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The *Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* were developed under the auspices of the Clinical & Scientific Section of the Canadian Diabetes Association. The following committee members contributed to these guidelines. All Committee members were volunteers and received no remuneration or honoraria for their participation.

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Notes to Readers

Overview

The Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada are intended to guide practice and are not intended to serve as a comprehensive text of diabetes management, nor are they intended to set criteria for research protocols. These guidelines are intended to inform general patterns of care. These guidelines are also intended to enhance diabetes prevention efforts in Canada and to reduce the burden of diabetes complications in people living with this disease.

As per the *Canadian Medical Association Handbook on Clinical Practice Guidelines* (Davis D, et al. Ottawa, ON: Canadian Medical Association; 2007), guidelines should not be used as a legal resource in malpractice cases as “their more general nature renders them insensitive to the particular circumstances of the individual cases.” Healthcare professionals must consider the needs, values and preferences of individual patients, use clinical judgement and work with available human and healthcare service resources in their settings. These guidelines were developed using the best available evidence. It is incumbent upon healthcare professionals to stay current in this rapidly changing field.

Unless otherwise specified, these guidelines pertain to the care of adults with diabetes. Two chapters—Type 1 Diabetes in Children and Adolescents and Type 2 Diabetes in Children and Adolescents—are included to highlight aspects of care that must be tailored to the pediatric population.

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Clinical Practice Guidelines

Introduction

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Alice Y.Y. Cheng MD, FRCPC

Every 5 years, since 1992, the Clinical & Scientific Section (C&SS) of the Canadian Diabetes Association has published comprehensive, evidence-based recommendations for healthcare professionals to consider in the prevention and management of diabetes in Canada. They have served as a helpful resource and aid for anyone caring for people with diabetes and are recognized, not only in Canada but also internationally, as high-quality, evidence-based clinical practice guidelines (1). In fact, an analysis by Bennett et al (1) demonstrated that the Canadian Diabetes Association clinical practice guidelines are among the best in the world with respect to quality, rigour and process (1). For these 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada, volunteer members of the Clinical Practice Guidelines Expert Committee assessed the peer reviewed evidence published since 2008 relevant to the prevention and management of diabetes. They then incorporated the evidence into revised diagnostic, prognostic and therapeutic recommendations for the care of Canadians living with diabetes, as well as recommendations for measures to delay the onset of diabetes for populations at high risk of developing type 2 diabetes.

A number of important changes have occurred in the development of the 2013 clinical practice guidelines:

- Expansion of the Expert Committee to include 120 healthcare professional volunteers from across Canada; Expert Committee members bring expertise from diverse practice settings and include professionals from family medicine, endocrinology, internal medicine, infectious disease, neurology, nephrology, cardiology, urology, psychology, obstetrics, ophthalmology, pediatrics, nursing, dietetics, pharmacy, exercise physiology and others.
- Inclusion and active participation of people with diabetes on the Expert Committee to ensure that their views and preferences informed the guideline development process and the recommendations.
- Update and expansion of previous chapters and, in some cases, amalgamation of previous chapters into others to increase utility and relevance.
- Inclusion of a drug cost appendix for pharmacological therapies as a reference for clinicians.
- Update and expansion of our Methodology process (e.g. updated literature searches throughout the guideline development process, expansion of the Duality of Interest policy) (see Methods chapter, p. S4).
- Inclusion of a "Practical Tips" box, where appropriate, to facilitate implementation of the recommendations.

- Expanded harmonization of recommendations through collaboration with other organizations, including the Canadian Hypertension Education Program (CHEP), the Society of Obstetricians and Gynecologists of Canada (SOGC), the Canadian Cardiovascular Society (CCS) and the Canadian Cardiovascular Harmonization of National Guidelines Endeavour (C-CHANGE).
- Expanded dissemination and implementation strategy with increased use of technology.

It is hoped that primary care physicians and other healthcare professionals who care for people with diabetes or those at risk of diabetes will continue to find the evidence compiled in these guidelines a vital aid and resource in their efforts. We are confident that, ultimately, if applied properly, these guidelines will lead to improved quality of care, reduced morbidity and mortality from diabetes and its complications, and a better quality of life for people living with this chronic disease.

The Challenge of Diabetes

Diabetes mellitus is a serious condition with potentially devastating complications that affects all age groups worldwide. In 1985, an estimated 30 million people around the world were diagnosed with diabetes; in 2000, that figure rose to over 150 million; and, in 2012, the International Diabetes Federation (IDF) estimated that 371 million people had diabetes (2). That number is projected to rise to 552 million (or 1 in 10 adults) by 2030, which equates to 3 new cases per second (2). Although the largest increase is expected to be in countries with developing economies, Canada also will be impacted significantly. As of 2009, the estimated prevalence of diabetes in Canada was 6.8% of the population—2.4 million Canadians (3)—a 230% increase compared to prevalence estimates in 1998. By 2019, that number is expected to grow to 3.7 million (3). Diabetes is the leading cause of blindness, end stage renal disease (ESRD) and nontraumatic amputation in Canadian adults. Cardiovascular disease is the leading cause of death in individuals with diabetes and occurs 2- to 4-fold more often than in people without diabetes. People with diabetes are over 3 times more likely to be hospitalized with cardiovascular disease, 12 times more likely to be hospitalized with ESRD and over 20 times more likely to be hospitalized for a nontraumatic lower limb amputation compared to the general population (3). Diabetes and its complications increase costs and service pressures on Canada's publicly funded healthcare system. Among adults aged 20 to 49 years, those with

diabetes were 2 times more likely to see a family physician and 2 to 3 times more likely to see a specialist (3). Also, people with diabetes were 3 times more likely to require hospital admission in the preceding year with longer lengths of stay (3). Therefore, the impact of diabetes is significant not only for individuals but also for their families and for society as a whole.

Delaying the Onset of Type 2 Diabetes

Prevention of type 1 diabetes has not yet been successful, but remains an active area of research. However, there is good evidence that delaying the onset of type 2 diabetes results in significant health benefits, including lower rates of cardiovascular disease and renal failure (4). In 2007, the IDF released a “Consensus on Type 2 Diabetes Prevention” and called upon the governments of all countries to develop and implement a National Diabetes Prevention Plan (4). The IDF proposed that strategies be implemented for 2 separate groups: those at high risk of developing type 2 diabetes, and the entire population at large. Among those at high risk, the proposed 3-step approach was to A) identify those who may be at higher risk, B) measure the risk, and C) intervene to delay/prevent the onset of type 2 diabetes using predominantly health behaviour strategies to affect the modifiable risk factors for type 2 diabetes. As of 2013, Canada does not have such a strategy in place. There remains an urgent and increasing need for governments to invest in research to define effective strategies and programs to prevent and treat obesity and to encourage physical activity. In addition, Canada’s diverse population, with some ethnic groups disproportionately affected by diabetes, requires that health promotion, and disease prevention and management strategies be culturally appropriate and tailored to specific populations. They also should include policies aimed at addressing poverty and other systemic barriers to healthcare (5).

Optimal Care of Diabetes

Effective diabetes care should be delivered within the framework of the Chronic Care Model and centred around the individual who is practicing, and supported in, self-management (see Organization of Care chapter, p. S20). To achieve this, an interprofessional team with the appropriate expertise is required, and the system needs to support and allow for sharing and collaboration between primary care and specialist care as needed. A multifactorial approach utilizing an interprofessional team addressing healthy behaviours, glycemic control, blood pressure control, lipid management and vascular protection measures has been shown to effectively and dramatically lower the risk of development and progression of serious complications for individuals with diabetes (6–9). In addition, individuals with diabetes must be supported in the skills of self-management since their involvement in disease management is absolutely necessary for success. People with diabetes require training in goal setting, problem solving and health monitoring, all of which are critical components of self-management. They also need access to a broad range of tools, including medications, devices and supplies to help them achieve the recommended blood glucose, cholesterol and blood pressure targets. Health outcomes depend on managing the disease effectively, and, without access to the necessary tools and strategies, Canadians living with diabetes will not be able to achieve optimal results. All levels of government should commit to investing in chronic care management and support of the tools needed for successful self-management to ensure that optimal care can be delivered.

Research

Canada continues to be a world leader in diabetes research. This research is essential for continued improvement in the lives of people

with diabetes. Regulatory agencies should not apply these guidelines in a rigid way with regard to clinical research in diabetes. It is suggested that study protocols may include guideline recommendations, but individual decisions belong in the domain of the patient-physician relationship. The merits of each research study must be assessed individually so as to not block or restrict the pursuit of new information. The Canadian Diabetes Association welcomes the opportunity to work with regulatory agencies to enhance research in Canada and, ultimately, to improve the care of people with diabetes.

Cost Considerations

When it comes to the issue of cost, caution is required when identifying direct, indirect and induced costs for treating diabetes (10). In fact, the 2011 Diabetes in Canada report from the Public Health Agency of Canada could not report the total economic burden of diabetes, but concluded that the costs will only increase substantially as the prevalence of the disease increases over time (3). Nonetheless, in 2009, the Canadian Diabetes Association commissioned a report to evaluate the economic burden of diabetes using a Canadian Diabetes Cost Model, which utilizes the data from the Canadian National Diabetes Surveillance System (NDSS) and the Economic Burden of Illness in Canada (EBIC) (11). In this report, the estimated economic burden of diabetes was \$12.2 billion in 2010 and projected to increase by another \$4.7 billion by 2020. It is certainly the hope and expectation of all stakeholders that the evidence-based prevention and management of diabetes in a multifactorial fashion will reduce the economic burden of the disease (3,6,12).

These clinical practice guidelines, like those published before, have purposefully not taken into account cost effectiveness in the evaluation of the evidence surrounding best practice. The numerous reasons for this have been outlined in detail previously (13). Some of these reasons include the paucity of cost-effectiveness analyses using Canadian data, the difficulty in truly accounting for all the important costs (e.g. hypoglycemia) in any cost-effectiveness analysis, the lack of expertise and resources to properly address the cost-effectiveness analyses needed for all the clinical questions within these clinical practice guidelines and, perhaps more importantly, the philosophical question of which is more important: clinical benefit to the patient or cost to the system? At what level of cost effectiveness should one consider a therapy worth recommending? For these 2013 clinical practice guidelines, the question of whether the committee should incorporate cost considerations was discussed again, and a Cost Consideration Working Group, consisting of health economists and health outcomes researchers, was convened. The mandate of the group was to develop a proposal to the Clinical Practice Guidelines Steering Committee describing how cost issues might be incorporated into the guidelines, considering feasibility and impact. Based on issues of feasibility and philosophical considerations of our role as recommendation developers, it was decided that cost would not be included in the recommendations to ensure that they reflect the best available clinical evidence for the patient. The issue of evidence-based vs. cost-effective healthcare is an ethical debate that should involve all citizens because the outcome of this debate ultimately impacts every Canadian. However, it is recognized and acknowledged that both the healthcare professional and the patient should consider cost when deciding on therapies. Therefore, drug costs are included in Appendix 5, allowing for easy reference for both clinicians and patients alike.

Other Considerations

In Canada, the glycated hemoglobin (A1C) continues to be reported using National Glycohemoglobin Standardization Program (NGSP) units (%). In 2007, a consensus statement from the American Diabetes Association, the European Association for the Study of

Diabetes and the IDF called for A1C reporting worldwide to change to dual reporting of A1C with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) SI units (mmol/mol) and derived NGSP units (%) with the hope of fully converting to exclusive reporting in SI units (14). However, this has not been adopted worldwide, with both Canada and the United States still using the NGSP units (%) (15). Although there are some advantages to reporting in SI units, the most notable disadvantage is the massive education effort that would be required to ensure recognition and adoption of the new units. At this time, Canada is not performing dual reporting. Therefore, throughout this document, the A1C will still be written in NGSP units (%). For those who wish to convert NGSP units to SI units, the following equation can be used: (16) $IFCC = 10.93(NGSP) - 23.50$.

Dissemination and Implementation

Despite the strength of the evidence supporting the multifactorial treatment of people with diabetes to reduce complications, a recent national cross-sectional survey conducted around World Diabetes Day (November 14, 2012) demonstrated that only 13% of 5123 patients with type 2 diabetes had achieved all 3 metabolic targets (glycemia, lipids and blood pressure) (17). Therefore, a care gap remains and the effective dissemination and implementation of these 2013 clinical practice guidelines is critical. A Dissemination & Implementation Chair was appointed at the beginning of the guidelines process. Strategies were developed to increase practitioner implementation and to improve patient care and health outcomes. A Dissemination & Implementation Committee was created to develop a strategic plan to be implemented at the launch of the guidelines and to continue for years thereafter. These volunteers from across Canada are involved in creating a 3-year plan to translate the evidence compiled in the guidelines into community practice. An Executive Summary will be distributed to healthcare professionals in Canada. The full guidelines will continue to be available online, and summary articles will be strategically placed in journals and newsletters. In addition, key messages and tools supporting specific themes from the guidelines will be highlighted in technology-based and paper-based awareness campaigns over the next few years. Primary care physicians, healthcare providers, government officials, Canadians living with diabetes and the general public continue to be the audiences for these campaigns.

Clinical Practice Guidelines and Clinical Judgement

“Neither evidence nor clinical judgment alone is sufficient. Evidence without judgment can be applied by a technician. Judgment without evidence can be applied by a friend. But the integration of evidence and judgment is what the healthcare provider does in order to dispense the best clinical care.” (Hertzel Gerstein, 2012)

People with diabetes are a diverse and heterogeneous group; therefore, it must be emphasized that treatment decisions need to be individualized. Guidelines are meant to aid in decision making by providing recommendations that are informed by the best available evidence. However, therapeutic decisions are made at the level of the relationship between the healthcare professional and the patient. That relationship, along with the importance of clinical judgement, can never be replaced by guideline recommendations. Evidence-based guidelines try to weigh the benefit and harm of various treatments; however, patient preferences are not always included in clinical research, and, therefore, patient values and preferences must be incorporated into clinical decision making (18). For some of the clinical decisions that we need to make with our patients, strong evidence is available to inform those decisions, and these are reflected in the recommendations within these guidelines. However, there are many other clinical situations where

strong evidence may not be available, or may never become available, for reasons of feasibility. In those situations, the consensus of expert opinions, informed by whatever evidence is available, is provided to help guide and aid the clinical decisions that need to be made at the level of the patient. It is also important to note that clinical practice guidelines are not intended to be a legal resource in malpractice cases as outlined in the *Canadian Medical Association Handbook on Clinical Practice Guidelines* (19).

Conclusions

Diabetes is a complex and complicated disease. The burgeoning evidence on new technologies and therapeutic treatments is rapidly expanding our knowledge and ability to manage diabetes and its complications; at the same time, however, it is challenging for physicians and other healthcare professionals who care for people with diabetes. These 2013 clinical practice guidelines contain evidence-based recommendations that provide a useful reference tool to help healthcare professionals translate the best available evidence into practice. The hope is that these guidelines will provide government officials with the evidence they need when rationalizing access to healthcare so that the potentially beneficial health outcomes are maximized for people living with diabetes. Healthcare professionals are encouraged to judge independently the value of the diagnostic, prognostic and therapeutic recommendations published in the 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada.

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Clinical Practice Guidelines

Methods

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Gillian Booth MD, MSc, FRCPC,
Alice Y.Y. Cheng MD, FRCPC

Process

Following the process used to develop previous Canadian Diabetes Association clinical practice guidelines (1,2), an Executive Committee, Steering Committee and Expert Committee with broad expertise and geographic representation were assembled. In total, 120 volunteers, including health professionals from family medicine, endocrinology, internal medicine, infectious disease, neurology, nephrology, cardiology, urology, psychology, obstetrics, ophthalmology, pediatrics, nursing, dietetics, pharmacy, exercise physiology and others, as well as people with diabetes, participated in the guideline development process.

The following basic principles were adopted to ensure that the values and empirical basis underlying each recommendation were explicitly identified and to facilitate the critical scrutiny and analysis of each recommendation by other organizations and individuals.

Elements covered by the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument were incorporated into the guideline development process.

- Each recommendation had to address a clinically important question related to 1 or more of the following: detection, prognosis, prevention or management of diabetes and its sequelae. Health benefits, risks and side effects of interventions were considered in formulating the recommendations. Patient preferences and values were sought from expert panel members with diabetes and the literature (where available).
- Whenever possible, each recommendation had to be justified by the strongest clinically relevant, empirical evidence that could be identified; the citation(s) reporting this evidence had to be noted adjacent to the relevant guideline.
- The strength of this evidence, based on prespecified criteria from the epidemiological literature and other guidelines processes, had to be noted (3–8).
- Each recommendation had to be assigned a grade based on the available evidence, its methodological strength and its applicability to the Canadian population.
- Each recommendation had to be approved by the Steering Committee and Executive Committee, with 100% consensus.
- Guidelines based on biological or mechanistic reasoning, expert opinion or consensus had to be explicitly identified and graded as such; harmonization was sought with other Canadian guideline bodies, including the Canadian Cardiovascular Society (CCS), the Canadian Hypertension Education Program

(CHEP), the Canadian Cardiovascular Harmonization of National Guidelines Endeavour (C-CHANGE) and the Society of Obstetricians and Gynecologists of Canada (SOGC).

Identifying and Appraising the Evidence

Authors for each chapter were assembled based on their relevant fields of expertise. Each chapter had 1 lead author, 1 or 2 “evidence resource” persons trained or experienced in clinical epidemiology or clinical research methodology, and additional authors, as needed. At the outset of the process, committee members from each section of the guidelines attended a workshop on evidence-based methodology, in order to ensure a consistent approach to the development of recommendations. Committee members identified clinically important questions related to diagnosis, prognosis, prevention and treatment of diabetes and its complications, which were used as a basis for our literature search strategy (outlined below).

Authors were to explicitly define A) the population to which a guideline would apply; B) the test, risk factor or intervention being addressed; C) the “gold standard” test or relevant intervention to which the test or intervention in question was compared; and D) the clinically relevant outcomes being targeted. This information was used to develop specific, clinically relevant questions that were the focus of literature searches. For each question, individual strategies were developed combining diabetes terms with methodological terms. A librarian with expertise in literature reviews performed a comprehensive search of the relevant English-language, published, peer-reviewed literature using validated search strategies (<http://hiru.mcmaster.ca/hiru/>) of electronic databases (MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Trials, and PsycINFO [where appropriate]). This was complemented by the authors' own manual and electronic searches.

For topics that were covered in the 2008 guidelines, the literature searches focused on new evidence published since those guidelines, including literature published in September 2007 or later. For new topics, the search time frame included the literature published since 1990 or earlier, where relevant. Updated literature searches were performed at regular intervals throughout the development process.

Key citations retrieved from the literature searches were then reviewed. Each citation that was used to formulate or revise a recommendation was assigned a level of evidence according to the prespecified criteria in Table 1, reflecting the methodological quality of the paper. When evaluating papers, authors were required to use standardized checklists that highlighted the most important

Table 1

Criteria for assigning levels of evidence to the published studies

Level	Criteria
Studies of diagnosis	
Level 1	a) Independent interpretation of test results (without knowledge of the result of the diagnostic or gold standard) b) Independent interpretation of the diagnostic standard (without knowledge of the test result) c) Selection of people suspected (but not known) to have the disorder d) Reproducible description of both the test and diagnostic standard e) At least 50 patients with and 50 patients without the disorder
Level 2	Meets 4 of the Level 1 criteria
Level 3	Meets 3 of the Level 1 criteria
Level 4	Meets 1 or 2 of the Level 1 criteria
Studies of treatment and prevention	
Level 1A	Systematic overview or meta-analysis of high quality RCTs a) Comprehensive search for evidence b) Authors avoided bias in selecting articles for inclusion c) Authors assessed each article for validity d) Reports clear conclusions that are supported by the data and appropriate analyses OR Appropriately designed RCT with adequate power to answer the question posed by the investigators a) Patients were randomly allocated to treatment groups b) Follow-up at least 80% complete c) Patients and investigators were blinded to the treatment* d) Patients were analyzed in the treatment groups to which they were assigned e) The sample size was large enough to detect the outcome of interest
Level 1B	Nonrandomized clinical trial or cohort study with indisputable results
Level 2	RCT or systematic overview that does not meet Level 1 criteria
Level 3	Nonrandomized clinical trial or cohort study; systematic overview or meta-analysis of level 3 studies
Level 4	Other
Studies of prognosis	
Level 1	a) Inception cohort of patients with the condition of interest but free of the outcome of interest b) Reproducible inclusion/exclusion criteria c) Follow-up of at least 80% of subjects d) Statistical adjustment for extraneous prognostic factors (confounders) e) Reproducible description of outcome measures
Level 2	Meets criterion a) above, plus 3 of the other 4 criteria
Level 3	Meets criterion a) above, plus 2 of the other criteria
Level 4	Meets criterion a) above, plus 1 of the other criteria

RCT, randomized, controlled trial.

* In cases where such blinding was not possible or was impractical (e.g. intensive vs. conventional insulin therapy), the blinding of individuals who assessed and adjudicated study outcomes was felt to be sufficient.

elements of a well-conducted study. The level of evidence was then determined by the cited paper's objectives, methodological rigour, susceptibility to bias and generalizability (Table 1). Because they could not be critically appraised, meeting abstracts, narrative review articles, news reports and other sources could not be used to support recommendations. Papers evaluating the cost effectiveness of therapies or diagnostic tests also were not included.

A number of considerations were made when evaluating the evidence within a given area. For example, people with diabetes are at high risk for several sequelae that are not exclusive to diabetes (e.g. cardiovascular disease, renal failure and erectile dysfunction). As such, some evidence relating to these problems was identified that either excluded, did not report on or did not focus on people with diabetes.

Whenever such evidence was identified, a level was assigned using the approach described above. Higher levels were assigned if A) people with diabetes comprised a predefined subgroup; B) the results in the diabetes subgroup were unlikely to have occurred by

chance; and C) the evidence was generated in response to questions that were formulated prior to the analysis of the results. Lower levels (than those indicated in Table 1) were assigned to evidence that did not meet these criteria.

Guideline Development

Expert Committee members evaluated the relevant literature, and guidelines were developed and initially reviewed by the Expert Committee. In the absence of new evidence since the publication of the 2008 clinical practice guidelines, recommendations from the 2008 document were not changed.

The studies used to develop and support each recommendation are cited beside the level of evidence. In some cases, key citations that influenced the final recommendation were not assigned the same level of evidence but rather were of varying levels of evidence. In those circumstances, all relevant studies were cited, regardless of the grading assigned to the recommendation. The final grading depended on the overall evidence available, including the relative strengths of the studies from a methodological perspective and the studies' findings. Studies with conflicting outcomes were also considered and cited in the final recommendation where relevant. Further details on the grading process are described below.

Finally, several treatment recommendations were based on evidence generated from the use of one therapeutic agent from a given class (e.g. one of the statins). Whenever evidence relating to 1 or more agents from a recognized class of agents was available, the recommendation was written so as to be relevant to the class, but specifically studied therapeutic agents were identified within the recommendation and/or cited reference(s). Only medications with Health Canada Notice of Compliance granted by February 15, 2013 were included in the recommendations.

Grading the Recommendations

After formulating new recommendations or modifying existing ones based on new evidence, each recommendation was assigned a grade from A through D (Table 2). The highest possible grade that a recommendation could have was based on the strength of evidence that supported the recommendation (i.e. the highest level of evidence assigned to studies on which the recommendation was based). However, the assigned grading was lowered in some cases, for example, if the evidence was found not to be applicable to the Canadian population or, if based on the consensus of the Steering and Executive Committees, there were additional concerns regarding the recommendation. In some situations, the grading also was lowered for subgroups that were not well represented in the study or in whom the beneficial effect of an intervention was less clear. Grading also was lowered if the findings from relevant (and equally rigorous) studies on the topic were conflicting. Thus, a recommendation based on Level 1 evidence, deemed to be very applicable to Canadians and supported by strong consensus, was assigned a grade of A. A recommendation not deemed to be applicable to Canadians, or judged to require further supporting evidence, was assigned a lower grade. Where available, the number of patients that would need to be treated in order to prevent 1 clinical event (number needed to treat [NNT]) or to cause an adverse event (number needed to harm [NNH]) was considered in assessing the impact of a particular intervention.

Table 2

Criteria for assigning grades of recommendations for clinical practice

Grade	Criteria
Grade A	The best evidence was at Level 1
Grade B	The best evidence was at Level 2
Grade C	The best evidence was at Level 3
Grade D	The best evidence was at Level 4 or consensus

The degree to which evidence derived from other populations was felt to be relevant to diabetes also was reflected in the wording and grading of the recommendation. Finally, in the absence of Level 1, 2 or 3 supporting evidence, or if the recommendation was based on the consensus of the Steering and Executive Committees, the highest grade that could be assigned was D.

Interpreting the Assigned Grade of a Recommendation

The grade assigned to each recommendation is closely linked to the methodological rigour and robustness of the relevant clinical research. Therefore, as noted above, a high grade reflects a high degree of confidence that following the recommendation will lead to the desired outcome. Similarly, a lower grade reflects weaker evidence and a greater possibility that the recommendation will change when more evidence is generated in the future. Of note, the assigned grade contains no subjective information regarding the importance of the recommendation or how strongly members of the committee felt about it; it only contains information regarding the evidence upon which the recommendation is based. Thus, many Grade D recommendations were deemed to be very important to the contemporary management of diabetes, based on clinical experience, case series, physiological evidence and current concepts of disease pathophysiology. However, the paucity of clinical evidence addressing the areas of therapy, prevention, diagnosis or prognosis precluded the assignment of a higher grade.

Clearly, clinicians need to base clinical decisions on the best available relevant evidence that addresses clinical situations. However, they also frequently are faced with having to act in the absence of clinical evidence, and there are many situations where good clinical evidence may be impossible, impractical or too expensive to generate (which implies that it would be impossible to develop Grade A recommendations). For example, it took the United Kingdom Prospective Diabetes Study (UKPDS) Group >20 years to collect and publish Level 1 evidence leading to a Grade A recommendation in support of the role of tight glycemic control to reduce microvascular disease in people with type 2 diabetes. Prior to the publication of the UKPDS results, the recommendation for glycemic control to prevent microvascular consequences was a Grade B recommendation (9).

Varying grades of recommendations, therefore, reflect varying degrees of certainty regarding the strength of inference that can be drawn from the evidence in support of the recommendation. Therefore, these evidence-based guidelines and their graded recommendations are designed to satisfy 2 important needs: 1) the explicit identification of the best research upon which the recommendation is based and an assessment of its scientific relevance and quality (captured by the assignment of a level of evidence to each citation); and 2) the explicit assignment of strength of the recommendation based on this evidence (captured by the grade). In this way, they provide a convenient summary of the evidence to facilitate clinicians in the task of “weighting” and incorporating ever increasing evidence into their daily clinical decision making. They also facilitate the ability of clinicians, healthcare planners, healthcare providers and society, in general, to critically examine any recommendation and arrive at their own conclusions regarding its appropriateness. Thus, these guidelines facilitate their own scrutiny by others according to the same principles that they use to scrutinize the literature.

It is important to note that the system chosen for grading recommendations differs from the approach used in some other guideline documents, such as the one pertaining to the periodic health examination in Canada, in which harmful practices were assigned a grade of D (8). In this Canadian Diabetes Association guidelines document, recommendation to avoid any harmful practices would be graded in the same manner as all other

recommendations. However, it should be noted that the authors of these guidelines focused on clinical practices that were thought to be potentially beneficial and did not seek out evidence regarding the harmfulness of interventions.

External Peer Review and Independent Methodological Review

In May 2012, a draft document was circulated nationally and internationally for review by numerous stakeholders and experts in relevant fields. This input was then considered by the Executive and Steering Committees, and revisions were made accordingly. Subsequently, a panel of 6 methodologists, who were not directly involved with the initial review and assessment of the evidence, independently reviewed each recommendation, its assigned grade and supportive citations. Based on this review, the wording, assigned level of evidence and grade of each recommendation were reassessed and modified as necessary. Revised recommendations were reviewed and approved by the Executive and Steering Committees. Selected recommendations were presented at a public forum at the Canadian Diabetes Association/Canadian Society of Endocrinology and Metabolism Professional Conference and Annual Meetings in Vancouver, British Columbia, on October 13, 2012.

Disclosure of Duality of Interest

Committee members were volunteers and received no remuneration or honoraria for their participation. Members of all committees signed an annual duality of interest form listing all financial interests or relationships with manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services. Dualities of interest were discussed during deliberations where relevant. In the case of a potential duality or outright conflict of interest, committee members removed themselves from discussions. Funding for the development of the guidelines was provided from the general funds of the Canadian Diabetes Association and from unrestricted educational grants from Novo Nordisk Canada Inc, Eli Lilly Canada Inc, Merck Canada Inc, Bristol-Myers Squibb and AstraZeneca, and Novartis Pharmaceuticals Canada Inc. These companies were not involved in any aspect of guideline development, literature interpretation, the decision to publish or any other aspect related to the publication of these guidelines, and they did not have access to guideline meetings, guideline drafts or committee deliberations.

Guideline Updates

A process to update the full guidelines will commence within 5 years and will be published in 2018. Updates to individual chapters may be published sooner in the event of significant changes in evidence supporting the recommendations. The Executive and Steering Committees of the 2013 revision will continue to remain intact to deliberate any potential updates to individual chapters until such time as the Executive and Steering Committees for the 2018 revision have been created.

Other Relevant Guidelines

Introduction, p. S1

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Clinical Practice Guidelines

Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- The chronic hyperglycemia of diabetes is associated with significant long-term microvascular and macrovascular complications.
- A fasting plasma glucose level of ≥ 7.0 mmol/L, a 2-hour plasma glucose value in a 75 g oral glucose tolerance test of ≥ 11.1 mmol/L or a glycated hemoglobin (A1C) value of $\geq 6.5\%$ can predict the development of retinopathy. This permits the diagnosis of diabetes to be made on the basis of each of these parameters.
- The term “prediabetes” refers to impaired fasting glucose, impaired glucose tolerance or an A1C of 6.0% to 6.4%, each of which places individuals at high risk of developing diabetes and its complications.

Definition of Diabetes and Prediabetes

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (CVD). The diagnostic criteria for diabetes are based on thresholds of glycemia that are associated with microvascular disease, especially retinopathy.

“Prediabetes” is a practical and convenient term referring to impaired fasting glucose (IFG), impaired glucose tolerance (IGT) (1) or a glycated hemoglobin (A1C) of 6.0% to 6.4%, each of which places individuals at high risk of developing diabetes and its complications.

Classification of Diabetes

The classification of type 1 diabetes, type 2 diabetes and gestational diabetes mellitus (GDM) is summarized in Table 1. Appendix 1 addresses the etiologic classification of diabetes. Distinguishing between type 1 and type 2 diabetes is important because management strategies differ, but it may be difficult at the time of diagnosis in certain situations. Physical signs of insulin resistance and autoimmune markers, such as anti-glutamic acid decarboxylase (GAD) or anti-islet cell antibody (ICA) antibodies, may be helpful, but have not been adequately studied as diagnostic tests in this setting. While very low C-peptide levels measured after

months of clinical stabilization may favour type 1 diabetes (2), they are not helpful in acute hyperglycemia (3). Clinical judgement with safe management and ongoing follow-up is a prudent approach.

Diagnostic Criteria

Diabetes

The diagnostic criteria for diabetes are summarized in Table 2 (1). These criteria are based on venous samples and laboratory methods.

A fasting plasma glucose (FPG) level of 7.0 mmol/L correlates most closely with a 2-hour plasma glucose (2hPG) value of ≥ 11.1 mmol/L in a 75 g oral glucose tolerance test (OGTT), and each predicts the development of retinopathy (5–11).

The relationship between A1C and retinopathy is similar to that of FPG or 2hPG with a threshold at around 6.5% (5–7,11,12). Although the diagnosis of diabetes is based on an A1C threshold for developing microvascular disease, A1C is also a continuous cardiovascular (CV) risk factor and a better predictor of macrovascular events than FPG or 2hPG (13,14). Although many people identified by A1C as having diabetes will not have diabetes by traditional glucose criteria and vice versa, there are several advantages to using A1C for diabetes diagnosis (15). A1C can be measured at any time of day and is more convenient than FPG or 2hPG in a 75 g OGTT. A1C testing also avoids the problem of day-to-day variability of glucose values as it reflects the average plasma glucose (PG) over the previous 2 to 3 months (1).

In order to use A1C as a diagnostic criterion, A1C must be measured using a validated assay standardized to the National Glycohemoglobin Standardization Program-Diabetes Control and Complications Trial reference. It is important to note that A1C may be misleading in individuals with various hemoglobinopathies, iron deficiency, hemolytic anaemias, and severe hepatic and renal disease (16). In addition, studies of various ethnicities indicate that African Americans, American Indians, Hispanics and Asians have A1C values that are up to 0.4% higher than those of Caucasian patients at similar levels of glycemia (17,18). The frequency of retinopathy begins to increase at lower A1C levels in American blacks than in American whites, which suggests a lower threshold for diagnosing diabetes in black persons (19). Research is required

Table 1
Classification of diabetes (1)

<ul style="list-style-type: none"> • Type 1 diabetes* encompasses diabetes that is primarily a result of pancreatic beta cell destruction and is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown. • Type 2 diabetes may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance. • Gestational diabetes mellitus refers to glucose intolerance with onset or first recognition during pregnancy. • Other specific types include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use (Appendix 1).
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* Includes latent autoimmune diabetes in adults (LADA); the term used to describe the small number of people with apparent type 2 diabetes who appear to have immune-mediated loss of pancreatic beta cells (4).

to determine if A1C levels differ in African Canadians or Canadian First Nations. A1C values also are affected by age, rising by up to 0.1% per decade of life (20,21). More studies may help to determine if age- or ethnic-specific adjusted A1C thresholds are required for diabetes diagnosis. Also, A1C is not recommended for diagnostic purposes in children, adolescents, pregnant women or those with suspected type 1 diabetes.

The decision of which test to use for diabetes diagnosis (Table 2) is left to clinical judgement. Each diagnostic test has advantages and disadvantages (Table 3). In the absence of symptomatic hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. In the case of symptomatic hyperglycemia, the diagnosis has been made and a confirmatory test is not required before treatment is initiated. In individuals in whom type 1 diabetes is likely (younger or lean or symptomatic hyperglycemia, especially with ketonuria or ketonemia), confirmatory testing should not delay initiation of treatment to avoid rapid deterioration. If results of 2 different tests are available and both are above the diagnostic cutpoints, the diagnosis of diabetes is confirmed. When the results of more than 1 test are available (among

Table 2
Diagnosis of diabetes

FPG ≥ 7.0 mmol/L
Fasting = no caloric intake for at least 8 hours
or
A1C $\geq 6.5\%$ (in adults)
Using a standardized, validated assay in the absence of factors that affect the accuracy of the A1C and not for suspected type 1 diabetes (see text)
or
2hPG in a 75 g OGTT ≥ 11.1 mmol/L
or
Random PG ≥ 11.1 mmol/L
Random = any time of the day, without regard to the interval since the last meal

In the absence of symptomatic hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. In the case of symptomatic hyperglycemia, the diagnosis has been made and a confirmatory test is not required before treatment is initiated. In individuals in whom type 1 diabetes is likely (younger or lean or symptomatic hyperglycemia, especially with ketonuria or ketonemia), confirmatory testing should not delay initiation of treatment to avoid rapid deterioration. If results of 2 different tests are available and both are above the diagnostic cutpoints, the diagnosis of diabetes is confirmed.

2hPG, 2-hour plasma glucose; A1C, glycated hemoglobin; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PG, plasma glucose.

Table 3
Advantages and disadvantages of diagnostic tests for diabetes* (22)

Parameter	Advantages	Disadvantages
FPG	<ul style="list-style-type: none"> • Established standard • Fast and easy • Single sample • Predicts microvascular complications 	<ul style="list-style-type: none"> • Sample not stable • High day-to-day variability • Inconvenient (fasting) • Reflects glucose homeostasis at a single point in time
2hPG in a 75 g OGTT	<ul style="list-style-type: none"> • Established standard • Predicts microvascular complications 	<ul style="list-style-type: none"> • Sample not stable • High day-to-day variability • Inconvenient • Unpalatable • Cost
A1C	<ul style="list-style-type: none"> • Convenient (measure any time of day) • Single sample • Predicts microvascular complications • Better predictor of macrovascular disease than FPG or 2hPG in a 75 g OGTT • Low day-to-day variability • Reflects long-term glucose concentration 	<ul style="list-style-type: none"> • Cost • Misleading in various medical conditions (e.g. hemoglobinopathies, iron deficiency, hemolytic anaemia, severe hepatic or renal disease) • Altered by ethnicity and aging • Standardized, validated assay required • Not for diagnostic use in children, adolescents, pregnant women or those with suspected type 1 diabetes

2hPG, 2-hour plasma glucose; A1C, glycated hemoglobin; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.

* Adapted from Sacks D. A1C versus glucose testing: a comparison. Diabetes Care. 2011;34:518–523.

FPG, A1C, 2hPG in a 75 g OGTT) and the results are discordant, the test whose result is above the diagnostic cutpoint should be repeated and the diagnosis made on the basis of the repeat test.

Prediabetes

The term “prediabetes” refers to IFG, IGT or an A1C of 6.0% to 6.4% (Table 4), each of which places individuals at high risk of developing diabetes and its complications. Not all individuals with prediabetes will necessarily progress to diabetes. Indeed, a significant proportion of people who are diagnosed with IFG or IGT will revert to normoglycemia. People with prediabetes, particularly in the context of the metabolic syndrome, would benefit from CV risk factor modification.

While people with prediabetes do not have the increased risk for microvascular disease as seen in diabetes, they are at risk for the development of diabetes and CVD (23). IGT is more strongly associated with CVD outcomes than is IFG. Individuals identified as having both IFG and IGT are at higher risk for diabetes as well as CVD. While there is no worldwide consensus on the definition of IFG (24,25), the Canadian Diabetes Association defines IFG as an FPG value of 6.1 to 6.9 mmol/L due to the higher risk of developing diabetes in these individuals compared to defining IFG as an FPG value of 5.6 to 6.9 mmol/L (25).

While there is a continuum of risk for diabetes in individuals with A1C levels between 5.5% and 6.4%, population studies demonstrate that A1C levels of 6.0% to 6.4% are associated with

Table 4
Diagnosis of prediabetes

Test	Result	Prediabetes category
FPG (mmol/L)	6.1–6.9	IFG
2hPG in a 75 g OGTT (mmol/L)	7.8–11.0	IGT
A1C (%)	6.0–6.4	Prediabetes

2hPG, 2-hour plasma glucose; A1C, glycated hemoglobin; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

Table 5
Harmonized definition of the metabolic syndrome: ≥3 measures to make the diagnosis of metabolic syndrome* (29)

Measure	Categorical cutpoints	
	Men	Women
Elevated waist circumference (population- and country-specific cutpoints):		
• Canada, United States	≥102 cm	≥88 cm
• Euroid, Middle Eastern, sub-Saharan African, Mediterranean	≥94 cm	≥80 cm
• Asian, Japanese, South and Central American	≥90 cm	≥80 cm
Elevated TG (drug treatment for elevated TG is an alternate indicator [†])	≥1.7 mmol/L	
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator [†])	<1.0 mmol/L in males, <1.3 mmol/L in females	
Elevated BP (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg	
Elevated FPG (drug treatment of elevated glucose is an alternate indicator)	≥5.6 mmol/L	

BP, blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.
Three or more criteria are required for diagnosis.

* Adapted from Alberti KGMM, Eckel R, Grundy S, et al. Harmonizing the metabolic syndrome. *Circulation*. 2009;120:1640-1645.
[†] The most commonly used drugs for elevated TG and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high TG and reduced HDL-C. High-dose omega-3 fatty acids presumes high TG.

a higher risk for diabetes compared to levels between 5.5% and 6.0% (26). While the American Diabetes Association defines prediabetes as an A1C between 5.7% and 6.4%, the Canadian Diabetes Association has based the definition on a higher risk group and includes an A1C of 6.0% to 6.4% as a diagnostic criterion for prediabetes (1). However, A1C levels below 6.0% can indeed be associated with an increased risk for diabetes (26). The combination of an FPG of 6.1 to 6.9 mmol/L and an A1C of 6.0% to 6.4% is predictive of 100% progression to type 2 diabetes over a 5-year period (27).

Metabolic syndrome

Prediabetes and type 2 diabetes are often manifestations of a much broader underlying disorder (28), including the metabolic

syndrome—a highly prevalent, multifaceted condition characterized by a constellation of abnormalities that include abdominal obesity, hypertension, dyslipidemia and elevated blood glucose. Individuals with the metabolic syndrome are at significant risk of developing CVD. While metabolic syndrome and type 2 diabetes often coexist, those with metabolic syndrome without diabetes are at significant risk of developing diabetes. Evidence exists to support an aggressive approach to identifying and treating people, not only those with hyperglycemia but also those with the associated CV risk factors that make up the metabolic syndrome, such as hypertension, dyslipidemia and abdominal obesity, in the hope of significantly reducing CV morbidity and mortality.

Various diagnostic criteria for the metabolic syndrome have been proposed. In 2009, a harmonized definition of the metabolic syndrome was established, with at least 3 or more criteria required for diagnosis (Table 5) (29).

RECOMMENDATIONS

1. Diabetes should be diagnosed by any of the following criteria:
 - FPG ≥7.0 mmol/L [Grade B, Level 2 (11)]
 - A1C ≥6.5% (for use in adults in the absence of factors that affect the accuracy of A1C and not for use in those with suspected type 1 diabetes) [Grade B, Level 2 (11)]
 - 2hPG in a 75 g OGTT ≥11.1 mmol/L [Grade B, Level 2 (11)]
 - Random PG ≥11.1 mmol/L [Grade D, Consensus]
2. In the absence of symptomatic hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. In the case of symptomatic hyperglycemia, the diagnosis has been made and a confirmatory test is not required before treatment is initiated. In individuals in whom type 1 diabetes is likely (younger or lean or symptomatic hyperglycemia, especially with ketonuria or ketonemia), confirmatory testing should not delay initiation of treatment to avoid rapid deterioration. If results of two different tests are available and both are above the diagnostic cutpoints, the diagnosis of diabetes is confirmed [Grade D, Consensus].
3. Prediabetes (defined as a state which places individuals at high risk of developing diabetes and its complications) is diagnosed by any of the following criteria:
 - IFG (FPG 6.1–6.9 mmol/L) [Grade A, Level 1 (23)]
 - IGT (2hPG in a 75 g OGTT 7.8–11.0 mmol/L) [Grade A, Level 1 (23)]
 - A1C 6.0%–6.4% (for use in adults in the absence of factors that affect the accuracy of A1C and not for use in suspected type 1 diabetes) [Grade B, Level 2 (26)].

Abbreviations:
2hPG, 2-hour plasma glucose; A1C, glycated hemoglobin; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose.

Other Relevant Guidelines

- Screening for Type 1 and Type 2 Diabetes, p. S12
- Reducing the Risk of Developing Diabetes, p. S16
- Type 1 Diabetes in Children and Adolescents, p. S153
- Type 2 Diabetes in Children and Adolescents, p. S163

Relevant Appendix

- Appendix 1. Etiologic Classification of Diabetes Mellitus

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Clinical Practice Guidelines

Screening for Type 1 and Type 2 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- In the absence of evidence for interventions to prevent or delay type 1 diabetes, screening for type 1 diabetes is not recommended.
- Screening for type 2 diabetes using a fasting plasma glucose (FPG) and/or glycated hemoglobin (A1C) should be performed every 3 years in individuals ≥ 40 years of age or in individuals at high risk using a risk calculator.
- Diabetes will be diagnosed if A1C is $\geq 6.5\%$ (see Definition, Classification and Diagnosis chapter, p. S8).
- Testing with a 2-hour plasma glucose (2hPG) in a 75 g oral glucose tolerance test (OGTT) should be undertaken in individuals with an FPG of 6.1–6.9 mmol/L and/or an A1C of 6.0%–6.4% in order to identify individuals with impaired glucose tolerance (IGT) or diabetes.
- Testing with a 2hPG in a 75 g OGTT may be undertaken in individuals with an FPG 5.6–6.0 mmol/L and/or A1C 5.5%–5.9% and ≥ 1 risk factor in order to identify individuals with IGT or diabetes.

The clinical spectrum of diabetes ranges from a low-risk to a higher-risk individual or to the symptomatic patient who needs immediate treatment. Screening for diabetes implies testing for diabetes in individuals without symptoms who are unaware of their condition. Screening for diabetes will also detect individuals at increased risk for diabetes (prediabetes) or individuals with less severe states of dysglycemia who may still be at risk for type 2 diabetes. Screening strategies vary according to the type of diabetes and evidence of effective interventions to prevent progression of prediabetes to diabetes and/or reduce the risk of complications associated with diabetes. The growing importance of diabetes screening is undeniable (1).

In contrast to other diseases, there is no distinction between screening and diagnostic testing. Therefore, to screen for diabetes and prediabetes, the same tests would be used as for diagnosis of both medical conditions (see Definition, Classification and Diagnosis chapter, p. S8).

Screening for Type 1 Diabetes

Type 1 diabetes mellitus is primarily a result of pancreatic beta cell destruction due to an immune-mediated process that is likely incited by environmental factors in genetically predisposed individuals. An individual's risk of developing type 1 diabetes can be estimated by considering family history of type 1 diabetes with attention to age of onset and sex of the affected family members (2) and profiling

immunity and genetic markers (3). The loss of pancreatic beta cells in the development of type 1 diabetes passes through a subclinical prodrome that can be detected reliably in first- and second-degree relatives of persons with type 1 diabetes by the presence of pancreatic islet autoantibodies in their sera (4). However, in a recent large study, one-time screening for glutamic acid decarboxylase antibodies (GADAs) and islet antigen-2 antibodies (IA-2As) in the general childhood population in Finland would identify 60% of those individuals who will develop type 1 diabetes over the next 27 years. Initial positivity for GADAs and/or IA-2As had a sensitivity of 61% (95% confidence interval [CI] 36–83%) for type 1 diabetes. The combined positivity for GADAs and IA-2As had both a specificity and a positive predictive value of 100% (95% CI 59–100%) (5). Ongoing clinical studies are testing different strategies for preventing or reversing early type 1 diabetes in the presence of positive autoimmunity. Given that the various serological markers are not universally available and in the absence of evidence for interventions to prevent or delay type 1 diabetes, no widespread recommendations for screening for type 1 diabetes can be made.

Screening for Type 2 Diabetes

Adults

Undiagnosed type 2 diabetes may occur in $>2.8\%$ of the general adult population (6), and the number increases to $>10\%$ in some populations (7,8). Tests for hyperglycemia can identify these individuals, many of whom will have, or will be at risk for, preventable diabetes complications (5,6). To be effective, population-based screening would have to involve wide coverage and would have the goal of early identification and subsequent intervention to reduce morbidity and mortality. Using various multistaged screening strategies, the ADDITION-Europe study showed that 20% to 94% of eligible people in primary care practices attended the first blood glucose test of the screening process, and diabetes was detected in 0.33% to 1.09% of the target populations, which was lower than expected (9). In the subsequent ADDITION-Europe cluster randomized trial of intensive multifaceted cardiovascular risk factor management vs. routine diabetes care among screening-identified type 2 diabetes patients, intensive management did not reduce cardiovascular events (hazard ratio 0.83; 95% CI 0.65–1.05) or all-cause mortality (hazard ratio 0.91;

Table 1

Risk factors for type 2 diabetes

- Age ≥ 40 years
- First-degree relative with type 2 diabetes
- Member of high-risk population (e.g. Aboriginal, African, Asian, Hispanic or South Asian descent)
- History of prediabetes (IGT, IFG or A1C 6.0%–6.4%)*
- History of gestational diabetes mellitus
- History of delivery of a macrosomic infant
- Presence of end organ damage associated with diabetes:
 - Microvascular (retinopathy, neuropathy, nephropathy)
 - Macrovascular (coronary, cerebrovascular, peripheral)
- Presence of vascular risk factors:
 - HDL cholesterol level <1.0 mmol/L in males, <1.3 mmol/L in females*
 - Triglycerides ≥ 1.7 mmol/L*
 - Hypertension*
 - Overweight*
 - Abdominal obesity*
- Presence of associated diseases:
 - Polycystic ovary syndrome*
 - Acanthosis nigricans*
 - Psychiatric disorders (bipolar disorder, depression, schizophrenia[†])
 - HIV infection[‡]
 - OSA[§]
- Use of drugs associated with diabetes:
 - Glucocorticoids
 - Atypical antipsychotics
 - HAART[‡]
 - Other (see Appendix 1)
- Other secondary causes (see Appendix 1)

A1C, glycated hemoglobin; HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein; HIV, human immunodeficiency virus-1; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OSA, obstructive sleep apnea.

* Associated with insulin resistance.

[†] The incidence of type 2 diabetes is at least 3 times higher in people with schizophrenia than in the general population (25,26). Using data collected in 1991, the prevalence of diabetes was assessed in $>20,000$ individuals diagnosed with schizophrenia. The rate of diagnosed diabetes was 9% to 14%, exceeding rates for the general population prior to the widespread use of new antipsychotic drugs (27).

[‡] HIV and HAART increase the risk of prediabetes (IGT) and type 2 diabetes by 1.5- to 4-fold compared to the general population (28).

[§] OSA is an independent risk factor for diabetes (hazard ratio 1.43) (29).

95% CI 0.69–1.21) (10). Of note, a very high proportion of the routine care group also received optimal cardiovascular risk factor management, which may have diluted any potential benefits. In ADDITION-Cambridge, population-based screening for type 2 diabetes was not associated with a reduction in all-cause, cardiovascular or diabetes-related mortality within 10 years compared to a no-screening control group. However, the low rate of type 2 diabetes in the screened population (3%) was likely too small to affect overall population mortality (11). Nonetheless, there is no current evidence of clinical benefit to support a strategy of population-based screening for type 2 diabetes.

Although the relatively low prevalence of diabetes in the general population makes it unlikely that mass screening will be cost effective, testing for diabetes in people with risk factors for type 2 diabetes or with diabetes-associated conditions is likely to result in more benefit than harm and will lead to overall cost savings (12–17). Routine testing for type 2 diabetes is, therefore, justifiable in some but not all settings (18,19). Screening individuals as early as age 40 years in family physicians' offices has proved to be useful in detecting unrecognized diabetes (20).

While fasting plasma glucose (FPG) and/or glycated hemoglobin (A1C) are the recommended screening tests, a 75 g oral glucose tolerance test (OGTT) is indicated when the FPG is 6.1 to 6.9 mmol/L (14) and/or A1C is 6.0% to 6.4%. It may be indicated when the FPG is 5.6 to 6.0 mmol/L and/or A1C is 5.5% to 5.9% and suspicion of type 2 diabetes or impaired glucose tolerance (IGT) is high (e.g. for individuals with risk factors listed in Table 1) (Figure 1).

People with prediabetes, especially those with IGT or an A1C of 6.0% to 6.4%, not only are at increased risk of developing type 2 diabetes, but they also have an increased risk of macrovascular

complications, particularly in the context of the metabolic syndrome (21). These individuals would benefit from cardiovascular risk factor reduction strategies (1). Members of high-risk ethnic populations (Table 1) should be screened for prediabetes and type 2 diabetes using the recommended screening tests, such as FPG, OGTT and A1C. However, the high prevalence of hemoglobinopathies among these populations may considerably reduce the accuracy of A1C as a reliable screening tool in these populations. Furthermore, high-risk ethnic groups may have A1C levels that are slightly higher than those of Caucasians at the same level of glycemia, and more studies may help determine ethnic-specific A1C thresholds for diabetes diagnosis (see Definition, Classification and Diagnosis chapter, p. S8).

Risk prediction tools for type 2 diabetes mellitus

A number of risk scores based on clinical characteristics have been developed to identify individuals at high risk of having undiagnosed diabetes. However, the impact of known risk factors

RECOMMENDATIONS

1. All individuals should be evaluated annually for type 2 diabetes risk on the basis of demographic and clinical criteria [Grade D, Consensus].
2. Screening for diabetes using FPG and/or A1C should be performed every 3 years in individuals ≥ 40 years of age or at high risk using a risk calculator [Grade D, Consensus]. More frequent and/or earlier testing with either FPG and/or A1C or 2hPG in a 75 g OGTT should be considered in those at very high risk using a risk calculator or in people with additional risk factors for diabetes [Grade D, Consensus]. These risk factors include:
 - First-degree relative with type 2 diabetes
 - Member of high-risk population (e.g. Aboriginal, African, Asian, Hispanic or South Asian descent)
 - History of prediabetes (IGT, IFG, or A1C 6.0%–6.4%)
 - History of gestational diabetes mellitus
 - History of delivery of a macrosomic infant
 - Presence of end organ damage complications associated with diabetes:
 - Microvascular (retinopathy, neuropathy, nephropathy)
 - Macrovascular (coronary, cerebrovascular, peripheral)
 - Presence of vascular risk factors:
 - HDL cholesterol <1.0 mmol/L in males, <1.3 mmol/L in females
 - Triglycerides ≥ 1.7 mmol/L
 - Hypertension
 - Overweight
 - Abdominal obesity
 - Presence of associated diseases:
 - Polycystic ovary syndrome
 - Acanthosis nigricans
 - Obstructive sleep apnea
 - Psychiatric disorders (bipolar disorder, depression, schizophrenia)
 - HIV infection
 - Use of drugs associated with diabetes:
 - Glucocorticoids
 - Atypical antipsychotics
 - HAART
 - Other (see Appendix 1)
 - Other secondary causes (see Appendix 1)
3. Testing with 2hPG in a 75 g OGTT should be undertaken in individuals with FPG 6.1–6.9 mmol/L and/or A1C 6.0%–6.4% in order to identify individuals with IGT or diabetes [Grade D, Consensus].
4. Testing with 2hPG in a 75 g OGTT may be undertaken in individuals with FPG 5.6–6.0 mmol/L and/or A1C 5.5%–5.9% and ≥ 1 risk factor(s) in order to identify individuals with IGT or diabetes [Grade D, Consensus].

Abbreviations:

2hPG, 2-hour plasma glucose; A1C, glycated hemoglobin; FPG, fasting plasma glucose; HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein; HIV, human immunodeficiency virus-1; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

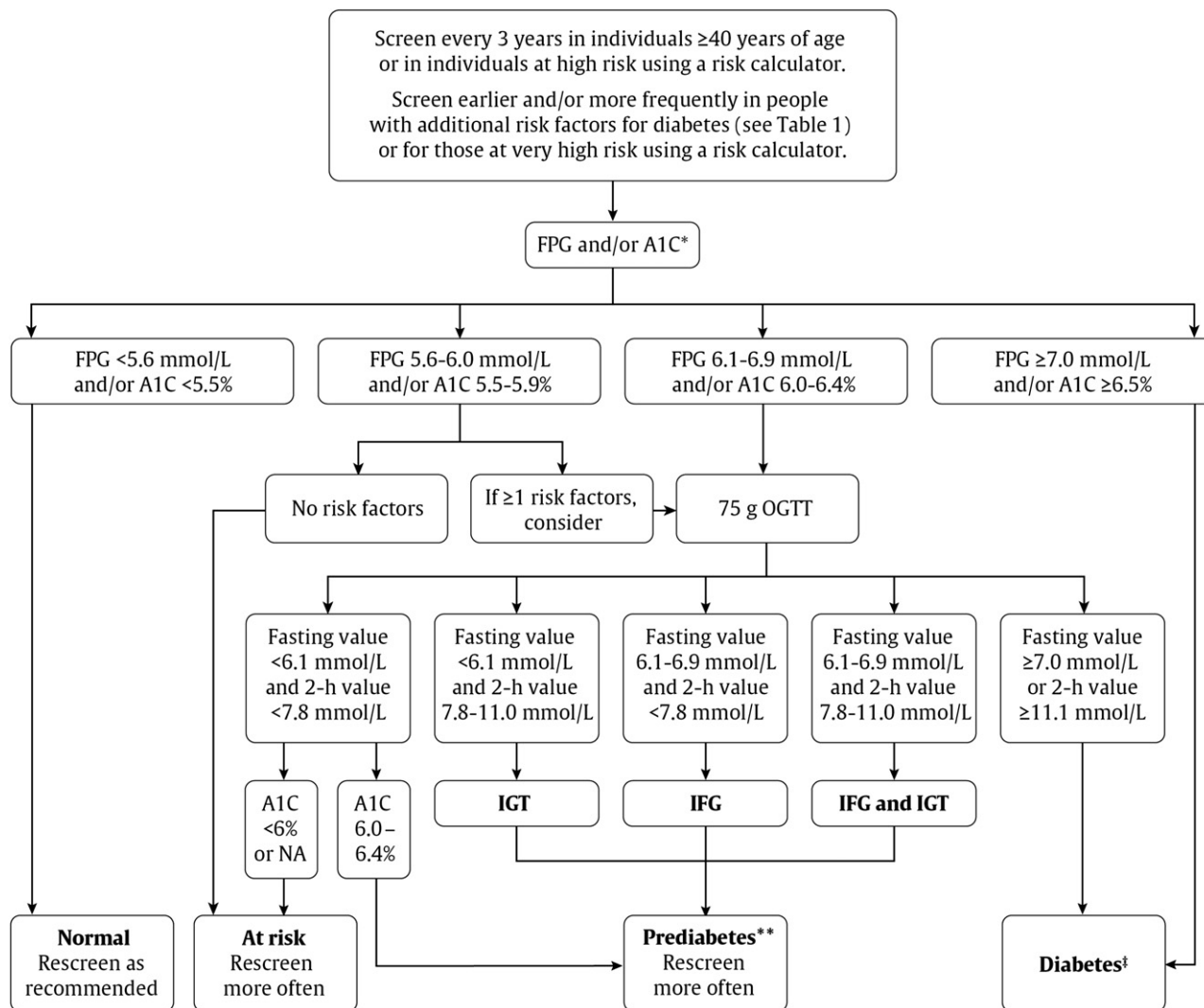


Figure 1. Screening and diagnosis algorithm for type 2 diabetes.

*If both fasting plasma glucose (FPG) and glycated hemoglobin (A1C) are available but discordant, use the test that appears furthest to the right side of the algorithm.

**Prediabetes = impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or A1C 6.0% to 6.4% (see Table 4 in Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome, p. S8). †In the absence of symptomatic hyperglycemia, if a single laboratory test is in the diabetes range, a repeat confirmatory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation. If results of 2 different tests are available and both are above the diagnostic cutpoints, the diagnosis of diabetes is confirmed. NA = not available; OGTT = oral glucose tolerance test.

on having undiagnosed type 2 diabetes differs between populations of different ethnic origins, and risk scores developed in Caucasian populations cannot be applied to populations of other ethnic groups (22). Furthermore, the prevalence of individuals at risk for developing type 2 diabetes varies considerably according to the scoring system. Risk scoring systems must, therefore, be validated for each considered population in order to adequately detect individuals at risk and eventually implement efficacious preventative strategies (23). The Canadian Diabetes Risk Assessment Questionnaire (CANRISK) is a statistically valid tool that may be suitable for diabetes risk assessment in the Canadian population and is available on the Internet at www.phac-aspc.gc.ca/cd-mc/diabetes-diabete/canrisk/index-eng.php (24).

Other Relevant Guidelines

Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome, p. S8

Reducing the Risk of Developing Diabetes, p. S16

Type 1 Diabetes in Children and Adolescents, p. S153

Type 2 Diabetes in Children and Adolescents, p. S163

Relevant Appendix

Appendix 1. Etiologic Classification of Diabetes Mellitus

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Clinical Practice Guidelines

Reducing the Risk of Developing Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- As safe and effective preventive therapies for type 1 diabetes have not yet been identified, any attempts to prevent type 1 diabetes should be undertaken only within the confines of formal research protocols.
- Intensive and structured lifestyle modification that results in loss of approximately 5% of initial body weight can reduce the risk of progression from impaired fasting glucose or impaired glucose tolerance to type 2 diabetes by almost 60%.
- Progression from prediabetes to type 2 diabetes can also be reduced by pharmacological therapy with metformin (~30% reduction), acarbose (~30% reduction) and thiazolidinediones (~60% reduction).

Introduction

Ideal preventive strategies for both type 1 and type 2 diabetes should range from focusing efforts on individuals identified as being at risk for developing diabetes to broader, more group- or population-based strategies. For the practicing healthcare professional, it is the individualized strategies that are sought. The prevention or delay of diabetes not only would alleviate the individual of the burden of disease but also could decrease associated morbidity and mortality. Preventive strategies would differ depending on the type of diabetes. Given the increasing incidence and prevalence of diabetes, development of safe and cost-effective interventions to reduce the risk of diabetes are needed to help decrease the burden of diabetes on individuals and the healthcare system.

Reducing the Risk of Developing Type 1 Diabetes

Type 1 diabetes is a chronic autoimmune condition characterized by destruction of pancreatic beta cells. The causes are multifactorial, with both genetic and environmental factors playing a part. There is a long preclinical period before the onset of overt symptoms, which may be amenable to therapeutic intervention to prevent disease. The exact nature of causative environmental factors continues to be debated. Immunotherapeutic interventions continue to be the main focus of disease prevention. Enhancement of “regulatory” immune mechanisms currently shows the most promise in terms of slowing the progression of the disease and preserving beta cell mass (secondary prevention).

Two major trials of interventions to prevent or delay the onset of type 1 diabetes have been completed. The European Nicotinamide Diabetes Intervention Trial (ENDIT), a randomized, double-blind, placebo-controlled trial of high-dose nicotinamide therapy, recruited first-degree relatives of people who were <20 years old when diagnosed with type 1 diabetes, were islet cell antibody positive, were <40 years of age and had a normal oral glucose tolerance test (OGTT) result. Although nicotinamide had proved protective in animal studies, no effect was observed in ENDIT during the 5-year trial period (1). The Diabetes Prevention Trial-Type 1 (DPT-1) studied the efficacy of low-dose insulin injections in high-risk (projected 5-year risk of >50%) first-degree relatives of subjects with type 1 diabetes. Overall, the insulin treatments had no effect (2), but in a subset of participants with high levels of insulin autoantibodies, a delay, and perhaps a reduction, in the incidence of type 1 diabetes was observed (3). A third large trial, the ongoing Trial to Reduce IDDM in the Genetically at Risk (TRIGR) study, is investigating the effect of excluding cow's milk protein and replacing it with hydrolyzed formula milk in genetically at-risk infants until 6 to 8 months of age. Preliminary data suggest there were fewer autoantibody-positive children at 10 years (4), but data on the overt development of diabetes by age 10 will not be available until 2017.

A second strategy is to try and halt, at the time of diagnosis, the immune-mediated destruction of beta cells so as to preserve any residual capacity to produce insulin. Progress in the field has been appropriately slow due to important ethical considerations. Namely, side effects from excessive immunosuppression/modulation cannot be tolerated because of the reasonable life expectancy with insulin substitution therapy.

As safe and effective preventive therapies for type 1 diabetes have not yet been identified, any attempts to prevent type 1 diabetes should be undertaken only within the confines of formal research protocols.

Reducing the Risk of Developing Type 2 Diabetes

Preventing type 2 diabetes may result in significant public health benefits, including lower rates of cardiovascular disease (CVD), renal failure, blindness and premature mortality. An epidemiological analysis projected that if all diabetes could be avoided in white American males through effective primary prevention, the

risk of all-cause and cardiovascular mortality in the entire population could be reduced by up to 6.2% and 9.0%, respectively (5). Data from the US indicate that 28% of cardiovascular expenditures are attributable to diabetes (6). Primary approaches to preventing diabetes in a population include the following: 1) programs targeting high-risk individuals in the community (such as those with impaired glucose tolerance [IGT] or obesity); 2) programs targeting high-risk subgroups of the population, such as high-risk ethnic groups; and 3) programs for the general population, such as those designed to promote physical activity and healthy eating in adults or children (7–9). Prospective cohort studies have identified historical, physical and biochemical variables associated with the subsequent development of type 2 diabetes. These include older age, certain ethnic backgrounds, obesity (especially abdominal obesity), physical inactivity, history of gestational diabetes mellitus, overt coronary artery disease, high fasting insulin levels and IGT (10–12). Results of large, well-designed studies assessing lifestyle and pharmacological interventions in adults to prevent the progression from IGT to diabetes have been published. No pharmacological agent is approved for diabetes prevention in Canada.

Lifestyle

Changes in lifestyle were assessed in the Finnish Diabetes Prevention Study (DPS) (13) and the Diabetes Prevention Program (DPP) (14). Dietary modification that targeted a low-calorie, low-fat, low-saturated fat, high-fibre diet and moderate-intensity physical activity of at least 150 minutes per week resulted in a moderate weight loss of approximately 5% of initial body weight. In both studies, the risk reduction for diabetes was 58% at 4 years. These studies included comprehensive, sustained programs to achieve these outcomes. On the basis of the observed benefits of lifestyle in the DPP, all participants were offered further lifestyle interventions for a median of 5.7 more years and benefits were sustained for up to 10 years (15).

In another lifestyle intervention trial, 458 Japanese males with IGT were randomly assigned in a 4:1 ratio to a standard intervention ($n=356$) or an intensive intervention ($n=102$) and followed for 4 years (16). Intensive treatment was associated with a 67.4% reduction in risk of diabetes ($p<0.001$). IGT and diabetes were diagnosed using a 100 g OGTT and the following diagnostic criteria: IGT = 2-hour plasma glucose (2hPG) 8.8 to 13.1 mmol/L; diabetes = 2hPG ≥ 13.2 mmol/L (16). These levels corresponded to the 1980 World Health Organization (WHO) diagnostic criteria using a 75 g OGTT (17,18).

In a more recent trial, 641 overweight Japanese men (aged 30 to 60 years) with impaired fasting glucose (IFG) were randomized to either a frequent intervention group ($n=311$) or a control group ($n=330$) for 36 months. The frequent intervention group received individual instructions and follow-up support for lifestyle modification from medical staff 9 times. The control group received similar individual instructions 4 times at 12-month intervals during the same period. Results showed an incidence of type 2 diabetes of 12.2% in the frequent intervention group and 16.6% in the control group, with an adjusted hazard ratio (HR) in the frequent intervention group of 0.56 (95% confidence interval [CI] 0.36–0.87). Post hoc subgroup analyses showed the HR reduced to 0.41 (95% CI 0.24–0.69) among participants with IGT at baseline and to 0.24 (95% CI 0.12–0.48) among those with a baseline A1C level $>5.6\%$ (19).

A 20-year follow-up of the Chinese Da Qing Diabetes Prevention Trial showed that after 6 years of active lifestyle interventions vs. no treatment and an additional 14 years of passive follow-up, a 43% (95% CI 19–59) relative risk reduction for incident diabetes persisted, and vision-threatening retinopathy was reduced by 47% (95% CI 1–71). There were, however, no identified reductions in nephropathy, neuropathy, cardiovascular events or mortality (20,21).

Pharmacotherapy

Metformin

Metformin was used in a second arm of the DPP (14). A dosage of 850 mg bid for an average of 2.8 years significantly decreased progression to diabetes by 31%. In the DPP population, metformin did not have any significant effect in the older age group (≥ 60 years) and in less obese subjects (body mass index [BMI] <35 kg/m²). To determine whether the observed benefit was a transient pharmacological effect or was more sustained, a repeat OGTT was undertaken after a short washout period. The results of this study suggested that 26% of the diabetes prevention effect could be accounted for by the pharmacological action of metformin (which did not persist when the drug was stopped). After the washout, the incidence of diabetes was still reduced by 25% (22). The benefits persisted for up to 10 years (15).

Thiazolidinediones

The DPP Research Group published the results from the troglitazone arm, which was part of the original protocol (23). The drug was discontinued after a mean follow-up of 0.9 years due to liver toxicity. Troglitazone 400 mg once daily resulted in a relative risk reduction of 75% ($p=0.02$) during the short period of time. This effect was not sustained after discontinuation of troglitazone.

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial randomized 5269 subjects with IGT and/or IFG, in a 2×2 factorial fashion, to ramipril (up to 15 mg/day) and/or rosiglitazone (8 mg/day) vs. placebo (24,25). Eligible subjects were 30 years old and not known to have CVD. The primary outcome of DREAM was a composite of development of diabetes or death. The conclusion of the DREAM investigators was that the results suggest that ramipril may have favourable effects on glucose metabolism, a finding that is consistent with other reports. However, not all trials have found such an association. For now, the routine use of ramipril for the express purpose of preventing diabetes is not indicated." Treatment with rosiglitazone resulted in a 60% reduction in the primary composite outcome of diabetes or death (HR 0.40, 95% CI 0.35–0.46), primarily due to a 62% relative reduction in the risk of progression to diabetes (HR 0.38, 95% CI 0.33–0.44). Although the trial was not powered to provide a definitive estimate of the effect of rosiglitazone on CV outcomes, there was a trend toward an increase in risk of the CV composite outcome with rosiglitazone (HR 1.37, 95% CI 0.97–1.94) driven primarily by a significant increase in nonfatal congestive heart failure (HR 7.03, 95% CI 1.60–30.9; $p=0.01$).

In the Actos Now for the Prevention of Diabetes (ACT NOW) study, 602 high-risk IGT subjects were randomized to receive pioglitazone or placebo and were followed for 2.4 years. Pioglitazone decreased the conversion of IGT to type 2 diabetes by 72% ($p<0.00001$) (26).

Despite the favourable effects of thiazolidinediones on delaying the development of type 2 diabetes, the multiple potential adverse effects of this class of medication makes it difficult to recommend their widespread use in IFG or IGT.

Combination therapy

The combination of metformin 500 mg twice daily and rosiglitazone 2 mg twice daily was found to reduce the progression to diabetes by 66% (95% CI 41–80) among 103 people with IGT compared to 104 people randomized to placebo over a median of 3.9 years (27).

Alpha-glucosidase inhibitors

The Study to Prevent Non-Insulin Dependent Diabetes (STOP-NIDDM) used acarbose at a dosage of 100 mg tid in a 5-year study with a mean follow-up of 3.3 years (28). Overall, there was a 25% reduction in the risk of progression to diabetes when the diagnosis was based on 1 OGTT and a 36% reduction in the risk of progression

to diabetes when the diagnosis was based on 2 consecutive OGTTs. This beneficial effect was not affected by age or BMI. However, when the drug was discontinued, the effect of acarbose did not persist (28). In this IGT population, acarbose treatment was also associated with a 49% reduction in CV events ($p=0.032$) and a 50% reduction in the progression of carotid intima-media thickness (29,30). In another trial, 1780 Japanese patients with IGT were randomly assigned to oral voglibose 0.2 mg three times per day ($n=897$) or placebo ($n=883$). Results showed that, over a mean of 48.1 weeks, voglibose was better than placebo at reducing the progression to type 2 diabetes (5.6% vs. 11.9%; HR 0.595, 95% CI 0.433–0.818; $p=0.0014$). More subjects in the voglibose group achieved normoglycemia than in the placebo group (66.8% vs. 51.5%; HR 1.539, 95% CI 1.357–1.746; $p<0.0001$).

Orlistat

The Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study examined the effect of orlistat in combination with an intensive lifestyle modification program (diet and exercise) on the prevention of diabetes in 3305 obese individuals (31). Subjects were randomized to orlistat 120 mg or placebo tid with meals for 4 years. Weight loss was observed in both groups, but the orlistat group lost significantly more (5.8 vs. 3 kg; $p<0.001$). Compared to placebo, orlistat treatment was associated with a further 37% reduction in the incidence of diabetes. However, 2 important methodological limitations affect the interpretation of these results. First, there was a very high dropout rate—48% in the orlistat group and 66% in the placebo group. Second, the last observation carried forward was used for analysis, which is generally not favoured for prevention or survival studies. Nonetheless, the significant weight loss would be expected to decrease the risk of diabetes as already shown in the DPS and the DPP.

Incretin-based therapies

Liraglutide has been shown to effectively prevent IGT conversion to type 2 diabetes and cause reversion to normoglycemia (32). In a 20-week study, liraglutide was administered to 564 obese individuals who did not have diabetes, 31% of whom had IGT. Subjects were randomized to 1 of 4 liraglutide doses (1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg; $n=90$ –95) or to placebo ($n=98$), or to orlistat (120 mg; $n=95$) three times daily. A1C was reduced by 0.14% to 0.24%. The prevalence of prediabetes decreased by 84% to 96% with liraglutide 1.8 mg, 2.4 mg and 3.0 mg doses.

Diabetes prevention in high-risk ethnicities

Ethnic groups, such as South Asians, Hispanics and Aborigines, are at very high risk for and have a high prevalence of type 2 diabetes (12%–15% in the Western world) (33,34).

The reasons for this are multifactorial and include genetic susceptibility, altered fat distribution (more visceral fat with greater insulin resistance) and higher prevalence of metabolic syndrome. Many of them develop diabetes at a younger age and often have complications at the time of diagnosis due to long-standing, preexistent diabetes. As a result, there may be a benefit of delaying the onset of diabetes in this population. The Indian Diabetes Prevention Programme showed similar results in preventing diabetes with both lifestyle and pharmacological interventions where the progression to diabetes from IGT was quite high (55%) over 3 years (35). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian subjects with IGT (IDPP-1).

This approach of prevention may lead to cost savings, fewer complications and lower morbidity, but it remains to be proven with hard clinical endpoints. Lifestyle measures not only reduce the risk of diabetes but have other health benefits, so the overall benefit is positive with little harm. One must keep in mind that the measures of prevention must be delivered in a culturally sensitive manner to these populations.

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RECOMMENDATIONS

- A structured program of lifestyle modification that includes moderate weight loss and regular physical activity should be implemented to reduce the risk of type 2 diabetes in individuals with IGT [Grade A, Level 1A (13,14)] and IFG [Grade B, Level 2 (18)] and A1C 6.0%–6.4% [Grade D, Consensus].
- In individuals with IGT, pharmacological therapy with metformin [Grade A, Level 1A (14)] or acarbose [Grade A, Level 1A (27)] may be used to reduce the risk of type 2 diabetes.

Abbreviations:

A1C, glycated hemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

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Clinical Practice Guidelines

Organization of Diabetes Care

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetes care should be organized around the person living with diabetes who is practising self-management and is supported by a proactive, interprofessional team with specific training in diabetes.
- Diabetes care should be delivered using as many elements as possible of the chronic care model.
- The following strategies have the best evidence for improved outcomes and should be used: promotion of self-management, including self-management support and education; interprofessional team-based care with expansion of professional roles, in cooperation with the collaborating physician, to include monitoring or medication adjustment and disease (case) management, including patient education, coaching, treatment adjustment, monitoring and care coordination.
- Diabetes care should be structured, evidence based and supported by a clinical information system that includes electronic patient registries, clinician and patient reminders, decision support, audits and feedback.

HELPFUL HINTS BOX: ORGANIZATION OF CARE

Recognize: Consider diabetes risk factors for all of your patients and screen appropriately for diabetes.

Register: Develop a registry for all of your patients with diabetes.

Resource: Support self-management through the use of interprofessional teams which could include the primary care provider, diabetes educator, dietitian, nurse, pharmacist and other specialists.

Relay: Facilitate information sharing between the person with diabetes and the team for coordinated care and timely management changes.

Recall: Develop a system to remind your patients and caregivers of timely review and reassessment.

Introduction

In Canada, there is a care gap between the clinical goals outlined in evidence-based guidelines for diabetes management and real-life clinical practice (1,2). Since almost 80% of the care of people with diabetes takes place in the primary care setting, there has been a shift toward delivering diabetes care in the primary care

setting using the chronic care model (CCM) (3–5). The CCM is an organizational approach as well as a quality improvement (QI) strategy in caring for people with chronic diseases, the elements of which are evidence based. These elements facilitate planning and coordination among providers while helping patients play an informed role in managing their own care (6). Previous recommendations in this chapter, in 2008, focused on the daily commitment of the individual with diabetes to self-management, with the support of the interprofessional diabetes healthcare team. Although these are still critical elements of diabetes care, increasing evidence suggests that the CCM, which includes elements beyond the patient and healthcare provider, provides a framework for the optimal care of persons with diabetes (6–8). This chapter has been revised to reflect the importance of the CCM design, delivery and organization of diabetes care. Despite the use of new terminology (Table 1), many of the previous recommendations have remained the same but have been reorganized to fall under specific components of the CCM and broadened to include elements such as the health system and the community (9). This is intended to assist the readers in increasing their understanding and use of the CCM framework in their daily practice.

The CCM and Organization of Diabetes Care

In many ways, diabetes care has been the prototype for the CCM (Figure 1). Developed in the late 1990s, this model aims to transform the care of patients with chronic illnesses from acute and reactive to proactive, planned and population based. This model has been adopted by many countries as well as several provinces in Canada (13). Early studies showed that the following interventions improved care in the chronically ill: educating and supporting the patient, team-based care, increasing the healthcare provider's skills and use of registry-based information systems (7,8,10). The current CCM has expanded on this evidence to include the following 6 elements that work together to strengthen the provider-patient relationship and improve health outcomes: 1) delivery systems design, 2) self-management support, 3) decision support, 4) clinical information systems, 5) the community, and 6) health systems. A recent systematic review found that primary care practices were able to successfully implement the CCM (6). Furthermore, incorporating most or all of the CCM elements has been associated with improved quality of care and disease outcomes in patients with various chronic illnesses, including

Table 1
Definition of terms (9–12)

Terminology	
Chronic care model (CCM)	The CCM is an organizational approach to caring for people with chronic diseases as well as a quality improvement strategy, the elements of which are evidence based. These elements facilitate planning and coordination among providers while helping patients play an informed role in managing their own care. This model has evolved from the original Wagner CCM (1999) to the expanded care model (9).
Elements of CCM	1) Delivery systems designs 2) Self-management support 3) Decision support 4) Clinical information 5) The community 6) Health systems
Primary care	First contact and ongoing healthcare: family physicians, general practitioners and nurse practitioners
Shared care	Joint participation of primary care physicians and specialty care physicians in the planned delivery of care, informed by an enhanced information exchange over and above routine discharge and referral notices Can also refer to the sharing of responsibility for care between the patient and provider or team
Quality Improvement Strategies	
Audit and feedback	Summary of provider or group performance on clinical or process indicators delivered to clinicians to increase awareness of performance
Clinical information systems	The part of an information system that helps organize patient and population data to facilitate efficient and effective care. May provide timely reminders for providers and patients, identify relevant subpopulations for proactive care, facilitate individual patient care planning, and share information with patients and providers to coordinate care or monitor performance of practice team and care system.
Clinician reminders	Paper-based or electronic system to prompt healthcare professionals to recall patient-specific information (e.g. A1C) or do a specific task (e.g. foot exam)
Collaboration	A collaborative intervention is a method used to help healthcare organizations apply continuous quality improvement techniques and affect organizational change.
Continuous quality improvement	Techniques for examining and measuring clinical processes, designing interventions, testing their impacts and then assessing the need for further improvement
Decision support	Integration of evidence-based guidelines into the flow of clinical practice
Disease (case) management	A structured, multifaceted intervention that supports the practitioner/patient relationship and plan of care; emphasizes prevention of exacerbations and complications utilizing evidence-based practice guidelines and patient empowerment strategies May include education, coaching, treatment adjustment, monitoring and care coordination, often by a nurse, pharmacist or dietitian
Facilitated relay of information to clinician	Clinical information collected from patients and sent to clinicians, other than the existing medical record (e.g. pharmacist sending SMBG results)
Patient registry	A list of patients sharing a common characteristic, such as a diabetes registry May be paper based but increasingly is electronic, ranging from a simple spreadsheet to one embedded in an electronic health record
Patient reminders	Any effort to remind patients about upcoming appointments or aspects of self-care (e.g. glucose monitoring)
Self-management education (SME)	A systematic intervention that involves active patient participation in self-monitoring (physiological processes) and/or decision making (managing) (see Self-Management Education chapter, p. S26)
Self-management support	In addition to SME strategies that enhance patients' ability to manage their condition, including internal and community resources, such as disease management with patient reminders, monitoring and linkage to self-management support/interest groups
Team changes	Changes to the structure of a primary healthcare team, such as: <ul style="list-style-type: none"> • Adding a team member or shared care, such as a physician, nurse specialist or pharmacist • Using an interdisciplinary team in primary routine management • Expansion of professional role (e.g. nurse or pharmacist has a more active role in monitoring or adjusting medications)
Other Terms	
Lay leader	Trained and accredited non-healthcare professional delivering a program that adopts a philosophy of self-management rather than the medical model
Telehealth	Delivery of health-related services and information via telecommunications technology

A1C, glycated hemoglobin; SMBG, self-monitoring of blood glucose.

diabetes (6,8,10,14–16). A recent systematic review and meta-analysis of QI strategies on the management of diabetes concluded that interventions targeting the system of chronic disease management along with patient-mediated QI strategies should be an important component of interventions aimed at improving care. Although some of the improvements were modest, it may be that, when the QI components are used together, there is a synergistic effect as noted in the above studies (12).

CCM in Diabetes

Initial analyses of CCM interventions for improving diabetes care suggested that a multifaceted intervention was the key to QI

(8,15,17). Organizations that provided diabetes care in accordance with the CCM provided better quality care than did organizations that were less likely to use elements of this model (18). Furthermore, the degree to which care delivered in a primary care setting conforms to the CCM has been shown to be an important predictor of the 10-year risk of coronary heart disease (CHD) in patients with type 2 diabetes (19). Initially, it appeared as if only process outcomes, such as behaviours of patients and caregivers, are improved with the CCM; however, with longer-term use of the model in clinical practice, improvements in clinical outcomes also are noted, such as reductions in glycated hemoglobin (A1C) and low-density lipoprotein cholesterol (LDL-C) levels (20). A large, 2-arm, cluster-randomized, QI trial, using all 6 dimensions of the

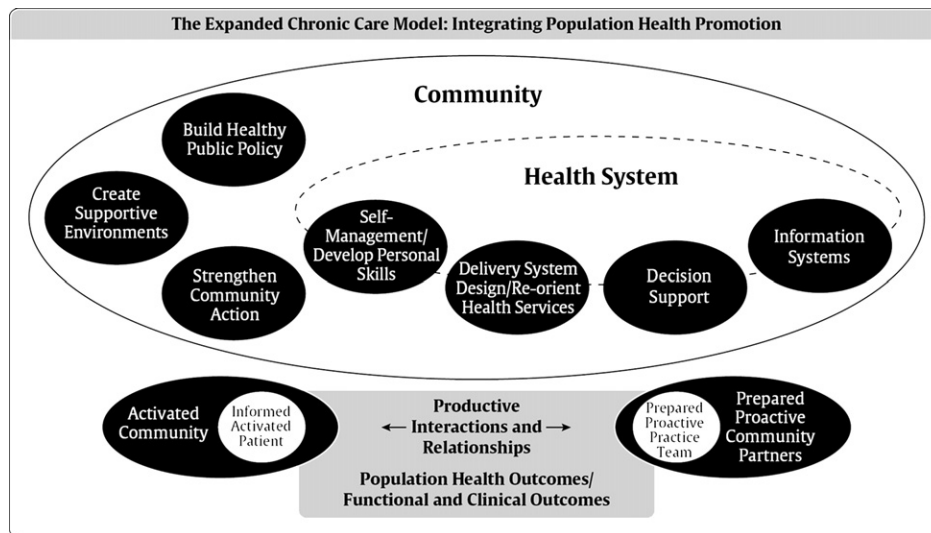


Figure 1. The Expanded Chronic Care Model: Integrating Population Health Promotion.

Used with permission from Barr VJ, Robinson S, Marin-Link B, et al. The expanded chronic care model: an integration of concepts and strategies from population health promotion and the chronic care model. *Hosp Q*. 2003;7:73–80.

CCM, found significant improvements in A1C and LDL-C and an increase in the use of statins and antiplatelet therapy among patients with diabetes (5). A recent meta-analysis of randomized controlled trials (RCTs) assessing the effectiveness of disease management programs for improving glycemic control found significant reductions in A1C with programs that included the fundamental elements of the CCM (21). Other trials found that use of the CCM improved cardiovascular (CV) risk factors in patients with diabetes (19,22). One large-scale analysis of a nationwide disease management program using the CCM and based in primary care reduced overall mortality as well as drug and hospital costs (23). The Assessment of Chronic Illness Care (ACIC) is a practical assessment as well as a research tool. It can help teams strategically involve themselves in a structured way to assess and identify gaps to develop into a more robust CCM (11).

Elements of the CCM that Improve Care

Delivery systems design

The team

Current evidence continues to support the importance of a multi- and interprofessional team with specific training in diabetes within the primary care setting (10,12,21). The team should work collaboratively with the primary care provider who, in turn, should be supported by a diabetes specialist. Specialist support may be direct or indirect through shared care, an interdisciplinary team member or educational support (5,12). In adults with type 2 diabetes, this care model has been associated with improvements in A1C, blood pressure (BP), lipids and care processes compared to care that is delivered by a specialist or primary care physician alone (5,24–27). A reduction in preventable, diabetes-related emergency room visits also has been noted when the team includes a specifically trained nurse who follows detailed treatment algorithms for diabetes care (25). In Canada, observational data from primary care networks, whose approach is to improve access and coordinate care, suggest that patients who are part of these interdisciplinary teams have better outcomes and fewer hospital visits than patients who are not (28).

Team membership may be extensive and should include various disciplines. Those disciplines associated with improved diabetes outcomes include nurses, nurse practitioners, dietitians, pharmacists and providers of psychological support.

Nurses have always been, and continue to be, core members of the team. A systematic review (26) and recent meta-analysis (29) found that case management led by specialist nurses or dietitians improved both glycemic control and CV risk factors. Another study found improved BP outcomes with nurse-led interventions vs. usual care, particularly when nurses followed algorithms and were able to prescribe (30). In addition, a large RCT found that nurse-led, guideline-based, collaborative care management was associated with improvements in A1C, lipids, BP and depression in patients with depression and type 2 diabetes and/or CHD (31). Practices with nurse practitioners also were found to have better diabetes process outcomes than those with physicians alone or those employing only physician assistants (32). Small-group or individualized nutrition counselling by a registered dietitian with expertise in diabetes management is another important element of team-based care. A variety of individual and community health-care support systems, particularly psychological support, can also improve glycemic control (33).

Recent meta-analyses involving people with both type 1 and type 2 diabetes showed a significant 0.76% drop in A1C (34) as well as improved adherence and quality of life (QOL) and reductions in adverse drug reactions and LDL-C with collaborative pharmacist intervention (35). A Canadian randomized trial that added a pharmacist to primary care teams showed a significant reduction in BP for people with type 2 diabetes (36). Therefore, pharmacists can play a key role in diabetes management, beyond that of dispensing medications.

Roles within the team and disease management

Flexibility in the operation of the team is important. Team changes, such as adding a team member, active participation of professionals from more than one discipline and role expansion, have been associated with improved clinical outcomes (10,12,21). The greatest body of evidence for improved clinical outcomes in diabetes is with promotion of self-management, team changes and case or disease management programs (5,10,12,21,27,37,38). In a systematic review and meta-analysis of QI strategies, the following QI strategy improved clinical outcomes, such as A1C, BP and cholesterol, as well as process outcomes, medication use and screening for complications: promotion of self-management, team changes, case management, patient education, facilitated relay, electronic patient registries, patient reminders, audits and feedback, and clinician reminders. The effectiveness of different QI

strategies may vary based on the baseline A1C, with QI targeting professionals only beneficial when the baseline A1C control is poor. In practice, many of these QI strategies occur in concert with one another through the use of interprofessional teams.

Another recent meta-analysis by Pimouguet et al. (21) defines disease management as the “ongoing and proactive follow-up of patients that includes at least 2 of the following 5 components: patient education, coaching, treatment adjustment (where the manager is able to start or modify treatment with or without prior approval from the primary care physician), monitoring, care coordination (where the manager reminds the patient about upcoming appointments or important aspects of self-care and informs the physician about complications, treatment adjustments, or therapeutic recommendations).” The meta-analysis found that a high frequency of patient contact and the ability of the disease manager to start or modify treatment with or without prior approval from the primary care physician had the greatest impact on A1C lowering. Disease management programs also were more effective for patients with poor glycemic control ($A1C \geq 8\%$) at baseline (21). Other disease management strategies that have been associated with positive outcomes are the delegation of prescription authority and the monitoring of complications using decision support tools (26,27,30).

The primary care provider, who is usually a family physician, has a unique role in the team, particularly with regard to providing continuity of care. He or she is often the principal medical contact for the person with diabetes and has a comprehensive understanding of all health issues and social supports (39). In the past, there was some debate over whether specialist care or primary care yields better diabetes outcomes (40–43). Although physicians practising in hospital-based diabetes centres may be more likely to adhere to guidelines (44), general practice-based care is associated with higher patient follow-up (45). Certainly, there are patients with diabetes who may require ongoing, specialized care, such as children and pregnant women. There is also evidence that specialized care may be more beneficial in people with type 1 diabetes (46,47). In the CCM, collaborative, shared care is the ideal. However, the results of one Cochrane review did not support shared care (48). It should be noted, however, that several of the studies included in this analysis did not use all the elements of the CCM. Other, more recent studies have supported the shared care model (49) and have shown that specialist input into specialized diabetes teams at the interface of primary and secondary care improves care (5,50).

Self-management support

Self-management support, including self-management education, is the cornerstone of diabetes care in the CCM. Self-management education goes well beyond didactic disease-specific information. It is a systematic intervention that involves active patient participation in self-monitoring (physiological processes) and/or decision making (managing). Self-management enables the person with diabetes to take an active role in managing his or her own care through problem solving and goal setting, which can be facilitated through the use of motivational interviewing techniques. Self-management support, often through disease or case management, with strategies such as patient reminders, helps the individual in self-management. Evidence for diabetes self-management support and education is robust (12) and is covered in more detail in the next chapter (see Self-Management Education chapter, p. S26).

Decision support

Providing healthcare practitioners with best practice information at the point of care to help support decision making has been shown to improve outcomes. In a systematic review, evidence-based guideline interventions, particularly those that used

interactive computer technology to provide recommendations and immediate feedback of personally tailored information, were the most effective in improving patient outcomes (51). A randomized trial using electronic medical record (EMR) decision support in primary care found improvement in A1C (52), and a cluster randomized trial of a QI program found that the provision of a clear treatment protocol—supported by tailored postgraduate education of the primary care physician and case coaching by an endocrinologist—substantially improved the overall quality of diabetes care provided, as well as major diabetes-related outcomes (50). Incorporation of evidence-based treatment algorithms has been shown in several studies to be an integral part of diabetes case management (10,26,30,31). Even the use of simple decision support tools, such as clinical flow sheets, have been associated with improved adherence to clinical practice guidelines for diabetes (53).

Clinical information systems

Clinical information systems (CIS) that allow for a population-based approach to diabetes assessment and management, such as EMRs or electronic patient registries, have been shown to have a positive impact on evidence-based diabetes care (10,12,54,55). Practice-level clinical registries give an overview of an entire practice, which may assist in the delivery and monitoring of patient care. In addition to providing clinical information at the time of a patient encounter, CIS also can help promote timely management and reduce the tendency toward clinical inertia (56). Provincial- and national-level registries are also essential for benchmarking, tracking diabetes trends, determining the effect of QI programs, and for resource planning.

Other quality improvement strategies

Audits and feedback generally lead to small but potentially important improvements in professional practice and seem to depend on baseline performance and how the feedback is provided (57). Facilitated relay of information to clinicians may include electronic or web-based methods through which patients provide self-care data and the clinician reviews have been shown to improve care. Ideally, this should occur in case management with a team member who has prescribing or ordering ability (12). Physician and patient reminders also have shown benefit (12,50).

Community

Environmental factors, such as food security, the ability to lead an active lifestyle, as well as access to care and social supports, also impact diabetes outcomes. Although community resources have not traditionally been integrated into care, community partnerships should be considered as a means of obtaining better care for patients with diabetes. For example, in addition to the diabetes health team, peer- or lay leader-led self-management groups have been shown to be beneficial in persons with type 2 diabetes (58,59).

Health systems

Support for diabetes care from the broader level of the health-care system, such as the national and provincial systems, is essential. A number of provinces have adopted an expanded CCM (9) that includes health promotion and disease prevention (13). Many provinces and health regions also have developed diabetes strategies, diabetes service frameworks and support diabetes collaboratives. Some trials on diabetes-specific collaboratives have been shown to improve clinical outcomes (22,50,60), although a recent meta-analysis on continuous QI failed to show benefit (12).

Provider incentives represent another area of health system support. Some provinces have added incentive billing codes for

patients with diabetes so that providers can be financially compensated for the use of flow sheets as well as time spent collaborating with the patient for disease planning (61). Pay-for-performance programs, which encourage the achievement of goals through reimbursement, are more commonly used outside of Canada. To date, these programs have had mixed results (62–64). Various payment systems also have been studied, but it is still unclear which of these may improve diabetes outcomes (65,66). Incentives to physicians to enroll patients and provide care within a nation-wide disease management program appears to be effective (23), as does infrastructure incentive payments that encourage the CCM (16). A meta-analysis that included physician incentives as a QI has shown mixed results for improved outcomes (12).

Telehealth

Although not a specific element of the CCM, telehealth technologies may help facilitate many components of this model. These technologies may be used for conferencing or education of team members; telemonitoring of health data, such as glucose readings

or BP; disease management via telephone or internet; or teleconsultation with specialists. Telehealth also appears to be effective for diabetes self-management education and has been associated with improvements in metabolic control and reductions in CV risk (67). One RCT and 2 systematic reviews of telemonitoring of various disease management parameters, ranging from blood glucose results to foot temperature, found improved outcomes with telemonitoring, such as A1C lowering, a lower incidence of foot ulcerations and better QOL (4,68,69). These benefits were noted regardless of whether the teleconsultation was asynchronous or synchronous (69).

Other Relevant Guidelines

Self-Management Education, p. S26

Type 1 Diabetes in Children and Adolescents, p. S153

Type 2 Diabetes in Children and Adolescents, p. S163

Diabetes and Pregnancy, p. S168

Relevant Appendix

Appendix 2. Sample Diabetes Patient Care Flow Sheet for Adults

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RECOMMENDATIONS

- Diabetes care should be proactive, incorporate elements of the chronic care model (CCM), and be organized around the person living with diabetes who is supported in self-management by an interprofessional team with specific training in diabetes [Grade C, Level 3 (6,23)].
- The following quality improvement strategies should be used, alone or in combination, to improve glycemic control [Grade A, Level 1 (12)]:
 - Promotion of self-management
 - Team changes
 - Disease (case) management
 - Patient education
 - Facilitated relay of clinical information
 - Electronic patient registries
 - Patient reminders
 - Audit and feedback
 - Clinician education
 - Clinician reminders (with or without decision support)
- Diabetes care management by an interprofessional team with specific training in diabetes and supported by specialist input should be integrated within diabetes care delivery models in the primary care [Grade A, Level 1A (12,21)] and specialist care [Grade D, Consensus] settings.
- The role of the diabetes case manager should be enhanced, in cooperation with the collaborating physician [Grade A, Level 1A (12,21)], including interventions led by a nurse [Grade A, Level 1A (29,30)], pharmacist [Grade B, Level 2 (34)] or dietitian [Grade B, Level 2 (70)], to improve coordination of care and facilitate timely diabetes management changes.
- As part of a collaborative, shared care approach within the CCM, an interprofessional team with specialized training in diabetes, and including a physician diabetes expert, should be used in the following groups:
 - Children with diabetes [Grade D, Level 4 (71)]
 - Type 1 diabetes [Grade C, Level 3 (46)]
 - Women with diabetes who require preconception counselling [Grade C, Level 3 (72–74)] and women with diabetes in pregnancy [Grade D, Consensus]
 - Individuals with complex (multiple diabetes-related complications) type 2 diabetes who are not reaching targets [Grade D, Consensus]
- Telehealth technologies may be used as part of a disease management program to:
 - Improve self-management in underserved communities [Grade B, Level 2 (67)]
 - Facilitate consultation with specialized teams as part of a shared-care model [Grade A, Level 1A (69)]

Abbreviation:

CCM, chronic care model.

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Clinical Practice Guidelines

Self-Management Education

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Offer collaborative and interactive self-management education (SME) interventions as they are more effective than didactic SME.
- Incorporate problem-solving skills for ongoing self-management of medical, social and emotional aspects of care into the traditional knowledge and technical skills content of educational interventions.
- Design patient-centred learning to empower individuals to make informed decisions toward achievement of patient-chosen goals.
- Individualize SME interventions according to type of diabetes and recommended therapy, the patient's ability and motivation for learning and change, and his or her culture and literacy level.
- Provide ongoing SME and comprehensive healthcare collaboratively to make SME most effective.

Introduction

Self-management education (SME) is defined as a systematic intervention that involves active patient participation in self-monitoring (physiological processes) and/or decision making (managing) (1). It recognizes that patient-provider collaboration and the enablement of problem-solving skills are crucial to the individual's ability for sustained self-care (2).

Several meta-analyses have demonstrated that SME is associated with clinically important benefits in persons with type 2 diabetes, such as reductions in glycated hemoglobin (A1C) of 0.36% to 0.81% (1,3,4). Improved quality of life (QOL) for persons with either type 1 or type 2 diabetes also has been demonstrated (5), as have other important self-care outcomes in those with type 2 diabetes, such as sustained weight loss and cardiovascular (CV) fitness for up to 4 years (6). One systematic review involving both type 1 and type 2 diabetes found that, as measures progressed from immediate to long-term outcomes, percentage of improved outcomes reduced (immediate learning 78.6%, intermediate behaviour change 50.0%, long-term clinical improvement 38.5%) (7). A 5-year follow-up of a patient-centred type 2 diabetes SME program resulted in no worsening of A1C, whereas the A1C in the control group rose 1.3% over the 5 years (8).

Diabetes SME is evolving from a traditional didactic teaching program to one using a variety of educational, psychological and behavioural interventions, and a combination of didactic, interactive and collaborative teaching methods that are tailored to the

individual's specific needs (9). The content and skill-training components of SME must be individualized according to the type of diabetes and recommended therapy, the patient's ability, barriers, motivation for learning and change, culture and literacy level, and available resources (4,10,11). Models for systematizing, organizing and/or guiding the development of SME programs (12,13) share a 5-step problem-solving process aligned with the empowerment protocol (14) based on the principle that adults are more likely to make and maintain behaviour changes if these changes are personally meaningful and freely chosen (14). In order to meet the definition of "self-management education," problem-solving skills for ongoing self-management of medical, social and emotional aspects of care must be integrated into the traditional knowledge and technical skills content of educational interventions (2). These skills are needed to inform decisions and increase the individual's capacity and confidence to apply these skills in daily life situations (2). SME refers to any of the educational processes that provide persons with the knowledge, skills and motivation required to inform decisions and increase the individual's capacity and confidence to apply these skills in daily life situations. Self-management support (addressed in the Organization of Care chapter, p. S20) refers to policies and people that may support continuation of self-management behaviours across the lifespan but that are not specific to educational processes.

Self-identification of a problem or need for self-care behaviour by the individual is crucial to all cognitive-behavioural interventions (14,15). The healthcare provider's role is to collaboratively facilitate this awareness process (2). Standardized instruments, such as the Problem Areas in Diabetes (PAID) (16), Self-care Inventory-Revised (SCI-R 2005) (17) or Summary of Diabetes Self-Care Activities (18), may have value in this process (19), although they have been used mainly for research purposes.

Interventions targeting knowledge and skills

Basic knowledge and skill areas that are essential for SME are monitoring of relevant health parameters, healthy eating, physical activity, pharmacotherapy, prevention and management of hypo-/hyperglycemia, and prevention and surveillance of complications. Skill training should include using self-monitoring of blood glucose (SMBG), making appropriate dietary choices, incorporating an exercise regimen, using medications as recommended and adjusting medication (20,21).

In general, education sessions provided to patients with diabetes have resulted in positive changes in diabetes-related knowledge (22), as well as psychological (23–26) and behavioural (23,27) domains. With respect to A1C, most trials involving group-based education have shown sustained A1C reductions (i.e. between 4 and 12 months), ranging from 0.4% to 0.7% (22,23,26,28). The Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND) trial, a structured group education program for persons with newly diagnosed type 2 diabetes, resulted in greater improvements in weight loss, smoking cessation and positive improvements in illness beliefs up to 12 months after diagnosis; however, no significant effect on A1C was noted at 12-month follow-up (25).

In those studies that used print-based education, significant changes in behaviours related to physical activity (27), stage-of-change progression (29), weight loss (27) and improvements in glucose control (30) have been noted. Randomized trials of computer- or video-based education models have demonstrated improvements in at least 1 behaviour change related to healthy eating and physical activity (7,31).

All trials evaluating a culturally appropriate education module (which incorporated cultural or religious beliefs, were offered in the patient's native language, adapted dietary advice to reflect cultural traditions and the patient's needs, and/or involved family members) have noted improvements in diabetes-related knowledge, self-management behaviours and clinical outcomes, with A1C reductions ranging from 0.5% to 1.8% (32–35). These findings demonstrate the importance of creating culturally relevant educational materials.

Interventions for content and materials geared toward patients with low literacy and numeracy can be successful in improving outcomes, such as A1C, self-efficacy and blood pressure (BP) (36). Training healthcare professionals in specific communication skills to address low literacy can also be effective (37,38).

While the majority of randomized controlled trials (RCTs) examining skill-training interventions used face-to-face individual sessions (39–43), some have used face-to-face group sessions (44), a combination of face-to-face group and individual sessions (26) and video-based programs for home viewing (45). One study that compared insulin-initiation skills training provided in a group vs. an individual setting found no difference in A1C, rate of hypoglycemia, BP, lipid profile or QOL between the 2 approaches; however, differences in weight gain and time spent in follow-up appointments or calls favoured individual training sessions (44). Most interventions were delivered by nurses (26,39,43,44) or diabetes educators (42). In general, skill-training interventions demonstrated positive changes or no significant differences in outcomes compared to control. For example, contrasting results were found in the 2 trials examining the impact of SMBG skills training: 1 study found an improvement in A1C, low-density lipoprotein cholesterol (LDL-C), body mass index (BMI) and self-care activities with skills training (40), whereas the other found no difference in A1C and BMI but an improvement in total cholesterol (TC) and TC to high-density lipoprotein cholesterol (HDL-C) ratio (41).

Cognitive-behavioural interventions

The acquisition of knowledge should be augmented with behavioural interventions to achieve longer-term change in self-care behaviours (3,23,25,46). Behavioural interventions had a larger effect size (ES) on self-management behaviours (ES –0.92) and on metabolic outcomes (ES 0.63) than knowledge-based or other psychological interventions (9). The more appropriate term may be “cognitive behavioural” interventions, which include cognitive restructuring, problem solving, cognitive-behavioural therapy (CBT), stress management, goal setting and relaxation. All

of these recognize that personal awareness and alteration of causative (possibly unconscious) thoughts and emotions are essential for effective behaviour change (47).

Several trials have found various cognitive-behavioural interventions to be effective in lowering A1C (4,15,48), improving QOL (49,50) and increasing self-care behaviours (15,23), whereas others have shown mixed results (3,46). Interventions that combine strategies for knowledge acquisition and self-care management (25,46) have been proven to be more effective in increasing knowledge, self-efficacy and self-care behaviours and in achieving metabolic control than programs that are didactic and knowledge oriented alone (4,9,15,51). Cognitive-behavioural interventions share common elements, including a patient-centred approach, shared decision making, the development of problem-solving skills, and the use of action plans directed toward patient-chosen goals (23,25,52).

A trusting, collaborative patient-healthcare professional relationship is also important for improving self-care behaviours (4). Frequent communication is a key indicator for successful interventions, whether done by a multidisciplinary team in a hospital or a community setting (33,53). Effective patient-clinician communication may improve adherence to recommendations (54). Communication technologies, such as e-Health and telemedicine with videoconferencing and teletransmission of home glucose monitoring, show promise for delivering individualized messages over an extended time period (52). Using a combination of different instructional methods that consistently incorporate an interactive component has been found to have somewhat more favourable effects than didactic programs (9,53).

Family and social support has positively impacted metabolic control and self-care behaviours (32,33,55). In both type 1 and type 2 diabetes, interventions that have targeted the family's ability to cope with stress have resulted in fewer conflicts, and having partners involved in care has been found to impact glycemic control (55).

Family and culturally tailored interventions are particularly relevant in minority communities. Several RCTs and systematic reviews have demonstrated that culturally competent healthcare interventions have resulted in lower A1C levels and improvements in diabetes-related knowledge and QOL (32,33,49).

Both individual and group settings have been used for cognitive-behavioural interventions, but there is no definitive conclusion as to which setting is superior (9,23). In general, group settings have been found to be more effective for weight loss and short-term glycemic control, whereas group interventions combined with individual follow-up sessions have resulted in lower A1C levels than either setting alone (10). Connecting with community partners and other chronic care model programs has proven to be a successful adjunct to cognitive-behavioural interventions (49,52,56). RCTs have concluded that different behavioural strategies are needed at different times to sustain behaviour change in the long term (56,57).

SME reinforcers and technological innovation

Incorporating booster sessions enhances the effectiveness of SME interventions (9). While healthcare providers play an essential role in SME delivery, patients are largely responsible for the majority of their own diabetes management. Historically, healthcare providers have been challenged with providing continued self-management support between visits. More recently, however, the availability of several different technologies (e.g. the internet, web-based education, text messaging [58–62], email, automatic telephone reminders [63], telehealth/telephone education [64–67] and reinforcement [68–72]) has provided an effective and time-efficient means of providing this ongoing support.

Several small trials have demonstrated improved outcomes when utilizing these technologies, reminder systems and

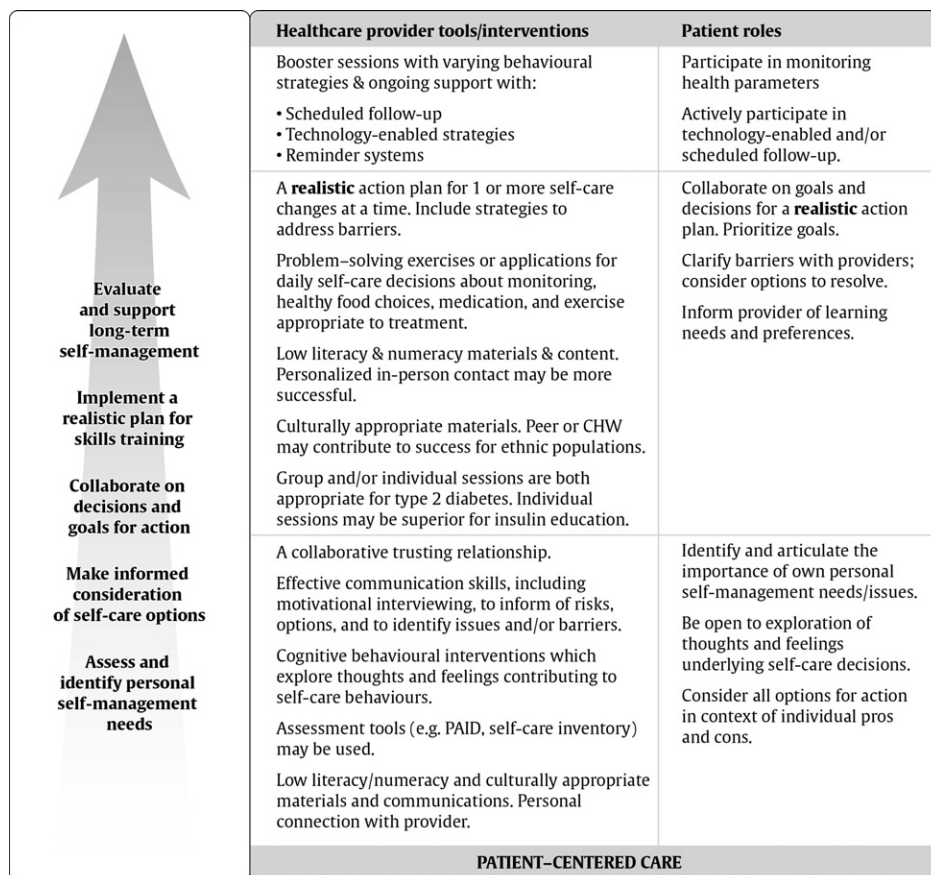


Figure 1. Steps to success in SME.

CHW, community health worker. PAID, Problem Areas In Diabetes scale.

scheduled follow-ups compared to controls. Outcomes include increased frequency of SMBG (58,63,71), improved adherence to treatment algorithms (31), improved self-efficacy (64–66) and QOL (70), as well as improved clinical outcomes, including reductions in A1C (59–62,65,69,73) and weight (67,68). However, 1 study of online diabetes education found no improvement in outcomes with the use of reinforcement methods (74).

A meta-analysis of studies examining the use of telemonitoring, home monitoring, telecare and telemedicine demonstrated a significant impact at the behavioural, clinical and structural levels (75). These strategies also resulted in significant reductions in A1C and diabetes-related complications, patient empowerment and improved patient understanding. However, the magnitude of the effect varied across studies and appeared to be dependent on the background characteristics of the patient population (e.g. ability for self-management, medical condition), sample selection and the approach to the treatment of control subjects.

Professional and peer delivery

Peer facilitators may augment multidisciplinary team practices in providing SME and/or social support, especially when developed as culturally relevant behavioural interventions for underserved populations (35). Two studies of the 6-week Diabetes Self-Management Program (DSMP) demonstrated the feasibility, but mixed effectiveness, of peer delivery of this standardized diabetes education program in Hispanic (71) and non-Hispanic populations (76). The DSMP was associated with significant A1C reductions in the Hispanic group (−0.4%) but not in the non-Hispanic group. Significant improvements in other outcomes, including decreased health distress, improved global health, decreased depressive

symptoms, improved self-efficacy and improved communication with physicians, were noted in both groups (71,76). In another study, a culturally tailored outreach and education program delivered by trained community health workers (CHW) was associated with significant improvements in self-care behaviours and similar A1C reductions compared to nurse-led case management and standard clinic care (77). Of note, the dropout rate was significantly lower in the CHW group (28% vs. 50% in the standard group), suggesting that the CHW may provide a trusted, culturally relevant and sustainable component to standard diabetes care (77).

The superiority of peer-delivered programs over similar programs delivered by health professionals has not been demonstrated in general populations with type 2 diabetes. A large study found that a peer-support intervention (i.e. 9 group sessions over 2 years) was not effective when targeted at all patients with type 2 diabetes (78). Another large study comparing specialist (nurse and physician) delivery to peer delivery of a 6-week, structured, interactive diabetes education program found no significant differences in either knowledge or A1C outcomes between the groups. However, the specialist group scored significantly higher in process and participant evaluations (79). Studies of the incremental effect of peer educators show much variability in terms of behaviour change and clinical outcomes (80,81). The specifics of training requirements for peer educators have not been clarified, and significant variations in training, scope of practice and issues of governance remain.

Delivery

No particular delivery strategy (e.g. video, web-based/online, phone, face-to-face, mixed) appears to result in consistently

superior outcomes in persons with type 2 diabetes; however, larger effect sizes have been noted with strategies that involve personal contact with healthcare providers, either via face-to-face interactions or by telephone (9). A combination of didactic and interactive teaching methods, as well as group and individual sessions, appears to be most effective for persons with type 2 diabetes (9).

Conclusions

Since 2004, there has been a clear increase in the use of multifaceted programs that incorporate behavioural/psychosocial interventions, as well as knowledge and skills training, with a marked reduction in didactic educational programs that focus on knowledge or skill acquisition only (3). Interventions that include face-to-face delivery, a cognitive-behavioural method and the practical application of content are more likely to improve glycemic control (11,48). The most effective behavioural interventions involve a patient-centred approach, shared decision making, the enablement of problem-solving skills and the use of action plans directed toward patient-chosen goals. Steps to success in SME are summarized in Figure 1.

RECOMMENDATIONS

1. People with diabetes should be offered timely diabetes education that is tailored to enhance self-care practices and behaviours [Grade A, Level 1A (3,11,53)].
2. All people with diabetes who are able should be taught how to self-manage their diabetes [Grade A, Level 1A (53)].
3. SME that incorporates cognitive-behavioural educational interventions, such as problem solving, goal setting, and self-monitoring of health parameters, should be implemented for all individuals with diabetes [Grade B, Level 2 (11,23,48,82)].
4. Interventions that increase patient participation and collaboration in healthcare decision making should be used by providers [Grade B, Level 2 (53)].
5. For people with type 2 diabetes, SME interventions should be offered in small group and/or one-on-one settings, since both may be effective [Grade A, Level 1A (83,84)].
6. In both type 1 and 2 diabetes, interventions that target families' ability to cope with stress or diabetes-related conflict should be included in educational interventions when indicated [Grade B, Level 2 (55)].
7. Technologically based home blood glucose monitoring systems may be integrated into SME interventions in order to improve glycemic control [Grade C, Level 3 (75,85)].
8. Culturally appropriate SME, which may include peer or lay educators, may be used to increase diabetes-related knowledge and self-care behaviours and to decrease A1C [Grade B, Level 2 (32,34,77)].
9. Adding literacy- and numeracy-sensitive materials to a comprehensive diabetes management and education program may be used to improve knowledge, self-efficacy and A1C outcomes for patients with low literacy [Grade C, Level 3 (36)].

Abbreviations:

A1C, glycated hemoglobin; SME, self-management education.

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Other Relevant Guidelines

Organization of Diabetes Care, p. S20
Monitoring Glycemic Control, p. S35
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Clinical Practice Guidelines

Targets for Glycemic Control

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Optimal glycemic control is fundamental to the management of diabetes.
- Both fasting and postprandial plasma glucose levels correlate with the risk of complications and contribute to the measured glycated hemoglobin (A1C) value.
- Glycemic targets should be individualized based on the individual's age, duration of diabetes, risk of severe hypoglycemia, presence or absence of cardiovascular disease and life expectancy.

Introduction

Optimal glycemic control is fundamental to the management of diabetes. In epidemiological analyses, glycated hemoglobin (A1C) levels $>7.0\%$ are associated with a significantly increased risk of both microvascular and macrovascular complications, regardless of underlying treatment (1–3). Data from the Diabetes Control and Complications Trial (DCCT; type 1 diabetes) (2) and the United Kingdom Prospective Diabetes Study (UKPDS; type 2 diabetes) (3) demonstrated a continuous relationship between A1C and diabetes complications, with no apparent threshold of benefit. In the DCCT, a 10% reduction in A1C was associated with a 40% to 50% lower risk of retinopathy progression, although the absolute reduction in risk was substantially less at lower A1C levels (2). In the UKPDS, this relationship was directly linear, with each 1.0% (absolute) reduction in mean A1C associated with a 37% decline in the risk of microvascular complications, a 14% lower rate of myocardial infarction (MI) and a 21% reduction in deaths from diabetes (3).

Both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) are directly correlated to the risk of complications, with some evidence that postprandial might constitute a stronger risk factor for cardiovascular (CV) complications (4–9). In a meta-analysis of 102 prospective studies, FPG >5.6 mmol/L was associated with an increased risk of CV events (10). Postprandial hyperglycemia and the 2-hour post-challenge PG appears to be a better predictor of cardiovascular disease (CVD) and all-cause mortality than FPG (7). This association between CVD and 2-hour postprandial PG appears to be linear (6,7). Values >7.8 mmol/L are associated with an increase in all-cause mortality (8), and

values >10.0 mmol/L are associated with both microvascular complications (11) and the highest risk of MI (12).

There is compelling evidence from randomized controlled studies that improved glycemic control reduces the risk of microvascular complications but has no significant effect on macrovascular outcomes in recently diagnosed type 1 (13) and type 2 diabetes (1,11,14), as well as more long-standing type 2 diabetes (15–19). The initial prospective randomized controlled trials were conducted in patients with recently diagnosed diabetes. These trials—the DCCT in type 1 diabetes (13) and the Kumamoto (11) and the UKPDS (1,14) in type 2 diabetes—confirmed that improved glycemic control significantly reduced the risk of microvascular complications but had no significant effect on macrovascular (particularly CV) outcomes. Subsequent observational data from long-term follow-up of both the DCCT and UKPDS cohorts showed a persistence of significant microvascular benefits in patients who had previously been in the intensively treated groups despite the fact that, during the subsequent follow-up period, their glycemic control became similar to that of patients who were previously in the standard arm (20–22). The follow-up data from these 2 studies also demonstrated a beneficial effect of improved glycemic control on CV outcomes. In the DCCT cohort, there was a significant reduction in CV outcomes (42%) as well as non-fatal MI, stroke and CV death (57%) in previously intensively treated patients compared with those who were previously in the standard arm (23). Similarly, there was a significant reduction in MI (15%–33%) and all-cause mortality (13%–27%) in the UKPDS cohort in patients who had been originally randomized to intensive treatment (22).

Three major trials—the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT)—looked at the effect of intensive glycemic control on patients with long-standing type 2 diabetes. The ACCORD trial randomly assigned 10 251 patients to intensive therapy targeting an A1C $<6.0\%$ or standard therapy targeting an A1C level of 7.0% to 7.9% (17,24). Patients included had either a previous history of CVD or multiple risk factors for CVD, and a baseline A1C level $\geq 7.5\%$. At inclusion, participants had a mean age of 62 years, diabetes duration of 10 years and a median baseline A1C level of 8.1%. A difference in A1C was rapidly obtained

and maintained throughout the trial at 6.4% and 7.5% in the intensive and standard therapy groups, respectively. The primary outcome of this study was a composite of major CV events: non-fatal MI, nonfatal stroke or death from CV causes. The intensive glucose control arm was prematurely terminated after 3.5 years due to higher mortality associated with assignment to this treatment (17,24).

The ADVANCE trial randomly assigned 11 140 patients to standard (targeting A1C based on local guidelines) or intensive glucose control therapy aimed at reducing A1C levels to $\leq 6.5\%$ (15). Patients were at least 55 years old with a history of major macrovascular or microvascular disease or at least 1 other risk factor for vascular disease. Median baseline A1C level and diabetes duration were lower than in the ACCORD trial at 7.2% and 8 years, respectively, whereas mean age was slightly higher at 66 years. The difference in A1C in both arms was obtained less rapidly, and, after a 5-year follow-up, mean A1C was 6.5% in the intensive group and 7.3% in the standard group. The primary outcome in the ADVANCE trial was a composite of microvascular events (nephropathy and retinopathy) and macrovascular disease defined by major adverse CV events.

VADT randomly assigned 1791 United States military veterans with poor glycemic control ($\geq 7.5\%$) to either standard or intensive glucose therapy, which aimed for an overall reduction in A1C levels by 1.5% (18,19). Following a median follow-up of 5.6 years, A1C levels were 8.4% and 6.9% in the standard and intensive therapy groups, respectively. The primary outcome of the study was the time from randomization to the first occurrence of a major CV event (18,19).

These 3 trials confirmed the benefit of intensive glycemic control on microvascular outcomes. In the VADT study, the progression to albuminuria was significantly reduced in the intensive-treatment patients, with 9.1% of patients having significantly reduced progression compared to 13.8% in the standard therapy group (19). Similarly, intensive therapy in ACCORD patients showed a favourable effect on microvascular outcomes, particularly albuminuria and diabetic retinopathy (16). In ADVANCE, patients in the intensive control group demonstrated a reduction in the incidence of major microvascular events, mainly through a 21% relative reduction in nephropathy (15). A recent meta-analysis confirmed the positive impact of intensive glycemic control on microalbuminuria (25).

None of the above studies independently confirmed a significant benefit of tight glycemic control on macrovascular outcomes. However, meta-analysis of clinical trials designed to assess differences in CV outcomes in patients who had achieved lower versus higher levels of glycemia demonstrated that those treated with more intensive therapy, compared to less intensive glycemic control, were found to have a 10% to 15% reduction in the risk of major CV events, primarily because of a 15% reduced risk of MI, but with no effect on stroke, CV death or all cause mortality (26). Intensive glycemic control, however, was associated with more than a 2-fold increase in the risk of severe hypoglycemia (25).

The unexpected higher mortality rates seen in the intensive arm of the ACCORD study and the lack of clear macrovascular benefit in the ADVANCE and VADT trials have been further reviewed. Several potential reasons for these findings have been suggested, including patient age, duration of diabetes, presence of CVD, history of severe hypoglycemic events, weight gain and the rapid decrease in A1C values. Increased mortality associated with intensive treatment could not be explained by the type of pharmacological treatment, rapidity to implement the intensive strategy or weight gain (24). Hypothesis-generating secondary analysis from the ACCORD trial reported a nonsignificant trend toward lower all-cause mortality in individuals assigned to the standard arm who were younger than 65 years at baseline (27). Similarly, the ADVANCE trial also reported a nonsignificant trend toward fewer events among younger patients in the intensive therapy group (15). Duration of diabetes

also may have played a role. Compared with the UKPDS and the DCCT, which were conducted in younger individuals with recent-onset diabetes, the duration of diabetes in the ACCORD, ADVANCE and VADT trials ranged from 8 to 11.5 years. Further emphasis of the importance of duration of diabetes was identified in a substudy of the VADT patients when measurement of the coronary calcium score, utilizing computed tomography, revealed fewer CVD events in these younger patients enrolled in the intensive treatment arm (28). The frequency of severe hypoglycemia in these trials was 2 to 3 times higher in the intensive therapy groups, and a higher mortality was reported in participants with 1 or more episodes of severe hypoglycemia in both the ACCORD (29) and the ADVANCE (30) trials, irrespective of the different treatment arms in which individual patients were allocated. However, these subanalyses confirmed that hypoglycemic events could not account for the difference in mortality between the intensive and standard therapy groups. Finally, in the ACCORD trial, mortality was increased in patients randomized in the intensive arm but who failed to reduce their A1C despite treatment intensification (31).

These findings suggest that microvascular and macrovascular events may be reduced by intensifying therapy targeting an A1C $< 7.0\%$ in younger patients with recently diagnosed diabetes and a lower initial A1C value but with an increased risk of hypoglycemic risk. Individualized and higher A1C targets may be indicated in older type 2 patients with longer duration of diabetes, established CV risk factors, severe hypoglycemia episodes and/or without A1C reduction despite treatment intensification. Similarly, individualization of A1C targets may be needed in some patients with type 1 diabetes who are unable to achieve an A1C $< 7.0\%$ without being at increased risk of severe hypoglycemia.

It also must be recognized that A1C measurement is a component of both the FPG and PPG. When A1C values are higher, the major contribution is the FPG levels, but as the A1C value approaches the target value of $\leq 7.0\%$, there is a greater contribution from PPG values (32,33). Another study using continuous glucose monitoring demonstrated that a 2-hour postprandial PG < 8.0 mmol/L correlates best with A1C $< 7.0\%$ (34). In view of this, if A1C targets cannot be achieved with a postprandial target of 5.0 to 10.0 mmol/L, further postprandial BG lowering to 5.0 to 8.0 mmol/L can be considered. The role of pre- vs. postprandial glucose control on reducing CV outcomes has been controversial (35,36).

A major difficulty in attempting to use evidence-based observations to determine the value of tighter postprandial glucose control has been the lack of well-designed, long-term outcome studies where assessing postprandial glucose values is the major objective of the study. Most of the large outcome trials conducted so far have been mostly based on preprandial glucose and A1C targets. Although there is evidence in type 2 diabetes that targeting postprandial hyperglycemia to < 8.0 mmol/L reduces progression of carotid atherosclerosis (35), a randomized controlled trial of type 2 diabetes patients treated with insulin therapy after acute MI showed no benefit of insulin regimen targeting postprandial hyperglycemia compared with the regimen targeting preprandial glucose (36).

Conclusions

Contrasting results from recent studies should not discourage physicians from controlling blood glucose levels. Intensive glucose control, lowering A1C values to $\leq 7\%$ in both type 1 and type 2 diabetes, provides strong benefits for microvascular complications and, if achieved early in the disease, might also provide a significant macrovascular benefit, especially as part of a multifactorial treatment approach. More intensive glucose control, A1C $\leq 6.5\%$, may be sought in patients with a shorter duration of diabetes, no evidence of significant CVD and longer life expectancy, provided this does

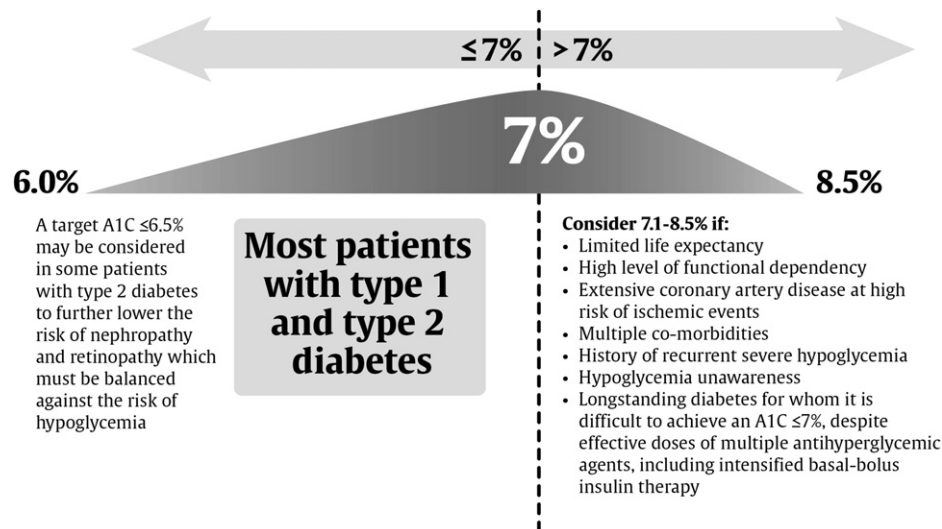


Figure 1. Recommended targets for glycemic control.

not result in a significant increase in hypoglycemia. An A1C target $\leq 8.5\%$ may be more appropriate in type 1 and type 2 patients with limited life expectancy, higher level of functional dependency, a history of severe hypoglycemia, advanced comorbidities, and a failure to attain established glucose targets despite treatment intensification (Figure 1).

RECOMMENDATIONS

- Glycemic targets should be individualized based on age, duration of diabetes, risk of severe hypoglycemia, presence or absence of cardiovascular disease, and life expectancy [Grade D, Consensus].
- Therapy in most individuals with type 1 or type 2 diabetes should be targeted to achieve an A1C $\leq 7.0\%$ in order to reduce the risk of microvascular [Grade A, Level 1A (1,2)] and, if implemented early in the course of disease, macrovascular complications [Grade B, Level 3 (22,23)].
- An A1C $\leq 6.5\%$ may be targeted in some patients with type 2 diabetes to further lower the risk of nephropathy [Grade A, Level 1 (15)] and retinopathy [Grade A, Level 1 (24)], but this must be balanced against the risk of hypoglycemia [Grade A, Level 1 (15)].
- Less stringent A1C targets (7.1%–8.5% in most cases) may be appropriate in patients with type 1 or type 2 diabetes with any of the following [Grade D, Consensus]:
 - Limited life expectancy
 - High level of functional dependency
 - Extensive coronary artery disease at high risk of ischemic events
 - Multiple comorbidities
 - History of recurrent severe hypoglycemia
 - Hypoglycemia unawareness
 - Longstanding diabetes for whom it is difficult to achieve an A1C $\leq 7.0\%$ despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy
- In order to achieve an A1C $\leq 7.0\%$, people with diabetes should aim for:
 - FPG or preprandial PG target of 4.0–7.0 mmol/L and a 2-hour PPG target of 5.0–10.0 mmol/L [Grade B, Level 2 (2) for type 1; Grade B, Level 2 (1,11) for type 2 diabetes].
 - If an A1C target $\leq 7.0\%$ cannot be achieved with a PPG target of 5.0–10.0 mmol/L, further PPG lowering to 5.0–8.0 mmol/L should be achieved [Grade D, Consensus, for type 1 diabetes; Grade D, Level 4 (32,33) for type 2 diabetes].

Abbreviations:

A1C, glycated hemoglobin; BG, blood glucose; FPG, fasting plasma glucose; PG, plasma glucose; PPG, postprandial plasma glucose.

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Clinical Practice Guidelines

Monitoring Glycemic Control

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Glycated hemoglobin (A1C) is a valuable indicator of treatment effectiveness and should be measured every 3 months when glycemic targets are not being met and when diabetes therapy is being adjusted.
- Awareness of both measures of glycemia, self-monitoring of blood glucose (SMBG) results and A1C, provide the best information to assess glycemic control.
- SMBG should not be viewed as an intervention but rather as an aid to assess interventions and hypoglycemia.
- Timing and frequency of SMBG should be determined individually based on the type of diabetes, the treatment prescribed, the need for information about blood glucose (BG) levels and the individual's capacity to use the information from testing to modify behaviours or adjust medications.
- SMBG and continuous glucose monitoring (CGM) should be linked with a structured educational and therapeutic program designed to facilitate behaviour change for improving BG levels.

Glycated Hemoglobin Testing

Glycated hemoglobin (A1C) is a reliable estimate of mean plasma glucose (PG) levels over the previous 3 to 4 months for most individuals (1). The mean level of blood glucose (BG) in the 30 days immediately preceding the blood sampling (days 0 to 30) contributes 50% of the result and the prior 90 to 120 days contributes 10% (2,3). In uncommon circumstances, where the rate of red blood cell turnover is significantly shortened or extended, or the structure of hemoglobin is altered, A1C may not accurately reflect glycemic status (Table 1).

A1C is the preferred standard for assessing glycated hemoglobin, and laboratories are encouraged to use assay methods for this test that are standardized to the Diabetes Control and Complications Trial (DCCT) reference (4–6). A1C is a valuable indicator of treatment effectiveness and should be measured every 3 months when glycemic targets are not being met and when diabetes therapy is being adjusted. Testing at 6-month intervals may be considered in situations where glycemic targets are consistently achieved (4). A1C is now also being used for diagnosis of diabetes (see Screening for Type 1 and Type 2 Diabetes chapter, p. S12).

In Canada, the A1C continues to be reported using the National Glycohemoglobin Standardization Program (NGSP) units (%). In 2007, a consensus statement from the American Diabetes Association, European Association for the Study of Diabetes and the International Diabetes Federation called for A1C reporting worldwide to change to dual reporting of A1C with the International Federation

of Clinical Chemistry and Laboratory Medicine (IFCC) SI units (mmol/mol) and derived NGSP units (%) with the hope of fully converting to exclusive reporting in SI units (7). However, this has not been adopted worldwide, with both Canada and the United States still using the NGSP units (%) (8). Although there are some advantages to reporting in SI units, the most notable disadvantage is the massive education effort that would be required to ensure recognition and adoption of the new units. At this time, Canada is not performing dual reporting. Therefore, throughout this document, the A1C will still be written in NGSP units (%). For those who wish to convert NGSP units to SI units, the following equation can be used: IFCC = 10.93(NGSP) – 23.50 (9) (see Appendix 11 for conversion of A1C from NGSP units to IFCC SI units).

Self-Monitoring of Blood Glucose

Self-monitoring of blood glucose (SMBG) can serve as a useful adjunct to other measures of glycemia, including A1C. Most people with diabetes will benefit from SMBG for a variety of individual reasons (10,11). SMBG is the only way to confirm, and appropriately treat, hypoglycemia. It can provide feedback on the results of lifestyle and pharmacological treatments, and increase patient empowerment and adherence to treatment. It can provide information to both the patient and healthcare professionals to facilitate longer-term treatment modifications and titrations as well as shorter-term treatment decisions, such as insulin dosing for people with type 1 or type 2 diabetes. In situations where A1C does not accurately reflect glycemia (Table 1), SMBG is essential (12).

SMBG is most effective when combined with an educational program that incorporates behavioural changes (lifestyle modification and/or oral hypoglycemic agents) in response to BG values (13–17). As part of this education, patients should receive instruction on (1) how and when to perform SMBG, (2) how to record the results in an organized fashion, (3) the meaning of various BG levels, and (4) how behaviour and actions affect SMBG results.

Frequency of SMBG

The recommended frequency of SMBG must be individualized to each person's unique circumstances. Factors influencing this recommendation will include type of diabetes, type of therapy, adequacy of glycemic control, literacy and numeracy skills, propensity to hypoglycemia, awareness of hypoglycemia, occupational requirements and acute illness.

Table 1
Factors that can affect A1C (74)

Factor	Increased A1C	Decreased A1C	Variable Change in A1C
Erythropoiesis	Iron deficiency B12 deficiency Decreased erythropoiesis	Use of erythropoietin, iron or B12 Reticulocytosis Chronic liver disease	
Altered hemoglobin			Fetal hemoglobin Hemoglobinopathies Methemoglobin Genetic determinants
Altered glycation	Alcoholism Chronic renal failure Decreased erythrocyte pH	Ingestion of aspirin, vitamin C or vitamin E Hemoglobinopathies Increased erythrocyte pH	
Erythrocyte destruction	Increased erythrocyte lifespan: Splenectomy	Decreased erythrocyte lifespan: Chronic renal failure Hemoglobinopathies Splenomegaly Rheumatoid arthritis Antiretrovirals Ribavirin Dapsone	
Assays	Hyperbilirubinemia Carbamylated hemoglobin Alcoholism Large doses of aspirin Chronic opiate use	Hypertriglyceridemia	Hemoglobinopathies

A1C, glycated hemoglobin.

Type 1 and type 2 treated with insulin

For people with type 1 diabetes, SMBG is an essential daily activity. In a large cohort study, performance of ≥ 3 self-tests per day was associated with a statistically and clinically significant 1.0% absolute reduction in A1C (7). The evidence is less certain in people with type 2 diabetes treated with insulin, although the above principles likely apply (7). In a large, nonrandomized study of individuals with stable type 2 diabetes using insulin, testing at least 3 times a day was associated with improved glycemic control (18).

More frequent testing, including preprandial and 2-hour postprandial PG (18,19) and occasional nocturnal BG measurements, is often required to provide the information needed to reduce hypoglycemia risk, including unrecognized nocturnal hypoglycemia (20–24).

Type 2 diabetes not treated with insulin

For people with type 2 diabetes treated with lifestyle management, with or without oral antihyperglycemic agents, the effectiveness of SMBG in terms of improving glycemic control, as well as the optimal frequency, is less clear (10,11,25–34). However, a series of recent meta-analyses, all using different methodologies and inclusion criteria, have generally shown a small benefit to reducing A1C in those individuals performing SMBG compared to those who did not (35–41). The magnitude of the benefit was small, with (absolute) A1C reductions in these meta-analyses ranging from 0.2% to 0.5%. These analyses demonstrated greater A1C reductions in those performing SMBG when the baseline A1C was $>8\%$ (17,35,38,42). SMBG has been demonstrated to be most effective in persons with type 2 diabetes within the first 6 months after diagnosis (43). Also of significance, there is no evidence that SMBG affects patient satisfaction, general well-being or general health-related quality of life (43).

It is important to recognize that most trials in non-insulin-treated patients with type 2 diabetes are of limited value as baseline A1C levels were typically $<8.0\%$, and these trials did not include a component of educational and therapeutic intervention in response to BG values. Several recent, well-designed randomized controlled trials that have included this component have demonstrated reductions in A1C (17,44,45). In the STeP trial, 483 poorly

controlled subjects, not on insulin (mean A1C $>8.9\%$), were randomized to either an active control group with enhanced usual care or a structured testing group with enhanced usual care and at least quarterly use of structured SMBG (17). At 1 year, there was a significantly greater reduction in mean A1C in the structured testing group compared with the active control group (-0.3% , $p=0.04$). Significantly, more structured testing group subjects received a treatment change recommendation compared with active control group subjects. In the ROSES (Role of Self-Monitoring of Blood Glucose and Intensive Education in Patients with Type 2 Diabetes Not Receiving Insulin) trial, subjects were randomly allocated to either a self-monitoring-based disease management strategy with education on how to modify lifestyle according to SMBG readings or to usual care (44). Results of SMBG were discussed during monthly telephone contact. After 6 months, significantly greater reductions in mean A1C (-0.5% , $p=0.04$) and body weight (-4.0 kg, $p=0.02$) were observed in the SMBG group compared with the usual care group. In the St. Carlos trial, newly diagnosed patients with type 2 diabetes were randomized to either an SMBG-based intervention or an A1C-based intervention (45). In the SMBG intervention group, SMBG results were used as both an educational tool to adhere to lifestyle changes as well as a therapeutic tool for adjustment of pharmacologic therapy. Treatment decisions for the A1C cohort were based strictly on A1C test results. After 1 year of follow-up, the median A1C level and body mass index (BMI) were significantly reduced in patients in the SMBG intervention group (from 6.6% to 6.1%, $p<0.05$; and from 29.6 to 27.9 kg/m², $p<0.01$). In the A1C group, there was no change in median A1C or BMI.

The evidence is less clear about how often, once recommended, SMBG should be performed by persons with type 2 diabetes not treated with insulin. Separate from one's ability to use SMBG in order to lower A1C, SMBG should be considered for the prevention, recognition and treatment of hypoglycemia in persons whose regimens include an insulin secretagogue due to the higher risk of hypoglycemia with this class of agents (46). On the other hand, for patients with type 2 diabetes who are managed with lifestyle, with or without oral antihyperglycemic agents associated with low risk of hypoglycemia, and who are meeting glycemic targets, very infrequent checking may be needed.

The Canadian Diabetes Association has published the “Self-Monitoring of Blood Glucose (SMBG) Recommendation Tool for Healthcare Providers,” which defines basic SMBG requirements to provide guidance to healthcare professionals regarding appropriate utilization of SMBG (Appendix 4) (available at: http://www.diabetes.ca/documents/for-professionals/SMBG_HCP_Tool_9.pdf).

Verification of accuracy of SMBG performance and results

Variability can exist between BG results obtained using SMBG devices and laboratory testing of PG. At BG levels >4.2 mmol/L, a difference of $<20\%$ between SMBG and simultaneous venous FPG is considered acceptable (47). In order to ensure accuracy of SMBG, results should be compared with a laboratory measurement of FPG at least annually or when indicators of glycemic control (A1C) do not match SMBG readings. Periodic re-education on correct SMBG technique may improve the accuracy of SMBG results (48,49). In rare situations, therapeutic interventions may interfere with the accuracy of some SMBG devices. For example, icodextrin-containing peritoneal dialysis solutions may cause falsely high readings in meters utilizing glucose dehydrogenase. Care should be taken to select an appropriate meter in such situations.

Alternate site testing

Meters are available that allow SMBG using blood samples from sites other than the fingertip (forearm, palm of the hand, thigh). Accuracy of results over a wide range of BG levels and during periods of rapid change in BG levels is variable across sites. During periods of rapid change in BG levels (e.g. after meals, after exercise and during hypoglycemia), fingertip testing has been shown to more accurately reflect glycemic status than forearm or thigh testing (50,51). In comparison, blood samples taken from the palm near the base of the thumb (the thenar area) demonstrate a closer correlation to fingertip samples at all times of day and during periods of rapid change in BG levels (52,53).

Ketone Testing

Ketone testing is recommended for all individuals with type 1 diabetes during periods of acute illness accompanied by elevated BG, when preprandial BG levels remain elevated (>14.0 mmol/L), or when symptoms of diabetic ketoacidosis (DKA), such as nausea, vomiting or abdominal pain, are present (4). If all of these conditions are present in type 2 diabetes, ketone testing should be considered, as DKA also can occur in these individuals.

During DKA, the equilibrium that is usually present between ketone bodies shifts toward formation of beta-hydroxybutyric acid (beta-OHB). As a result, testing methods that measure blood beta-OHB levels may provide more clinically useful information than those that measure urine acetoacetate or acetone levels. Assays that measure acetoacetate through urine testing may not identify the onset and resolution of ketosis as quickly as those that quantify beta-OHB levels in blood, since acetoacetate or acetone can increase as beta-OHB decreases with effective treatment (47). Meters that quantify beta-OHB from capillary sampling may be preferred for self-monitoring of ketones, as they have been associated with earlier detection of ketosis and may provide information required to prevent progression to DKA (54–56). This may be especially useful for individuals with type 1 diabetes using continuous subcutaneous insulin infusion, as interruption of insulin delivery can result in rapid onset of DKA (54).

Continuous Glucose Monitoring Systems

Continuous glucose monitoring systems (CGMSs) measure glucose concentrations in the interstitial fluid. Two types of devices are available. The “real time” (also called “personal”) CGMS provides information directly to the user by displaying moment-to-moment absolute glucose levels and trending arrows, and by providing alarm notifications in the event that the glucose level is above or below a preset limit. A “blinded” (sometimes referred to as “professional”) CGMS captures, but does not display, the glucose readings, which are then downloaded onto a computer for viewing and retrospective analysis by the healthcare provider (typically in conjunction with the user).

Continuous glucose monitoring (CGM) technology incorporates a subcutaneously inserted sensor, an attached transmitter and, in the case of real-time CGM, a display unit (which may be a stand-alone unit or be integrated into an insulin pump). In professional

RECOMMENDATIONS

1. For most individuals with diabetes, A1C should be measured every 3 months to ensure that glycemic goals are being met or maintained. Testing at least every 6 months should be performed in adults during periods of treatment and lifestyle stability when glycemic targets have been consistently achieved [Grade D, Consensus].
2. For individuals using insulin more than once a day, SMBG should be used as an essential part of diabetes self-management [Grade A, Level 1 (21), for type 1 diabetes; Grade C, Level 3 (10), for type 2 diabetes] and should be undertaken at least 3 times per day [Grade C, Level 3 (10,18)] and include both pre- and postprandial measurements [Grade C, Level 3 (18,19,73)]. In those with type 2 diabetes on once-daily insulin in addition to oral antihyperglycemic agents, testing at least once a day at variable times is recommended [Grade D, Consensus].
3. For individuals with type 2 diabetes not receiving insulin therapy, SMBG recommendations should be individualized depending on type of antihyperglycemic agents, level of glycemic control and risk of hypoglycemia [Grade D, Consensus].
 - When glycemic control is not being achieved, SMBG should be instituted [Grade B, Level 2 (33,38)] and should include periodic pre- and postprandial measurements and training of healthcare providers and patients on methods to modify lifestyle and medications in response to SMBG values [Grade B, Level 2 (17)].
 - If achieving glycemic targets or receiving medications not associated with hypoglycemia, infrequent SMBG is appropriate [Grade D, Consensus].
4. In many situations, for all individuals with diabetes, more frequent testing should be undertaken to provide information needed to make behavioural or treatment adjustments required to achieve desired glycemic targets and avoid risk of hypoglycemia [Grade D, Consensus].
5. In people with type 1 diabetes, real-time continuous glucose monitoring may be used to improve glycemic control [Grade B, Level 2 (58)] and reduce hypoglycemia [Grade B, Level 2 (65,69)].
6. In order to ensure accuracy of BG meter readings, meter results should be compared with laboratory measurement of simultaneous venous FPG at least annually and when indicators of glycemic control do not match meter readings [Grade D, Consensus].
7. Individuals with type 1 diabetes should be instructed to perform ketone testing during periods of acute illness accompanied by elevated BG, when preprandial BG levels remain >14.0 mmol/L or in the presence of symptoms of DKA [Grade D, Consensus]. Blood ketone testing methods may be preferred over urine ketone testing, as they have been associated with earlier detection of ketosis and response to treatment [Grade B, Level 2 (55)].

Abbreviations:

BG, blood glucose; DKA, diabetic ketoacidosis; FPG, fasting plasma glucose; SMBG, self-monitoring of blood glucose.

CGM, the “transmitter” captures and retains the data. In Canada, one real-time CGMS and two professional CGMSs are available. Real-time CGM has been consistently shown to reduce A1C in both adults (57–66) and children (58,60,62,63,65–67) with type 1 diabetes, and to reduce A1C in adults with type 2 diabetes (68). Real-time CGM also has been shown to reduce the time spent in hypoglycemia (65,69). Professional CGM has been shown to reduce A1C in adults with type 2 diabetes (70) and in pregnant women with type 1 or type 2 diabetes (71).

Successful use of CGM is, unsurprisingly, dependent on adherence with using the CGMS; the greater the time wearing the device, typically the better the A1C (59,60,63,64,67,72). Like SMBG, CGM provides the best outcomes if it is associated with structured educational and therapeutic programs. CGM is not a replacement for SMBG because SMBG is still required for calibration of the CGM device and, for real-time CGM, to confirm interstitial measurements prior to making therapeutic changes or treating suspected hypoglycemia.

Other Relevant Guidelines

Self-Management Education, p. S26
Targets for Glycemic Control, p. S31
Hypoglycemia, p. S69
Type 1 Diabetes in Children and Adolescents, p. S153
Type 2 Diabetes in Children and Adolescents, p. S163
Diabetes and Pregnancy, p. S168

Relevant Appendix

Appendix 4. Self-Monitoring of Blood Glucose (SMBG) Recommendation Tool for Healthcare Providers

Appendix 11. A1C Conversion

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Clinical Practice Guidelines

Physical Activity and Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Moderate to high levels of physical activity and cardiorespiratory fitness are associated with substantially lower morbidity and mortality in men and women with and without diabetes.
- For most people, being sedentary has far greater adverse health consequences than exercise would. However, before beginning a program of physical activity more vigorous than walking, people with diabetes should be assessed for conditions that might place the individual at increased risk for an adverse event associated with certain types of exercise.
- For people with type 2 diabetes, supervised exercise programs have been particularly effective in improving glycemic control, reducing the need for antihyperglycemic agents and insulin, and producing modest but sustained weight loss.
- Both aerobic and resistance exercise are beneficial for patients with diabetes, and it is optimal to do both types of exercise. At least 150 minutes per week of aerobic exercise, plus at least two sessions per week of resistance exercise, is recommended.

Types of Exercise

Aerobic exercise is physical activity, such as walking, bicycling or jogging, that involves continuous, rhythmic movements of large muscle groups lasting for at least 10 minutes at a time. **Resistance exercise** is physical activity involving brief repetitive exercises with weights, weight machines, resistance bands or one's own body weight (e.g. pushups) to increase muscle strength and/or endurance. **Flexibility exercise** is a form of activity, such as lower back or hamstring stretching, that enhances the ability of joints to move through their full range of motion. Some types of exercise, such as yoga, can incorporate elements of both resistance and flexibility exercise.

Benefits of Physical Activity

Physical activity can help people with diabetes achieve a variety of goals, including increased cardiorespiratory fitness, increased vigour, improved glycemic control, decreased insulin resistance, improved lipid profile, blood pressure reduction and maintenance of weight loss (1–4). The terms “physical activity” and “exercise” are used interchangeably in this chapter.

Benefits of Aerobic Exercise

Moderate to high levels of aerobic physical activity and higher levels of cardiorespiratory fitness are associated with substantial reductions in morbidity and mortality in both men and women and in both type 1 and type 2 diabetes. Large cohort studies have demonstrated that, in people with type 2 diabetes, regular physical activity (5–7) and/or moderate to high cardiorespiratory fitness (8) are associated with reductions in cardiovascular and overall mortality of 39% to 70% over 15 to 20 years of follow-up. Similarly, a cohort study in people with type 1 diabetes found that 7-year mortality was 50% lower in those reporting more than 2000 kcal of weekly exercise (equivalent to about 7 hours per week of brisk walking) compared to those reporting <1000 kcal of physical activity per week (9). Additional benefits of aerobic exercise include increased cardiorespiratory fitness in both type 1 and type 2 diabetes (10) and slowing of the development of peripheral neuropathy (11). In contrast to trials in type 2 diabetes, most clinical trials evaluating exercise interventions in people with type 1 diabetes have not demonstrated a beneficial effect of exercise on glycemic control (12).

Benefits of Resistance Exercise

A systematic review of randomized trials found that resistance training improves glycemic control (as reflected by reduced glycated hemoglobin [A1C]), decreases insulin resistance and increases muscular strength in adults with type 2 diabetes (13). Additionally, resistance training has been shown to increase lean muscle mass (14) and bone mineral density (15,16), leading to enhanced functional status and prevention of sarcopenia and osteoporosis. Resistance exercise in these studies was carried out using weight machines and/or free weights, and cannot necessarily be generalized to other types of resistance exercise, such as resistance bands or exercises utilizing only one's own body weight.

Benefits of Other Types of Exercise

To date, evidence for the beneficial effects of other types of exercise is not as extensive or as supportive as the evidence for aerobic and resistance exercise. For example, we found no study demonstrating any impact of a pure flexibility program on metabolic control, injury risk or any diabetes-related outcome.

A systematic review found that tai chi had no significant effects on glycemic control or quality of life (17). In one trial, 40 people with type 2 diabetes were randomized to whole-body vibration, strength training or flexibility training (18). A1C decreased nonsignificantly in the vibration group while it increased nonsignificantly in the strength and flexibility training groups. Baseline A1Cs were 7.3%, 6.8%, and 6.7% in vibration, strength and flexibility groups, respectively. This study's sample size was small ($n=13$ to 14 per group) so statistical power was limited; therefore, further studies would be needed before we can be confident regarding the degree of effectiveness of vibration therapy. A systematic review of trials evaluating yoga as an intervention for type 2 diabetes found modest reductions in A1C, fasting glucose and total cholesterol, as well as modest increases in high-density lipoprotein cholesterol (HDL-C) (19). The quality of the included studies was low, results were highly heterogeneous and there was evidence of significant publication bias. A trial published after this systematic review's search date found that Hatha yoga reduced A1C, fasting glucose, total cholesterol, body mass index and blood pressure to the same extent as aerobic exercise, with fewer self-reported symptoms of hypoglycemia (20,21). It is important to note that the Hatha yoga program in this trial incorporated elements of both strength training (where the resistance load was the individual's body weight) and aerobic exercise (repeated movements, done in a flowing manner, resulting in increased heart rate), and that it involved three 2-hour exercise sessions per week. This study's findings cannot necessarily be extrapolated to all Hatha Yoga programs or to other forms of yoga.

Supervised vs. Unsupervised Exercise

A systematic review and meta-analysis found that supervised programs involving aerobic or resistance exercise improved glycemic control in adults with type 2 diabetes, whether or not they included dietary co-intervention (22). The same meta-analysis found that unsupervised exercise only improved glycemic control if there was concomitant dietary intervention. A 1-year randomized trial compared exercise counselling plus twice-weekly supervised aerobic and resistance exercise vs. exercise counselling alone in patients with type 2 diabetes and the metabolic syndrome (23). Although self-reported total physical activity increased substantially in both groups, the group receiving the supervised aerobic and resistance exercise training had significantly better results: greater reductions in A1C, blood pressure, body mass index, waist circumference and estimated 10-year cardiac risk, and greater increases in aerobic fitness, muscle strength and HDL-C.

Minimizing Risk of Exercise-Related Adverse Events

People with diabetes should be prescribed and encouraged to incorporate regular exercise as a key part of their treatment plan. For most people with and without diabetes, being sedentary is associated with far greater health risks than exercise would be. However, before beginning a program of vigorous physical activity, people with diabetes should be assessed for conditions that might increase risks associated with certain types of exercise or predispose them to injury (2,24). Examples of such conditions include severe autonomic neuropathy, severe peripheral neuropathy, preproliferative or proliferative retinopathy and unstable angina. Preproliferative or proliferative retinopathy should be treated and stabilized prior to commencement of vigorous exercise. People with severe peripheral neuropathy should be instructed to inspect their feet daily, especially on days they are physically active, and to wear appropriate footwear. Although previous guidelines stated that persons with severe peripheral neuropathy should avoid weight-bearing activity, recent studies indicate that individuals

with peripheral neuropathy may safely participate in moderate weight-bearing exercise provided they do not have active foot ulcers (25). Studies also suggest that patients with peripheral neuropathy in the feet, who participate in daily weight-bearing activity, are at decreased risk of foot ulceration compared with those who are less active (26).

A resting electrocardiogram (ECG) should be performed, and an exercise ECG stress test should be considered, for individuals with possible cardiovascular disease who wish to undertake exercise more intense than brisk walking, especially if they are considering intense, prolonged endurance exercise, such as marathon running. Maximal exercise testing can be useful for exercise prescription. Exercise intensity can be prescribed and assessed more accurately when the actual maximum heart rate or maximum oxygen consumption (VO_{2max}) is known from exercise testing, as opposed to estimating target heart rate or work rate from age-predicted calculations. In addition, in cases where ischemia or arrhythmias are induced at higher exercise intensities, exercise test results could be used to keep exercise intensity below the ischemic threshold. Exercise testing also can be useful for risk stratification, given that lower aerobic capacity (27) and the presence of ischemic changes on ECG (28) are each associated with higher risks of cardiovascular and overall morbidity and mortality. Exercise testing can also sometimes detect previously unsuspected coronary disease. However, no trial has specifically assessed whether exercise stress testing before beginning an exercise program reduces coronary morbidity or mortality. Furthermore, a recent randomized trial found that screening of asymptomatic people with diabetes and additional cardiac risk factors using exercise ECG stress testing (or dipyridamole single photon emission computed tomography for those unable to exercise) did not reduce the risk of major cardiovascular events in the subsequent 3.5 years compared to a no-screening strategy (29). Another trial, in which 1123 asymptomatic people aged 50 to 75 years with type 2 diabetes were randomized to screening adenosine-stress radionuclide myocardial perfusion imaging or usual care found that screening had no impact on major cardiovascular events over the subsequent 5 years (30). Subjects in these 2 screening trials were not necessarily planning to begin exercise programs. Nevertheless, the evidence for exercise ECG stress testing of asymptomatic individuals with type 2 diabetes before beginning an exercise program is neither strong nor clear-cut.

The risk of hypoglycemia during exercise is of concern for people with diabetes, particularly those with type 1 diabetes, and to a lesser extent in those with type 2 diabetes using insulin or insulin secretagogues (sulfonylureas and meglitinides). In these individuals, if pre-exercise blood glucose levels are <5.5 mmol/L, approximately 15 to 30 g carbohydrate should be ingested before exercise. (The actual amount will be dependent on injected insulin dose, exercise duration and intensity, and results of blood glucose monitoring). In individuals whose diabetes is controlled by lifestyle or oral hypoglycemic agents that do not increase insulin levels, the risk of developing hypoglycemia during exercise is minimal, and most individuals will not need to monitor their blood glucose levels or be required to supplement with carbohydrate for exercise lasting <1 hour.

Hyperglycemia prior to exercise also may be of concern in people with diabetes. In individuals with type 1 diabetes who are severely insulin deficient (e.g. due to insulin omission or illness), hyperglycemia can be worsened by exercise. In patients with type 1 diabetes, if capillary glucose is >16.7 and the patient does not feel well, blood or urine ketones should be tested. If ketone levels are elevated, it is suggested that vigorous exercise be postponed and the patient take additional insulin. If ketones are negative and the patient feels well, it is not necessary to defer exercise due to hyperglycemia. Individuals with type 2 diabetes generally do not need to postpone exercise because of high blood glucose, provided they feel well. If capillary glucose levels are elevated >16.7 mmol/L, it is important to ensure

proper hydration and monitor for signs and symptoms (e.g. increased thirst, nausea, severe fatigue, blurred vision or headache), especially for exercise to be performed in the heat.

Minimizing Risk of Heat-Related Illness

People with diabetes may have greater susceptibility to adverse effects from heat than those without diabetes (31). Metabolic, cardiovascular and neurological dysfunctions associated with diabetes, along with associated health issues and advanced age, reduce the body's ability to detect heat and impair its capacity to dissipate heat (32–34). Reductions in sweating (32,33) and skin blood flow (35–37) decrease the body's ability to maintain core temperature at safe levels, especially during extended heat exposure and/or exercise in the heat. Patients with diabetes, especially those who are elderly and/or have autonomic neuropathy, cardiac or pulmonary disease, should be aware that they are at higher risk for heat illness. Whenever possible, exercise should be performed in a cool environment, such as an air-conditioned training centre. When weather is hot, exercise outdoors should be performed in the early or later hours of the day when the temperatures are cooler and the sun is not at its peak.

Acute Effects of Exercise on Blood Glucose

During and after all but the most intense exercise, blood glucose tends to decline due to increased glucose disposal and insulin sensitivity (38). However, during, and especially after, brief, very intense exercise (e.g. competitive track and field, hockey, basketball, intense resistance training), blood glucose often increases as a result of increases in glucose production that exceed increases in glucose disposal (39). These diverging effects of exercise on blood glucose concentrations can make management challenging, particularly for patients with type 1 diabetes, although some strategies are provided below.

Exercise Prescription Details

Both aerobic and resistance exercise are recommended for most people with diabetes (Tables 1 and 2). Walking is often the most popular and most feasible type of aerobic exercise in overweight, middle-aged, and elderly people with diabetes. For those who struggle with pain upon walking (e.g. due to osteoarthritis), semi-recumbent cycling may provide an alternative. For most middle-aged individuals, moderately brisk walking on level ground or semirecumbent cycling would be an example of moderate aerobic exercise, while brisk walking up an incline or jogging would be vigorous aerobic exercise. Resistance exercise performed 2 or 3 times per week may provide benefits that complement those of aerobic

Table 1
Aerobic exercise

Definition and recommended frequency	Intensity	Examples
Rhythmic, repeated and continuous movements of the same large muscle groups for at least 10 minutes at a time	Moderate: 50%–70% of person's maximum heart rate	<ul style="list-style-type: none"> • Biking • Brisk walking • Continuous swimming • Dancing • Raking leaves • Water aerobics
Recommended for a minimum of 150 minutes per week (moderate intensity)	Vigorous: >70% of person's maximum heart rate	<ul style="list-style-type: none"> • Brisk walking up an incline • Jogging • Aerobics • Hockey • Basketball • Fast swimming • Fast dancing

Table 2
Resistance exercise

Definition	Recommended frequency	Examples
Activities of brief duration involving the use of weights, weight machines or resistance bands to increase muscle strength and endurance	Three times per week <ul style="list-style-type: none"> • Start with 1 set using a weight with which you can perform 15 to 20 repetitions while maintaining proper form. • Progress to 2 sets and decrease the number of repetitions to 10–15 while increasing the weight slightly. If you cannot complete the required repetitions while maintaining proper form, reduce the weight. • Progress to 3 sets of 8 repetitions performed using an increased weight, ensuring proper form is maintained. 	<ul style="list-style-type: none"> • Exercise with weight machines • Exercise with free weights

Initial instruction and periodic supervision are recommended.

Note: The evidence supporting exercise with resistance bands is not as strong as the evidence for free weights or weight machines.

training (e.g. increased strength and vigour, reduced body fat, increased resting metabolic rate) (3,13,40). The studies reporting the greatest impact of resistance exercise on A1C had subjects progress to 3 sets (with approximately 8 repetitions per set) of resistance-type exercises at moderate to high intensity (i.e. the maximum weight that can be lifted 8 times while maintaining proper form), 3 times per week (41,42) or more (43,44). However, significant reductions in A1C and body fat have been achieved with twice-weekly resistance exercise in combination with regular aerobic exercise (23,45). The effects of resistance exercise and aerobic exercise on glycemic control are additive (46). Individuals who wish to begin resistance exercise should receive initial instruction and periodic supervision by a qualified exercise specialist to maximize benefits while minimizing risk of injury. A meta-analysis found that trials evaluating resistance exercise with less supervision showed less beneficial impact on glycemic control, insulin resistance and body composition than studies with greater supervision (13). Individuals with diabetes should also be recommended to reduce the amount of time spent doing sedentary activities.

Physical Activity in Children with Type 2 Diabetes

The pathophysiology of type 2 diabetes in children is similar to that of type 2 diabetes in adults; therefore, it seems logical to expect similar benefits from physical activity in children with type 2 diabetes as has been achieved in adults. A recent systematic review found no good-quality studies directly assessing the effects of physical activity in youth with type 2 diabetes (47). In the absence of direct evidence in this population, it is reasonable to recommend that children with type 2 diabetes strive to achieve the same activity level recommended for children in general: 60 minutes daily of moderate to vigorous physical activity and limit sedentary screen time to no more than 2 hours per day. Canadian physical activity guidelines for children and youth are available from the Canadian Society for Exercise Physiology (www.csep.ca).

Beginning Exercise in People with Low Baseline Fitness Levels

Previously sedentary individuals with limited exercise tolerance may have to gradually build up their amount of exercise, starting with as little as 5 to 10 minutes per day. Multiple, shorter exercise sessions (each lasting at least 10 minutes) in the course of a day should be considered as this regimen is as effective as a single longer session of equivalent length and intensity (48).

Exercise in Type 1 Diabetes

Moderate intensity aerobic exercise causes increased insulin sensitivity during, and for many hours after, the activity in people with and without diabetes. In type 1 diabetes, there is little or no endogenous insulin secretion and no physiological regulation of insulin levels. Therefore, if exogenous insulin and/or carbohydrate ingestion is not adjusted, hypoglycemia often occurs. Fear of hypoglycemia is an important barrier to exercise in people with type 1 diabetes (49) and advice on physical activity to patients with type 1 diabetes should include strategies to reduce risk of hypoglycemia. Small studies have explored several types of strategies for the prevention of hypoglycemia in type 1 diabetes. These strategies include the consumption of extra carbohydrates for exercise (50), limiting preprandial bolus insulin doses (51) and altering basal insulin for insulin pump users (52). These strategies can be used alone or in combination (53,54). Another strategy to avoid hypoglycemia is to perform intermittent, very brief (10 seconds), maximal-intensity sprints either at the beginning (55) or end (56) of an otherwise moderate-intensity exercise session, or intermittently during an exercise session (57). The attenuation of hypoglycemia is due to transiently reduced glucose disposal (58). Another strategy is to perform resistance exercise immediately prior to aerobic exercise (59). Exercise performed late in the day or in the evening can be associated with increased risk of overnight hypoglycemia in people with type 1 diabetes (50). To reduce this risk, one can reduce bedtime intermediate or long-acting injected insulin dose, or reduce overnight basal insulin infusion rates by approximately 20% from bedtime to 3 AM for insulin pump users (60). For more detailed, case-based discussions of insulin and carbohydrate adjustment for exercise in type 1 diabetes, see references 53 and 54.

Hyperglycemia can occur after very intense exercise. If it occurs, it can be addressed by giving a small bolus of a short-acting insulin analogue or, in insulin pump users, by temporarily increasing the basal insulin infusion until euglycemia is restored.

Motivating People with Diabetes to Be Physically Active

Physicians and other healthcare professionals can heighten awareness of the importance of physical activity by promoting regular exercise as a key component of therapy and identifying resources in the community (61). Patients should be encouraged to set specific physical activity goals, anticipate likely barriers to physical activity (e.g. weather, competing time commitments) and develop strategies to overcome these barriers (62). Having patients record their daily physical activity has been shown to increase physical activity levels and improve self-efficacy (confidence in one's own ability to successfully carry out a behaviour) (63). Self-efficacy is a very strong cognitive predictor of both aerobic and resistance exercise participation in people with diabetes (64). Some studies have found that structured physical activity counselling by a physician (65), skilled healthcare personnel or case managers (66,67) increases physical activity levels, improves glycemic control (66), reduces the need for oral antihyperglycemic agents and insulin (67), and produces modest but sustained weight loss (68). However, the impact of physical activity counselling on glycemic control, fitness, body composition and lipids is not as great as can be achieved through a supervised aerobic and resistance exercise program (23). Having social support (e.g. exercising with a friend or partner) facilitates regular physical activity, especially for women (69).

In youth with type 1 diabetes, physical activity adherence levels can be increased through structured programs involving pedometers, text messaging, social media and exercise trainers (70–72).

RECOMMENDATIONS

1. People with diabetes should accumulate a minimum of 150 minutes of moderate- to vigorous-intensity aerobic exercise each week, spread over at least 3 days of the week, with no more than 2 consecutive days without exercise [Grade B, Level 2, for type 2 diabetes (1,3,22); Grade C, Level 3, for type 1 diabetes (9)].
2. People with diabetes (including elderly people) should perform resistance exercise at least twice a week (23) and preferably 3 times per week [Grade B, Level 2 (13)] in addition to aerobic exercise [Grade B, Level 2 (23,45,46)]. Initial instruction and periodic supervision by an exercise specialist are recommended [Grade C, Level 3 (13)].
3. People with diabetes should set specific physical activity goals, anticipate likely barriers to physical activity (e.g. weather, competing commitments), develop strategies to overcome these barriers [Grade B, Level 2 (61)] and keep records of their physical activity [Grade B, Level 2 (62)].
4. Structured exercise programs supervised by qualified trainers should be implemented when feasible for people with type 2 diabetes to improve glycemic control, CVD risk factors and physical fitness [Grade B, Level 2 (22,23)].
5. People with diabetes with possible CVD or microvascular complications of diabetes who wish to undertake exercise that is substantially more vigorous than brisk walking should have medical evaluation for conditions that might increase exercise-associated risk. The evaluation would include history, physical examination (including funduscopic exam, foot exam, and neuropathy screening), resting ECG and, possibly, exercise ECG stress testing [Grade D, Consensus].

Abbreviations:

CVD, cardiovascular disease; ECG, electrocardiogram.

Other Relevant Guidelines

Monitoring Glycemic Control, p. S35

Pharmacotherapy in Type 1 Diabetes, p. S56

Hypoglycemia, p. S69

Screening for the Presence of Coronary Artery Disease, p. S105

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Clinical Practice Guidelines

Nutrition Therapy

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- People with diabetes should receive nutrition counselling by a registered dietitian.
- Nutrition therapy can reduce glycated hemoglobin (A1C) by 1.0% to 2.0% and, when used with other components of diabetes care, can further improve clinical and metabolic outcomes.
- Reduced caloric intake to achieve and maintain a healthier body weight should be a treatment goal for people with diabetes who are overweight or obese.
- The macronutrient distribution is flexible within recommended ranges and will depend on individual treatment goals and preferences.
- Replacing high glycemic index carbohydrates with low glycemic index carbohydrates in mixed meals has a clinically significant benefit for glycemic control in people with type 1 and type 2 diabetes.
- Intensive lifestyle interventions in people with type 2 diabetes can produce improvements in weight management, fitness, glycemic control and cardiovascular risk factors.
- A variety of dietary patterns and specific foods have been shown to be of benefit in people with type 2 diabetes.
- Consistency in carbohydrate intake and in spacing and regularity in meal consumption may help control blood glucose and weight.

Introduction

Nutrition therapy and counselling are an integral part of the treatment and self-management of diabetes. The goals of nutrition therapy are to maintain or improve quality of life and nutritional and physiological health; and to prevent and treat acute and long-term complications of diabetes, associated comorbid conditions and concomitant disorders.

It is well documented that nutrition therapy can improve glycemic control (1) by reducing glycated hemoglobin (A1C) by 1.0% to 2.0% (2–5) and, when used with other components of diabetes care, can further improve clinical and metabolic outcomes (3,4,6,7), resulting in reduced hospitalization rates (8). Furthermore, frequent follow-up (i.e. every 3 months) with a registered dietitian (RD) has been associated with better dietary adherence in type 2 diabetes (7).

Nutrition therapy provided by an RD with expertise in diabetes management (9,10), delivered in either a small group and/or an individual setting (11–13), has demonstrated benefits for those with, or at risk for, diabetes. Individual counselling may be

preferable for people of lower socioeconomic status (8), while group education has been shown to be more effective than individual counselling when it incorporates principles of adult education, including hands-on activities, problem solving, role playing and group discussions (14). Additionally, in people with type 2 diabetes, culturally sensitive peer education has been shown to improve A1C, nutrition knowledge and diabetes self-management (15), and web-based care management has been shown to improve glycemic control (16). Diabetes education programs serving vulnerable populations should evaluate the presence of barriers to healthy eating (e.g. cost of healthy food, stress-related overeating) (17) and work toward solutions to facilitate behaviour change.

In general, people with diabetes should follow the healthy diet recommended for the general population in *Eating Well with Canada's Food Guide* (18). This involves consuming a variety of foods from the 4 food groups (vegetables and fruits; grain products; milk and alternatives; meat and alternatives), with an emphasis on foods that are low in energy density and high in volume to optimize satiety and discourage overconsumption. This diet may help a person attain and maintain a healthy body weight while ensuring an adequate intake of carbohydrate (CHO), fibre, fat and essential fatty acids, protein, vitamins and minerals.

Overall, nutrition counselling should be individualized, regularly evaluated and reinforced in an intensive manner (19–21), and incorporate self-management education (22). As evidence is limited for the rigid adherence to any single dietary prescription (23,24), nutrition therapy and meal planning should be individualized to accommodate the individual's age, type and duration of diabetes, concurrent medical therapies, treatment goals, values, preferences, needs, culture, lifestyle, economic status (25), activity level, readiness to change and abilities. Applying the evidence from the sections that follow, [Figure 1](#) and [Table 1](#) present an algorithm which allows for this level of individualization of therapy in an evidence-based framework.

Energy

As an estimated 80% to 90% of people with type 2 diabetes are overweight or obese, strategies that include energy restriction to achieve weight loss are a primary consideration (26). A modest weight loss of 5% to 10% of initial body weight can substantially improve insulin sensitivity, glycemic control, hypertension and

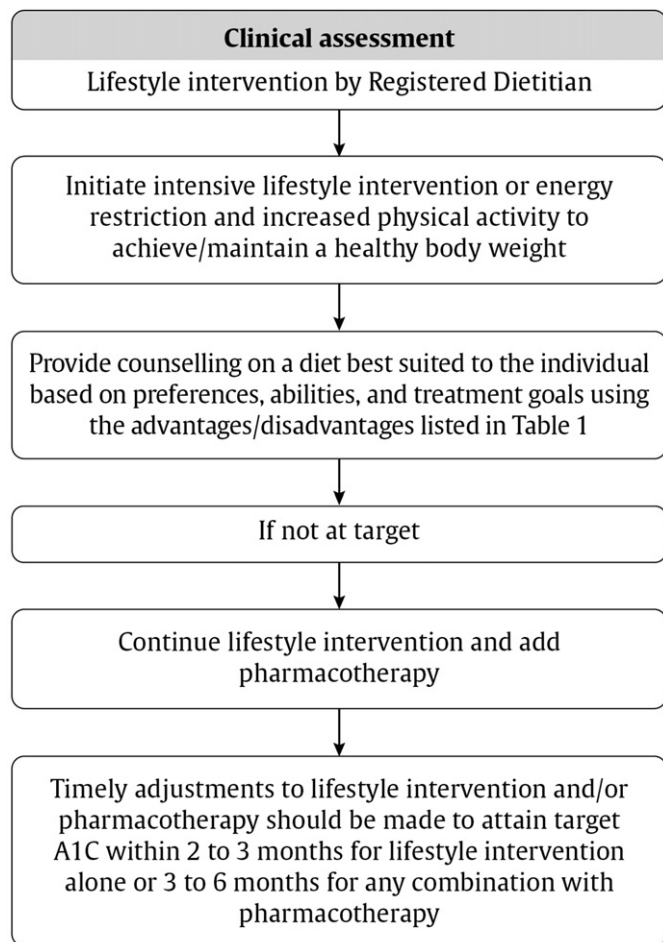


Figure 1. Nutritional management of hyperglycemia in type 2 diabetes.

dyslipidemia in people with type 2 diabetes and those at risk for type 2 diabetes (27–29). The sustainability of weight loss remains an important issue. Long-term follow-up of 7 to 10 years of intensive lifestyle intervention (ILI) programs targeting 5% to 7% weight loss in people at risk for type 2 diabetes suggests that there is some weight regain following discontinuation of the intervention, although the diabetes prevention benefits persist (30,31). Total calories should reflect the weight management goals for overweight and obese people with diabetes (i.e. to prevent further weight gain, to attain and maintain a healthy or lower body weight for the long term or to prevent weight regain).

Macronutrients

The ideal macronutrient distribution for the management of diabetes may vary, depending on the quality of the various macronutrients, the goals of the dietary treatment regimen and the individual's preferences and lifestyle.

Carbohydrate

The current recommended minimum intake for CHO is not less than 130 g/day, to provide glucose to the brain (32). A systematic review and meta-analysis of controlled feeding studies in people with type 2 diabetes found that CHO-restricted diets (mean CHO from 4% to 45% of total energy per day) improved A1C and triglycerides (TG), but not total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) or body weight compared with higher-CHO diets over

the short term (33). The long-term sustainability and safety of these diets, however, remain uncertain. Very-low-CHO diets may not ensure sufficient vitamin, mineral and fibre intake. It is recommended that the percentage of total daily energy from CHO should be no less than 45% to prevent high intakes of fat, as this is associated with reduced risk of chronic disease for adults (32). If CHO is derived from low glycemic index (GI) and high-fibre foods, it may contribute up to 60% of total energy, with improvements in glycemic and lipid control in adults with type 2 diabetes (34).

Glycemic index

The GI provides an assessment of the quality of CHO-containing foods based on their ability to raise blood glucose (BG) (35). To decrease the glycemic response to dietary intake, low-GI CHO foods are exchanged for high-GI CHO foods. Examples of typical low-GI food sources include beans, peas, lentils, pasta, pumpernickel or rye breads, parboiled rice, bulgur, barley, oats, quinoa and temperate fruit (apples, pears, oranges, peaches, plums, apricots, cherries, berries). Examples of higher-GI food sources include white or whole wheat bread, potatoes, highly extruded or crispy puffed breakfast cereals (corn flakes, puffed rice, puffed oats, puffed wheat), and tropical fruit (pineapple, mango, papaya, cantaloupe, watermelon). More detailed lists can be found in the *International Tables of Glycemic Index and Glycemic Load Values* (36).

Meta-analyses of controlled feeding trials of interventions replacing high-GI CHO with low-GI CHO in mixed meals have shown clinically significant improvements in glycemic control over 2 weeks to 6 months in people with type 1 or type 2 diabetes (37–39). This dietary strategy also leads to improvements in cardiovascular risk factors, such as TC, over 2 to 24 weeks (38), improvements in postprandial glycemia and high-sensitivity C-reactive protein (hsCRP) over 1 year (40) in people with type 2 diabetes, and reduces the number of hypoglycemic events over 24 to 52 weeks in adults and children with type 1 diabetes (39). Dietary advice to consume a low-GI diet was shown to sustain improvements in glycemic control and HDL-C compared with a high cereal fibre diet over 6 months (41), and to improve beta-cell function compared with a low-CHO, high monounsaturated fat diet over 1 year (42) in people with type 2 diabetes. A low-GI diet has also been shown to improve glycemic control compared with dietary advice based on the nutritional recommendations of the Japanese Diabetes Society over 3 months in Japanese people with impaired glucose tolerance (IGT) or type 2 diabetes (43) and to decrease the need for antihyperglycemic medications compared with the nutritional recommendations of the American Diabetes Association over 1 year in people with poorly controlled type 2 diabetes (44). Teaching a person to use the GI is recommended, but should be based on the individual's interest and ability.

Dietary fibre

Evidence suggests that the addition of soluble dietary fibre (e.g. eggplant, okra, oat products, beans, psyllium, barley) slows gastric emptying and delays the absorption of glucose in the small intestine, thereby improving postprandial BG control (45). In addition, cohort studies demonstrate that diets high in dietary fibre, especially cereal fibre, are associated with a decreased risk of cardiovascular disease (46). Due to the recognized beneficial effects of dietary fibre intake in people with diabetes, higher intakes than those recommended for the general population [25 g and 38 g for women and men, and 21 g and 30 g for women and men over 51 years, respectively (47)] are recommended for adults with diabetes (25 to 50 g/day or 15 to 25 g per 1000 kcal) (45,48).

Table 1
Properties of dietary interventions

Properties of dietary interventions (listed in the order they are presented in the text)			
Dietary interventions	A1C*	Advantages	Disadvantages
Macronutrients			
Hi-CHO (low-glycemic index)	↓	↑ HDL-C, ↓ CRP, ↓ hypoglycemia, ↓ diabetes medications	–
Hi-CHO (hi-fibre)	↓	↓ TC, ↓ LDL-C, ↓ diabetes medications	↓ HDL-C, GI side effects
Hi-MUFA	↓	↓ TG	–
Lo-CHO	↔	↓ TG	↓ Micronutrients, ↑ renal load
Hi-protein	↓	↓ BP, ↓ TG, preserve lean mass	↓ Micronutrients, ↑ renal load
Long chain omega 3 fatty acids	↔	↓ TG	Methyl-Hg exposure, environmental impact
Dietary patterns			
Vegetarian diets	↓	↓ LDL-C, ↑ HDL-C, ↓ BMI, ↓ non-HDL-C [†] , ↓ TC [†]	↓ Vitamin B12
Mediterranean diets	↓	↓ BP, ↓ CRP, ↓ TC, ↑ HDL-C, ↓ TC:HDL-C, ↓ TG, major CV events	–
DASH	↓	↓ Weight, ↓ BP, ↓ CRP, ↓ LDL-C, ↑ HDL-C	–
Popular weight loss diets			
Atkins diet	↔	↓ Weight, ↓ TC, ↑ HDL-C, ↓ TC:HDL-C, ↓ TG	↑ LDL-C, ↓ micronutrients, ↓ adherence, ↑ renal load
Protein Power Plan	↓	↓ Weight	↓ Micronutrients, ↓ adherence, ↑ renal load
Ornish diet	–	↓ Weight, ↓ LDL-C:HDL-C	↔ FPG, ↓ adherence
Weight Watchers diet	–	↓ Weight, ↓ LDL-C:HDL-C	↔ FPG, ↓ adherence
Zone diet	–	↓ Weight, ↓ LDL-C:HDL-C	↔ FPG, ↓ adherence, ↑ renal load
Diets emphasizing specific foods			
Dietary pulses	↓	↓ TC, ↓ LDL-C	GI side effects
Nuts	↓	↓ LDL-C, ↓ apo-B, ↓ apo-B:apo-A1, ↓ TG	–
Meal replacements	↓	↓ Weight	Temporary intervention

*↓ = <1% decrease in A1C. † adjusted for medication changes.

A1C = glycated hemoglobin; BMI = body mass index; BP = blood pressure; CHO = carbohydrate; CRP = C reactive protein; CV = Cardiovascular; FPG = fasting plasma glucose; GI = gastrointestinal; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MUFA = monounsaturated fatty acid; TC = total cholesterol; TG = triglycerides.

Sugars

Added sucrose intake of up to 10% of total daily energy (e.g. 50 to 65 g/day in a 2000 to 2600 kcal/day diet) is acceptable, as there is no evidence that sucrose intake up to this level has any deleterious effect on glycemic control or lipid profile in people with type 1 or type 2 diabetes (49–51). Intake of sucrose >10% of total daily energy may increase BG and TG concentrations in some individuals (52,53).

Systematic reviews and meta-analyses of controlled feeding trials have shown that consumption of added fructose in place of equal amounts of other sources of CHO (mainly starch or sucrose) is unlikely to have any harmful effect on body weight (54,55), blood pressure (56) or uric acid (55,57), and may even lower A1C (55,58,59) in most people with diabetes. However, at doses >60 g/day or >10% of total daily energy, fructose may have a small TG-raising effect in people with type 2 diabetes (60). As a source of excess energy, fructose has also been shown to contribute to weight gain and an adverse metabolic profile in people without diabetes (54,57).

Eating Well with Canada's Food Guide recommends up to 7 to 10 servings of vegetables and fruit per day (18). Consuming naturally occurring fructose obtained from fruit does not show evidence of harm. A randomized controlled feeding trial showed that naturally occurring fructose from fruit at a level providing ~60 g/day decreased body weight without adverse effects on lipids, blood pressure, uric acid or insulin resistance compared with a low-fructose control diet under matched hypocaloric feeding

conditions in overweight subjects without diabetes (61). Encouraging low-GI fruit over high-GI fruit as sources of small doses of fructose also provided glycemic benefit without adverse metabolic effects in people with type 2 diabetes over 6 months (62).

Fat

Current recommendations for the general population to consume fats in the range of 20% to 35% of energy intake apply equally to people with diabetes (47). As the risk of coronary artery disease (CAD) in people with diabetes is 2 to 3 times that of those without diabetes, saturated fats (SFAs) should be restricted to <7% of total daily energy intake (63), and trans fatty acids arising from industrial hydrogenation should be kept to a minimum. Meal plans should favour fats rich in monounsaturated fatty acids (MUFAs) (e.g. olive oil, canola oil) with up to 20% of total calories (63). Polyunsaturated fats (PUFAs), such as plant oils (e.g. canola, walnut, flax, salba) and long-chain omega-3 fatty acids (e.g. fatty fish) should be included in the diet up to 10% of total energy intake (63).

A comprehensive review found that although long-chain omega-3 fatty acids from fish oils, which include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), do not show an effect on glycemic control, these fatty acids do improve lipid profile, modify platelet aggregation and decrease cardiovascular mortality in people with diabetes (64). In a prospective cohort study of women with type 2 diabetes, higher consumption (1 to 3 servings

per month) of omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs) from fish was associated with a 40% reduction in CAD compared with those with a low intake (<1 serving per month) (65). Those who consumed fatty fish >5 times per week had a 64% reduction in CAD compared with those in the low-intake category (65). A cohort analysis of the Diabetes Control and Complications Trial (DCCT) also showed that higher consumptions of omega-3 LC-PUFAs from fish are associated with a decrease in the degree of albuminuria in type 1 diabetes (66).

Large clinical outcome trials of supplementation with omega-3 LC-PUFAs have shown a significant reduction in cardiovascular events in participants, including people with diabetes who have elevated TC (67), those with chronic heart failure (68) or those who had a previous myocardial infarction (MI) (69). Although the Alpha OMEGA trial did not show a significant mortality benefit after 3.5 years of supplementation with omega-3 LC-PUFAs in all participants who had a previous MI, it did show a significant reduction in incident cardiovascular disease and death from coronary heart disease (CHD) in the subgroup of participants with diabetes (70). However, there remains uncertainty regarding the benefits of supplementation with omega-3 LC-PUFAs. The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial failed to show a cardiovascular or mortality benefit of supplementation with omega-3 LC-PUFAs in 12 536 people with or at risk for diabetes (71). When the data from this trial were included in the most recent meta-analysis, the overall risk estimates for cardiovascular events and mortality were not significant (72). There remains a need for more evidence related to the benefits of supplementation with omega-3 LC-PUFAs in people with diabetes. The Study of Cardiovascular Events in Diabetes (ASCEND) in 15 480 people with diabetes free of cardiovascular disease (clinicaltrials.gov registration number NCT00135226) will provide more data on the outcomes of supplementation with omega-3 LC-PUFAs.

Protein

There is no evidence that the usual protein intake for most individuals (1 to 1.5 g per kg body weight per day), representing 15% to 20% of total energy intake, needs to be modified for people with diabetes (73). However, this intake in grams per kg per day should be maintained or increased with energy-reduced diets.

In people with diabetes who have chronic kidney disease (CKD), targeting a level of intake that does not exceed the recommended dietary allowance (RDA) of 0.8 g per kilogram body weight per day is an important consideration (74). This level of restriction is based on evidence of reductions in end stage renal disease or mortality seen in a single randomized controlled trial in people with type 1 diabetes who have CKD (75), as well as improvements in albuminuria or proteinuria and A1C from meta-analyses of randomized controlled trials from 6 months to 4 years of follow-up in people with varying degrees of diabetic nephropathy (76). Protein quality has been shown to be another important consideration in this cohort. Several randomized trials have shown that replacement of animal protein with plant protein (mainly from soy) results in improvements in albuminuria or proteinuria, LDL-C, TG and CRP up to 4 years (77–79). Replacement of red meat with either chicken or a low-protein diet with vegetable and dairy sources of protein has also been shown to result in significant reductions in albuminuria after 4 weeks in a randomized trial (80). In patients on low-protein diets, harm due to malnutrition should not be ignored (81). Both the quantity and quality (high biological value) of protein intake must be optimized to meet requirements for essential amino acids, necessitating adequate clinical and laboratory monitoring of nutritional status in the individual with diabetes and CKD. Greater incorporation of plant sources of protein may also require closer monitoring of potassium as CKD progresses.

Macronutrient substitutions

The ideal macronutrient distribution for the management of diabetes may need to be individualized based on individual preferences and perceived palatability, as several studies suggest that wide variations can be effective (82). For example, similar beneficial effects on body weight, body composition, cardiovascular risk factors and glycemic control have been reported in individuals with type 2 diabetes who followed either a high-MUFA diet (46% CHO, 15% protein, 38% fat, half MUFAs) or a higher CHO diet (54% CHO, 15% protein, 28% fat) for 1 year (83). Similarly, 6-week crossover feeding trials comparing high MUFA with high CHO isoenergetic diets, emphasizing natural foods, vegetables and fish, showed similar energy balance, glycemic control and lipid profile (82). Furthermore, it has been shown that a high MUFA diet is as successful as a conventional diet in improving metabolic and anthropometric parameters in persons with type 2 diabetes (84). However, postprandial glucose, insulin and LDL-C concentrations are lower in response to a meal with a low GI and low glycemic load compared with a MUFA-rich meal (85).

Replacing fat with refined CHOs should be avoided as it has been shown to elevate fasting insulin, TG, postprandial glucose and insulin concentrations and to lower HDL-C (86). A 15% increase of energy from dietary protein with a parallel decrease in fat, while maintaining CHO intake constant, does not affect postprandial plasma glucose and insulin concentrations in obese individuals with type 2 diabetes and, over 4 weeks, improves TG and blood pressure (87). Furthermore, in nondiabetic adults, increasing protein intake to 1.5 to 2 g per kilogram body weight was shown to promote satiety (88) and preserve lean body mass (89), which would be of potential benefit in energy-reduced diets.

There may be benefit of replacing SFAs with PUFAs. A systematic review and meta-analysis of large clinical outcome trials replacing SFAs with PUFAs showed a 19% reduction in MI or CHD death in people with and without CHD, in which some of the trials included people with diabetes (90). This result was supported by a pooled analysis of prospective cohort studies, which showed similar reductions in the risk of CHD in people without diabetes (91). The pooled analysis, however, did not show a cardiovascular benefit of replacing SFAs with MUFAs, and neither the pooled analysis nor the Women's Health Initiative Randomized Controlled Dietary Modification Trial in postmenopausal women—of whom approximately 5% were treated for diabetes and 36% had the metabolic syndrome (92)—showed a cardiovascular benefit of replacing SFAs with CHO. The CHO in these studies, however, was not differentiated by its GI.

A 12-month study comparing a high-protein/low-fat vs. a high-CHO/low-fat diet in the treatment of type 2 diabetes showed that neither diet was superior in helping to manage type 2 diabetes (93). Rather, it is the degree of energy reduction, not the variation in diet macronutrient composition, which was related to the long-term improvement in glycemic control (93,94). Better improvement of cardiovascular risk profile has been observed with a high- vs. low-protein diet in persons with type 2 diabetes despite similar weight loss with normal renal function being maintained (95). Two eggs per day, provided as part of a high-protein, low-saturated-fat, energy-reduced diet, improved HDL-C compared with a similar low-cholesterol diet, without adversely affecting other blood lipids in individuals with type 2 diabetes (96). Adjustments in medication type and dosage may be required when embarking on a different macronutrient distribution (97) or energy reduction (98).

Intensive Lifestyle Intervention

ILI programs in diabetes usually consist of behavioural interventions combining dietary modification and increased physical activity. A multidisciplinary team, including RDs, nurses and

kinesiologists, usually leads the ILI programs, with the intensity of follow-up varying from weekly to every 3 months with gradually decreasing contact as programs progress. Large, randomized, clinical trials have shown benefit of ILI programs using different lifestyle approaches in diabetes. Twenty-year follow-up of the China Da Qing Diabetes Prevention Outcome Study showed that 6 years of an ILI program targeting an increase in vegetable intake, decrease in alcohol and sugar intake, weight loss through energy restriction in overweight and obese participants, and an increase in leisure-time physical activity (e.g. 30 minutes walking per day) reduced severe retinopathy by 47%, whereas nephropathy and neuropathy outcomes were not affected compared with usual care in high-risk people with IGT (99). Interim analyses of the Look AHEAD (Action for Health in Diabetes) trial have shown that an ILI program targeting at least a 7% weight loss through a restriction in energy (1200 to 1800 total kcal/day based on initial weight), a reduction in fat (<30% of energy as total fat and <10% as saturated fat), an increase in protein ($\geq 15\%$ of energy) and an increase in physical activity (175 min/week with an intensity similar to brisk walking) produced sustained weight loss and improvements in fitness, glycemic control and cardiovascular risk factors (blood pressure, TG and HDL-C) compared with diabetes support and education over 4 years of follow-up in overweight people with type 2 diabetes (29). In 2012, the Look AHEAD trial was stopped early as it was determined that 11 years of an ILI did not decrease the occurrence of cardiovascular events compared to the control group and further intervention was unlikely to change this result. It was noted, however, that both groups had a lower number of cardiovascular events compared to previous studies of people with diabetes (<http://www.nih.gov/news/health/oct2012/niddk-19.htm>). The Lifestyle Over and Above Drugs in Diabetes (LOADD) trial showed that a 6-month ILI program of individualised dietary advice (according to the nutritional recommendations of the European Association for the Study of Diabetes) (100) improved glycemic control and anthropometric measures compared with usual care in persons with type 2 diabetes who had unsatisfactory glycemic control ($A1C > 7\%$) on optimized antihyperglycemic drug treatment (101). The Mediterranean Lifestyle Program (MLP) trial showed that a comprehensive 6-month ILI promoting a Mediterranean-style dietary pattern increased physical activity (including aerobic, strength-training and stress management exercises) and led to weight loss and improvements in glycemic control and quality of life in postmenopausal women with type 2 diabetes (102). Although the available trials suggest an overall benefit of different ILI programs in people with diabetes, the feasibility of implementing an ILI program will depend on the availability of resources and access to a multidisciplinary team.

Dietary Patterns

There are now several large studies that have suggested that a variety of dietary patterns are beneficial for people with diabetes. An individual's values, preferences and abilities may influence the decisions to use these dietary patterns.

Vegetarian diets

A low-fat, ad libitum vegan diet has been shown to be just as beneficial as conventional American Diabetes Association dietary guidelines in promoting weight loss and improving fasting BG, TC and LDL-C over 74 weeks in adults with type 2 diabetes, and, when taking medication changes into account, the vegan diet improved glycemia and plasma lipids more than the conventional diet (103). One must note that, with both diets, weekly or biweekly nutrition and cooking instruction was provided by a dietitian or cooking instructor (103). Similarly, a calorie-restricted vegetarian diet was shown to improve body mass index (BMI) and LDL-C more than

a conventional diet in people with type 2 diabetes (104). While both diets were effective in reducing A1C, more participants on the vegetarian diet had a decrease in diabetes medications compared to those on the conventional diet (43% vs. 5%, respectively).

Mediterranean diets

A "Mediterranean diet" primarily refers to a plant-based diet first described in the 1960s (105). General features include a high consumption of fruits, vegetables, legumes, nuts, seeds, cereals and whole grains; moderate-to-high consumption of olive oil (as the principal source of fat); low to moderate consumption of dairy products, fish and poultry; and low consumption of red meat, as well as low to moderate consumption of wine, mainly during meals (105,106). A systematic review of randomized controlled feeding trials showed that a Mediterranean-style dietary pattern improves glycemic control and cardiovascular risk factors, including systolic blood pressure, TC, HDL-C, TC:HDL-C ratio, and TG in type 2 diabetes (107). Individually, well-powered, randomized controlled trials in people with type 2 diabetes have also shown evidence of long-term benefits. A low-CHO Mediterranean-style diet reduced A1C and delayed the need for antihyperglycemic drug therapy compared with a low-fat diet in overweight individuals with newly diagnosed type 2 diabetes at 4 years (108). The Dietary Intervention Randomized Controlled Trial (DIRECT) showed that a calorie-reduced, Mediterranean-style diet lowered fasting plasma glucose compared with calorie-reduced low-fat or low-CHO diets in a subgroup of moderately obese people with type 2 diabetes at 2 years (109). Compared with a diet based on the American Diabetes Association recommendations, both traditional and low-CHO Mediterranean-style diets were shown to decrease A1C and TG, whereas only the low-CHO Mediterranean-style diet improved LDL-C and HDL-C at 1 year in overweight persons with type 2 diabetes (110). These metabolic advantages of a Mediterranean diet appear to have benefits for the primary prevention of cardiovascular disease in people with type 2 diabetes. The Prevención con Dieta Mediterránea (PREDIMED) study, a Spanish multicentre, randomized trial of the effect of a Mediterranean diet supplemented with extra-virgin olive oil or mixed nuts compared with a low-fat control diet on major cardiovascular events in 7447 participants at high cardiovascular risk (including 3614 participants [49%] with type 2 diabetes), was stopped early for benefit. Both types of Mediterranean diets were shown to reduce the incidence of major cardiovascular events by approximately 30% without any subgroup differences between participants with and without diabetes over a median follow-up of 4.8 years (111).

DASH and low-sodium dietary patterns

Dietary approaches to reducing blood pressure have focused on sodium reduction and the Dietary Approaches to Stop Hypertension (DASH) dietary pattern. Although advice to the general population over 1 year of age is to achieve a sodium intake that meets the adequate intake (AI) target of 1000 to 1500 mg/day (depending on age, sex, pregnancy and lactation) (112), there is recent concern from prospective cohort studies that low sodium intakes may be associated with increased mortality in people with type 1 (113) and type 2 diabetes (114).

The DASH dietary pattern does not target sodium reductions but rather emphasizes vegetables, fruits and low-fat dairy products, and includes whole grains, poultry, fish and nuts. It contains smaller amounts of red and processed meat, sweets and sugar-containing beverages, total and saturated fat, and cholesterol, and larger amounts of potassium, calcium, magnesium, dietary fibre and protein than typical Western diets (115,116). The DASH dietary pattern has been shown to lower systolic and diastolic blood

pressure compared with a typical American diet matched for sodium intake in people with and without hypertension, inclusive of people with well-controlled diabetes (115,116). These improvements in blood pressure have been shown to hold across high (3220 mg), medium (2300 mg), and low (1495 mg) levels of matched sodium intake (116). In people with type 2 diabetes, the DASH dietary pattern compared with a control diet matched for a moderate sodium intake (2400 mg) has been shown to decrease systolic and diastolic blood pressure, as well as decrease A1C, fasting BG, weight, waist circumference, LDL-C and CRP and to increase HDL-C over 8 weeks (117,118).

Popular weight-loss diets

Numerous popular weight-loss diets are available to people with diabetes. Several of these diets, including the Atkins, Zone, Ornish, Weight Watchers, and Protein Power Lifeplan diets, have been subjected to investigation in longer-term, randomized controlled trials in overweight and obese participants that included some people with diabetes, although no available trials have been conducted exclusively in people with diabetes. A systematic review and meta-analysis of 4 trials of the Atkins diet and one trial of the Protein Power Lifeplan diet (a diet with a similar extreme CHO restriction) showed that these diets were no more effective than conventional energy-restricted, low-fat diets in inducing weight loss with improvements in TG and HDL-C offset by increases in TC and LDL-C for up to 1 year (119). The Protein Power Lifeplan diet, however, did show improved A1C compared with an energy-reduced, low-fat diet at 1 year in a subset of participants with type 2 diabetes (120). DIRECT showed that, although an Atkins diet produced weight loss and improvements in the TC:HDL-C ratio, HDL-C and TG compared with a calorie-restricted, low-fat conventional diet, its effects were not different from that of a calorie-restricted Mediterranean-style diet at 2 years (109). Furthermore, the Mediterranean-style diet had a more favourable effect on fasting plasma glucose at 2 years in the subgroup of participants with type 2 diabetes (109). Another trial comparing the Atkins, Ornish, Weight Watchers, and Zone diets showed similar weight loss and improvements in the LDL-C:HDL-C ratio without effects on fasting plasma glucose at 1 year in overweight and obese participants, of whom 28% had diabetes (121). A common finding across most of the available trials was poor dietary adherence (119,120), although greater adherence was associated with greater weight loss and reductions in cardiovascular risk factors irrespective of the diet (121). The development of nutritional deficiencies must also be considered in the context of diets that restrict food groups. The available evidence on popular weight-loss diets supports the approach of selecting the diet best suited to the preferences and treatment goals of the individual; however, more studies conducted specifically in people with diabetes are warranted.

Diets emphasizing specific foods

A systematic review and meta-analysis of randomized controlled trials found that diets high in dietary pulses (e.g. beans, peas, chickpeas, lentils), either alone or as part of low-GI or high-fibre diets, lowered fasting BG and/or glycated blood proteins, including A1C, in people with and without diabetes (122). In addition to decreasing fasting BG, an increase in HDL-C was also found in a randomized controlled trial of a combination of dietary pulses and whole grains in partial replacement for rice in the diet of people with type 2 diabetes (123). Another systematic review and meta-analysis of randomized controlled trials found that diets high in dietary pulses reduced TC and LDL-C compared with

Table 2

Acceptable daily intake of sweeteners

Sweetener	Acceptable daily intake (mg/kg body weight/day)
Acesulfame potassium	15
Aspartame	40
Cyclamate	11
Erythritol	1,000
Neotame	2
Saccharin	5
Steviol glycosides	4
Sucralose	8.8
Tagatose	80
Thaumatin	0.9

macronutrient and energy-matched control diets in nondiabetic participants with normal to high cholesterol (124).

Another novel, and yet simple, technique of encouraging intake of vegetables first and other CHOs last at each meal was also successful in achieving better glycemic control (A1C) than an exchange-based meal plan after 24 months of follow-up in people with type 2 diabetes (125).

Two ounces of mixed, unsalted nuts daily (or 50 to 75 g, depending on individual energy needs of participants) for 13 weeks as a replacement for CHO foods in people with type 2 diabetes lowered A1C, TC and LDL-C with no decrease in HDL-C, resulting in an improved TC:HDL-C ratio and no concomitant weight gain (126). In studies of shorter duration and/or with smaller sample sizes, similar results have been reported. In 1 pilot study in people with type 2 diabetes, five 28-g servings of almonds per week for 12 weeks resulted in improvements in A1C and BMI (127). In another study, 60 g of almonds per day for 4 weeks, compared to a National Cholesterol Education Program (NCEP) Step II diet, in people with type 2 diabetes, improved fasting glucose, percentage of body fat, TC, LDL-C and LDL-C:HDL-C ratio (128). Furthermore, in a pooled analysis of 25 nut intervention trials in people with normolipidemia or hypercholesterolemia, including 1 trial in people with type 2 diabetes (129), it was concluded that different types of nuts were effective in reducing TC and LDL-C, with no decrease in HDL-C, and a decrease in TG only in those with elevated TG levels. Overall, the effect of nut consumption was dose dependent, and the greatest lipid-lowering benefits were seen in those with high baseline LDL-C, low BMI and consumers of Western diets (130). While more research in people with diabetes would be beneficial, these studies support the inclusion of nuts as a dietary strategy to improve lipid and A1C levels in this population.

Special Considerations for People with Type 1 Diabetes and Type 2 Diabetes on Insulin

Consistency in CHO intake (131), and spacing and regularity in meal consumption, may help control BG levels (21,131,132). Inclusion of snacks as part of a person's meal plan should be individualized based on meal spacing, metabolic control, treatment regimen and risk of hypoglycemia, and should be balanced against the potential risk of weight gain (133,134).

Intensively treated individuals with type 1 diabetes show worse diabetes control with diets high in total and saturated fat and low in CHO (135). People with type 1 diabetes or type 2 diabetes requiring insulin, using a basal-bolus regimen, should adjust their insulin based on the CHO content of their meals. Intensive insulin therapy regimens that include multiple injections of rapid-acting insulin matched to CHO allow for flexibility in meal size and frequency (136,137). Improvements in A1C, BG and quality of life, as well as less requirement for insulin, can be achieved when individuals with type 1 diabetes (138) or type 2 diabetes (139) receive education on matching insulin to CHO content (e.g. CHO counting) (140,141). In doing so,

dietary fibre and sugar alcohol should be subtracted from total CHO. In addition, new interactive technologies, utilizing mobile phones to provide information, CHO/insulin bolus calculations and telemedicine communications with care providers, have been shown to decrease both weight gain and the time required for education. They also improved individual quality of life and treatment satisfaction (142).

Other Considerations

Nonnutritive sweeteners

Acesulfame potassium, aspartame, cyclamate, neotame, saccharin, steviol glycosides, sucralose, tagatose and thaumatin have been approved by Health Canada for use as either table-top sweeteners or food additives, or for use in chewing gum (Personal Communication with Health Canada, <http://www.hc-sc.gc.ca/fn-an/securit/addit/list/9-sweetener-edulcorant-eng.php>, and <http://www.hc-sc.gc.ca/fn-an/securit/addit/sweeten-edulcor/index-eng.php>). Health Canada has set acceptable daily intake (ADI) values, which are expressed on a body weight basis and are considered safe daily intake levels over a lifetime (Table 2). These levels are considered high and are rarely achieved. Indeed, 1 can of pop contains about 42 mg Ace-K or 200 mg aspartame, 1 packet of sweeteners, 12 mg sucralose or 12 mg saccharin. Most have been shown to be safe when used by people with diabetes (143); however, there are limited data on the newer sweeteners, such as neotame and thaumatin. Stevia extracts are approved by Health Canada for use in foods and beverages. The ADI is set at 4 mg/kg/day of steviol, a level in agreement with that of the Food and Agricultural Organization (FAO) and the World Health Organization (WHO) (144). Intake of up to 1 g steviol glycosides per day was shown to be safe in people with type 1 or type 2 diabetes and was not associated with hypoglycemia or hypotension (145,146).

Sugar alcohols (erythritol, isomalt, lactitol, maltitol, mannitol, sorbitol, xylitol) are also approved for use in Canada; however, there is no ADI (except for erythritol) as their use is considered self-limiting due to the potential for adverse gastrointestinal symptoms. They vary in the degree to which they are absorbed, and their conversion rate to glucose is slow, variable and usually minimal, and may have no significant effect on BG. Thus, matching rapid-acting insulin to the intake of sugar alcohols is not recommended (147). Although there are no long-term, randomized controlled trials of consumption of sugar alcohols by people with diabetes, consumption of up to 10 g/day by people with diabetes does not appear to result in adverse effects (148).

Dietary advanced glycation endproducts

Thermal food processing at very high temperatures, such as frying, broiling and grilling, results in formation of dietary advanced glycation endproducts (dAGEs), a class of pro-oxidants of which 10% are absorbed. Meals high in dAGEs increase markers of endothelial and adipocyte dysfunction in adults with type 2 diabetes (149) and impair vascular function (150). A 4-month, randomized dietary study in 36 participants with or without type 2 diabetes showed that restricting dAGEs by cooking foods at a low temperature, preferably in liquid, improved insulin resistance in those with diabetes; however, A1C was not measured (151).

Meal replacements

Weight loss programs for people with diabetes may use partial meal replacement plans. Commercially available, portion-controlled, vitamin- and mineral-fortified meal replacement products usually replace 1 or 2 meals per day in these plans. Randomized controlled feeding trials have shown partial meal

replacement plans to result in comparable (152) or better (153,154) weight loss compared with conventional reduced-calorie diets up to 1 year with maintenance up to 86 weeks in overweight people with type 2 diabetes. This weight loss results in greater improvements in glycemic control over 3 months to 34 weeks (154,155) and reductions in the need for antihyperglycemic medications up to 1 year (153,155) without an increase in adverse or hypoglycemic events (153–155).

Meal replacements have also shown benefit as part of ILIs. Overweight participants with type 2 diabetes during week 3 to week 19 on the ILI intervention arm of the Look AHEAD trial were prescribed meal replacements: Glucerna (Abbott Laboratories, Abbott Park, USA), HMR (Health Management Resources Corp., Boston, USA), Optifast (Nestlé, Vevey, Switzerland) or Slimfast (Unilever, London, UK and Rotterdam, Netherlands). Those participants in the highest quartile of meal replacement usage were approximately 4 times more likely to reach the 7% and 10% weight loss goal than participants in the lowest quartile (156). Meal replacements with differing macronutrient compositions designed for people with diabetes have shown no clear advantage, although studies remain lacking (157,158).

Alcohol

The same precautions regarding alcohol consumption in the general population apply to people with diabetes (159). Alcohol consumption should be limited to ≤ 2 standard drinks per day and < 10 drinks per week for women and ≤ 3 standard drinks per day or < 15 drinks per week for men (1 standard drink: 10 g alcohol, 341 mL 5% alcohol beer, 43 mL 40% alcohol spirits, 142 mL 12% alcohol wine) (160).

Alcohol ingestion may mask the symptoms of hypoglycemia (161), reduce hepatic production of glucose and increase ketones (162). Moderate alcohol consumption (6 to 18 g/day) is associated with a 25% to 66% lower risk of total and fatal CHD in persons with type 2 diabetes (163) and, consumed with food, does not cause hyperglycemia or hypoglycemia (164). Daily moderate red wine consumption for 12 months reverses the increased oxidative stress and inflammation associated with MI in persons with type 2 diabetes (165) and shows renoprotective effects and lower blood pressure after 6 months in those with nephropathy; effects not observed with white wine (166). In contrast, visual acuity declines, but retinopathy does not, with increasing amounts of alcohol intake (167). Chronic high intake (~ 44 g ethanol per day) is associated with elevated blood pressure and TG in men with type 2 diabetes (168), while light to moderate intake shows an inverse association with A1C (169).

For people with type 1 diabetes, moderate consumption of alcohol with, or 2 or 3 hours after, an evening meal may result in delayed hypoglycemia the next morning after breakfast or as late as 24 hours after alcohol consumption (161,170) and may impede cognitive performance during mild hypoglycemia (171). The same concern may apply to sulphonylurea- and insulin-treated individuals with type 2 diabetes (172). Healthcare professionals should discuss alcohol use with their patients (173) to inform them of the potential weight gain and risks of hypoglycemia (172).

Vitamin and mineral supplements

People with diabetes should be encouraged to meet their nutritional needs by consuming a well-balanced diet by following *Eating Well with Canada's Food Guide* (18). Routine vitamin and mineral supplementation is generally not recommended. Supplementation with 10 μ g (400 IU) vitamin D is recommended for people > 50 years of age (18). Supplementation with folic acid (0.4 to 1.0 mg) is recommended for women who could become

RECOMMENDATIONS

1. People with diabetes should receive nutrition counselling by a registered dietitian to lower A1C levels [Grade B, Level 2 (3)], for those with type 2 diabetes; Grade D, Consensus, for type 1 diabetes] and to reduce hospitalization rates [Grade C, Level 3 (8)].
2. Nutrition education is effective when delivered in either a small group or a one-on-one setting [Grade B, Level 2 (13)]. Group education should incorporate adult education principles, such as hands-on activities, problem solving, role playing and group discussions [Grade B, Level 2 (14)].
3. Individuals with diabetes should be encouraged to follow *Eating Well with Canada's Food Guide* (18) in order to meet their nutritional needs [Grade D, Consensus].
4. In overweight or obese people with diabetes, a nutritionally balanced, calorie-reduced diet should be followed to achieve and maintain a lower, healthier body weight [Grade A, Level 1A (28,29)].
5. In adults with diabetes, the macronutrient distribution as a percentage of total energy can range from 45% to 60% carbohydrate, 15% to 20% protein and 20% to 35% fat to allow for individualization of nutrition therapy based on preferences and treatment goals [Grade D, Consensus].
6. Adults with diabetes should consume no more than 7% of total daily energy from saturated fats [Grade D, Consensus] and should limit intake of trans fatty acids to a minimum [Grade D, Consensus].
7. Added sucrose or added fructose can be substituted for other carbohydrates as part of mixed meals up to a maximum of 10% of total daily energy intake, provided adequate control of BG and lipids is maintained [Grade C, Level 3 (50,51,54,58,60)].
8. People with type 2 diabetes should maintain regularity in timing and spacing of meals to optimize glycemic control [Grade D, Level 4 (132)].
9. Dietary advice may emphasize choosing carbohydrate food sources with a low glycemic index to help optimize glycemic control [type 1 diabetes: Grade B, Level 2 (34,35,169); type 2 diabetes: Grade B, Level 2 (41)].
10. Alternative dietary patterns may be used in people with type 2 diabetes to improve glycemic control, (including):
 - a. Mediterranean-style dietary pattern [Grade B, Level 2 (107,108)]
 - b. Vegan or vegetarian dietary pattern [Grade B, Level 2 (103,104)]
 - c. Incorporation of dietary pulses (e.g. beans, peas, chick peas, lentils) [Grade B, Level 2 (122)]
 - d. Dietary Approaches to Stop Hypertension (DASH) dietary pattern [Grade C, Level 2 (118)]
11. An intensive lifestyle intervention program combining dietary modification and increased physical activity may be used to achieve weight loss and improvements in glycemic control and cardiovascular risk factors [Grade A, Level 1A (29)].
12. People with type 1 diabetes should be taught how to match insulin to carbohydrate quantity and quality [Grade C, Level 2 (138)] or should maintain consistency in carbohydrate quantity and quality [Grade D, Level 4 (131)].
13. People using insulin or insulin secretagogues should be informed of the risk of delayed hypoglycemia resulting from alcohol consumed with or after the previous evening's meal [Grade C, Level 3 (170,172)] and should be advised on preventive actions such as carbohydrate intake and/or insulin dose adjustments and increased BG monitoring [Grade D, Consensus].

Abbreviation:
BG, blood glucose.

pregnant (18). The need for further vitamin and mineral supplements needs to be assessed on an individual basis. As vitamin and mineral supplements are regulated as Natural Health products (NHP) in Canada, the evidence for their therapeutic role in diabetes has been reviewed in the Natural Health Products chapter.

Other Relevant Guidelines

Self-Management Education, p. S26
Physical Activity and Diabetes, p. S40
Weight Management in Diabetes, p. S82
Natural Health Products, p. S97
Dyslipidemia, p. S110
Treatment of Hypertension, p. S117
Type 1 Diabetes in Children and Adolescents, p. S153
Type 2 Diabetes in Children and Adolescents, p. S163
Diabetes and Pregnancy, p. S168
Type 2 Diabetes in Aboriginal Peoples, p. S191

Related Websites

- Canadian Diabetes Association (<http://www.diabetes.ca>)
- Alcohol and Diabetes. Available at: <http://www.diabetes.ca/for-professionals/resources/nutrition/alcohol>. Accessed March 3, 2013.
- Basic Carbohydrate Counting for Diabetes Management. Available at: <http://www.diabetes.ca/for-professionals/resources/nutrition/basic-carb-counting>. Accessed March 3, 2013.
- Cholesterol and Diabetes. Available at: <http://www.diabetes.ca/for-professionals/resources/nutrition/cholesterol-diabetes>. Accessed March 3, 2013.
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- The Glycemic Index. Available at: <http://www.diabetes.ca/for-professionals/resources/nutrition/glycemic-index>. Accessed March 3, 2013.
- Handy Portion Guide. Available at: <http://www.diabetes.ca/diabetes-and-you/nutrition/portion-guide>. Accessed March 3, 2013.
- Just the Basics: Tips for Healthy Eating, Diabetes Prevention and Management. Available at: <http://www.diabetes.ca/for-professionals/resources/nutrition/just-basics>. Accessed March 3, 2013.
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Clinical Practice Guidelines

Pharmacotherapy in Type 1 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Basal-bolus insulin regimens (e.g. multiple daily injections or continuous subcutaneous insulin infusion) are the insulin regimens of choice for all adults with type 1 diabetes.
- Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self-management.
- All individuals with type 1 diabetes should be counseled about the risk, prevention and treatment of insulin-induced hypoglycemia.

Introduction

Insulin is lifesaving pharmacological therapy for people with type 1 diabetes. Insulin preparations are primarily produced by recombinant DNA technology and are formulated either as structurally identical to human insulin or as a modification of human insulin (insulin analogues) to alter pharmacokinetics. Human insulin and insulin analogues are preferred and used by most adults with type 1 diabetes; however, preparations of animal-sourced insulin are still accessible in Canada (1).

Insulin preparations are classified according to their duration of action and are further differentiated by their time of onset and peak actions (Table 1). Premixed insulin preparations are available and are not generally suitable for intensive treatment in patients with type 1 diabetes in whom frequent adjustments of insulin are required.

There may be a role for adjunctive therapy in some people with type 1 diabetes to aid in achieving optimal glycemic targets. Pharmacotherapy for prevention of complications and treatment of risk factors will be addressed in other chapters.

Insulin Delivery Systems

Insulin can be administered by syringe, pen or pump (continuous subcutaneous insulin infusion [CSII]). Insulin pen devices facilitate the use of multiple injections of insulin. CSII therapy is a safe and effective method of intensive insulin therapy in type 1 diabetes and has shown improvements in glucose control over NPH-based regimens and, in fewer studies, over long-acting analogue regimens with less severe hypoglycemia (2,3). Advancements in basal insulins may lessen the value of CSII in type 1 diabetes. CSII may provide some advantages over other methods of

intensive therapy, particularly in individuals with higher baseline glycated hemoglobin (A1C) (4–9). In patients using CSII, insulin aspart and insulin lispro have been shown to be superior to regular insulin by improving postprandial glycemic control and reducing hypoglycemia (10–13). Advances in continuous glucose monitoring systems (CGMSs) may augment CSII (14,15). For CSII and CGMS, adverse events, cost and mortality data are lacking (3).

Initiation of Insulin Therapy

Patients with type 1 diabetes will be initiated on insulin therapy immediately at diagnosis. This will involve both the selection of an insulin regimen and the start of education. Patients must receive initial and ongoing education that includes comprehensive information on how to care for and use insulin; prevention, recognition and treatment of hypoglycemia; sick-day management; adjustments for food intake (e.g. carbohydrate counting) and physical activity; and self-monitoring of blood glucose (SMBG).

Insulin Regimens

Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self-management. Social and financial aspects also should be considered. After insulin initiation, some patients go through a “honeymoon period,” during which insulin requirements may decrease. This period is, however, transient (usually weeks to months), and insulin requirements will increase with time.

While fixed-dose regimens (conventional therapy) once were common and still may be used in some circumstances, they are not preferred. The Diabetes Control and Complications Trial (DCCT) conclusively demonstrated that intensive treatment of type 1 diabetes significantly delays the onset and slows the progression of microvascular and macrovascular complications (16,17). The most successful protocols for type 1 diabetes rely on basal-bolus (basal-prandial) regimens that are used as a component of intensive diabetes therapy. Basal insulin is provided by an intermediate-acting insulin or a long-acting insulin analogue once or twice daily. Bolus insulin is provided by a short-acting insulin or a rapid-acting insulin analogue given at each meal. Such protocols attempt to duplicate normal pancreatic insulin secretion. Prandial insulin dose must take into account the carbohydrate content and glycemic index of the carbohydrate consumed, exercise around mealtime

Table 1
Types of insulin

Insulin type (trade name)	Onset	Peak	Duration
Bolus (prandial) insulins			
Rapid-acting insulin analogues (clear)			
Insulin aspart (NovoRapid®)	10–15 min	1–1.5 h	3–5 h
Insulin glulisine (Apidra®)	10–15 min	1–1.5 h	3–5 h
Insulin lispro (Humalog®)	10–15 min	1–2 h	3.5–4.75 h
Short-acting insulins (clear)			
Humulin®-R	30 min	2–3 h	6.5 h
Novolin® ge Toronto			
Basal insulins			
Intermediate-acting (cloudy)			
Humulin®-N	1–3 h	5–8 h	Up to 18 h
Novolin® ge NPH			
Long-acting insulin analogues (clear)			
Insulin detemir (Levemir®)	90 min	Not applicable	Up to 24 h
Insulin glargine (Lantus®)			(glargine 24 h, detemir 16–24 h)
Premixed insulins			
Premixed regular insulin–NPH (cloudy)	A single vial or cartridge contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)		
Humulin® 30/70			
Novolin® ge 30/70, 40/60, 50/50			
Premixed insulin analogues (cloudy)			
Biphasic insulin aspart (NovoMix® 30)			
Insulin lispro/lispro protamine (Humalog® Mix25 and Mix50)			

Physicians should refer to the most current edition of *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) and product monographs for detailed information.

and the fact that the carbohydrate-to-insulin ratio may not be the same for each meal (breakfast, lunch and dinner). Prandial insulins also can be used for correction doses to manage hyperglycemia.

Compared with regular insulin, insulin aspart, insulin glulisine or insulin lispro, in combination with adequate basal insulin, results in improved postprandial glycemic control and A1C while minimizing the occurrence of hypoglycemia (when using insulin lispro or insulin aspart) (18–23). Regular insulin should ideally be administered 30 to 45 minutes prior to a meal. In contrast, insulin aspart, insulin glulisine and insulin lispro should be administered 0 to 15 minutes before meals. In fact, their rapid onset of action allows for these insulins to be administered up to 15 minutes after a meal. However, preprandial injections achieve better postprandial control and, possibly, better overall glycemic control (22,24,25). Insulin aspart has been associated with improved quality of life (26). Insulin glulisine has been shown to be equivalent to insulin lispro for glycemic control, with greater A1C reduction when given preprandially as opposed to postprandially (22,27).

When used as a basal insulin in patients with good glycemic control, the long-acting analogues, insulin detemir and insulin glargine (with regular insulin or rapid-acting insulin analogues for meals), result in lower fasting plasma glucose levels and less nocturnal hypoglycemia compared with once- or twice-daily NPH insulin (18,28–37). Given the potential severe consequences of nocturnal hypoglycemia (discussed below), the avoidance of this complication is of critical clinical importance. Patients report increased treatment satisfaction and quality of life with use of insulin glargine compared with use of NPH in a basal-bolus insulin regimen (38,39).

When compared with 4-times-daily NPH insulin, insulin glargine was associated with lower A1C and less hypoglycemia (32). Among people with type 1 diabetes, insulin glargine has been shown to have a longer duration of action compared with detemir

(40); however, 15% to 30% of patients using insulin glargine will experience preinjection hyperglycemia, which is prevented by twice daily administration of the insulin (41). Insulin detemir has a flatter pharmacodynamic profile than NPH insulin (33). Twice-daily insulin detemir as the basal component of a basal-bolus insulin regimen has been shown to reduce nocturnal hypoglycemia compared with twice-daily NPH insulin (34,42). There has been a trend toward improved A1C with both insulin detemir and insulin glargine that has reached significance in several studies (36,38,42–46). Due to concerns that alterations in the pharmacokinetics may occur, mixing detemir or glargine with other insulins in the same syringe is not recommended by the manufacturers.

An ultra-long-acting insulin analogue, insulin degludec, has been shown to have comparable safety and tolerability to insulin glargine when used as a basal insulin in type 1 diabetes and less hypoglycemia (47).

Adjunctive therapy for glycemic control

As the incidents of obesity and overweight increase in the population, including those with type 1 diabetes, there is increasing interest in the potential use of oral medications that improve insulin sensitivity for these patients. The use of metformin in type 1 diabetes reduces insulin requirements and the total cholesterol/low-density lipoprotein ratio and may lead to modest weight loss, but it does not result in improved A1C (48). Metformin use in type 1 diabetes is off-label and potentially harmful in the setting of renal or heart failure.

Hypoglycemia

Insulin-induced hypoglycemia is a major obstacle for individuals trying to achieve glycemic targets. Hypoglycemia can be severe and result in confusion, coma or seizure, requiring the assistance of other individuals. Significant risk of hypoglycemia often necessitates less stringent glycemic goals. The negative social and emotional impact of hypoglycemia may make patients reluctant to intensify therapy. The diabetes healthcare team should review the patient's experience with hypoglycemia at each visit. This should include an estimate of cause, frequency, symptoms, recognition, severity and treatment, as well as the risk of driving mishaps with hypoglycemia.

Intensive vs. conventional insulin therapy

Hypoglycemia is the most common adverse effect of intensive insulin therapy in patients with type 1 diabetes. In the DCCT, 35% of patients in the conventional treatment group and 65% in the intensive group experienced at least 1 episode of severe hypoglycemia (49,50). In a meta-analysis of 14 trials, the median incidence of severe hypoglycemia was 4.6 and 7.9 episodes per 100 patient-years in the conventionally treated and intensively treated patients, respectively (51). Studies have suggested that with adequate self-management education, appropriate glycemic targets, SMBG and professional support, intensive therapy may result in less hypoglycemia than reported in the DCCT (52–55). CSII leads to reductions in severe hypoglycemia compared to multiple daily injections (56). CGMS used in addition to CSII or with multiple daily injections is associated with less hypoglycemia than with the use of traditional glucose testing (57,58).

Insulin analogues vs. regular and intermediate-acting insulins

Although there are no differences in the magnitude and temporal pattern of the physiological, symptomatic and counter-regulatory hormonal responses to hypoglycemia induced by

regular human insulin or rapid-acting analogues (59,60), the frequency of hypoglycemic events has been shown to be reduced with rapid-acting insulin analogues compared with regular insulin (18–21).

Long-acting insulin analogues may reduce the incidence of hypoglycemia and nocturnal hypoglycemia when compared to intermediate-acting insulin as the basal insulin (36,37,61–64).

Lifestyle factors

Deviations from recommended or appropriate self-management behaviours (e.g. eating less food, taking more insulin, engaging in more activity) account for 85% of hypoglycemic episodes (65,66). For patients managed with fixed-dose insulin regimens, care should be taken to develop an individualized meal and activity plan that the person can and will follow (67). Adding bedtime snacks may be helpful to prevent nocturnal hypoglycemia among those taking NPH as the basal insulin or in those individuals at high risk of severe hypoglycemia (regardless of insulin type), particularly when bedtime plasma glucose levels are <7.0 mmol/L (68,69).

Knowledge of the acute effects of exercise is mandatory. Low- to moderate-intensity exercise lowers blood glucose (BG) levels both during and after the activity, increasing the risk of a hypoglycemic episode. These effects on BG levels can be modified by altering diet, insulin, and the type and timing of exercise. In contrast, high-intensity exercise raises BG levels during and immediately after the event. SMBG before, during and especially for many hours after exercise is important for establishing response to exercise and guiding the appropriate management of exercise. If ketosis is present (urine ketone level >8.0 mmol/L or blood ketone level >3.0 mmol/L), exercise should not be performed as metabolic deterioration will occur (70). Exercise-induced hypoglycemia may be lessened with the use of detemir as the basal insulin (71).

Hypoglycemia unawareness and nocturnal hypoglycemia

Hypoglycemia unawareness occurs when the threshold for the development of autonomic warning symptoms is close to, or lower than, the threshold for the neuroglycopenic symptoms, such that the first sign of hypoglycemia is confusion or loss of consciousness. Severe hypoglycemia is often the primary barrier to achieving glycemic targets in people with type 1 diabetes (72) and occurs frequently during sleep or in the presence of hypoglycemia unawareness (73,74). The sympathoadrenal response to hypoglycemia is reduced during sleep (75,76). Asymptomatic nocturnal hypoglycemia is common and often lasts >4 hours (73,77–80). Severe hypoglycemia, resulting in seizures, is more likely to occur at night than during the day (81). To reduce the risk of asymptomatic nocturnal hypoglycemia, individuals using intensive insulin therapy should periodically monitor overnight BG levels at a time that corresponds with the peak action time of their overnight insulin.

In type 1 diabetes, hypoglycemia was reported to occur at a mean rate of approximately 2 episodes per week. Frequent hypoglycemia can decrease normal responses to hypoglycemia (82) and lead to hypoglycemia unawareness and defective glucose counterregulation. Both hypoglycemia unawareness and defective glucose counterregulation are potentially reversible. Strict avoidance of hypoglycemia for a period of 2 days to 3 months has been associated with improvement in the recognition of severe hypoglycemia, the counterregulatory hormone responses or both (52,82–88). Structured educational and psychobehavioural programs (e.g. BG awareness training) may help improve detection of hypoglycemia and reduce the frequency of severe hypoglycemia (89,90).

RECOMMENDATIONS

Insulin regimens for type 1 diabetes

1. To achieve glycemic targets in adults with type 1 diabetes, basal-bolus insulin regimens or CSII as part of an intensive diabetes management regimen should be used [Grade A, Level 1A (16)].
2. Rapid-acting bolus insulin analogues, in combination with adequate basal insulin, should be used instead of regular insulin to minimize the occurrence of hypoglycemia, improve A1C [Grade B, Level 2 (19,21,23)] and achieve postprandial glucose targets [Grade B, Level 2 (23,91)].
3. Rapid-acting insulin analogues (aspart or lispro) should be used with CSII in adults with type 1 diabetes [Grade B, Level 2 (10,11)].
4. A long-acting insulin analogue (detemir, glargine) may be used as the basal insulin [Grade B, Level 2 (28–31)] to reduce the risk of hypoglycemia [Grade B, Level 2 (63) for detemir; Grade C, Level 3 (64) for glargine], including nocturnal hypoglycemia [Grade B, Level 2 (63) for detemir; Grade D, Consensus for glargine].

Hypoglycemia

5. All individuals with type 1 diabetes should be counselled about the risk and prevention of insulin-induced hypoglycemia, and risk factors for severe hypoglycemia should be identified and addressed [Grade D, Consensus].
6. In individuals with hypoglycemia unawareness, the following strategies may be used to reduce the risk of hypoglycemia and to attempt to regain hypoglycemia awareness:
 - a. Increased frequency of SMBG, including periodic assessment during sleeping hours [Grade D, Consensus]
 - b. Less stringent glycemic targets with avoidance of hypoglycemia for up to 3 months [Grade C, Level 3 (87,88)]
 - c. A psychobehavioural intervention program (blood glucose awareness training) [Grade B, Level 2 (90)]

Abbreviations:

CSII, continuous subcutaneous insulin infusion; SMBG, self-monitoring of blood glucose.

Other Relevant Guidelines

Targets for Glycemic Control, p. S31
 Monitoring Glycemic Control, p. S35
 Physical Activity and Diabetes, p. S40
 Pharmacologic Management of Type 2 Diabetes, p. S61
 Hypoglycemia, p. S69
 In-hospital Management of Diabetes, p. S77
 Management of Acute Coronary Syndromes, p. S119
 Type 1 Diabetes in Children and Adolescents, p. S153
 Type 2 Diabetes in Children and Adolescents, p. S163
 Diabetes and Pregnancy, p. S168
 Diabetes in the Elderly, p. S184

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Clinical Practice Guidelines

Pharmacologic Management of Type 2 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- If glycemic targets are not achieved within 2 to 3 months of lifestyle management, antihyperglycemic pharmacotherapy should be initiated.
- Timely adjustments to, and/or additions of, antihyperglycemic agents should be made to attain target glycated hemoglobin (A1C) within 3 to 6 months.
- In patients with marked hyperglycemia ($A1C \geq 8.5\%$), antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to initiating combination therapy with 2 agents, 1 of which may be insulin.
- Unless contraindicated, metformin should be the initial agent of choice, with additional antihyperglycemic agents selected on the basis of clinically relevant issues, such as contraindication to drug, glucose lowering effectiveness, risk of hypoglycemia and effect on body weight.

Introduction

As people with type 2 diabetes form a heterogeneous group, treatment regimens and therapeutic targets should be individualized. As type 2 diabetes is characterized by insulin resistance and ongoing decline in beta cell function, glucose levels likely will worsen over time (1), and treatment must be dynamic as therapeutic requirements increase with longer duration of disease. The number of available antihyperglycemic agents is ever expanding, requiring the clinician to consider many of the following factors when choosing medications: degree of hyperglycemia, risk of hypoglycemia, medication effectiveness at reducing diabetes complications (microvascular and/or macrovascular), medication effects on body weight, medication side effects, concomitant medical conditions, ability to adhere to regimen and patient preferences. Lifestyle modification, including nutritional therapy and physical activity, should continue to be emphasized while pharmacotherapy is being used as many agent classes can cause weight gain as a side effect.

Treatment Regimens

The diagnosis of type 2 diabetes is often delayed, and 20% to 50% of people with type 2 diabetes present with microvascular and/or

macrovascular complications at the time of diagnosis (2,3). When lifestyle interventions fail to control blood glucose (BG) levels adequately, pharmacological treatment becomes necessary.

In the face of more severe hyperglycemia (i.e. glycated hemoglobin [A1C] $\geq 8.5\%$), combinations of agents are usually required. The lag period before adding other antihyperglycemic agent(s) should be kept to a minimum, taking into account the characteristics of the different medications. With timely adjustments to and/or additions of antihyperglycemic agents, the target A1C level should be attainable within 3 to 6 months.

In general, A1C will decrease by about 0.5% to 1.5% with monotherapy, depending on the agent used and the baseline A1C level, with the maximum effect of oral antihyperglycemic agent monotherapy seen at 3 to 6 months (4,5). By and large, the higher the baseline A1C, the greater the A1C reduction seen for each given agent. In general, as A1C levels decrease toward target levels ($<7.3\%$), postprandial BG control assumes greater importance for further A1C reduction (6). Several classes of antihyperglycemic agents have greater efficacy at lowering postprandial BG levels (7–20), although adopting an approach of specifically targeting postprandial BG control has not been shown to be effective at reducing macrovascular diabetes complications (21).

The initial use of combinations of submaximal doses of antihyperglycemic agents produces more rapid and improved glycemic control and fewer side effects compared to monotherapy at maximal doses (22–25). Furthermore, many patients on monotherapy with the late addition of another antihyperglycemic agent may not readily attain target BG levels (1). When combining antihyperglycemic agents with or without insulin, classes of agents that have different mechanisms of action should be used. Simultaneous use of agents within the same class and/or from different classes but with similar mechanisms of action (e.g. sulfonylureas and meglitinides or dipeptidyl peptidase [DPP]-4 inhibitors and glucagon-like peptide [GLP]-1 agonists) is currently untested, may be less effective at improving glycemia and is not recommended at this time. Table 1 identifies the mechanism of action for all classes of antihyperglycemic agents to aid the reader in avoiding the selection of agents with overlapping mechanisms.

There is debate over which antihyperglycemic agent (including insulin) should be used initially and which agents should be added subsequently. There is also debate over which agents within a given

Table 1
Antihyperglycemic agents for use in type 2 diabetes

Class ^a and mechanism of action	Drug (brand name)	Expected [†] decrease in A1C	Relative [†] A1C lowering	Hypoglycemia	Other therapeutic considerations
Alpha-glucosidase inhibitor: inhibits pancreatic alpha-amylase and intestinal alpha-glucosidase	Acarbose (Glucobay) (7,81,82)	0.6%	↓	Negligible risk as monotherapy	<ul style="list-style-type: none"> • Not recommended as initial therapy in people with marked hyperglycemia (A1C ≥8.5%) • Weight neutral as monotherapy • GI side effects
Combined formulations	Avandamet (metformin + rosiglitazone)	0.8%	↓↓	Negligible risk as monotherapy	<ul style="list-style-type: none"> • See metformin, TZDs, DPP-4 inhibitors and sulfonylureas
	Janumet (metformin + sitagliptin)	0.7%	↓↓		
	Jentadueto (metformin + linagliptin)				
	Avandaryl (glimepiride + rosiglitazone)	1.6%	↓↓↓	Moderate risk	
DPP-4 inhibitor: amplifies incretin pathway activation by inhibition of enzymatic breakdown of endogenous GLP-1 and GIP (45)	Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Trajenta)	0.7%	↓↓	Negligible risk as monotherapy	<ul style="list-style-type: none"> • Weight neutral • Improved postprandial control • Rare cases of pancreatitis
GLP-1 receptor agonist: activates incretin pathway by utilizing DPP-4 resistant analogue to GLP-1 (45–48)	Exenatide (Byetta) Liraglutide (Victoza)	1.0%	↓↓ to ↓↓↓	Negligible risk as monotherapy	<ul style="list-style-type: none"> • Improved postprandial control • Significant weight loss • Nausea and vomiting • Administration parenteral • Rare cases of pancreatitis • Parafollicular cell hyperplasia • Contraindicated with personal/family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
Insulin: activates insulin receptors to regulate metabolism of carbohydrate, fat and protein (3,10,11,50,53,83–85)	Bolus (prandial) insulins <i>Rapid-acting analogues</i> Aspart (NovoRapid) Glulisine (Apidra) Lispro (Humalog) <i>Short-acting</i> Regular (Humulin-R, Novolin ge Toronto) Basal insulins <i>Intermediate-acting</i> NPH (Humulin-N, Novolin ge NPH) <i>Long-acting basal analogues</i> Detemir (Levemir) Glargine (Lantus) Premixed insulins Premixed Regular-NPH (Humulin 30/70; Novolin ge 30/70, 40/60, 50/50) Biphasic insulin aspart (NovoMix 30) Insulin lispro/lispro protamine suspension (Humalog Mix25, Mix50)	0.9%–1.1% ↓↓↓		Significant risk (hypoglycemia risk highest with regular and NPH insulin)	<ul style="list-style-type: none"> • Potentially greatest A1C reduction and no maximal dose • Numerous formulations and delivery systems (including subcutaneous-injectable) • Allows for regimen flexibility • When initiating insulin, consider adding bedtime long-acting basal analogue or intermediate-acting NPH to daytime oral antihyperglycemic agents (although other regimens can be used) • Basal-bolus regimen recommended if above fails to attain glycemic targets • Increased risk of weight gain relative to sulfonylureas and metformin

Insulin secretagogue: activates sulfonylurea receptor on beta cell to stimulate endogenous insulin secretion	Sulfonylureas Gliclazide (Diamicon, Diamicon MR, generic) (86,87) Glimepiride (Amaryl) (88–90) Glyburide (Diabeta, Euglucon, generic) (3) (Note: Chlorpropamide and tolbutamide are still available in Canada but rarely used)	0.8%	↓↓	Minimal/moderate risk	<ul style="list-style-type: none"> • Relatively rapid BG-lowering response • All insulin secretagogues reduce glycemia similarly (except nateglinide, which is less effective) • Postprandial glycemia is especially reduced by meglitinides • Hypoglycemia and weight gain are especially common with glyburide • Consider using other class(es) of antihyperglycemic agents first in patients at high risk of hypoglycemia (e.g. the elderly, renal/hepatic failure) • If a sulfonylurea must be used in such individuals, gliclazide is associated with the lowest incidence of hypoglycemia (94) and glimepiride is associated with less hypoglycemia than glyburide (90) • Nateglinide and repaglinide are associated with less hypoglycemia than sulfonylureas due to their shorter duration of action allowing medication to be held when forgoing a meal
	Meglitinides Nateglinide (Starlix) (91) Repaglinide (GlucosNorm) (92,93)	0.7%	↓ ↓↓	Minimal/moderate risk Minimal/moderate risk	
Metformin: enhances insulin sensitivity in liver and peripheral tissues by activation of AMP-activated protein kinase	Glucophage, Glumetza, generic (52,95)	1.0%–1.5%	↓↓	Negligible risk as monotherapy	<ul style="list-style-type: none"> • Improved cardiovascular outcomes in overweight subjects • Contraindicated if CrCl/eGFR <30 mL/min or hepatic failure • Caution if CrCl/eGFR <60 mL/min • Weight neutral as monotherapy, promotes less weight gain when combined with other antihyperglycemic agents, including insulin • B12 deficiency (96) • GI side effects
Thiazolidinedione (TZD): enhances insulin sensitivity in peripheral tissues and liver by activation of peroxisome proliferator-activated receptor-gamma receptors (28–30,33,35,97–104)	Pioglitazone (Actos) Rosiglitazone (Avandia)	0.8%	↓↓	Negligible risk as monotherapy	<ul style="list-style-type: none"> • Longer duration of glycemic control with monotherapy compared to metformin or glyburide • Mild BP lowering • Between 6 and 12 weeks required to achieve full glycemic effect • Weight gain • May induce edema and/or congestive heart failure • Contraindicated in patients with known clinical heart failure or evidence of left ventricular dysfunction on echocardiogram or other heart imaging • Higher rates of heart failure when combined with insulin[‡] • Rare occurrence of macular edema • Higher occurrence of fractures (29,30,33) • Possibility of increased risk of myocardial infarction with rosiglitazone (31,108) • Rare risk bladder cancer with pioglitazone (109)
Weight loss agent: inhibits lipase	Orlistat (Xenical) (105–107,110)	0.5%	↓	None	<ul style="list-style-type: none"> • Promote weight loss • Orlistat can cause diarrhea and other GI side effects

A1C, glycated hemoglobin; BG, blood glucose; BP, blood pressure; CrCl, creatinine clearance; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GIP, gastric inhibitory peptide; GLP-1, glucagon-like peptide 1; AMP, adenosine monophosphate.

Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and detailed prescribing information.

* Listed in alphabetical order.

[†] A1C percentage/relative reduction expected when agent from this class is added to metformin therapy (37,105,111) with exception of metformin where A1C percentage/relative reduction reflects expected monotherapy efficacy.

[‡] Combining insulin with a TZD is not an approved indication in Canada.

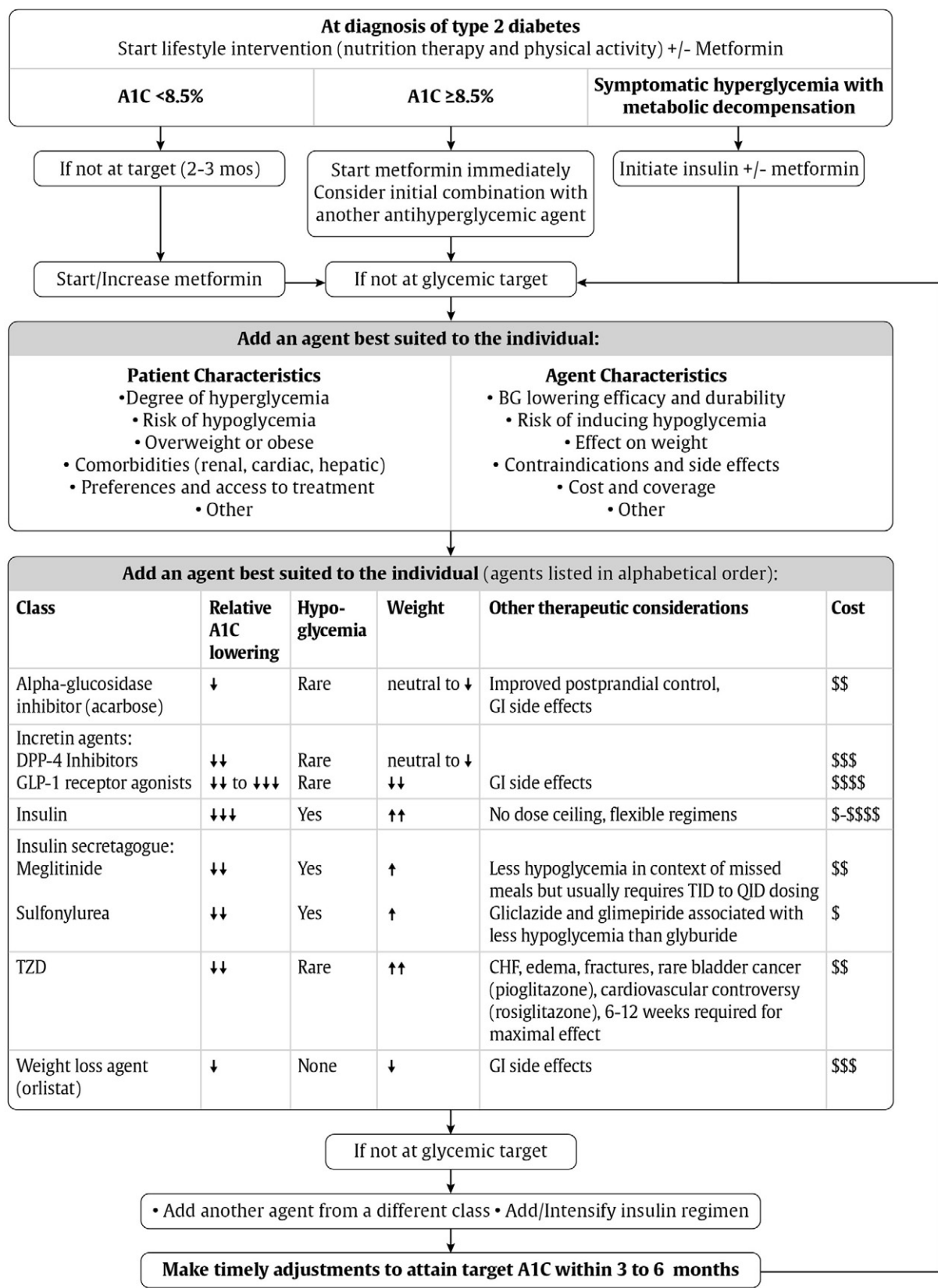


Figure 1. Management of hyperglycemia in type 2 diabetes. Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and for detailed prescribing information. A1C, glycated hemoglobin; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase 4; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; TZD, thiazolidinedione.

class might be preferred in specific situations. Symptomatic patients with high BG and A1C levels require agents that lower BG levels substantially and quickly (e.g. insulin). However, the issue of how to reach glycemic targets may be less important than the need to achieve that target. Improved BG and A1C levels are associated with better outcomes, even if recommended glycemic targets cannot be reached (3). Each of the agents listed in Table 1 and Figure 1 has advantages and disadvantages to consider. Figure 2 illustrates the basis on which agent selection is influenced by renal function as dictated by product monograph precautions.

The recommendation to use metformin as the initial agent in most patients is based on its effectiveness in lowering BG, its relatively mild side effect profile, its long-term safety track record, its negligible risk of hypoglycemia and its lack of causing weight gain. The demonstrated cardiovascular benefit in overweight patients is also cited as a reason to select metformin as first-line treatment (26), but more recent evidence has been equivocal on this matter (27). While monotherapy with the thiazolidinedione (TZD) rosiglitazone produces more long-lasting glycemic control compared to metformin or glyburide therapy (28), the edema, weight gain, risk of congestive heart failure (CHF), increased risk of fractures (29,30) and inconsistent data regarding myocardial infarction (MI) risk (31–33) significantly limit the clinical utility of this drug class. Although meta-analyses of smaller, underpowered studies suggested possible risk of MI with rosiglitazone (31,32), this has not been demonstrated in a larger randomized clinical trial (33,34). Conversely, the evidence for pioglitazone suggests a possible reduced risk of cardiovascular events, although heart failure and increased fractures are still concerning side effects (35,36).

Table 1 and Figure 1 provide information to aid decision making. In deciding upon which agent to add after metformin, there must be consideration of multiple factors. First of all, the agent's effectiveness at BG lowering must be considered in terms of both the degree of baseline hyperglycemia needing correction and any heightened concerns regarding hypoglycemia (e.g. elderly patients or those with renal or hepatic dysfunction). The relative BG and A1C lowering of the various antihyperglycemic agent classes when added to metformin is shown in both Table 1 and Figure 1 and is based on network meta-analysis allowing the comparison between classes that have not yet had direct head-to-head comparison in a randomized clinical trial (37). Ideally, consideration would be made towards the selection of agents with evidence demonstrating ability to not only lower glucose levels, but also reduce the risk of diabetic microvascular and/or macrovascular complications. Unfortunately, the majority of evidence remains equivocal in this regard as most clinical trials compared varying levels of glycemic lowering as opposed to direct comparison between agents used to achieve such glycemic control (38–40). More recent studies looking at the benefits seen with select agents are of such short duration that their results are still preliminary with respect to proving clinical event reduction (41–44) and confirmation awaits the results of more definitive long-term studies.

Multiple other agent-specific advantages and disadvantages should be weighed as treatment is individualized to best suit the patient's needs and preferences. In particular, attention should be paid to the agent's effects on body weight as this is a clinically relevant issue for many people with type 2 diabetes, and some agents cause significant weight gain while others can help to promote significant weight loss. GLP-1 receptor agonists are particularly effective at promoting concomitant glycemic control and weight reduction (45–48), but long-term efficacy and safety data are currently lacking for this class.

A combination of oral antihyperglycemic agents and insulin often effectively controls glucose levels. When insulin is added to oral antihyperglycemic agent(s), a single injection of intermediate-acting (NPH) (49) or a long-acting insulin analogue

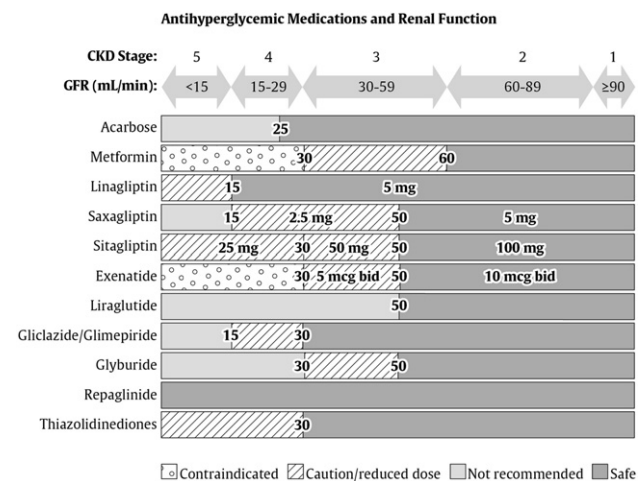


Figure 2. Antihyperglycemic medications and renal function. Based on product monograph precautions. CKD, chronic kidney disease; GFR, glomerular filtration rate; TZD, thiazolidinedione. Designed by and used with the permission of Jean-François Yale MD CSPQ FRCPC.

(insulin glargine or insulin detemir) (50) may be added. This approach may result in better glycemic control with a smaller dose of insulin (51), and may induce less weight gain and less hypoglycemia than that seen when oral agents are stopped and insulin is used alone (52). The addition of bedtime insulin to metformin therapy leads to less weight gain than insulin plus a sulfonylurea or twice-daily NPH insulin (53). While combining insulin with a TZD is not an approved indication in Canada, the addition of such agents to insulin in carefully selected patients improves glycemic control and reduces insulin requirements (54). Such combinations can result in increased weight, fluid retention and, in few patients, CHF. DPP-4 inhibitors and GLP-1 receptor agonists have been shown to be effective at further lowering glucose levels when combined with insulin therapy (55–58).

Insulin can be used at diagnosis in individuals with marked hyperglycemia and can also be used temporarily during illness, pregnancy, stress or for a medical procedure or surgery. There is no evidence that exogenous insulin accelerates the risk of macrovascular complications of diabetes, and its appropriate use should be encouraged (59,60). The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial studied the use of basal insulin titrated to a fasting glucose of ≤ 5.3 mmol/L in people at high cardiovascular risk with prediabetes or early type 2 diabetes over 6 years. There was a neutral effect on cardiovascular outcomes and cancer, a reduction in new-onset diabetes and a slight increase in hypoglycemia and weight. Indeed, use of insulin earlier in the course of type 2 diabetes can be an effective strategy over oral antihyperglycemic agents (60,61). When insulin is used in type 2 diabetes, the insulin regimen should be tailored to achieve good metabolic control while trying to avoid excessive hypoglycemia. With intensive glycemic control, there is an increased risk of hypoglycemia, but this risk is lower in people with type 2 diabetes than in those with type 1 diabetes. The number of insulin injections (1 to 4 per day) and the timing of injections may vary, depending on each individual's situation (62). The reduction in A1C achieved with insulin therapy depends on the dose and number of injections per day (63). Insulin regimens based on basal or bolus insulin appear to be equally effective (21,64) and superior with respect to glycemic lowering compared to biphasic insulin-based regimens (63).

As type 2 diabetes progresses, insulin requirements will likely increase, additional doses of basal insulin (intermediate-acting or

long-acting analogues) may need to be added and bolus insulin (short-acting or rapid-acting analogues) may also be required. Generally, once bolus insulin is introduced into a treatment regimen, either as a separate meal time bolus or as part of a pre-mixed containing regimen, insulin secretagogues, such as sulfonylureas and meglitinides, are usually discontinued. Concomitant metformin therapy, unless contraindicated, should be continued with regimens containing bolus insulin, including intensive basal-bolus regimen, to allow for improved glycemic control with less risk of weight gain and hypoglycemia (65).

Although not commonly practiced, the use of intensive insulin therapy (basal-bolus regimen or continuous subcutaneous insulin infusion pump), for a transient period of approximately 2 to 3 weeks at the time of diagnosis or early in the disease course, has been shown to induce diabetes remission, subsequently allowing adequate glycemic control with lifestyle management alone (66). This normoglycemic state is often transient, however, and such interventions have been tested only in patients early in the course

of disease where the degree of residual beta cell function is relatively preserved (67).

Epidemiological evidence suggesting a possible link between insulin glargine and cancer has not been substantiated in review of clinical trial data for either glargine or detemir (60,68,69).

Hypoglycemia

Medication-induced hypoglycemia is the most common cause of hypoglycemia. It is estimated that hypoglycemia of any severity occurs annually in up to approximately 20% of patients taking insulin secretagogues (70). Although these hypoglycemic episodes are rarely fatal, they can be associated with serious clinical sequelae. Therefore, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin secretagogues. Few large, randomized clinical trials have compared the rates of hypoglycemia between these agents.

In the United Kingdom Prospective Diabetes Study (UKPDS), the proportion of adults with type 2 diabetes who experienced a severe hypoglycemic episode per year was significantly higher in the intensive group than in the conventional group, particularly for patients using insulin therapy (3). Although the risk of hypoglycemia was less than that seen in the patients with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT), each year approximately 3% of patients treated with insulin in the UKPDS experienced a severe hypoglycemic episode, and 40% had a hypoglycemic episode of any severity (3). Protocols designed to achieve normoglycemia targets ($A1C \leq 6.5\%$) further increase the risk of severe hypoglycemia without providing any substantial reduction in the incidence of diabetes complications (71,72).

Lower rates of hypoglycemia have been observed in some studies of patients with type 2 diabetes treated with rapid-acting insulin analogues (insulin aspart, insulin lispro, insulin glulisine) compared to those treated with short-acting (regular) insulin (19,73,74). Use of long-acting basal insulin analogues (insulin detemir, insulin glargine) reduces the risk of nocturnal hypoglycemia compared to treatment with NPH insulin (19,50,75–79).

Other Relevant Guidelines

Targets for Glycemic Control, p. S31
 Pharmacotherapy in Type 1 Diabetes, p. S56
 Hypoglycemia, p. S69
 Weight Management in Diabetes, p. S82
 Type 2 Diabetes in Children and Adolescents, p. S163
 Diabetes and Pregnancy, p. S168
 Diabetes in the Elderly, p. S184

Relevant Appendix

Appendix 3: Examples of Insulin Initiation and Titration Regimens in People With Type 2 Diabetes

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RECOMMENDATIONS

- In people with type 2 diabetes, if glycemic targets are not achieved using lifestyle management within 2 to 3 months, antihyperglycemic agent therapy should be initiated [Grade A, Level 1A (3)]. Metformin may be used at the time of diagnosis, in conjunction with lifestyle management (Grade D, Consensus).
 - If $A1C \geq 8.5\%$, antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to initiating combination therapy with 2 agents, one of which may be insulin (Grade D, Consensus).
 - Individuals with symptomatic hyperglycemia and metabolic decompensation should receive an initial antihyperglycemic regimen containing insulin [Grade D, Consensus].
- Metformin should be the initial drug used [Grade A, Level 1A (26,80) for overweight patients; Grade D, Consensus for nonoverweight patients].
- Other classes of antihyperglycemic agents, including insulin, should be added to metformin, or used in combination with each other, if glycemic targets are not met, taking into account the information in Figure 1 and Table 1 [Grade D, Consensus], and these adjustments to and/or additions of antihyperglycemic agents should be made in order to attain target $A1C$ within 3 to 6 months [Grade D, Consensus].
- Choice of pharmacological treatment agents should be individualized, taking into consideration [Grade D, Consensus]:
 - Patient characteristics:
 - Degree of hyperglycemia
 - Presence of comorbidities
 - Patient preference and ability to access treatments
 - Properties of the treatment:
 - Effectiveness and durability of lowering BG
 - Risk of hypoglycemia
 - Effectiveness in reducing diabetes complications
 - Effect on body weight
 - Side effects
 - Contraindications
- When basal insulin is added to antihyperglycemic agents, long-acting analogues (detemir or glargine) may be used instead of intermediate-acting NPH to reduce the risk of nocturnal and symptomatic hypoglycemia [Grade A, Level 1A (19,78,79)].
- When bolus insulin is added to antihyperglycemic agents, rapid-acting analogues may be used instead of regular insulin to improve glycemic control [Grade B, Level 2 (20)] and to reduce the risk of hypoglycemia [Grade D, Consensus].
- All individuals with type 2 diabetes currently using or starting therapy with insulin or insulin secretagogues should be counseled about the prevention, recognition and treatment of drug-induced hypoglycemia [Grade D, Consensus].

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Clinical Practice Guidelines

Hypoglycemia

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- It is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin or insulin secretagogues.
- The goals of treatment for hypoglycemia are to detect and treat a low blood glucose (BG) level promptly by using an intervention that provides the fastest rise in BG to a safe level, to eliminate the risk of injury and to relieve symptoms quickly.
- It is important to avoid overtreatment, since this can result in rebound hyperglycemia and weight gain.

Introduction

Drug-induced hypoglycemia is a major obstacle for individuals trying to achieve glycemic targets. Hypoglycemia can be severe and result in confusion, coma or seizure, requiring the assistance of other individuals. Significant risk of hypoglycemia often necessitates less stringent glycemic goals. Frequency and severity of hypoglycemia negatively impact on quality of life (1) and promote fear of future hypoglycemia (2,3). This fear is associated with reduced self-care and poor glucose control (4–6). As such, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin or insulin secretagogues (see Pharmacotherapy in Type 1 Diabetes, p. S56, and Pharmacologic Management of Type 2 Diabetes, p. S61, for further discussion of drug-induced hypoglycemia).

Definition of Hypoglycemia

Hypoglycemia is defined by 1) the development of autonomic or neuroglycopenic symptoms (Table 1); 2) a low plasma glucose level (<4.0 mmol/L for patients treated with insulin or an insulin secretagogue); and 3) symptoms responding to the administration of carbohydrate (7). The severity of hypoglycemia is defined by clinical manifestations (Table 2).

Complications of Severe Hypoglycemia

Short-term risks of hypoglycemia include the dangerous situations that can arise while an individual is hypoglycemic, whether at home or at work (e.g. driving, operating machinery). In addition, prolonged coma is sometimes associated with

transient neurological symptoms, such as paresis, convulsions and encephalopathy. The potential long-term complications of severe hypoglycemia are mild intellectual impairment and permanent neurologic sequelae, such as hemiparesis and pontine dysfunction. The latter are rare and have been reported only in case studies.

Recurrent hypoglycemia may impair the individual's ability to sense subsequent hypoglycemia (8,9). The neurohormonal counterregulatory responses to hypoglycemia may become blunted; however, this is potentially reversible (see Pharmacotherapy in Type 1 Diabetes, p. S56).

Retrospective studies have suggested a link between frequent severe hypoglycemia (≥ 5 episodes since diagnosis) and a decrease in intellectual performance. These changes were small but, depending on an individual's occupation, could be clinically meaningful. Prospective studies in type 1 diabetes have not found an association between intensive insulin therapy and cognitive function (10–12). A meta-analysis concluded that lowered cognitive performance in people with type 1 diabetes appeared to be associated with the presence of microvascular complications but not with the occurrence of severe hypoglycemic episodes or with poor metabolic control (13). Unlike patients with type 1 diabetes, those with type 2 diabetes and previous severe hypoglycemia requiring presentation to the hospital have increased risk of subsequent dementia (14).

In patients with type 2 diabetes and established, or very high risk for, cardiovascular disease, symptomatic hypoglycemia (<2.8 mmol/L) is associated with increased mortality (15). The mechanism for this increase is not certain; however, acute hypoglycemia is proinflammatory (16) and may affect cardiac conduction (depolarization, QT prolongation). This effect, however, may be related to sympathetic tone rather than glucose per se (17,18).

Table 1
Symptoms of hypoglycemia

Neurogenic (autonomic)	Neuroglycopenic
Trembling	Difficulty concentrating
Palpitations	Confusion
Sweating	Weakness
Anxiety	Drowsiness
Hunger	Vision changes
Nausea	Difficulty speaking
Tingling	Headache
	Dizziness

Table 2

Severity of hypoglycemia

Mild: Autonomic symptoms are present. The individual is able to self-treat.
Moderate: Autonomic and neuroglycopenic symptoms are present. The individual is able to self-treat.
Severe: Individual requires assistance of another person. Unconsciousness may occur. PG is typically <2.8 mmol/L.

PG, plasma glucose.

The major risk factors for severe hypoglycemia in patients with type 1 diabetes include prior episode of severe hypoglycemia (19–21), current low glycated hemoglobin (A1C) (<6.0%) (20,22–24), hypoglycemia unawareness (25), long duration of diabetes (23,26), autonomic neuropathy (27), adolescence (28) and preschool-age children unable to detect and/or treat mild hypoglycemia on their own. Risk factors for hypoglycemia in patients with type 2 diabetes include advancing age (29), severe cognitive impairment (30), poor health literacy (31), food insecurity (32), increased A1C (29,33), hypoglycemia unawareness (34), duration of insulin therapy, renal impairment and neuropathy (33). In patients with type 2 diabetes and established cardiovascular disease (CVD) or age >54 years and 2 CVD risk factors, the risk of hypoglycemia is also increased by female gender (29). Patients at high risk for severe hypoglycemia should be informed of their risk and counselled, along with their significant others, on preventing and treating hypoglycemia (including use of glucagon), preventing driving and industrial accidents through self-monitoring of blood glucose (BG) and taking appropriate precautions prior to the activity, and documenting BG readings taken during sleeping hours. Individuals may need to have their insulin regimen adjusted appropriately to lower their risk. Risk factors for severe hypoglycemia are listed in Table 3.

Treatment of Hypoglycemia

The goals of treatment for hypoglycemia are to detect and treat a low BG level promptly by using an intervention that provides the fastest rise in BG to a safe level, to eliminate the risk of injury and to relieve symptoms quickly. It is also important to avoid over-treatment since this can result in rebound hyperglycemia and weight gain.

Evidence suggests that 15 g glucose (monosaccharide) is required to produce an increase in BG of approximately 2.1 mmol/L within 20 minutes, with adequate symptom relief for most people (Table 4) (35–39). This has not been well studied in patients with gastropathy. A 20 g oral glucose dose will produce a BG increment of approximately 3.6 mmol/L at 45 minutes (36,37). Other choices, such as milk and orange juice, are slower to increase BG levels and provide symptom relief (36,37). Glucose gel is quite slow (<1.0 mmol/L increase at 20 minutes) and must be swallowed to have a significant effect (35,40). Patients taking an alpha-

Table 3

Risk factors for severe hypoglycemia

<ul style="list-style-type: none"> • Prior episode of severe hypoglycemia • Current low A1C (<6.0%) • Hypoglycemia unawareness • Long duration of insulin therapy • Autonomic neuropathy • Low economic status • Food insecurity • Low health literacy • Cognitive impairment • Adolescence • Preschool-age children unable to detect and/or treat mild hypoglycemia on their own

A1C, glycated hemoglobin.

Table 4

Examples of 15 g carbohydrate for treatment of mild to moderate hypoglycemia

- 15 g glucose in the form of glucose tablets
- 15 mL (3 teaspoons) or 3 packets of table sugar dissolved in water
- 175 mL (3/4 cup) of juice or regular soft drink
- 6 LifeSavers (1 = 2.5 g carbohydrate)
- 15 mL (1 tablespoon) of honey

glucosidase inhibitor (acarbose) must use glucose (dextrose) tablets (41) or, if unavailable, milk or honey to treat hypoglycemia. Glucagon 1 mg given subcutaneously or intramuscularly produces a significant increase in BG (from 3.0 to 12.0 mmol/L) within 60 minutes (42). The effect is impaired in individuals who have consumed more than 2 standard alcoholic drinks in the previous few hours or in those who have advanced hepatic disease (43,44).

Hypoglycemia and driving

Individuals with diabetes are a heterogeneous group, and the risk of motor vehicle accidents and driving violations may be only slightly increased or markedly increased (relative risk [RR] 1.04 to 3.24) (45). Factors include age, level of A1C, degree of hypoglycemic awareness, miles driven, presence of complications and many others.

Advances in treatment, medical technology and self-monitoring have increased the ability of patients with diabetes to control their disease and operate a motor vehicle safely. The fitness of these patients to drive must be assessed on an individual basis. Individuals with diabetes should be encouraged to take an active role in assessing their ability to drive. Patients should have information concerning avoidance, recognition and appropriate therapeutic

RECOMMENDATIONS

1. Mild to moderate hypoglycemia should be treated by the oral ingestion of 15 g carbohydrate, preferably as glucose or sucrose tablets or solution. These are preferable to orange juice and glucose gels [Grade B, Level 2 (35)]. Patients should retest BG in 15 minutes and re-treat with another 15 g carbohydrate if the BG level remains <4.0 mmol/L [Grade D, Consensus]. *Note:* This does not apply to children. See Type 1 Diabetes in Children and Adolescents, p. S153, and Type 2 Diabetes in Children and Adolescents, p. S163, for treatment options in children.
2. Severe hypoglycemia in a conscious person should be treated by oral ingestion of 20 g carbohydrate, preferably as glucose tablets or equivalent. BG should be retested in 15 minutes and then re-treated with another 15 g glucose if the BG level remains <4.0 mmol/L [Grade D, Consensus].
3. Severe hypoglycemia in an unconscious individual
 - a. With no IV access: 1 mg glucagon should be given subcutaneously or intramuscularly. Caregivers or support persons should call for emergency services and the episode should be discussed with the diabetes healthcare team as soon as possible [Grade D, Consensus].
 - b. With IV access: 10–25 g (20–50 cc of D50W) of glucose should be given intravenously over 1–3 minutes [Grade D, Consensus].
4. For individuals at risk of severe hypoglycemia, support persons should be taught how to administer glucagon by injection [Grade D, Consensus].
5. Once the hypoglycemia has been reversed, the person should have the usual meal or snack that is due at that time of the day to prevent repeated hypoglycemia. If a meal is >1 hour away, a snack (including 15 g carbohydrate and a protein source) should be consumed [Grade D, Consensus].
6. Patients receiving antihyperglycemic agents that may cause hypoglycemia should be counselled about strategies for prevention, recognition and treatment of hypoglycemia related to driving and be made aware of provincial driving regulations [Grade D, Consensus].

Abbreviation:

BG, blood glucose.

intervention for hypoglycemia. Drivers with diabetes should be assessed for possible complications, including eye disease, neuropathy (autonomic, sensory, motor), renal disease and cardiovascular disease. In general, a patient is considered fit to drive if he or she is medically fit, is knowledgeable about controlling BG levels and is able to avoid severe hypoglycemic episodes.

Other Relevant Guidelines

Targets for Glycemic Control, p. S31
Monitoring Glycemic Control, p. S35
Pharmacotherapy in Type 1 Diabetes, p. S56
Pharmacologic Management of Type 2 Diabetes, p. S61
Type 1 Diabetes in Children and Adolescents, p. S153
Type 2 Diabetes in Children and Adolescents, p. S163
Diabetes and Pregnancy, p. S168
Diabetes in the Elderly, p. S184

Related Website

Begg IS, Yale J-F, Houlden RL, et al. Canadian Diabetes Association's clinical practice guidelines for diabetes and private and commercial driving. *Can J Diabetes*. 2003;27:128–140. Available at: <http://www.diabetes.ca/files/DrivingGuidelinesBeggJune03.pdf>. Accessed April 30, 2012.

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Clinical Practice Guidelines

Hyperglycemic Emergencies in Adults

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) should be suspected in ill patients with diabetes. If either DKA or HHS is diagnosed, precipitating factors must be sought and treated.
- DKA and HHS are medical emergencies that require treatment and monitoring for multiple metabolic abnormalities and vigilance for complications.
- A normal blood glucose does not rule out DKA in pregnancy.
- Ketoacidosis requires insulin administration (0.1 U/kg/h) for resolution; bicarbonate therapy should be considered only for extreme acidosis ($\text{pH} \leq 7.0$).

Note to readers: Although the diagnosis and treatment of diabetic ketoacidosis (DKA) in adults and in children share general principles, there are significant differences in their application, largely related to the increased risk of life-threatening cerebral edema with DKA in children and adolescents. The specific issues related to treatment of DKA in children and adolescents are addressed in the Type 1 Diabetes in Children and Adolescents chapter, p. S153.

Introduction

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are diabetes emergencies with overlapping features. With insulin deficiency, hyperglycemia causes urinary losses of water and electrolytes (sodium, potassium, chloride) and the resultant extracellular fluid volume (ECFV) depletion. Potassium is shifted out of cells, and ketoacidosis occurs as a result of elevated glucagon levels and absolute insulin deficiency (in the case of type 1 diabetes) or high catecholamine levels suppressing insulin release (in the case of type 2 diabetes). In DKA, ketoacidosis is prominent, while in HHS, the main features are ECFV depletion and hyperosmolarity.

Risk factors for DKA include new diagnosis of diabetes mellitus, insulin omission, infection, myocardial infarction, abdominal crisis, trauma and, possibly, treatment with insulin infusion pumps, thyrotoxicosis, cocaine, atypical antipsychotics and, possibly, interferon. HHS is much less common than DKA (1,2). In addition to the precipitating factors noted above for DKA, HHS also has been reported following cardiac surgery and with the use of certain drugs, including diuretics, glucocorticoids, lithium and atypical antipsychotics.

The clinical presentation of DKA includes symptoms of hyperglycemia, Kussmaul respiration, acetone-odoured breath, ECFV contraction, nausea, vomiting and abdominal pain. There also may be a decreased level of consciousness. In HHS, there is often more

profound ECFV contraction and decreased level of consciousness (proportional to the elevation in plasma osmolality). In addition, in HHS, there can be a variety of neurological presentations, including seizures and a stroke-like state that can resolve once osmolality returns to normal (2–4). In both conditions, there also may be evidence of a precipitating condition.

Prevention

Sick day management that includes capillary beta-hydroxybutyrate monitoring reduces emergency room visits and hospitalizations in young people (5).

Diagnosis

DKA or HHS should be suspected whenever patients have significant hyperglycemia, especially if they are ill or highly symptomatic (see above). As outlined in Figure 1, to make the diagnosis and determine the severity of DKA or HHS, the following should be assessed: plasma levels of electrolytes (and anion gap), glucose, creatinine, osmolality and beta-hydroxybutyric acid (beta-OHB) (if available), blood gases, serum and urine ketones, fluid balance, level of consciousness, precipitating factors and complications (6). Arterial blood gases may be required for sicker patients, when knowing the adequacy of respiratory compensation and the A-gradient is necessary. Otherwise, venous blood gases are usually adequate—the pH is typically 0.015 to 0.03 lower than arterial pH (7–9).

Point-of-care capillary blood beta-hydroxybutyrate measurement in emergency is sensitive and specific for DKA and, as a screening tool, may allow more rapid identification of hyperglycemic patients at risk for DKA (10–15).

There are no definitive criteria for the diagnosis of DKA. Typically, the arterial pH is ≤ 7.3 , serum bicarbonate is ≤ 15 mmol/L, and the anion gap is > 12 mmol/L with positive serum and/or urine ketones (6,16,17). Plasma glucose is usually ≥ 14.0 mmol/L but can be lower (18). DKA is more challenging to diagnose in the presence of the following conditions: 1) mixed acid-base disorders (e.g. associated vomiting, which will raise the bicarbonate level); 2) if there has been a shift in the redox potential favouring the presence of beta-OHB (rendering serum ketone testing negative); or 3) if the loss of keto anions with sodium or potassium in osmotic diuresis has occurred, leading to a return of the plasma anion gap toward normal. It is, therefore, important to measure ketones in both the serum and urine. If there is an elevated anion gap and serum ketones are negative, beta-OHB levels should be measured.

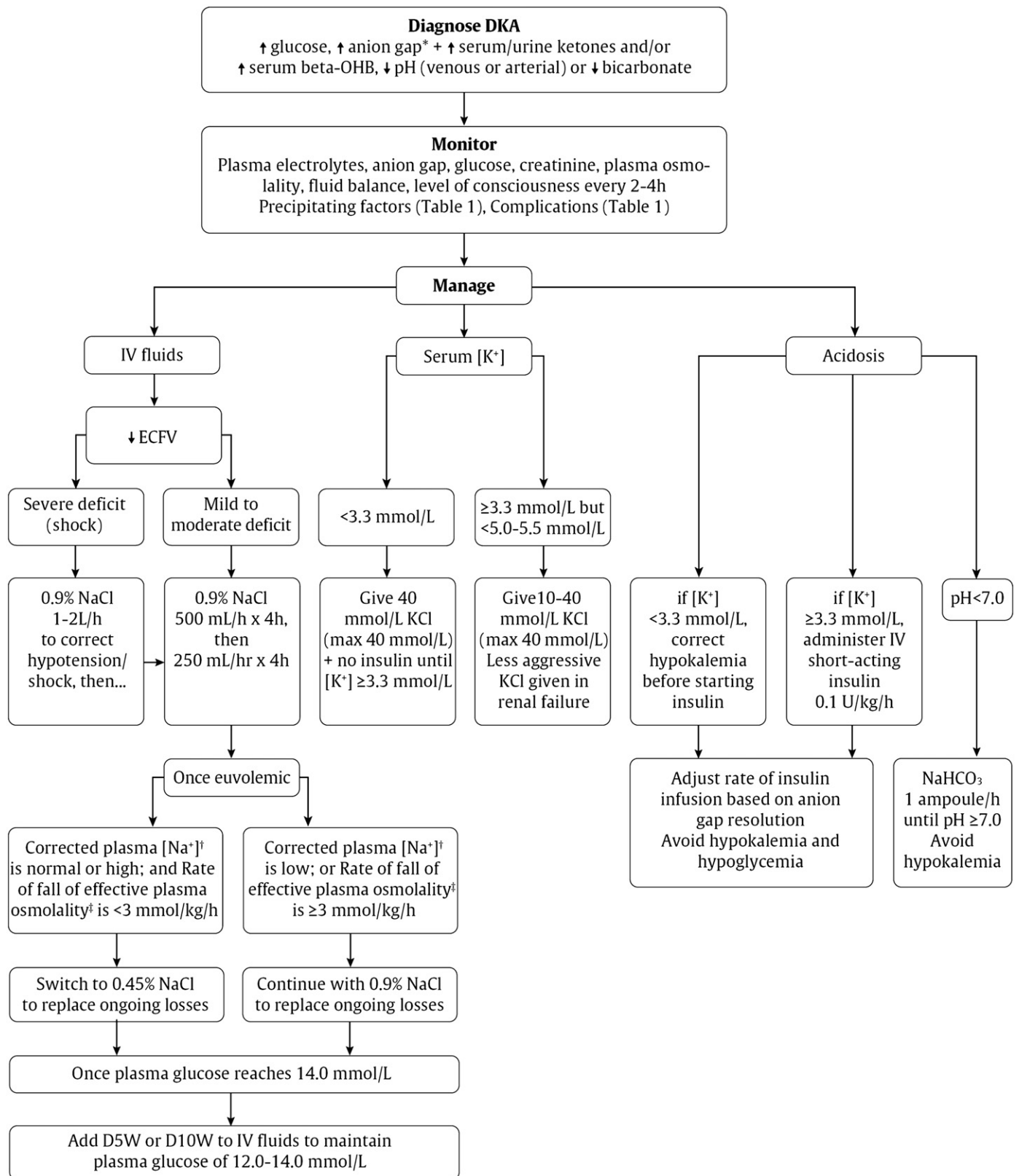


Figure 1. Management of diabetic ketoacidosis (DKA) in adults.

*Anion gap = Plasma $[\text{Na}^+]$ – Plasma $[\text{Cl}^-]$ – Plasma $[\text{HCO}_3^-]$. [†]Corrected plasma $[\text{Na}^+]$ = Measured $[\text{Na}^+]$ + $[3/10 \times ([\text{Glucose (mmol/L)}] - 5)]$. [‡]Effective plasma osmolality = $([\text{Na}^+] \times 2) + [\text{Glucose (mmol/L)}] + [\text{Urea (mmol/L)}]$ reported as mmol/kg. Beta-OHB, beta-hydroxybutyric acid; ECFV, extracellular fluid volume; IV, intravenous.

Measurement of serum lactate should be considered in hypoxic states. In HHS, a more prolonged duration of relative insulin insufficiency and inadequate fluid intake (or high glucose intake) results in higher glucose levels (typically ≥ 34.0 mmol/L) and greater ECFV contraction, but minimal acid-base disturbance (6,16).

Pregnant women in DKA typically present with lower glucose levels than nonpregnant women (19), and there are case reports of euglycemic DKA in pregnancy (20,21).

Management

Objectives of management include restoration of normal ECFV and tissue perfusion; resolution of ketoacidosis; correction of electrolyte imbalances and hyperglycemia; and the diagnosis and treatment of coexistent illness. The issues that must be addressed in the patient presenting with DKA or HHS are outlined in Table 1. A summary of fluid therapy is outlined in Table 2, and a management algorithm and formulas for calculating key measurements are provided in Figure 1.

Patients with DKA and HHS are best managed in an intensive care unit or step-down setting (6,16,17) with specialist care (22,23). Protocols, when followed, may be beneficial (24,25), but there can be challenges with achieving adherence (26,27). Volume status (including fluid intake and output), vital signs, neurological status, plasma concentrations of electrolytes, anion gap, osmolality and glucose need to be monitored closely, initially as often as every 2 hours (6,16,17). Precipitating factors must be diagnosed and treated (6,16,17).

ECFV contraction

The sodium deficit is typically 7–10 mmol/kg in DKA (28) and 5 to 13 mmol/kg in HHS (29), which, along with water losses (100 mL/kg and 100 to 200 mL/kg, respectively), results in decreased ECFV, usually with decreased intracellular fluid volume (28,29). Restoring ECFV improves tissue perfusion and reduces plasma glucose levels both by dilution and by increasing urinary glucose losses. ECFV re-expansion, using a rapid rate of initial fluid administration, was associated with an increased risk of cerebral edema (CE) in 1 study (30) but not in another (31). In adults, one should initially administer

Table 1
Priorities* to be addressed in the management of patients presenting with hyperglycemic emergencies

Metabolic	Precipitating cause of DKA/HHS	Other complications of DKA/HHS
<ul style="list-style-type: none"> • ECFV contraction • Potassium deficit and abnormal concentration • Metabolic acidosis • Hyperosmolality (water deficit leading to increased corrected sodium concentration plus hyperglycemia) 	<ul style="list-style-type: none"> • New diagnosis of diabetes • Insulin omission • Infection • Myocardial infarction • ECG changes may reflect hyperkalemia (57,58) • A small increase in troponin may occur without overt ischemia (59) • Thyrotoxicosis (60) • Drugs 	<ul style="list-style-type: none"> • Hyper/hypokalemia • ECFV overexpansion • Cerebral edema • Hypoglycemia • Pulmonary emboli • Aspiration • Hypocalcemia (if phosphate used) • Stroke • Acute renal failure • Deep vein thrombosis

ECFV, extracellular fluid volume; ECG, electrocardiographic; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state.

* Severity of issue will dictate priority of action.

Table 2
Summary of fluid therapy for DKA and HHS in adults

1. Administer IV normal saline initially. If the patient is in shock, give 1–2 L/h initially to correct shock; otherwise, give 500 mL/h for 4 hours, then 250 mL/h for 4 hours.
2. Add potassium immediately if patient is normo- or hypokalemic. Otherwise, if initially hyperkalemic, only add potassium once serum potassium falls to <5 to 5.5 mmol/L and patient is diuresing.
3. Once plasma glucose reaches 14.0 mmol/L, add glucose to maintain plasma glucose at 12.0–14.0 mmol/L.
4. After hypotension has been corrected, switch normal saline to half-normal saline (with potassium chloride). However, if plasma osmolality is falling more rapidly than 3 mmol/kg/h and/or the corrected plasma sodium is reduced, maintain IV fluids at higher osmolality (i.e. may need to maintain on normal saline).

DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; IV, intravenous.

intravenous (IV) normal saline 1 to 2 L/h to correct shock, otherwise 500 mL/h for 4 hours, then 250 mL/h of IV fluids (32,33).

Potassium deficit

The typical potassium deficit range is 2 to 5 mmol/kg in DKA and 4 to 6 mmol/kg in HHS (29,30). There have been no randomized trials that have studied strategies for potassium replacement. Typical recommendations suggest that potassium supplementation should be started for plasma potassium <5.0 to 5.5 mmol/L once diuresis has been established, usually with the second litre of saline. If the patient at presentation is normo- or hypokalemic, potassium should be given immediately, at concentrations in the IV fluid between 10 and 40 mmol/L, at a maximum rate of 40 mmol/h. In the case of frank hypokalemia (potassium <3.3 mmol/L), insulin should be withheld until potassium replacement at 40 mmol/h has restored plasma potassium to ≥ 3.3 mmol/L (6,16). It is reasonable to treat the potassium deficit of HHS in the same way.

Metabolic acidosis

Metabolic acidosis is a prominent component of DKA. Patients with HHS have minimal or no acidosis. Insulin is used to stop ketoacid production; IV fluid alone has no impact on parameters of ketoacidosis (34). Short-acting insulin (0.1 U/kg/h) is recommended (35–37). Although the use of an initial bolus of IV insulin is recommended in some reviews (6), there has been only 1 randomized controlled trial (RCT) in adults examining the effectiveness of this step (38). In this study, there were 3 arms: a bolus arm (0.07 units/kg, then 0.07 units/kg/h), a low-dose infusion group (no bolus, 0.07 units/kg/h), and a double-dose infusion group (no bolus, 0.14 units/kg/h). Outcomes were identical in the 3 groups, except 5 of 12 patients needed extra insulin in the no-bolus/low-dose infusion group, and the double dose group had the lowest potassium (nadir of 3.7 mmol/L on average). Unfortunately, this study did not examine the standard dose of insulin in DKA (0.1 units/kg/h). In children, using an initial bolus of IV insulin does not result in faster resolution of ketoacidosis (39,40) and increases the risk of CE. The use of subcutaneous boluses of rapid-acting insulin analogues at 1- to 2-hour intervals results in similar duration of ketoacidosis with no more frequent occurrence of hypoglycemia compared to short-acting IV insulin 0.1 U/kg/h (41–43). The dose of insulin should subsequently be adjusted based on ongoing acidosis (44), using the plasma anion gap or beta-OHB measurements. Plasma glucose levels will fall due to multiple mechanisms, including ECFV re-expansion (45), glucose losses via osmotic diuresis (34), insulin-mediated reduced glucose production and increased cellular uptake of glucose. Once plasma glucose reaches 14.0 mmol/L, IV glucose should be started to prevent hypoglycemia, targeting a plasma glucose of 12.0 to 14.0 mmol/L.

Similar doses of IV insulin can be used to treat HHS, although subjects are not acidemic, and the fall in plasma glucose concentration is predominantly due to re-expansion of ECFV and osmotic diuresis (45). Insulin has been withheld successfully in HHS (46), but generally its use is recommended to reduce plasma glucose levels (6,16).

Use of IV sodium bicarbonate to treat acidosis did not affect outcome in RCTs (47–49). Sodium bicarbonate therapy can be considered in adult patients in shock or with arterial pH ≤ 7.0 . For example, one can administer 1 ampoule (50 mmol) sodium bicarbonate added to 200 mL D5W (or sterile water, if available) over 1 hour, repeated every 1 to 2 hours until pH is ≥ 7.0 (6,16). Potential risks associated with the use of sodium bicarbonate include hypokalemia (50) and delayed occurrence of metabolic alkalosis.

Hyperosmolality

Hyperosmolality is due to hyperglycemia and a water deficit. However, serum sodium concentration may be reduced due to shift of water out of cells. The concentration of sodium needs to be corrected for the level of glycemia to determine if there is also a water deficit (Figure 1). In patients with DKA, plasma osmolality is usually ≤ 320 mmol/kg. In HHS, plasma osmolality is typically >320 mmol/kg. Because of the risk of CE with rapid reductions in osmolality (51), it has been recommended that the plasma osmolality be lowered no faster than 3 mmol/kg/h (6,16). This can be achieved by monitoring plasma osmolality, by adding glucose to the infusions when plasma glucose reaches 14.0 mmol/L to maintain it at that level and by selecting the correct concentration of IV saline. Typically, after volume re-expansion, IV fluid is switched to

half-normal saline because urinary losses of electrolytes in the setting of osmotic diuresis are usually hypotonic. The potassium in the infusion will also add to the osmolality. If osmolality falls too rapidly despite the administration of glucose, consideration should be given to increasing the sodium concentration of the infusing solution (6,16). Water imbalances can also be monitored using the corrected plasma sodium. Central pontine myelinolysis has been reported in association with overly rapid correction of hyponatremia in HHS (52).

Phosphate deficiency

There is currently no evidence to support the use of phosphate therapy for DKA (53–55), and there is no evidence that hypophosphatemia causes rhabdomyolysis in DKA (56). However, because hypophosphatemia has been associated with rhabdomyolysis in other states, administration of potassium phosphate in cases of severe hypophosphatemia may be considered for the purpose of trying to prevent rhabdomyolysis.

Complications

In Ontario, in-hospital mortality in patients hospitalized for acute hyperglycemia ranged from $<1\%$ at ages 20 to 49 years to 16% in those over 75 years (61). Reported mortality in DKA ranges from 0.65% to 3.3% (2,22,62–64). In HHS, recent studies found mortality rates to be 12% to 17%, but included patients with mixed DKA and hyperosmolality (1,3,65). About 50% of deaths occur in the first 48 to 72 hours. Mortality is usually due to the precipitating cause, electrolyte imbalances (especially hypo- and hyperkalemia) and CE.

Other Relevant Guidelines

Type 1 Diabetes in Children and Adolescents, p. S153

RECOMMENDATIONS

1. In adult patients with DKA, a protocol should be followed that incorporates the following principles of treatment: 1) fluid resuscitation, 2) avoidance of hypokalemia, 3) insulin administration, 4) avoidance of rapidly falling serum osmolality, and 5) search for precipitating cause (as illustrated in Figure 1) [Grade D, Consensus].
2. In adult patients with HHS, a protocol should be followed that incorporates the following principles of treatment: 1) fluid resuscitation, 2) avoidance of hypokalemia, 3) avoidance of rapidly falling serum osmolality, 4) search for precipitating cause, and 5) possibly insulin to further reduce hyperglycemia (as illustrated in Figure 1) [Grade D, Consensus].
3. Point-of-care capillary beta-hydroxybutyrate may be measured in the hospital in patients with type 1 diabetes with capillary glucose >14.0 mmol/L to screen for DKA, and a beta-hydroxybutyrate >1.5 mmol/L warrants further testing for DKA [Grade B, Level 2 (10–15)].
4. In individuals with DKA, IV 0.9% sodium chloride should be administered initially at 500 mL/h for 4 hours, then 250 mL/h for 4 hours [Grade B, Level 2 (32)] with consideration of a higher initial rate (1–2 L/h) in the presence of shock [Grade D, Consensus]. For persons with a HHS, IV fluid administration should be individualized based on the patient's needs [Grade D, Consensus].
5. In individuals with DKA, an infusion of short-acting IV insulin of 0.10 U/kg/h should be used ([Grade B, Level 2 (36,37)]). The insulin infusion rate should be maintained until the resolution of ketosis [Grade B, Level 2 (42)] as measured by the normalization of the plasma anion gap [Grade D, Consensus]. Once the plasma glucose concentration reaches 14.0 mmol/L, IV dextrose should be started to avoid hypoglycemia [Grade D, Consensus].

Abbreviations:

DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; IV, intravenous.

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Clinical Practice Guidelines

In-hospital Management of Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Hyperglycemia is common in hospitalized patients, even in those without a previous history of diabetes, and is associated with increased in-hospital complications, length of hospital stay and mortality.
- Insulin is the most appropriate agent for effectively controlling glycemia in-hospital. A proactive approach to management using scheduled basal, bolus and correction (supplemental) insulin is the preferred method. The use of sliding-scale insulin (SSI), which treats hyperglycemia after it has occurred, should be discouraged.
- For the majority of noncritically ill patients treated with insulin, preprandial blood glucose (BG) targets should be 5.0 to 8.0 mmol/L, in conjunction with random BG values <10.0 mmol/L, as long as these targets can be safely achieved. For critically ill patients, BG levels should be maintained between 8.0 and 10.0 mmol/L.

Introduction

Diabetes increases the risk for disorders that predispose individuals to hospitalization, including cardiovascular disease, nephropathy, infection, cancer and lower-extremity amputations. In-hospital hyperglycemia is common. Umpierrez et al. (1) reviewed the medical records of over 2000 adult patients admitted to a community teaching hospital in the United States (>85% were non-intensive care unit [non-ICU] patients) and found that hyperglycemia was present in 38% of patients. Of these patients, 26% had a known history of diabetes, and 12% had no history of diabetes prior to admission (1). Diabetes has been reported to be the fourth most common comorbid condition listed on all hospital discharges (2).

Acute illness results in a number of physiological changes (e.g. increases in circulating concentrations of stress hormones) or therapeutic choices (e.g. glucocorticoid use) that can exacerbate hyperglycemia. Hyperglycemia, in turn, causes physiological changes that can exacerbate acute illness, such as decreased immune function and increased oxidative stress. This leads to a vicious cycle of worsening illness and poor glucose control (3).

Although a growing body of literature supports the need for targeted glycemic control in the hospital setting, blood glucose (BG) continues to be poorly controlled and is frequently overlooked in general medicine and surgery services. This is largely explained by the fact that the majority of hospitalizations for patients with diabetes are not directly related to the metabolic state, and diabetes

management is rarely the primary focus of care. Therefore, glycemic control and other diabetes care issues are often not adequately addressed (4).

Diagnosis of Diabetes and Hyperglycemia in the Hospital Setting

A history of diabetes should be elicited in all patients admitted to hospital and, if present, should be clearly identified on the medical record. In view of the high prevalence of inpatient hyperglycemia with associated poor outcomes, an admission BG measurement should be considered for all patients even in the absence of a prior diagnosis of diabetes (1). In-hospital hyperglycemia is defined as any glucose value >7.8 mmol/L (5). A glycated hemoglobin (A1C) level should be drawn in all patients with known diabetes or with hyperglycemia if this has not been performed within 2 to 3 months of the admission. For patients with known diabetes, the A1C identifies patients who would benefit from efforts to improve glycemic control. For patients with newly recognized hyperglycemia, an elevated A1C may help differentiate patients with previously undiagnosed diabetes from those with stress-induced hyperglycemia (6).

Glycemic Control in the Noncritically Ill Patient

A number of studies have demonstrated that inpatient hyperglycemia is associated with increased morbidity and mortality in noncritically ill hospitalized patients (1,7–9). However, due to a paucity of randomized controlled trials on the benefits and risks of “loose” vs. “tight” glycemic control in noncritically ill patients, it is difficult to define glycemic targets for this population. Current recommendations are based on clinical experience and judgement. Glycemic targets for hospitalized patients are modestly higher than those routinely advised for outpatients with diabetes given that the hospital setting presents unique challenges for the management of hyperglycemia, such as variations in patient nutritional status and the presence of acute illness. For the majority of noncritically ill patients treated with insulin, preprandial glucose targets should be 5.0 to 8.0 mmol/L, in conjunction with random BG values <10.0 mmol/L, as long as these targets can be safely achieved. Lower targets may be considered in clinically stable patients with a prior history of successful tight glycemic control in the outpatient setting, while higher targets may be acceptable in terminally ill patients or in

those with severe comorbidities. If BG values are ≤ 3.9 mmol/L, the glucose-lowering therapy should be modified, unless the event is easily explained by other factors (e.g. a missed meal) (5).

Glycemic Control in the Critically Ill Patient

Acute hyperglycemia in the intensive care setting is not unusual and results from a number of factors, including stress-induced counterregulatory hormone secretion and the effects of medications administered in the ICU (10). Appropriate glycemic targets for patients with preexisting diabetes who are critically ill (ICU setting) have not been firmly established. Some trials showed that achieving normoglycemia (4.4 to 6.1 mmol/L) in cardiac surgery patients or patients in postoperative surgical ICU settings may reduce mortality (11). However, subsequent trials in mixed populations of critically ill patients did not show a benefit of targeting BG levels of 4.4 to 8.3 mmol/L. A meta-analysis of trials of intensive insulin therapy in the ICU setting suggested some benefit of intensive insulin therapy in surgical patients, but not in medical patients (12). However, this benefit in surgical ICU patients was not demonstrated in the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, the largest trial to date of intensive glucose control in critically ill patients (13). Furthermore, intensive insulin therapy has been associated with an increased risk of hypoglycemia in the ICU setting (12). Therefore, it is recommended to maintain BG levels between 8.0 and 10.0 mmol/L in critically ill patients; a lower BG target (but not < 6.0 mmol/L) may be appropriate in select patients. Insulin infusion protocols with proven efficacy and safety are recommended to minimize the risk of hypoglycemia (5).

Perioperative glycemic control

The management of individuals with diabetes at the time of surgery poses a number of challenges. Acute hyperglycemia is common secondary to the physiological stress associated with surgery. Preexisting diabetes-related complications and comorbidities may also influence clinical outcomes. Acute hyperglycemia has been shown to adversely affect immune function (14) and wound healing (15) in animal models. Observational studies in humans have shown that hyperglycemia increases the risk of postoperative infections (16–18) and renal allograft rejection (19), and is associated with increased resource utilization (20). In patients undergoing coronary artery bypass grafting (CABG), a preexisting diagnosis of diabetes has been identified as a risk factor for postoperative sternal wound infections, delirium, renal dysfunction, respiratory insufficiency and prolonged hospital stays (21–23). Intraoperative hyperglycemia during cardiopulmonary bypass has been associated with increased morbidity and mortality rates in individuals with and without diabetes (24–26).

Minor and moderate surgery

The appropriate perioperative glycemic targets for minor or moderate surgeries are less clear. There are few intervention studies assessing the impact of tight glycemic control on morbidity or mortality in these settings; however, a number of small studies that compared different methods of achieving glycemic control during minor and moderate surgeries did not demonstrate any adverse effects of maintaining perioperative glycemic levels between 5.0 and 11.0 mmol/L (27–29).

Rapid institution of perioperative control should be carefully considered in patients with poorly controlled type 2 diabetes undergoing monocular phacoemulsification cataract surgery with moderate to severe nonproliferative diabetic retinopathy because of the possible increased risk of postoperative progression of

retinopathy and maculopathy (30). The outcome of vitrectomy does not appear to be influenced by perioperative control (31).

Given the data supporting tighter perioperative glycemic control during major surgeries and the compelling data showing the adverse effects of hyperglycemia, it is reasonable to target glycemic levels between 5.0 and 10.0 mmol/L for minor and moderate surgeries. However, the benefits of improved perioperative glycemic control must be weighed against the risk of perioperative hypoglycemia. Anesthetic agents and postoperative analgesia may alter the patient's level of consciousness and awareness of hypoglycemia. The risk of hypoglycemia can be reduced by frequent BG monitoring and carefully designed management protocols.

Role of Subcutaneous Insulin

In general, insulin is the preferred treatment for hyperglycemia in hospitalized patients with diabetes (5). Patients with type 1 diabetes must be maintained on insulin therapy at all times to prevent diabetic ketoacidosis (DKA). Scheduled subcutaneous (SC) insulin administration that consists of basal, bolus (prandial) and correction (supplemental) insulin components is the preferred method for achieving and maintaining glucose control in non-critically ill patients with diabetes or stress hyperglycemia who are eating (5). Bolus insulin can be withheld or reduced in patients who are not eating regularly; basal insulin should not be withheld. Stable patients can usually be maintained on their home insulin regimen with adjustments made to accommodate for differences in meals and activity levels, the effects of illness and the effects of other medications. In the hospital setting, rapid-acting insulin analogues are the preferred SC bolus insulins (32). Sliding-scale insulin (SSI) (defined as the administration of a preestablished amount of short-acting insulin in response to hyperglycemia) as the sole regimen for the management of hyperglycemia in the hospital setting is ineffective in the majority of patients and, therefore, is not recommended (5,33–36). Insulin is often required temporarily in-hospital, even in patients with type 2 diabetes not previously treated with insulin. In these insulin-naïve patients, there is evidence demonstrating the superiority of basal-bolus-supplemental insulin regimens over SSI (37,38). These studies have typically started patients on 0.4 to 0.5 units of insulin per kilogram of body weight per day, with 40% to 50% of the total daily dose (TDD) given as basal insulin (detemir, glargine, NPH) and the balance given as bolus (rapid or short-acting) insulin divided equally before each meal (i.e. breakfast, lunch, and dinner); supplemental doses of the bolus insulin are to be provided if BG values are above target. The patient's BG measurements should be reviewed daily and the insulin dose adjusted as required.

Role of Oral Antihyperglycemic Drugs

To date, no large studies have investigated the use of oral antihyperglycemic drugs (OADs) on outcomes in hospitalized patients with diabetes. There are often short- and/or long-term contraindications to the use of OADs in the hospital setting, such as irregular eating, acute or chronic renal failure, and exposure to intravenous (IV) contrast dye (39). Stable patients without these contraindications can often have their home medications continued while in the hospital. However, if contraindications develop or if glycemic control is inadequate, these drugs should be discontinued and the patient should be started on a basal-bolus-supplemental insulin regimen.

Role of Medical Nutrition Therapy

Medical nutrition therapy is an essential component of inpatient glycemic management programs and should include nutritional

assessment and individualized meal planning. A consistent carbohydrate meal planning system may facilitate glycemic control in hospitalized patients and facilitate matching the prandial insulin dose to the amount of carbohydrate consumed (35,40).

Special Clinical Situations

Patients receiving enteral or parenteral feedings

In patients receiving parenteral nutrition (PN), insulin can be administered with the nutrition. An IV infusion of regular insulin is often used initially to estimate the TDD of insulin required. Approximately 80% of the TDD of insulin needed to maintain BG levels within the target range on IV insulin is added to the PN bags as regular insulin. SC correction (supplemental) insulin is often used in addition to the insulin mixed with PN for unusual hyperglycemia. The dose of insulin is adjusted based on BG monitoring results. To prevent ketoacidosis, patients with type 1 diabetes must be given subcutaneous insulin if the total parenteral nutrition (TPN) is interrupted. As an alternative to adding insulin to the PN, a separate IV insulin infusion may be used.

Since nutrition is being provided continuously in patients receiving continuous enteral feeds, the TDD of insulin can be administered as a long-acting, nonpeaking basal insulin alone (once-daily glargine or twice daily detemir). Patients receiving bolus enteral feeds are typically treated like patients who are eating meals. Approximately 50% of the TDD is provided as basal insulin and 50% as bolus insulin, which is administered in divided doses to match feed times (39). Short-acting regular insulin is usually selected over rapid-acting insulin in this group of patients because of the longer duration of action. Supplemental insulin should be administered as needed with the bolus insulin. In the event that tube feeds are interrupted, IV dextrose may be required to prevent hypoglycemia.

Patients receiving corticosteroid therapy

Hyperglycemia is a common complication of corticosteroid therapy, with prevalence between 20% and 50% among patients without a previous history of diabetes (41). Although the optimal management of hyperglycemia in patients receiving high-dose oral corticosteroids has not been clearly defined, glycemic monitoring for at least 48 hours is recommended for patients with or without a history of diabetes (5). For management, insulin is generally preferred, with an emphasis on adjusting bolus insulin doses. Depending on the glucose monitoring results, gradual, persistent insulin adjustments should be made to prevent hyper- and hypoglycemia. During corticosteroid tapers, insulin dosing should be proactively adjusted to prevent hypoglycemia.

Patients using insulin pump therapy

Patients on insulin pump therapy do not necessarily need to discontinue this form of therapy while hospitalized. However, to promote a collaborative relationship between the hospital staff and the patient, and to ensure patient safety, hospitals must have clear policies and procedures in place to guide the continued use of insulin pump therapy in the inpatient setting (42). All patients admitted to hospital using insulin pumps must be assessed for their physical and mental competency to use their respective device. Patients should be asked to demonstrate or describe how to adjust their basal rate, administer a bolus dose, insert an infusion set, fill a reservoir, suspend their pump and correct a capillary BG result outside their target range. The patient should also have adequate insulin pump supplies. If the patient cannot competently demonstrate and/or describe the above-mentioned actions, insulin pump

therapy should be discontinued and the patient placed on a SC insulin regimen or an IV insulin infusion.

Role of IV Insulin

Most patients with type 1 or type 2 diabetes admitted to general medical wards can be treated with SC insulin. IV insulin may be appropriate for patients who are critically ill, patients who are not eating or those who require prompt improvement in their glycemic control. Staff education is a critical component of the implementation of an IV insulin infusion protocol. IV insulin protocols should take into account the patient's current and previous BG levels (and, therefore, the rate of change in BG), and the patient's usual insulin dose. Several published insulin infusion protocols appear to be both safe and effective, with low rates of hypoglycemia; however, most of these protocols have only been validated in the ICU setting, where the nurse-to-patient ratio is higher than on general medical and surgical wards (3,43). BG determinations should be performed every 1 to 2 hours until BG stability has been demonstrated. With the exception of the treatment of hyperglycemic emergencies (e.g. DKA, hyperosmolar hyperglycemic state (HHS)), patients receiving IV insulin should receive some form of glucose (e.g. IV glucose or through TPN or enteral feeding).

Transition from IV insulin to SC insulin therapy

All patients with type 1 and type 2 diabetes should be transitioned to scheduled SC insulin therapy from IV insulin. Short- or rapid-acting insulin should be administered 1 to 2 hours before discontinuation of the IV insulin to maintain effective blood levels of insulin. If intermediate- or long-acting insulin is used, it should be given 2 to 3 hours prior to IV insulin discontinuation. Patients without a history of diabetes, who have hyperglycemia requiring more than 2 units of IV insulin per hour, should be transitioned to scheduled SC insulin therapy.

The initial dose and distribution of SC insulin at the time of transition can be determined by extrapolating the IV insulin requirement over the preceding 6- to 8-hour period to a 24-hour period. Administering 60% to 80% of the total daily calculated dose as basal insulin has been demonstrated to be safe and efficacious in surgical patients (44). Dividing the total daily dose as a combination of basal and bolus insulin has been demonstrated to be safe and efficacious in medically ill patients (44,45).

Organization of Care

Healthcare institutions should implement a program to improve glycemic control in the inpatient setting. This should include the formation of a multidisciplinary steering committee to provide educational programs, implement policies to assess and monitor the quality of glycemic management, and produce standardized order sets, protocols and algorithms for diabetes care within the institution. Order sets for basal-bolus-supplemental insulin regimens, insulin management algorithms (46,47), computerized order entry systems (48,49) and specialized nurses reviewing insulin orders (50) all have been shown to improve glycemic control and/or reduce adverse outcomes in hospitalized patients. The timely consultation of glycemic management teams has also been found to improve the quality of care provided, reduce the length of hospital stays and lower costs (51,52).

Patient self-management in the hospital setting may be appropriate for competent, adult patients who successfully self-manage their diabetes at home, have a stable level of consciousness and have the physical skills needed to self-administer insulin and perform self-monitoring of blood glucose (SMBG). For such individuals, a physician order for self-management should be written

with respect to selection of food, SMBG, self-determination and administration of insulin dose and type.

Transition from hospital to home

Patients and their family or caregivers should receive written and oral instructions regarding their diabetes management at the time of hospital discharge. The instructions should include recommendations for timing and frequency of home glucose monitoring; identification and management of hypoglycemia; a reconciled medication list, including insulin and other glucose-lowering medication; and identification and contact information for healthcare providers responsible for ongoing diabetes care and adjustment of glucose-lowering medication. Patients and their primary care providers should be aware of the need for potential adjustments in insulin therapy that may accompany adjustments of other medications prescribed at the time of discharge, such as corticosteroids or octreotide.

RECOMMENDATIONS

1. Provided that their medical conditions, dietary intake and glycemic control are acceptable, people with diabetes should be maintained on their prehospitalization oral antihyperglycemic agents or insulin regimens [Grade D, Consensus].
2. For hospitalized patients with diabetes treated with insulin, a proactive approach that includes basal, bolus and correction (supplemental) insulin, along with pattern management, should be used to reduce adverse events and improve glycemic control, instead of the reactive sliding-scale insulin approach that uses only short- or rapid-acting insulin [Grade B, Level 2 (37,38)].
3. For the majority of noncritically ill patients treated with insulin, preprandial BG targets should be 5.0 to 8.0 mmol/L in conjunction with random BG values <10.0 mmol/L, as long as these targets can be safely achieved [Grade D, Consensus].
4. For most medical/surgical critically ill patients with hyperglycemia, a continuous IV insulin infusion should be used to maintain glucose levels between 8 and 10 mmol/L [Grade D, Consensus].
5. To maintain intraoperative glycemic levels between 5.5 and 10.0 mmol/L for patients with diabetes undergoing CABG, a continuous IV insulin infusion protocol administered by trained staff [Grade C, Level 3 (60–62)] should be used.
6. Perioperative glycemic levels should be maintained between 5.0 and 10.0 mmol/L for most other surgical situations, with an appropriate protocol and trained staff to ensure the safe and effective implementation of therapy and to minimize the likelihood of hypoglycemia [Grade D, Consensus].
7. In hospitalized patients, hypoglycemia should be avoided.
 - Protocols for hypoglycemia avoidance, recognition and management should be implemented with nurse-initiated treatment, including glucagon for severe hypoglycemia when IV access is not readily available [Grade D, Consensus].
 - Patients at risk of hypoglycemia should have ready access to an appropriate source of glucose (oral or IV) at all times, particularly when NPO or during diagnostic procedures [Grade D, Consensus].
8. Healthcare professional education, insulin protocols and order sets may be used to improve adherence to optimal insulin use and glycemic control [Grade C, Level 3 (46)].
9. Measures to assess, monitor and improve glycemic control within the inpatient setting should be implemented, as well as diabetes-specific discharge planning [Grade D, Consensus].

Abbreviations:

BG, blood glucose; CABG, coronary artery bypass grafting; IV, intravenous; NPO, nothing by mouth.

Bedside BG monitoring

Currently, there are no studies that have examined the effect of the frequency of bedside BG testing on the incidence of hyper- or hypoglycemia in the hospital setting. The frequency and timing of bedside BG monitoring should be individualized; however, monitoring is typically performed before meals and at bedtime in patients who are eating, every 4 to 6 hours in patients who are NPO (nothing by mouth) or receiving continuous enteral feeding, and every 1 to 2 hours for patients on continuous IV insulin. Some bedside BG testing is indicated in individuals without known diabetes but receiving treatments known to be associated with hyperglycemia (glucocorticoids, octreotide, PN, enteral nutrition) (53). Healthcare institutions must implement and maintain a quality control program to ensure the accuracy of bedside BG testing (54,55). The use of meters with bar coding capability has been shown to reduce data entry errors in medical records (56). Data management programs that transfer bedside BG monitoring results into electronic records allow evaluation of hospital-wide glycemic control (57).

Safety

Hypoglycemia

Hypoglycemia remains a major barrier to achieving optimal glycemic control in hospitalized patients. Healthcare institutions should have standardized treatment protocols that address mild, moderate and severe hypoglycemia. Healthcare workers should be educated about factors that increase the risk of hypoglycemia, such as sudden reduction in oral intake, discontinuation of PN or enteral nutrition, unexpected transfer from the nursing unit after rapid-acting insulin administration or a reduction in corticosteroid dose (35).

Insulin administration errors

Insulin causes the most harm and severe adverse events of the high alert medications (58). A systems approach that includes preprinted, approved, unambiguous standard orders for insulin administration and/or a computerized order entry system may help reduce errors (59).

Other Relevant Guidelines

Pharmacotherapy in Type 1 Diabetes, p. S56

Pharmacologic Management of Type 2 Diabetes, p. S61

Hyperglycemic Emergencies in Adults, p. S72

Management of Acute Coronary Syndromes, p. S119

Treatment of Diabetes in Patients with Heart Failure, p. S126

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Clinical Practice Guidelines

Weight Management in Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- An estimated 80% to 90% of persons with type 2 diabetes are overweight or obese. Higher body mass index in people with diabetes is associated with increased overall mortality.
- A modest weight loss of 5% to 10% of initial body weight can substantially improve glycemic control and cardiovascular disease risk factors.
- Comprehensive health behaviour intervention should be implemented in overweight and obese people with diabetes or those at risk for diabetes to prevent weight gain and to achieve and maintain a reduced body weight. Many classes of antihyperglycemic medications are associated with weight gain, while some are weight neutral or associated with weight loss. The drug effects on body weight should be considered in glycemic management.
- Bariatric surgery may be considered for appropriate patients when other interventions fail to achieve and maintain a healthy body weight.

Introduction

Obesity is widely considered a chronic health problem that is often progressive and difficult to treat. An estimated 80% to 90% of persons with type 2 diabetes are also overweight or obese (1). Obesity is also becoming more prevalent in people with type 1 diabetes; a study has indicated a 7-fold increase in obesity in 20 years (2). Furthermore, intensive insulin therapy and some glucose-lowering medications are associated with weight gain (3,4). Weight loss has been shown to improve glycemic control by increasing insulin sensitivity and glucose uptake and diminishing hepatic glucose output (5). The risk of death from all causes, cardiovascular disease (CVD) and some forms of cancer increases with excessive body fat (6). This relationship between increasing body fat accumulation and adverse health outcomes exists throughout the range of overweight and obese men and women in all age groups, including those ≥ 75 years of age (7). Analysis of 57 prospective studies in $\sim 900,000$ adults by the Prospective Studies Collaboration indicated that each 5 kg/m^2 higher body mass index (BMI) above 25 kg/m^2 was associated with about 30% higher overall mortality (8).

Assessment of Overweight and Obesity

The initial assessment of people with diabetes should include the following measurements: height, weight, calculation

Table 1

Canadian guidelines for body weight classification in adults using BMI (8)

Classification	BMI* category (kg/m^2)	Risk of developing health problems
Underweight	<18.5	Increased
Normal weight	$18.5\text{--}24.9$	Least
Overweight	$25.0\text{--}29.9$	Increased
Obese	≥ 30.0	
Class I	$30.0\text{--}34.9$	High
Class II	$35.0\text{--}39.9$	Very High
Class III	≥ 40.0	Extremely High

* Body mass index (BMI) values are age and gender independent and may not be correct for all ethnic populations.

of BMI (kg/m^2) (Table 1) (9) and waist circumference (WC) to assess the degree of abdominal obesity (Table 2) (9). Metabolic comorbidities, such as hypertension, dyslipidemia and CVD risk factors, should also be assessed since they are highly correlated with increasing BMI (10,11). Excessive abdominal adiposity is a strong independent predictor of metabolic comorbidities (12,13). Cutoff values for WC vary among expert guidelines. Table 2 (14,15) lists National Cholesterol and Education Program Adult Treatment Panel III (NCEP-ATP III) WC values. The International Diabetes Federation has proposed population specific WC cutoff values (Table 3) (16). These guidelines have not been fully validated against the development of clinical events, and considerable population-based research is needed in this area.

Assessment of overweight and obese patients should include determining reasons for the previous or current positive energy balance that led them to become overweight or obese, or to continually gain weight. An etiological approach assessing causes of lower metabolic rates, such as medications and hormonal imbalances, should be considered (17). People with diabetes often take medications that are associated with weight gain; these include antihyperglycemic, antihypertensive, pain relief and antidepressant agents (18). Psychological aspects of eating behaviours, such as emotional eating, binge eating and depression, also should be assessed (19). Physical parameters that impede activity, such as osteoarthritis or dyspnea, should be assessed (20). Comorbid conditions, such as osteoarthritis and obstructive sleep apnea, can also impact the ability to lose weight (21). These conditions should be assessed and treated.

Table 2

NCEP-ATP III WC and risk of developing health problems (8)

WC cutoff points* [†]	Risk of developing health problems
Men ≥ 102 cm (40 inches)	Increased
Women ≥ 88 cm (35 inches)	Increased

* Waist circumference (WC) cutoffs may be lower in some populations (e.g. older individuals, Asian population [See Table 3]), especially in the presence of the metabolic syndrome (e.g. hypertriglyceridemia).

[†] Increased WC can also be a marker for increased risk, even in persons with normal weight.

Table 3

Ethnic-specific values for WC from International Diabetes Federation (13)

Country or ethnic group	Central obesity as defined by WC	
	Men	Women
Europid ^a	≥ 94 cm	≥ 80 cm
South Asian, Chinese, Japanese	≥ 90 cm	≥ 80 cm
South and Central American	Use South Asian cutoff points until more specific data are available.	
Sub-Saharan African	Use Europid cutoff points until more specific data are available.	
Eastern Mediterranean and Middle Eastern (Arab)	Use Europid cutoff points until more specific data are available.	

^a National Cholesterol and Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines (11,12) and Health Canada (6) define central obesity as waist circumference (WC) values ≥ 102 cm (40 inches) in men and ≥ 88 cm (35 inches).

Table 4

Checklist for weight management programs (46)

1. The program assesses and treats comorbid conditions.
2. The program provides individualized nutritional, exercise and behavioral programs and counselling.
3. Nutritional advice is provided by qualified experts (e.g. registered dietitians) and diets are not less than 900 kcal/day.
4. Exercise is encouraged but physical activity is promoted at a gradual pace.
5. Reasonable weight loss goals are set at 1 to 2 lb/week.
6. Cost is not prohibitive, and there are no financial contracts.
7. There is no requirement to buy products, supplements, vitamins or injections.
8. The program does not make unsubstantiated claims.
9. The program has an established maintenance program.

Treatment of Overweight and Obesity

The goals of therapy for overweight and obese people with diabetes are to achieve optimal glycemic and metabolic control initially through health behaviour intervention. Attaining and maintaining a healthy body weight and preventing weight regain are the short- and long-term goals. In general, obese people with diabetes have greater difficulty with weight loss compared to similarly obese people without diabetes (22). Many anti-hyperglycemic medications are associated with weight gain, and attempts should be made to minimize these medications without compromising glycemic control or to switch to alternative agents not associated with weight gain (18). For many patients, prevention of weight gain can be considered a realistic and sustainable outcome. A modest weight loss of 5% to 10% of initial body weight can substantially improve insulin sensitivity, glycemic control, high

Table 6

Glucose-lowering medications and their effects on weight (17)

Weight gain	Weight effect (lb)
Insulin (fast acting, NPH) (2)	+8.8 – +11.0
Thiazolidinediones (TZDs) (57)	+5.2 – +10.6
Sulphonylureas (2,57)	+3.5 – +5.7
Meglitinides (58)	+1.54 – +3.97
Weight neutral or decrease weight	Weight effect
Insulin (basal analogues, detemir, glargine) (59,60)	–0.22 – +0.88
Metformin (61)	–8.4 – +0.88
Alpha-glucosidase inhibitors (62,63)	+0.0 – +0.44
Dipeptidyl peptidase-4 (DPP-4) inhibitors (64,65)	+0.0 – +0.46
Glucagon-like peptide-1 (GLP-1) receptor agonists (66,67)	–6.6 – –3.5

blood pressure (BP) and dyslipidemia (23–27). The optimal rate of weight loss is 1 to 2 kg/month but is generally self-limiting due to physiological counterregulation (17,28). A negative energy balance of 500 kcal/day is typically required to achieve a weight loss of 0.45 kg/week (29). As individuals lose weight, adjustment in anti-hyperglycemic medications may be required to avoid hypoglycemia.

The National Institutes of Health (NIH)-sponsored multicenter Look AHEAD (Action for Health in Diabetes) trial, whose design is based largely on the United States (US) Diabetes Prevention Program, investigated the effects of lifestyle intervention on changes in weight, fitness, and CVD risk factors and events in people with type 2 diabetes (30). The 1- and 4-year interim data reported beneficial effects of modest weight loss of 5% to 10% in improving glycemic control, lowering of CV risk markers, BP and lipid levels (30,31). Greater improvement in risk factors occurred with greater weight losses. There was some expected weight regain at 4 years, yet there continued to be beneficial metabolic effects.

Healthy Behaviour Interventions

The overall goal of health behaviour intervention in people with diabetes who are overweight or obese is to improve health status and quality of life (32,33).

Health behaviour interventions that combine dietary modification, increased and regular physical activity and behaviour therapy are the most effective (34–37). Structured interdisciplinary programs have demonstrated better short- and long-term results (36).

All weight-loss diets must be well balanced and nutritionally adequate to ensure optimal health. In general, a carbohydrate intake of at least 100 g/day is required to spare protein breakdown and muscle wasting and to avoid large shifts in fluid balance and ketosis. High-fibre foods are associated with greater satiety. Adequate protein intake is required to maintain lean body mass and other essential physiological processes. Reduced intake of saturated fat and energy-dense foods should be emphasized. Very-low-calorie diets with <900 kcal/day are not recommended, except under medical supervision.

As understanding and adhering to healthy and nutritionally balanced meal plans can be challenging, people with diabetes should be counselled by qualified professionals on appropriate serving sizes, caloric and carbohydrate intake and how to select nutrient-rich meals (38,39).

Table 5

Medication approved for the treatment of obesity in type 2 diabetes (36)

Class	Generic (trade) name	Recommended regimen	Action	Adverse effects
Gastrointestinal lipase inhibitor	Orlistat (Xenical)	120 mg tid (during or up to 1 hour after each meal)	• Nonsystemic pancreatic lipase inhibitor reduces dietary fat digestion and absorption by about 30%	• Abdominal bloating, pain and cramping • Steatorrhea • Fecal incontinence

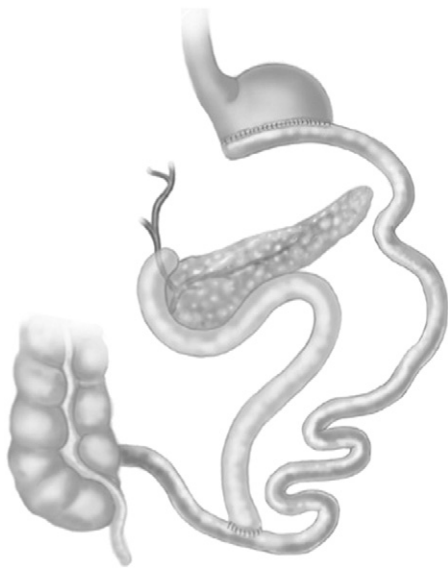


Figure 1. Biliopancreatic Diversion with Duodenal Switch. The stomach and small intestine are surgically reduced so that nutrients are absorbed only in a 50-cm “common limb.” (From Shukla A, Rubino F. Secretion and function of gastrointestinal hormones after bariatric surgery: their role in type 2 diabetes. *Can J Diabetes* 2011;35:115-122.)



Figure 3. Gastric Sleeve. A longitudinal (sleeve) resection of the stomach reduces the functional capacity of the stomach and eliminates the ghrelin-rich gastric fundus. (From Shukla A, Rubino F. Secretion and function of gastrointestinal hormones after bariatric surgery: their role in type 2 diabetes. *Can J Diabetes* 2011;35:115-122.)

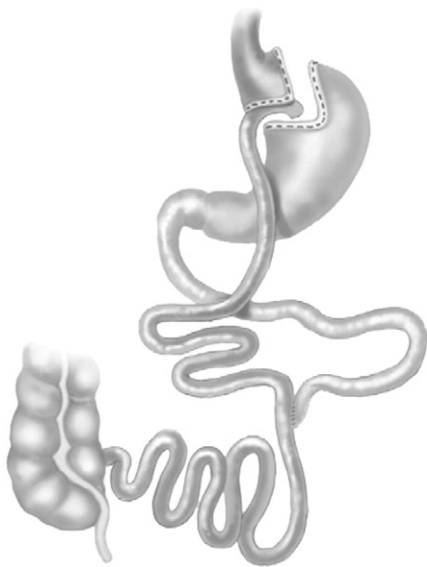


Figure 2. Roux-en-Y Gastric Bypass. A surgical stapler is used to create a small gastric pouch. Ingested food bypasses ~95% of the stomach, the entire duodenum and a portion of the jejunum. (From Shukla A, Rubino F. Secretion and function of gastrointestinal hormones after bariatric surgery: their role in type 2 diabetes. *Can J Diabetes* 2011;35:115-122.)



Figure 4. Adjustable Gastric Band. The upper part of the stomach is encircled with a constrictive saline-filled tube. The amount of restriction can be adjusted by injecting or withdrawing saline solution. (From Shukla A, Rubino F. Secretion and function of gastrointestinal hormones after bariatric surgery: their role in type 2 diabetes. *Can J Diabetes* 2011;35:115-122.)

Two large-scale reviews of >100 individual studies evaluating behaviour modification techniques support their effectiveness in promoting weight loss (40,41).

Members of the healthcare team should consider using a structured approach to providing advice and feedback on physical activity, healthy eating habits and weight loss (42–45). Programs and clinics dedicated to weight management may be beneficial, particularly those that adhere to the checklist in Table 4 (46).

Pharmacotherapy

Orlistat is currently the only approved medication in Canada for long-term management of obesity (Table 5) (47). When used to treat overweight and obese people with diabetes, orlistat has been demonstrated to improve glycemic control and to reduce the doses of antihyperglycemic agents that can promote weight gain (47).

However, pharmacotherapy options are limited in weight management, and many approved agents have been discontinued

by the developers or rejected by government drug approval boards due to unacceptable side effects (18). Pharmacotherapy can be considered for people with BMI ≥ 30.0 kg/m² with no obesity-related comorbidities or risk factors, or for those with BMI ≥ 27.0 kg/m² with obesity-related comorbidities or risk factors (29). Antiobesity drug therapy may be considered as an adjunct to nutrition therapy, physical activity and behaviour modification to achieve a target weight loss of 5% to 10% of initial body weight and for weight maintenance (32,48). There are several new antiobesity agents that may be available within the near future and that may have a beneficial impact on diabetes management.

Orlistat leads to greater weight loss when coupled with healthy behaviour interventions (47). Orlistat has been shown to be effective at improving glycemic and metabolic control in obese people with type 2 diabetes (47,49,50). In obese people with impaired glucose tolerance, orlistat also improves glucose tolerance and reduces the progression to type 2 diabetes (51). Clinical trials with antiobesity agents have confirmed a smaller degree of weight loss in people with diabetes compared with obese people who do not have diabetes (22,38). Orlistat should be avoided in patients with inflammatory or other chronic bowel disease.

Some antihyperglycemic medications are associated with weight gain (insulin, insulin secretagogues, thiazolidinediones), and the magnitude of weight gain can vary from 4 to 9 kg or more, depending on the choice of drugs (Table 6) (18). Insulin is associated with the most weight gain, whereas metformin, glucosidase inhibitors and the incretin class of antihyperglycemic agents typically are weight neutral or associated with a weight loss of about 3 kg (18).

Other available anti-obesity drugs, such as diethylpropion and phentermine, are sympathomimetic noradrenergic appetite suppressants that are approved only for short-term use of a few weeks. They are not recommended because of modest efficacy and frequent adverse side effects.

Bariatric Surgery

Bariatric surgery has emerged as an innovative alternative option in the management of type 2 diabetes. These procedures can result in sustained body weight loss and significant improvement in obesity-related comorbidities (52). Surgery is usually reserved for people with class III obesity (BMI ≥ 40.0 kg/m²) or class II obesity (BMI = 35.0 to 39.9 kg/m²) in the presence of comorbidities (52) and the inability to achieve weight loss maintenance following an adequate trial of health behaviour intervention. Individuals who are candidates for surgical procedures should be selected after evaluation by an interdisciplinary team with medical, surgical, psychiatric and nutritional expertise. Long-term, if not lifelong, medical surveillance after surgical therapy is necessary for most people. Bariatric surgery procedures can be classified as restrictive,

malabsorptive or combined restrictive and malabsorptive. Biliopancreatic diversion with duodenal switch procedure (Figure 1), roux-en-Y gastric bypass (Figure 2), gastric sleeve (Figure 3) and laparoscopic adjustable gastric banding (Figure 4) have all demonstrated significant improvements and even remission in type 2 diabetes (53–55).

Other Relevant Guidelines

Physical Activity and Diabetes, p. S40

Nutrition Therapy, p. S45

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RECOMMENDATIONS

1. An interdisciplinary weight management program (including a nutritionally balanced, calorie-restricted diet; regular physical activity; education; and counselling) for overweight and obese people with, or at risk for, diabetes should be implemented to prevent weight gain and to achieve and maintain a lower, healthy body weight [Grade A, Level 1A (30,56)].
2. In overweight or obese adults with type 2 diabetes, the effect of antihyperglycemic agents on body weight should be taken into account [Grade D, Consensus].
3. Adults with type 2 diabetes and class II or III obesity (BMI ≥ 35.0 kg/m²) may be considered for bariatric surgery when lifestyle interventions are inadequate in achieving healthy weight goals [Grade B, Level 2 (53–55)].

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Clinical Practice Guidelines

Diabetes and Mental Health

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Psychiatric disorders, particularly major depressive disorder (MDD), generalized anxiety disorder and eating disorders, are more prevalent in people with diabetes compared to the general population.
- People diagnosed with serious mental illnesses, such as MDD, bipolar disorder and schizophrenia, have a higher risk of developing diabetes than the general population.
- All individuals with diabetes should be regularly screened for the presence of depressive and anxious symptoms.
- Compared to those with diabetes only, individuals with diabetes and mental health disorders have decreased medication adherence, decreased compliance with diabetes self-care, increased functional impairment, increased risk of complications associated with diabetes, increased healthcare costs and an increased risk of early mortality.
- The following treatment modalities should be incorporated into primary care and self-management education interventions to facilitate adaptation to diabetes, reduce diabetes-related distress and improve outcomes: motivational interventions, stress management strategies, coping skills training, family therapy and collaborative case management.
- Individuals taking psychiatric medications, particularly atypical antipsychotics, benefit from regular screening of metabolic parameters.

Introduction

Research is increasingly demonstrating a relationship between mental health disorders and diabetes. Patients with serious mental illnesses, particularly those with depressive symptoms or syndromes, and patients with diabetes share reciprocal susceptibility and a high degree of comorbidity (Figure 1).

The mechanisms behind these relationships are multifactorial. Some evidence shows that treatment for mental health disorders may actually increase the risk of diabetes, particularly when second-generation (atypical) antipsychotic agents are prescribed (1). Biochemical changes due to the mental health disorders themselves also may play a role (2). Lifestyle changes and symptoms of mental health disorders are also likely to contribute (3).

Depression

The prevalence of clinically relevant depressive symptoms among patients with diabetes is in the range of 30% (4–6). The prevalence of major depressive disorder (MDD) is approximately 10% (7,8), which is double the overall prevalence in people without a chronic medical illness. Individuals with depression have an

approximately 60% increased risk of developing type 2 diabetes (9). The prognosis for comorbid depression and diabetes is worse than when each illness occurs separately (10). Depression in patients with diabetes amplifies symptom burden by a factor of about 4 (11). Episodes of MDD in individuals with diabetes are likely to last longer and have a higher chance of recurrence compared to those without diabetes (12).

Studies examining differential rates for the prevalence of depression in type 1 vs. type 2 diabetes have yielded inconsistent results (4,13). One study found that the requirement for insulin was the factor associated with the highest rate of depression, regardless of the type of diabetes involved (14).

Risk factors for developing depression in individuals with diabetes are as follows:

- Female gender
- Adolescents/young adults and older adults
- Poverty
- Few social supports
- Stressful life events
- Poor glycemic control, particularly with recurrent hypoglycemia
- Longer duration of diabetes
- Presence of long-term complications (15–19)

Risk factors (with possible mechanisms) for developing diabetes in patients with depression are as follows:

- Physical inactivity and obesity, which leads to insulin resistance, and
- Psychological stress, leading to chronic hypothalamic-pituitary-adrenal activation with cortisol release (20–25).

Comorbid depression worsens clinical outcomes in diabetes, possibly because the accompanying lethargy lowers motivation for self-care, resulting in lowered physical and psychological fitness, higher use of healthcare services and reduced adherence to medication regimens (26,27). Depression also appears to worsen cardiovascular mortality (28,29). Treating depressive symptoms more reliably improves mood than it does glycemic control (30–33).

Bipolar Disorder

Patients with bipolar disorder have been found to have prevalence rates estimated to be double that of the general population for metabolic syndrome and triple for diabetes (34–36).

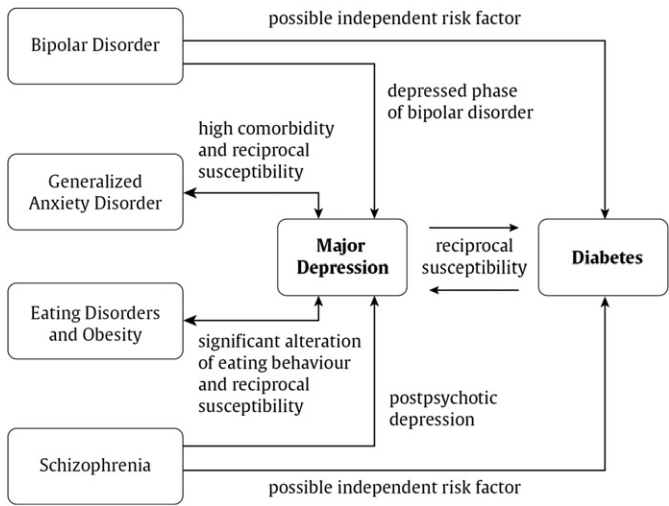


Figure 1. The interplay between diabetes, major depressive disorder, and other psychiatric conditions.

Anxiety

Anxiety is commonly comorbid with depressive symptoms (37). One study estimated that 14% of individuals with diabetes suffered from generalized anxiety disorder, with double this figure experiencing a subclinical anxiety disorder and triple this figure having at least some anxiety symptoms (38).

Eating Disorders

Eating disorders, such as anorexia nervosa, bulimia nervosa and binge eating, have been found to be more common in individuals with diabetes (both type 1 and type 2) than in the general population (39,40). Depressive symptoms are highly comorbid with eating disorders, affecting up to 50% of patients (41). Type 1 diabetes in young adolescent women appears to be a risk factor for development of an eating disorder, both in terms of an increased prevalence of established eating disorder features (42,43) as well as through deliberate insulin omission or underdosing (called diabulimia). Night eating syndrome (NES) has been noted to occur in individuals with type 2 diabetes who have depressive symptoms. This is characterized by the consumption of >25% of daily caloric intake after the evening meal and waking at night to eat, on average, at least 3 times per week. NES can result in weight gain, poor glycemic control and an increased number of diabetic complications (44).

Schizophrenia

Schizophrenia (SZ) and other psychotic disorders may contribute an independent risk factor for diabetes. People diagnosed with psychotic disorders were reported to have had insulin resistance/glucose intolerance prior to the advent of antipsychotic medication; however, this matter is still open to debate (45,46). The Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) study found, at baseline, that of the individuals with SZ who participated in the study, 11% had diabetes (type 1 and 2 combined) (1). The prevalence of metabolic syndrome was approximately twice that of the general population (47). Whether the increased prevalence of diabetes is due to the effect of the illness, antipsychotic medications or other factors, individuals with psychotic disorders represent a particularly vulnerable population.

Monitoring Metabolic Risks

Patients with diabetes and comorbid psychiatric illnesses are at an elevated risk for developing metabolic syndrome, possibly due to a combination of the following factors (48):

- Patient factors (e.g. lifestyle choices, diet, tobacco consumption, substance use, exercise, obesity, low degree of implementation of education programs)
- Illness factors (e.g. proinflammatory states from MDD or depressive symptoms, possible disease-related risks for developing diabetes) (49,50)
- Medication factors (i.e. psychiatric medications have a variable effect on glycemic control, weight and lipids)
- Environmental factors (e.g. access to healthcare, availability of screening and monitoring programs, social supports, education programs)

Psychiatric medications (primarily second-generation/atypical antipsychotics, but in some cases antidepressants as well) have the potential to affect weight, lipids and glycemic control in patients without diabetes (1,30,51). A weight gain of between 2 to 3 kg was found within a 1-year time frame with amitriptyline, mirtazapine and paroxetine (51). A study of patients with type 2 diabetes and SZ who were treated with antipsychotic medications also showed worsening glycemic control requiring the addition of insulin therapy over a 2-year period with a hazard ratio of 2.0 (52). The reported weight gain over a 1-year period ranges from <1 kg to >4 kg for various antipsychotic medications. Olanzapine and clozapine have been shown to have the greatest weight gain, with a mean increase of >6 kg over a 1-year span compared with 2 to 3 kg for quetiapine and risperidone, and 1 kg for aripiprazole and ziprasidone, also over a 1-year time frame. The main impact on lipid profile is an increase in triglyceride and total cholesterol levels, especially with clozapine, olanzapine and quetiapine (1,53).

Regular and comprehensive monitoring of metabolic parameters is recommended for all persons who receive antipsychotic medications, whether or not they have diabetes. Table 1 outlines a Psychiatric Medication Metabolic Monitoring Protocol adapted from recommendations made by various organizations, including the American Diabetes Association–American Psychiatric Association, Australian and Belgian consensus groups.

Psychological Effects of Diabetes

Diabetes, both type 1 and 2, is a psychologically challenging disease for patients and their family members (57). It interferes

Table 1
Psychiatric medication metabolic monitoring protocol

Parameter	Baseline	1 month	2 months	3 months	Every 3–6 months	Annually
Weight (BMI)	x	x	x	x	x	
Waist circumference	x			x		x
Blood pressure	x			x		x
Fasting glucose and/or A1C	x			x	x	
Fasting lipid profile	x			x	x	
Personal history, particularly alcohol, tobacco and recreational substance use	x			x		x
Family history	x					x

A1C, glycated hemoglobin; BMI, body mass index. Adapted from references 54–56.

Table 2

Comparison of main features and assessment methods: diabetes distress vs. depression

	Diabetes distress	Major depressive disorder
Assessment Instrument	Diabetes Distress Scale (17 items)	Patient Health Questionnaire for Depression: PHQ-9 (9 items)
Format	Self-report using ratings from 1–6 based on feelings and experiences over the past week	Self-report using ratings from 0–3 based on feelings and experiences over the past 2 weeks
Features	Emotional Burden Subscale (5 items) Physician-Related Distress Subscale (4 items) Regimen-Related Distress Subscale (5 items) Diabetes-Related Interpersonal Distress Subscale (3 items)	Vegetative symptoms, such as sleep, appetite and energy level changes Emotional symptoms, such as low mood and reduced enjoyment of usual activities Behavioural symptoms, such as agitation or slowing of movements Cognitive symptoms, such as poor memory or reduced concentration or feelings of guilt; thoughts of self-harm

with quality of life and is a risk factor for diabetes-related distress as well as the psychiatric disorders listed above. Challenges accompanying the diagnosis of diabetes include adjustment to the disease, adherence to the treatment regimen and psychosocial difficulties at both a personal and an interpersonal level (58,59). Stress, deficient social supports and negative attitudes toward diabetes can impact on self-care and glycemic control (60–64). Diabetes management strategies ideally incorporate a means of addressing the psychosocial factors that impact on individuals and their families. Both symptom measures (e.g. self-report measures of depressive or anxiety symptoms) and methods to arrive at mental disorder diagnoses (e.g. structured interviews leading to *Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition, Text Revision] [DSM-IV-TR] diagnoses [42]) have been assessed. Given that the person with diabetes carries out 95% of diabetes management (65), identifying depressive syndromes in diabetes is important since depression is a risk factor for poor diabetes self-management (66–68) and outcomes, including early mortality (69,70). MDD has been found to be underdiagnosed in people with diabetes (71).

Diabetes distress describes the despondency and emotional turmoil related specifically to having the condition, the need for continual monitoring and treatment, persistent concerns about complications and the potential erosion of personal and professional relationships. Distinguishing between diabetes distress, MDD and the presence of depressive symptoms is important (72,73) because these psychological experiences are different, and, of the three, diabetes distress may be most strongly related to adverse diabetes outcomes (72,74,75).

Screening for Psychological/Psychiatric Symptoms

Individuals with diabetes should be regularly screened for psychological distress and psychiatric disorders via directed interviews. No data presently demonstrate the superiority of one particular depression screening tool over another (76). Currently available screening instruments have a sensitivity of between 80% and 90% and a specificity of 70% to 85% (76). A website that contains a wide variety of downloadable scales that are in the public domain is https://www.outcometracker.org/scales_library.php. Patient Health Questionnaire (PHQ) Screeners are available at www.phqscreener.com.

Screening instruments fall into three categories:

- Diabetes-specific measures, such as the Problem Areas in Diabetes (PAID) Scale (77,78) or the Diabetes Distress Scale (DDS) (79)
- Quality of life measures, such as the WHO-5 screening instrument (80)
- Depressive/anxiety symptoms, such as the Hospital Anxiety and Depression Scale (HADS) (81), the Patient Health Questionnaire (PHQ-9) (82,83), the Centre for Epidemiological Studies–Depression Scale (CES-D) (84) or the Beck Depression Inventory (BDI) (85)

Table 2 illustrates the differences between the principal features and assessment methods of diabetes distress and MDD.

Treatment of Psychological/Psychiatric Risk Factors

Given the burden associated with the demands of diabetes self-management, efforts to promote well-being and moderate distress should be incorporated into diabetes management for all individuals (86). Motivational interventions (68,87,88), coping skills, self-efficacy enhancement, stress management (89,90) and family interventions (91–93) all have been shown to be helpful. Case management by a nurse working with the patient's primary care physician and providing guideline-based, patient-centred care resulted in improved glycated hemoglobin (A1C), lipids, blood pressure and depression scores (94). Individuals with diabetes distress and/or psychiatric disorders benefit from professional interventions, either some type of psychotherapy or prescription medication. Evidence from systematic reviews of randomized controlled trials supports cognitive behaviour therapies (CBT) and antidepressant medication, both solely or in combination (33,95). No evidence presently shows that the combination of CBT and medication is superior to these treatments given individually. A pilot study of 50 patients with type 2 diabetes who initially had a moderate level of depression at baseline showed an improvement in the severity of their depression (moving to the mild range) with a 12-week intervention of 10 CBT sessions combined with exercise in the form of 150 minutes of aerobic activity weekly. This effect was sustained at 3 months (96). Online resources are available to help healthcare providers learn CBT skills (e.g. www.moodgym.com).

Table 3

Features of cognitive behavioural therapy that can be applied to diabetes treatment (97)

Cognitive component	Behavioural component
Record keeping to identify distressing automatic thoughts	Strategies to help get the person moving (behavioural activation)
Understanding the link between thoughts and feelings	Scheduling pleasant events; learning assertive and effective communication skills
Learning the common "thinking errors" that mediate distress (e.g. all-or-nothing thinking, personalization, magnification, minimization, etc.)	Focusing on feelings of mastery and accomplishment
Analyzing negative thoughts and promoting more functional ones	Learning problem-solving strategies
Identifying basic assumptions about oneself (e.g. "unless I am very successful, my life is not worth living") and being encouraged to adopt healthier ones (e.g. "when I am doing my best, I should be proud of myself")	Exposure to new experiences
	Shaping behaviours by breaking them down into smaller steps to develop skills

org). Table 3 illustrates some of the major features of CBT as applied to diabetes care.

Gains from treatment with psychotherapy are more likely to benefit psychological symptoms and glycemic control in adults than will psychiatric medications (which usually only reduce psychological symptoms) (98). A meta-analysis of psychological interventions found that glycemic control (A1C) is improved in children and adolescents with type 1 diabetes (99). Furthermore, evidence suggests interventions are best implemented in a collaborative fashion and when combined with self-management interventions (95).

Treatment with Medication

Psychiatric medications have the capacity to affect metabolic parameters and cause changes in weight, glycemic control and lipid profile and, in some cases, can have immunomodulating effects (22,100–103). A key review estimated and compared the effects of antipsychotics—both the newer ones and the conventional ones—on body weight (104). The consensus statement issued by the American Diabetes Association in 2004 contains recommendations regarding almost all of the atypical agents currently available in Canada (55), as does the Canadian Diabetes Association position paper from 2005 (105). A comprehensive review and meta-analysis looked at the effect of antidepressants on body weight (51).

The CATIE study investigated 4 aspects of the effectiveness of antipsychotic medications: efficacy, tolerability, emergence of medical problems and patient choice (1,106). The results did indicate that some antipsychotic medications were more likely to cause weight gain, worsen glycemic control and induce unfavourable changes in lipid profile. However, when these effects were considered in the context of efficacy, tolerability and patient choice, no conclusive statements could be made about which medications to clearly use or which to clearly avoid. Consequently, all 4 aspects are important and reinforce the need for regular and comprehensive metabolic monitoring. Should medical problems arise while a patient is taking psychiatric medications, clinical judgement will dictate, on a case-by-case basis, as to whether modifications such as diet or exercise, adding a medication to address the emergent issue

(e.g. side effect or medical complication) or changing the psychiatric prescription, is the most reasonable step (107). Handbooks are available that allow clinicians to quickly review the major side effect profiles of psychiatric medications (108,109).

Other Relevant Guidelines

Organization of Diabetes Care, p. S20

Type 1 Diabetes in Children and Adolescents, p. S153

Type 2 Diabetes in Children and Adolescents, p. S163

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RECOMMENDATIONS

- Individuals with diabetes should be regularly screened for subclinical psychological distress and psychiatric disorders (e.g. depressive and anxiety disorders) by interview [Grade D, Consensus] or with a standardized questionnaire [Grade B, Level 2 (110)].
- Psychosocial interventions should be integrated into diabetes care plans, including
 - Motivational interventions [Grade D, Consensus]
 - Stress management strategies [Grade C, Level 3 (90)]
 - Coping skills training [Grade A, Level 1A for type 2 diabetes (111); Grade B, Level 2, for type 1 diabetes (112)]
 - Family therapy [Grade A, Level 1B (91,93,113)]
 - Case management [Grade B, Level 2 (94)]
- Antidepressant medication should be used to treat acute depression [Grade B, Level 2 (31)] and for maintenance treatment to prevent recurrence of depression [Grade A, Level 1A (32)]. Cognitive behaviour therapy (CBT) alone [Grade B, Level 2 (33)] or in combination with antidepressant medication [Grade A, Level 1 (95)] may be used to treat depression in individuals with diabetes.
- Antipsychotic medications (especially atypical/second generation) can cause adverse metabolic changes [Grade A, Level 1 (1)]. Regular metabolic monitoring is recommended for patients with and without diabetes who are treated with such medications [Grade D, Consensus].

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Clinical Practice Guidelines

Influenza and Pneumococcal Immunization

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Nadira Husein MD, FRCPC, Vincent Woo MD, FRCPC

KEY MESSAGES

- Influenza immunization can reduce hospitalization rates by approximately 40% for those individuals deemed to be at high risk.
- Pneumococcal immunization is desired in people with diabetes as they are considered as likely to be infected as those with other chronic diseases.
- For those who are >65 years of age, a 1-time revaccination is recommended if the original vaccine was administered when they were <65 years of age with at least 5 years between administrations.

Introduction

People with diabetes are considered to be at high risk for morbidity and mortality from influenza and pneumococcal disease (1,2). During recent influenza epidemics, diabetes was considered a significant risk factor for hospitalization (3). Influenza immunization is associated with up to a 40% risk reduction in mortality (2). Clinical recommendations for vaccination are derived from large cohort studies that included people with diabetes as trials specific to individuals with diabetes are currently lacking.

Influenza Immunization in Adults

Data regarding influenza morbidity and mortality in people with diabetes are based on retrospective analyses during influenza epidemics (3,4). A recent epidemiological analysis of pandemic influenza demonstrated that people with diabetes are more likely to be hospitalized or to require intensive care (5).

Over a period of 10 influenza seasons, influenza vaccination was shown to be effective in reducing both death and hospitalization from influenza and pneumonia in a cohort that included people with diabetes (6).

RECOMMENDATIONS

1. People with diabetes should receive an annual influenza immunization to reduce the risk of complications associated with influenza [Grade D, Consensus].
2. Pneumococcal immunization should be offered to people with diabetes. A single dose is recommended for those >18 years of age. A 1-time revaccination is recommended for those >65 years of age (if the original vaccine was given when they were <65 years of age) with at least 5 years between administrations [Grade D, Consensus].

A Dutch case control study documented that the incidence of complications was 2 times higher in the unvaccinated group compared to the vaccinated group (7). The rates of hospitalization for influenza, pneumonia, other acute respiratory diseases, myocardial infarction, congestive heart failure, and stroke or diabetes events were reduced by 70%.

Pneumococcal Immunization in Adults

People with diabetes are at increased risk of hospitalization for pneumococcal disease (1,8). Prior pneumococcal vaccination is associated with a reduction in death and complications in hospitalized adults with community-acquired pneumonia (9). It is accepted that people with diabetes are at similar risk of developing pneumococcal disease as those with other chronic conditions (1), and, therefore, those with diabetes are encouraged to receive pneumococcal vaccination. Revaccination is recommended as a 1-time event for individuals >65 years of age if the original vaccine was given when they were <65 years of age and >5 years earlier.

Related Websites

National Advisory Committee on Immunization. *Canadian Immunization Guide*. 7th ed. Ottawa, ON: Canadian Medical Association; 2006. Available at: <http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php>. Accessed November 2012.

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Clinical Practice Guidelines

Pancreas and Islet Transplantation

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Breay W. Paty MD, FRCPC, Angela Koh MD, Peter Senior MBBS, PhD, MRCP

KEY MESSAGES

- Simultaneous pancreas kidney transplantation in persons with type 1 diabetes and end stage renal disease can improve kidney graft survival and result in prolonged insulin independence.
- Successful pancreas or islet allotransplantation can stabilize glucose and possibly result in insulin independence in persons with type 1 diabetes and glycemic lability or recurrent hypoglycemia.
- Islet autotransplantation can stabilize glucose and possibly result in insulin independence in people undergoing total pancreatectomy for benign pancreatic disease.

Introduction

Restoring endogenous insulin secretion by whole pancreas or islet transplantation has been established as an alternative to insulin injection therapy in select individuals with type 1 diabetes (1,2). Nonrandomized studies demonstrate that both pancreas and islet transplantation can result in insulin independence and glucose stability, especially in the setting of glucose lability or frequent, severe hypoglycemia. Unfortunately, the absence of prospective randomized controlled trials makes it difficult to draw firm conclusions about the overall efficacy and safety of these therapies compared with exogenous insulin treatment. Also, the limited number of specialized islet and pancreas transplantation centres and the relatively small number of donor pancreases limit the availability of these treatments. Nevertheless, general recommendations regarding the role of pancreas and islet transplantation may be made in the context of current clinical experience.

Pancreas Transplantation

Pancreas transplantation can result in complete independence from exogenous insulin in the majority of cases (3). As shown in Table 1, worldwide, noncontrolled 1- and 3-year mean pancreas graft and patient survival rates differ slightly among the 3 major types of transplantations (4). Long-term pancreas graft survival declines with time, with a median graft survival of 9 years and <10% survival at 21 years (5).

Glycemic control and glycated hemoglobin (A1C) are markedly improved after successful pancreas transplantation, with most recipients achieving normal glucose tolerance, albeit with hyperinsulinemia (6,7). A reduction in albuminuria has been noted at 1 year (8), and improvements in the histological changes associated

with diabetic nephropathy have been reported 5 to 10 years post-transplantation (9,10). Whether successful simultaneous pancreas kidney (SPK) transplantation improves renal graft survival is unclear. In 1 study, recipients of SPK transplantations had better renal graft survival over 72 months than deceased-donor kidney transplantations but lower graft survival than living-donor kidney transplantations (11). The impact of pancreas transplantation on overall patient survival also is uncertain. Studies suggest lower short-term survival in the perioperative period up to 18 to 24 months after SPK, but for patients with successful functioning pancreas grafts at 12 months post-transplantation, survival was similar or improved compared to living- or deceased-donor kidney transplantation (12–14). A retrospective cohort study of individuals with diabetes and preserved kidney function who received a solitary pancreas transplantation suggested that overall survival was worse compared with wait-listed patients receiving conventional medical therapy (15). Improvement and/or stabilization of diabetic retinopathy have been demonstrated (16). Peripheral sensory and motor neuropathies also have been shown to improve after pancreas transplantation (17,18), but these findings are not consistent and may take years to achieve (19–21). Pancreas transplantation appears to improve cardiovascular (CV) function, carotid intimal medial thickness, blood pressure and lipid parameters (22–24). A single, small, non-randomized study showed a reduction in CV events in SPK recipients compared to those undergoing kidney transplantation alone (25); however, this has not been examined in a randomized controlled fashion. Finally, diabetes-related quality of life (QOL) appears to improve after pancreas transplantation, although overall QOL appears to be unchanged (26,27).

Islet Transplantation

Islet allotransplantation

Islet allotransplantation involves the infusion of islets isolated from cadaveric pancreata via the portal vein into the liver (28), either alone or in association with a renal transplantation (29,30). Successful islet transplantation can result in stable, near-normal glycemic control (A1C, glycemic variability) with a reduction or elimination of hypoglycemia (31) over and above what can be achieved with insulin injections or even insulin pump therapy (32). The ability of transplant recipients to achieve and maintain insulin independence varies between transplantation centres and is influenced by both donor and recipient factors (33,34). Insulin

Table 1

Reported graft survival rates according to type of pancreas transplantation (4)

Transplantation type	1 year	5 years	10 years	15 years
SPK	83%	69%	51%	33%
PAK	74%	45%	24%	13%
PTA	78%	54%	28%	9%

SPK, simultaneous pancreas kidney; PAK, pancreas after kidney; PTA, pancreas transplant alone.

independence can be achieved in most recipients but often requires 2 or more transplantation procedures. Insulin independence rates decline with time from approximately 70% at 1 year post-transplantation to approximately 10% after 5 years (31). However, patients who are not able to maintain insulin independence may still benefit from more stable blood glucose control (35) that results from ongoing graft function, as evidenced by the sustained secretion of C peptide and the reduced requirement for exogenous insulin (33). Small, short-term studies also suggest stabilization of retinopathy (36) and neuropathy (37) with islet allotransplantation. Renal outcomes vary, but recent reports suggest that the glomerular filtration rate achieved with the procedure does not differ significantly from that observed in the nondiabetic population (38,39). Successful islet transplantation can improve QOL by reducing the fear of hypoglycemia (40) but can be negatively impacted by adverse effects from immunosuppressive agents (27).

Islet autotransplantation

In islet autotransplantation, islets are isolated from an individual's own resected pancreas following pancreatectomy for benign pancreatic disease (e.g. chronic, painful pancreatitis) (41,42). Islet yields from a resected, diseased pancreas may be lower than those from cadaveric donors, but immunosuppression is not required. Even if insulin independence is not achieved, islet autotransplantation may result in reduced exogenous insulin requirements and a lower risk of hypoglycemia (43). As a result, the ratio of benefit to risk of this procedure may exceed that noted with islet allotransplantation (44).

Risks Associated with Pancreas and Islet Transplantation

Pancreas transplantation is associated with significant peri-operative risks, including graft thrombosis, hemorrhage,

Table 2

Comparison of beta cell replacement modalities

	Islet	Pancreas
Outcomes		
Reduce or eliminate hypoglycemia	Yes	Yes
Improve A1C	Yes	Yes
Insulin independence	Yes*	Yes
Effect on diabetes-related complications		
Microvascular	May be stabilized [†]	Improved
Macrovascular	Not known	May be improved
Risks		
Procedural risks	Minor procedural risk	Major surgical risk
Immunosuppression	Similar agents, [‡] life-long immunosuppression	
Other considerations		
ESRD	Avoid	Consider SPK
Functioning renal transplant	Consider IAK if glycemic lability or hypoglycemia [§]	Consider PAK if glycemic lability or hypoglycemia [§]

A1C, glycated hemoglobin; ESRD, end stage renal disease; IAK, islet after kidney; PAK, pancreas after kidney; SPK, simultaneous pancreas kidney.

* More than 1 islet infusion may be required.

[†] Retinopathy and neuropathy may be stabilized.

[‡] Steroids are avoided in islet transplantation but may be used in whole pancreas transplantation.

[§] No additional risk from immunosuppression.

RECOMMENDATIONS

1. Individuals with type 1 diabetes and ESRD who are being considered for kidney transplantation should also be considered for simultaneous pancreas transplantation [Grade D, Level 4 (12,14)].
2. Individuals with type 1 diabetes with preserved renal function, or who have undergone successful kidney transplantation but have persistent metabolic instability characterized by severe glycemic lability and/or severe hypoglycemia despite best efforts to optimize glycemic control, may be considered for pancreas or islet allotransplantation [Grade D, Consensus].
3. Individuals undergoing total pancreatectomy for benign pancreatic disease may be considered for islet autotransplantation but only in the context of an experienced islet transplantation centre [Grade D, Consensus].

Abbreviation:

ESRD, end stage renal disease.

pancreatitis, wound infection, peripancreatic abscesses and duodenal stump leakage (45). Islet transplantation is associated with fewer procedural risks, which may include intraperitoneal hemorrhage, partial portal vein thrombosis or gallbladder puncture. These complications occur in <10% of procedures and usually are self-limited (31,34). Both pancreas and islet transplantations require long-term immunosuppression, which is associated with a number of risks and side effects (46). Drug side effects are generally mild and often respond to dose or agent adjustment. Although rare, life-threatening opportunistic infections and malignancies have been reported (34,46). These risks must be carefully weighed against the potential benefits of transplantation for each individual. See Table 2 for a detailed comparison of pancreas vs. islet transplantation.

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Clinical Practice Guidelines

Natural Health Products

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Seventy-eight percent of patients with diabetes reported taking a natural health product (NHP) for various indications.
- Some NHPs have shown a lowering of A1C by $\geq 0.5\%$ in trials lasting ≥ 3 months in adults with type 2 diabetes, but most are single small trials so it would be premature to recommend their widespread use.
- Healthcare providers should always ask about the use of NHPs since some may result in side effects or drug interactions.

Introduction

Natural Health Products (NHPs) include herbal medicines, vitamins, minerals and other essential nutrients, probiotics and many other naturally occurring substances. Since 2004, they have been regulated in Canada by the Natural Health Products Directorate of Health Canada.

Management

These guidelines include NHPs because they are widely used by patients, but the evidence of their efficacy and safety is unknown to most prescribing physicians. In a recent Canadian study of 502 patients with diabetes, 78% reported taking an NHP, with similar frequency in people with type 1 and type 2 diabetes (1). While it is important to be aware of potential harms, side effects and drug interactions, some NHPs may be potentially important new therapeutic agents. Interestingly, metformin is derived from French lilac, a remedy used to treat diabetes since the Middle Ages, and identification of the active agent guanidine led to the synthesis of biguanides (2).

In general, the current level of evidence for the efficacy and safety of NHPs in people with type 2 diabetes is lower than that for pharmaceutical drug treatments. Trials tend to be of shorter duration and involve smaller sample sizes. At the present time, concerns remain about standardization and purity of available compounds, including their contamination with regular medications and, in some cases, toxic substances (3).

While a number of NHPs have been studied to evaluate their impact on cardiovascular and other outcomes in patients with type 2 diabetes, this guideline is limited to NHPs for improving glycemic control. Trials were considered for review if they were randomized, controlled, and reported changes in glycated hemoglobin (A1C) over at least 12 weeks of treatment. Positive trials were those that

demonstrated a reduction in the placebo-subtracted A1C of at least 0.5%.

The following NHPs lowered A1C by $\geq 0.5\%$ in trials lasting at least 3 months in adults with type 2 diabetes:

- *Coccinia cordifolia* (4)
- *Ganoderma lucidum* (5)
- *Salacia reticulata* (6)
- Soybean-derived pinitol extract (7)
- Touchi soybean extract (8)
- *Pterocarpus marsulium* (vijayasar) (9)
- *Gynostemma pentaphyllum* (10)
- Marine collagen peptides (11)
- Silymarin (12,13)
- *Citrullus colocynthis* (14)
- *Trigonella foenum-graecum* (fenugreek) (15)

These products are promising and merit consideration and further research, but, as they are mostly single, small trials, it is premature to recommend their widespread use.

The following NHPs failed to lower A1C by $\geq 0.5\%$ in trials lasting at least 3 months in adults with type 2 diabetes:

- *Tinospora crispa* (16)
- French maritime pine bark (17)
- Soy phytoestrogens (18)
- *Agaricus blazei* (19)
- Antioxidants (fruit/vegetable extract) (20), (pomegranate extract) (21)
- *Camellia sinensis* (22)
- *Cinnamomum* spp (cinnamon) (23–27)
- *Momordica charantia* (bitter melon or bitter gourd) (28)
- Flaxseed oil (29)
- Ginseng (30)
- Coenzyme Q10 (31)
- Vitamin C (32)
- Vitamin D (33–35)
- Vitamin E (36–38)

It should be noted that, in many cases, small sample sizes made the trials insufficiently powered to establish a significant benefit from NHP interventions.

The following NHPs have demonstrated conflicting effects on A1C in trials lasting at least 3 months in adults with type 2 diabetes:

- *Ipomoea batatas* (cayapo) (39,40)
- Chromium (41–52)
- Magnesium (53–57)
- L-carnitine (58–61)

It should be noted that vanadium, a trace element that is commonly used to treat type 2 diabetes, has not been studied in trials evaluating glycemic control over a period of 3 months or longer.

Complications

It is important to consider potential harm from the use of NHPs. In 1 trial of *Tinospora crispa*, hepatotoxicity was seen in 2 patients (16). Large doses of *Citrullus colocynthis* can induce diarrhea, but no side effects were reported in the lower doses used in 1 trial (14). *Momordica charantia*, an NHP commonly used for glycemic control, is an abortifacient (62). Most clinical trials have evaluated small sample sizes over relatively short periods of time and, thus, may not identify side effects or risks.

Drug-herb interactions may also occur. The most well described is *Hypericum perforatum* (St. John's wort), which can affect the metabolism of many drugs, including statins, by inducing CYP3A4. Some studies have reported poorer glycemic control in patients using glucosamine sulfate for osteoarthritis, but a systematic review concluded that the evidence does not support this concern (63).

Clinicians should ask all patients with diabetes about their use of NHPs. Potential concerns should be addressed using a patient-centered approach that ensures patient safety while respecting their views to maintain a positive therapeutic relationship. For more detailed information about specific NHPs, practitioners should consult previously published reviews (64).

RECOMMENDATIONS

1. Natural health products are not recommended for glycemic control for individuals with diabetes as there is insufficient evidence, at this time, regarding efficacy and safety [Grade D, Consensus].
2. Healthcare providers should ask about the use of natural health products [Grade D, Consensus].

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Clinical Practice Guidelines

Vascular Protection in People with Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetes promotes both the development and adverse impact of cardiovascular disease (CVD) risk factors (e.g. hypertension, dyslipidemia, renal dysfunction) and, as a consequence, accelerates cardiovascular age. Persons with diabetes generally have a cardiovascular age 10 to 15 years in advance of their chronological age (1).
- Advanced cardiovascular age substantially increases both the proximate and lifetime risk for CVD events, resulting in a reduced life expectancy of approximately 12 years (2).
- Although young patients with diabetes rarely will have a high proximate risk for CVD events, they have a relative proximate risk many fold greater than that of individuals without diabetes (1).
- All adults with diabetes require chronic disease care strategies that include health behaviour education and, for many individuals, pharmacological vascular protection, in order to promote CVD event risk reduction.
- The requirement for pharmacological vascular protection therapies (statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and acetylsalicylic acid) should be determined by both an individual's proximate and lifetime CVD event risk.

Proximate CVD Risk vs. Lifetime CVD Risk

Persons with both type 1 and type 2 diabetes mellitus are at significantly increased risk of atherosclerotic cardiovascular disease (CVD) presenting as coronary heart disease, stroke and peripheral vascular disease (1–3). For the vast majority of older persons with diabetes (age >40 years), both the proximate 10-year and lifetime CVD event risk becomes sufficiently high (>20%) to justify both health behaviour modification and pharmacological interventions. However, for many younger individuals with diabetes, their proximate 10-year CVD event risk may be low (4), yet both proximate and lifetime event rates are many times higher than for individuals of the same age without diabetes (1,5). For these persons, their vascular age far exceeds their chronological age, significantly increasing their relative risk of CVD events. The term “vascular age” refers to models of CVD event risk that predict an individual's CVD event risk and compare the event risk to age-adjusted CVD event risk (6). The greater the risk factor burden, the greater the vascular age and relative CVD event risk. Such a high relative risk indicates that early intervention before the arbitrary high-risk 10-year 20%

event rate is reached may be beneficial (6–10). Thus, the use of pharmacotherapy for CVD risk factor reduction in younger persons with diabetes, who are not at a high proximate risk and yet, as a consequence of diabetes, have a steep CVD event risk trajectory, can be justified by the potentially substantial long-term benefits of earlier interventions and lifelong therapy (8–11).

Traditional CVD event risk models predict an individual's proximate (5- to 10-year) CVD event risk based on risk factors, such as diabetes, dyslipidemia, hypertension and smoking. These models discriminate poorly between high- and low-risk individuals (12). Furthermore, they underestimate risk in younger individuals and have a low specificity; consequently, they cannot reliably exclude individuals with diabetes who are unlikely to benefit from long-term pharmacological vascular protection strategies before their proximate risk is high. Consequently, as most individuals with diabetes have a very high lifetime risk for a CVD event, a strategy that includes early vascular protection is justified (8–15).

Both type 1 and type 2 diabetes are associated with increased CVD risk. In young adults (aged 20 to 39 years), type 1 diabetes is an independent risk factor for premature CVD and mortality (16). The presence of CVD in people with type 1 diabetes is related to age, duration of diabetes, presence of retinopathy, higher glycated hemoglobin (A1C) levels and higher albumin excretion rates, as well as traditional CVD risk factors, such as elevated total cholesterol and low-density lipoprotein-cholesterol (LDL-C), smoking and excess body weight (17). For all age groups, the majority of people with type 1 diabetes have at least 1 CV risk factor (18). Even if an individual with type 1 diabetes has a low proximate risk of a CV event (i.e. younger and shorter duration of diabetes), his or her long-term risk is very high.

Vascular Protection in the Patient with Diabetes

Vascular protective measures in patients with diabetes include health behaviour interventions (diet, weight modification, increased physical activity, smoking cessation) and pharmacological therapies (anti-platelet agents, statins, angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs], glycemic and blood pressure [BP] control). A systematic approach to all vascular protective measures has been proven to reduce the

risk of CVD events. The STENO-2 trial showed the long-term benefits of an intensive multifactorial management strategy in patients with type 2 diabetes and microalbuminuria (8,9). Patients were randomized to receive either usual care or intensive multifactorial therapy, where the goal was to optimize health behaviour and control BP, cholesterol and blood glucose to the treatment targets recommended by clinical practice guidelines. In the intensively managed group, behaviour interventions were more frequently achieved, and BP, lipid and glycemic levels were lower than in the subjects receiving usual care, although treatment targets were usually not achieved. After 8 years of follow-up, there was a 53% relative risk reduction in major CVD events (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.24–0.73) compared to usual care with a 20% absolute risk reduction. This meant that only 5 patients with type 2 diabetes and microalbuminuria needed to be treated with the intensive multifactorial approach for 8 years to prevent 1 cardiovascular event. Microvascular complications were also substantially reduced. After 13 years, the originally intensively managed group had a significantly lower mortality rate (30% vs. 50%, $p=0.02$). The number needed to treat (NNT) for mortality after 13 years was 5. The STENO-2 trial shows that a process-driven, multifactorial management strategy optimizing behaviour and pharmacological interventions had a major impact on a wide range of CVD outcomes, including a 46% lower mortality. Thus, all patients with diabetes should participate in a multifactorial strategy to reduce CVD risk.

Strategies for Vascular Protection

Health behaviour interventions for all patients with diabetes

Smoking cessation

Smoking, in individuals with diabetes, is an independent risk factor for all-cause mortality. It increases the risk of myocardial infarction (MI) 3-fold, stroke by 30%, progression to end stage renal disease, and is associated with poorer glycemic control. Quitting smoking reduces CV risk, reduces the risk of renal disease and improves glycemic control (19,20).

Exercise and physical activity

Regular exercise and physical activity are key components in the vascular protection paradigm as they have been shown to significantly reduce morbidity and mortality in persons with diabetes (21). The benefits of regular physical activity are described in the Physical Activity and Diabetes chapter, p. S40.

Nutrition therapy

The benefits of a healthy diet are described in the Nutrition Therapy chapter, p. S45.

Weight modification

Achievement and maintenance of a healthy body weight are discussed in the Weight Management in Diabetes chapter, p. S82.

Pharmacological interventions

Glycemic control

While optimal glycemic control is central to the prevention of microvascular complications of diabetes, the benefits of tight glycemic control to reduce the risk for macrovascular disease have been more difficult to show. The goals for glycemic control and the cardiovascular benefits are discussed in the Targets for Glycemic Control chapter, p. S31, and options for glycemic control are discussed in the Pharmacotherapy in Type 1 Diabetes chapter,

p. S56, and the Pharmacologic Management of Type 2 Diabetes chapter, p. S61.

BP control

BP control is necessary in a high proportion of patients with diabetes. The goals of treatment and options to achieve BP targets are discussed in the Treatment of Hypertension chapter, p. S117.

Antiplatelet therapy

Platelets play a pivotal role in the development of atherothrombosis. As patients with diabetes have increased in vitro platelet reactivity and aggregation, they might be expected to have enhanced benefit from platelet inhibition with agents such as acetylsalicylic acid (ASA). However, in vitro tests of platelet aggregation suggest that patients with diabetes have platelets that are more likely to be resistant to the inhibitory effect of ASA (22,23). Despite the proven advantages of ASA therapy in patients with established CVD, the evidence for benefits of ASA therapy for the primary prevention of coronary artery disease (CAD) events in persons with diabetes is less robust.

ASA in primary prevention. In the general population, ASA reduces nonfatal MI in men without a history of CVD (24). In women without a history of CVD, the Women's Health Study (WHS) indicated that ASA reduces the risk for stroke but not for MI (25). Yet, the benefits in patients with diabetes are less apparent. The Antithrombotic Trialists meta-analysis included 95 randomized trials of antiplatelet therapy published up to 1997. Of these, only 9 trials with 5000 people had diabetes. Compared to a 22% reduction in the risk of major CV events among all 140 000 high-risk subjects on antiplatelet therapy, subjects with diabetes showed no significant benefit ($7\% \pm 8\%$ risk reduction) (26).

Primary CVD prevention trials conducted specifically in people with diabetes also have shown very little benefit. The Early Treatment of Diabetic Retinopathy Study (ETDRS) and the Japanese Prevention of Atherosclerosis with ASA in Diabetes (JPAD) trial included patients with diabetes without known atherosclerotic disease (27,28). The ETDRS trial with ASA 650 mg demonstrated a borderline significant reduction of fatal and nonfatal MI (relative risk [RR] 0.85, 95% CI 0.73–1.00) yet no reduction of stroke (RR 1.18, 95% CI 0.88–1.58) (27). The JPAD trial used ASA 81 to 100 mg and showed no significant benefit for either MI or stroke (28). The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial in patients with diabetes and peripheral vascular disease showed that ASA 100 mg did not reduce CAD, death, nonfatal MI or stroke (29). However, poor adherence to treatment, with only 50% of patients taking assigned therapy after 5 years, may have played a role in the apparently absent treatment effect in these patients with vascular disease.

Meta-analysis of the diabetes cohorts from large clinical trials, such as WHS, British Male Doctors (BMD), Hypertension Optimal Treatment (HOT), Primary Prevention Project (PPP), and Thrombosis Prevention Trial (TPT), also have suggested that ASA has little or no benefit for the primary prevention of CAD events (25,30–38). The Baigent meta-analysis included BMD, PHS, WHS, TPT, and HOT and showed a modest 12% reduction of CVD events (RR 0.88, 95% CI 0.82–0.94) (34). However, the other 4 meta-analyses that also included ETDRS, JPAD, and POPADAD showed no significant reduction in either CAD events or stroke for patients with diabetes (35–38).

ASA increases gastrointestinal bleeding 50% to 70% (39), but the absolute rates of bleeding are low, with a risk of approximately 3 per 10 000 in the overall population. It is likely the risk is higher in patients with diabetes, with an estimate of 1 to 2 per 1000 in

middle-aged individuals and as high as >5 per 1000 in people >70 years old (39).

In summary, pooled estimates suggest that for primary prevention of CVD events in people with diabetes, ASA results in no reduction of CAD events and stroke but an important increase in gastrointestinal hemorrhage. Thus, despite a plethora of data, there remains sufficient uncertainty about the use of ASA in the primary prevention of CAD events in persons with diabetes, and its routine use in primary CVD event prevention is not recommended.

ASA in secondary prevention. ASA has been shown to reduce CVD events in patients with established CVD disease (40). The clinical trial evidence, as reflected in the 2011 Canadian Cardiovascular Society Guidelines on the Use of Antiplatelet Therapy in the Outpatient Setting, supports the use of ASA 75 to 162 mg daily for the secondary prevention of CAD events in those with diabetes (41).

Renin-angiotensin-aldosterone system inhibition

The benefit of ACE inhibition for vascular protection with ramipril 10 mg daily was demonstrated by the Heart Outcomes Prevention Evaluation (HOPE) trial (42). It was also shown in the Micro-HOPE subset analysis of patients with diabetes, which enrolled individuals with diabetes, aged ≥ 55 years, with 1 other CV risk factor (total cholesterol > 5.2 mmol/L, high-density lipoprotein < 0.9 mmol/L, hypertension, microalbuminuria or smoking) or established CVD (43). In subjects with diabetes enrolled in the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) study, the benefits from perindopril 8 mg daily were similar to those observed in the overall group; however, in this subgroup, the sample size was too small to show a statistically significant benefit (44). More recently, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) indicated similar vascular protective effect from the ARB telmisartan 80 mg daily as the ACE inhibitor ramipril 10 mg daily in a subset of patients with diabetes (45).

Whether the benefits of ACE inhibition result from a reduction of BP remains controversial. The benefits of ACE inhibition in both the HOPE and EUROPA trials were observed in individuals with or without a history of hypertension, and in those with higher and lower BP readings (42,46). Furthermore, recent analyses of BP trials have indicated a benefit of ACE inhibition beyond that of BP lowering (47).

A recent meta-analysis indicates that ACE inhibitors and ARBs reduce CVD events in normotensive individuals with and without diabetes (48). Accordingly, the use of ACE inhibitors or ARBs for vascular protection with persons with diabetes ≥ 55 years or with any evidence of organ damage is recommended, even in the absence of hypertension. Furthermore, for patients with diabetes and hypertension, an ACE inhibitor or ARB should be considered as a first-line agent for BP control.

Lipid-modifying therapies

The role of lipid-modifying therapies in the protection against CAD events in persons with diabetes is presented in the Dyslipidemia chapter, p. S110. In 2008, the Canadian Diabetes Association recommended that all men with diabetes ≥ 45 years of age and women with diabetes ≥ 50 years of age be treated with a statin to reduce LDL-C to ≤ 2.0 mmol/L (49). The 2008 guidelines also recommended that, below these ages, patients with diabetes and higher CVD risk (e.g. those with established macrovascular disease,

microvascular disease, diabetes of > 15 years' duration and age > 30 years, and individuals with a very elevated single risk factor) should receive statin therapy.

There is clinical trial evidence of the benefits of statin therapy for primary prevention in patients with diabetes at ages prior to achieving a high proximate 10-year CVD risk. The Heart Protection Study (HPS) enrolled 5963 individuals from age 40 years with diabetes, of whom 49% had no evidence of CVD. CV events were reduced by 22% (95% CI 13–30) in the patients with diabetes receiving simvastatin 40 mg daily for the 5-year treatment period (50). The same relative benefit was observed in patients with or without evidence of CVD. In the 615 patients with type 1 diabetes, there was a similar (although not statistically significant) risk reduction as observed in the 5438 patients with type 2 diabetes (50). The Collaborative Atorvastatin Diabetes Study (CARDS) included 2838 patients with diabetes, 1 CV risk factor, and age > 40 years. They were treated for an average of 3.9 years with either atorvastatin 10 mg daily or placebo (51). CV events were reduced by 37% (95% CI –52% to –17%; $p=0.001$) by atorvastatin compared to placebo, with a 36% reduction of acute coronary heart disease, a 31% reduction of coronary revascularization and a 48% reduction of stroke. There was a strong trend toward a 27% reduction of all-cause mortality (95% CI –48% to 1%; $p=0.059$). Consequently, both the HPS and CARDS studies provided evidence supporting the use of statin therapy for all patients with diabetes ≥ 40 years of age with or without 1 CV risk factor. The CARDS study concluded with the statement: “The debate about whether all patients with type 2 diabetes warrant statin treatment should now focus on whether any patients can reliably be identified as being at sufficiently low risk for this safe and efficacious treatment to be withheld” (52).

As a direct reflection of this evidence, the current guidelines have taken into account the impact of diabetes on lifetime risk for CVD, increased vascular aging, premature development of CVD and shorter life expectancy for the individual with diabetes. In addition, the poor predictive value of current risk models does not allow adequate selection of individuals who are likely (or not) to benefit from statin therapy. Earlier treatment is predicted to result in enhanced cost-effective benefit (52). Consequently, the current guideline recommendations are for use of statins for primary prevention of CVD at the earliest time (or youngest age), supported by clinical trial evidence when there is no other compelling reason to use statins. Given the wealth of experience with statin use, there is little safety concern for their long-term use. The cost effectiveness of statin use for primary prevention in patients with diabetes has been shown to be similar to or greater than the benefits seen in individuals with established CVD and no diabetes (51). Furthermore, the number of years of life saved is greater the earlier treatment is initiated. Now, with highly effective generic statins available, cost effectiveness will likely improve further. Consequently, a reasonable position is to recommend statin therapy for primary CVD prevention for all patients with diabetes ≥ 40 years of age.

The current guidelines continue to support the use of statins in secondary prevention in those with evidence of end organ damage (macrovascular disease, microvascular disease, particularly microalbuminuria). In addition, there are other circumstances, not specific to diabetes, that may warrant statin therapy for a particular individual based on the 2012 Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia (53).

LDL reduction should aim to achieve targets recommended in the current guidelines, and statins should be prescribed up to the maximally tolerated and approved dose. However, the use of other lipid-lowering agents in addition to statins may be necessary in some patients to achieve LDL goals.

RECOMMENDATIONS

1. All individuals with diabetes (type 1 or type 2) should follow a comprehensive, multifaceted approach to reduce cardiovascular risk, including:
 - Achievement and maintenance of healthy body weight
 - Healthy diet
 - Regular physical activity
 - Smoking cessation
 - Optimal glycemic control (usually A1C $\leq 7\%$)
 - Optimal blood pressure control ($<130/80$ mm Hg)
 - Additional vascular protective medications in the majority of adult patients (see recommendations below) [Grade D, Consensus, for type 1 diabetes; Grade D, Consensus, for children/adolescents; Grade A, Level 1 (8,9), for those with type 2 diabetes age >40 years with microalbuminuria].
2. Statin therapy should be used to reduce cardiovascular risk in adults with type 1 or type 2 diabetes with any of the following features:
 - a. Clinical macrovascular disease [Grade A, Level 1 (50)]
 - b. Age ≥ 40 years [Grade A Level 1 (50,51), for type 2 diabetes; Grade D, Consensus for type 1 diabetes]
 - c. Age <40 years and 1 of the following:
 - Diabetes duration >15 years and age >30 years [Grade D, Consensus]
 - Microvascular complications [Grade D, Consensus]
 - Warrants therapy based on the presence of other risk factors according to the 2012 Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia (53). [Grade D, Consensus]
3. ACE inhibitor or ARB, at doses that have demonstrated vascular protection, should be used to reduce cardiovascular risk in adults with type 1 or type 2 diabetes with any of the following:
 - a. Clinical macrovascular disease [Grade A, Level 1 (43,45)]
 - b. Age ≥ 55 years [Grade A, Level 1 (43,45), for those with an additional risk factor or end organ damage; Grade D, Consensus, for all others]
 - c. Age <55 years and microvascular complications [Grade D, Consensus]

Note: Among women with childbearing potential, ACE inhibitors, ARBs or statins should only be used if there is reliable contraception.

4. ASA should not be routinely used for the primary prevention of cardiovascular disease in people with diabetes [Grade A, Level 2 (36)]. ASA may be used in the presence of additional cardiovascular risk factors [Grade D, Consensus].
5. Low-dose ASA therapy (81–325 mg) may be used for secondary prevention in people with established cardiovascular disease [Grade D, Consensus].
6. Clopidogrel 75 mg may be used in people unable to tolerate ASA [Grade D, Consensus].

Abbreviations:

A1C, glycated hemoglobin; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid.

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Clinical Practice Guidelines

Screening for the Presence of Coronary Artery Disease

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Compared to people without diabetes, people with type 1 and type 2 (especially women) are at higher risk of developing heart disease, and at an earlier age. Unfortunately, a large proportion will have no symptoms before either a fatal or a nonfatal myocardial infarction (MI). Hence, it is desirable to identify patients at high risk for vascular events, especially patients with established severe coronary artery disease (CAD).
- In individuals at high risk of CAD (based on age, gender, description of chest pain, history of prior MI, abnormal resting electrocardiogram and presence of several other risk factors), exercise stress testing is useful for the assessment of prognosis.
- Exercise capacity is frequently impaired in people with diabetes due to the high prevalence of obesity, sedentary lifestyle, peripheral neuropathy (both sensory and motor) and vascular disease. For those unable to perform an exercise test, functional imaging testing, such as pharmacologic or nuclear stress imaging, may be required. Most imaging techniques have been shown useful in prospective study in order to identify patients at higher risk. However, there is, so far, no head-to-head study showing which one will be best in a cost-effective way.

Cardiovascular Disease in Diabetes

The majority (65% to 80%) of people with diabetes will die from heart disease (1,2). Compared to people without diabetes, people with diabetes (especially women) are at higher risk of developing heart disease, and at an earlier age. A high proportion of deaths occur in patients with no prior signs or symptoms of cardiovascular disease (CVD). Furthermore, people with diabetes have a high prevalence of silent myocardial ischemia, and almost one-third of myocardial infarctions (MIs) occur without recognized or typical symptoms (silent MIs) (3). The goals of screening are to improve life expectancy and quality of life by preventing MI and heart failure through the early detection of coronary artery disease (CAD).

Role of Stress Testing

Exercise stress testing is useful in patients at high risk of CAD for the assessment of prognosis and the identification of individuals who may benefit from coronary artery revascularization to improve long-term survival. The most predictive clinical observation for CAD in the person with or without diabetes is a history of chest pain or discomfort, but these features will be absent in a significant number (20% to 50%) of people with diabetes (4–10). Clinical findings, such as dyspnea on exertion, resting electrocardiogram

(ECG) abnormalities or multiple risk factors for atherosclerosis, may also indicate the presence of CAD. Recognition of such features is of clinical importance, as the outcome of CAD events is worse in people with diabetes when shortness of breath is the primary symptom (4).

The presence of CAD risk factors and resting ECG abnormalities identify patients with diabetes at increased risk of important CAD burden and abnormal stress ECG or perfusion imaging results (11). A resting ECG at the time of diagnosis of diabetes also provides a baseline to which future ECGs can be compared. In patients considered to be at high risk for CAD, a repeat resting ECG may detect changes that result from silent MI and lead to earlier detection of critical CAD. There is evidence that early screening and intervention in people with diabetes and with silent ischemia is beneficial and may improve long-term survival (7,12). Screening with exercise ECG stress testing will find 3-vessel CAD in 13% to 15% of those with abnormal stress test findings (13) and lead to angiography with revascularization in 1% to 3% of asymptomatic individuals (13–15). The Definition of Ischemia in Asymptomatic Diabetes (DIAD) study was prospectively investigating the value of routine adenosine stress myocardial perfusion scanning in asymptomatic patients with type 2 diabetes ≥ 55 years for the prevention of coronary events (10). The baseline study showed either perfusion defects or stress-induced ECG abnormalities in 22% of patients and large defects in 6%. In this study, multiple risk factors for CAD did not help to predict the patients with positive screening tests for CAD. A substantial portion of the DIAD population was defined as having intermediate/high baseline cardiovascular risk. Nevertheless, their annual cardiac event rate was low and not altered by routine screening for inducible ischemia. Yet, a randomized pilot study on the impact of stress testing to screen for CAD in asymptomatic subjects with diabetes suggested a significant reduction in cardiac death and MI (16). Larger and adequately powered studies are necessary to support this provocative observation before clinical practice is changed. However, it is important to keep in mind that the goals of screening for CAD are to improve life expectancy and quality of life by preventing MI and heart failure through early detection.

The choice of initial stress test should be based on evaluation of the resting ECG, the individual's ability to exercise, and local expertise and technology. There are data with newer technology, but the add-on effect of the latter on prognosis and quality of life is not clear. ECG abnormalities that limit the diagnostic accuracy of a stress ECG include resting ST depression (≥ 1 mm), left bundle

branch block or right bundle branch block, an intraventricular conduction defect with QRS duration >120 ms, ventricular paced rhythm or preexcitation. Individuals with these resting ECG findings should have a stress test with an imaging modality, such as scintigraphic myocardial perfusion imaging or echocardiography. The role of other imaging modalities (anatomical imaging), such as coronary computed tomography (CT), calcium score, etc., in comparison to functional imaging, needs to be determined in individuals with diabetes.

The strongest and most consistent prognostic marker identified during exercise ECG stress testing is the person's maximum exercise capacity (4). Although exercise capacity is decreased in individuals with diabetes (17,18), it is still of prognostic importance (4). Silent ischemia is most likely to occur in individuals with diabetes who are older (mean age 65 years) and have elevated total cholesterol and proteinuria (14). An ECG with ST-T abnormalities at rest has been shown to be most predictive for silent ischemia (Odds Ratio (OR) 9.27, 95% confidence interval [CI], 4.44–19.38) and was the only significant predictor of silent ischemia in women (14). The relevance of ST-T abnormalities as a predictive factor for silent ischemia emphasizes the importance of recording a resting ECG in most individuals with type 2 diabetes. An abnormal ECG may indicate the need for further investigations and result in the earlier detection and treatment of CAD (14). An abnormal exercise ECG is associated with an annual CAD event rate of 2.1%, compared with 0.97% in subjects with normal exercise ECG (16). Myocardial ischemia (whether silent or symptomatic) detected during exercise stress testing in individuals with diabetes is associated with poorer long-term survival compared to individuals without diabetes (7). Silent MI is common (40%) in older asymptomatic people with type 2 diabetes, but is more frequent (65%) in those with diabetes who also have microalbuminuria (19). People with diabetes and silent ischemia have an annual event rate for CAD of 6.2% (50% of events were new-onset angina and 50% were cardiac death or MIs) (20). Thus, silent MI is a prelude not only to symptomatic ischemia, but also to potentially fatal events. Also, it has been shown in a randomized trial in patients with silent ischemia (the vast majority of whom did not have diabetes) that long-term anti-ischemic drug therapy (~11 years follow-up) reduces cardiac events (cardiac death, non-fatal MI, acute coronary syndrome, or revascularization) with preservation of ejection fraction (21).

Exercise capacity is frequently impaired in people with diabetes due to the high prevalence of obesity, sedentary lifestyle, peripheral neuropathy (both sensory and motor), and vascular disease in this population. Individuals who cannot adequately exercise on a stress test have a poorer prognosis than those who can, regardless of the reason for this incapacity. Perfusion imaging also provides important prognostic information. Myocardial perfusion imaging has similar predictive value for cardiac death and non-fatal MI in individuals with diabetes as in those without diabetes (22). For those unable to perform an exercise ECG stress test, pharmacologic stress imaging, using dipyridamole, adenosine, or dobutamine testing, is required. Stress echocardiography and stress nuclear imaging have similar values for cardiac events in the general population (23), but no comparative data are available for the person with diabetes. In a meta-analysis of perfusion imaging, an abnormal scan was predictive of future CAD events in subjects with and without diabetes. However, the cardiac event rate in individuals with diabetes was significantly greater than in those without diabetes (23). The choice of the optimal imaging modality to detect stress-induced MI is best determined by local availability and expertise. The utility of newer CAD diagnostic modalities, such as CT angiography, coronary artery calcium scoring, and cardiac magnetic resonance imaging, is currently unknown in terms of guiding management decisions in patients with type 2 diabetes (24).

CVD in Type 1 Diabetes

Incidence and prevalence of CVD

CVD complications are important causes of morbidity and mortality among individuals with type 1 diabetes which may have been under-recognized in the past. Reported prevalence rates of CVD in type 1 diabetes vary between 3% and 12.4% (25–27). It is important to emphasize that the cardiovascular risk burden and profile of patients with type 1 diabetes differs from type 2 diabetes. The Diabetes UK longitudinal cohort study, including more than 7,000 patients with type 1 diabetes, reported that type 1 diabetes is associated with markedly increased adjusted hazard ratio for major CAD events (median follow-up of 4.7 years) in both men (HR 3.6) and women (HR 9.6). Of such, these risk increments are comparable to those observed in patients with type 2 diabetes (27). Major CVD events occurred in type 1 diabetes on average 10 to 15 years earlier compared with matched nondiabetic controls. Despite the much younger age of onset, the age-adjusted relative risk for CVD in type 1 diabetes is ten times that of the general population (28–30). The Pittsburgh Epidemiology of Diabetes Complications (EDC) study demonstrated that the incidence of major CVD events in young adults with type 1 diabetes (age 28 to 38 years) was 0.98% per year (31) and was as high as 3% per year after age 55 years, making it the leading cause of death in that population (26,27,32). Gender and race/ethnicity are important features of increased risk of CVD; male gender and African-Americans have higher rates of CVD compared to Europeans (31).

Difference from type 2 diabetes

CVD in type 1 diabetes differs from type 2 diabetes, not only in that it presents at a younger age but also in relation to sex, silent presentation and disease severity (28,29). The risk of CAD mortality is comparable in women and men with type 1 diabetes, and there is a high prevalence of silent CAD in young adults with type 1 diabetes, which may be related to cardiac autonomic neuropathy. Finally, the disease process seems to be more severe in type 1 diabetes. Compared with nondiabetic controls, patients with type 1 diabetes are more likely to have severe coronary stenosis, involvement of all 3 major coronary arteries and distal segment disease, resulting in major cardiovascular events with poor outcome and/or early development of heart failure (28,29).

Coronary artery disease and cerebrovascular disease

CAD appears more common than stroke. The cumulative incidence of CAD ranges between 2.1% (26) and 19% (33) depending on the characteristics of the population studied. For the most part, studies report incidences around 15% (27,34,35). Mortality rates from CAD are reported between 6 and 8% (33,35), are likely higher in men than women (36), and in those >40 years of age compared to those <40 years of age (36). Stroke is still an important outcome in type 1 diabetes; the cumulative incidence of stroke was 3.3% over 6 years among African-Americans (27), 5.9% over 20 years in the WESDR (Wisconsin Epidemiologic Study of Diabetic Retinopathy) (34), and 0.74% per year in the EURODIAB Study (26). Also, prevalence of silent brain infarcts or leukoariosis is extremely high (34.5%) in type 1 diabetes (37).

Peripheral vascular disease

Peripheral vascular disease (PVD) is an important vascular complication of type 1 diabetes. Incidence rates of lower extremity amputation vary by age from 3.6 per 1000 person-years among individuals 25 to 44 years of age to as high as 7.2% (38). By

age 65, the cumulative probability of PVD is 11% in women and 20.7% in men (39). Compared to the general population, the rate of PVD among those with type 1 diabetes may be very high (39). If one considers ankle-brachial index (ABI) <0.9 as the criterion for the presence of peripheral atherosclerotic disease instead of overt clinical events, 45.6% of participants from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study developed PVD (41). Predictors of PVD include increasing age, male gender, history of sores or ulcers, diastolic blood pressure, low-density lipoprotein, glycated hemoglobin (A1C), diabetes duration, hypertension, albumin excretion rate, glomerular filtration rate, smoking and retinopathy (38,40,41). In addition to the clinical endpoints of CAD, stroke and PVD, subclinical carotid disease may be commonly associated with type 1 diabetes. Compared to age-/sex-matched healthy controls, greater carotid intima-media thickness (IMT) has been observed in studies of children with type 1 diabetes with a mean age as young as 11 years (42–45).

Time course of events

Although CAD rarely presents within the first 20 years of diagnosis, by age 30 years, many individuals will have had type 1 diabetes for 20 years and rates of CVD begin to approach the considered “high-risk” category (46). The recent decline in diabetic kidney disease has not been accompanied by a corresponding fall in CAD rates. Indeed, no temporal decline was noted for the cumulative incidence of MI/CAD death at 20, 25, or 30 years’ duration of diabetes in the Pittsburgh EDC, despite at least a 50% decrement of the cumulative incidence of overt nephropathy (31). In fact, nephropathy or microalbuminuria no longer precedes CAD in the majority of cases. In the EDC study, there was no difference in the cumulative incidence of CAD stratified according to year of diagnosis (1950–1980), despite substantial declines in renal failure as well as decline in overall mortality over the same time period (31). The DCCT intensive therapy intervention had a significant impact on the age and the duration of diabetes exposure at onset of CVD, despite the fact that no overt CVD was apparent at baseline (47). Thus, despite the well-recognized increase in CVD risk associated with proteinuria, it clearly explains only a portion of the CVD risk. In the DCCT study, the treatment group effect of intensive treatment therapy on CVD risk persisted after adjustment for microalbuminuria (hazard ratio [HR] 0.62) and albuminuria (HR 0.58), suggesting that, although diabetic kidney disease is important, differences in mean A1C are clearly significant drivers (47). In the same way, only 15% of the Oslo Study population had microalbuminuria, despite the fact that all participants had at least subclinical CAD (48). In the Pittsburgh EDC study, myocardial ischemia by ECG, as the initial manifestation of CAD, was less common and a documented MI as more common in those with prior renal disease compared to those without (49).

Effect of gender

Compared to women without diabetes, women with type 1 diabetes had a 3.5 times higher risk of having coronary artery calcifications (50). While standardized mortality rates from ischemic heart disease were higher in men than women at all ages in the general population, there was no difference in mortality from ischemic heart disease in men and women with type 1 diabetes <40 years of age (36). Men with type 1 diabetes age ≥40 years had a higher mortality rate from CVD than women with type 1 diabetes (51). In a large Norwegian cohort study, mortality rates from ischemic heart disease were higher in women with type 1 diabetes than in men or women without diabetes. However, men with type 1 diabetes had higher mortality rates than women with type 1

diabetes (52). The most recent population-based cohort study showed different results (53). This study found that among those with type 1 diabetes, women had a 2.5 to 3 times higher standardized mortality rate from CVD than men with type 1 diabetes. Although not all the findings are consistent, the common thread in all these studies is that the presence of type 1 diabetes (as well as in type 2 diabetes) seems to dramatically increase the risk for CVD, particularly in women.

Testing for CVD in type 1 diabetes

In the absence of data to the contrary, 1 approach to identifying CVD in patients with type 1 diabetes is to apply the same CAD risk assessment and diagnostic strategies used in type 2 diabetes (see discussion above) or in the population in general (54). This, however, does not support routine CAD screening beyond resting ECGs in patients with diabetes who do not have cardiovascular symptoms or an abnormal ECG, favouring instead global risk factor assessment and treatment.

Patients with type 1 diabetes who have symptoms suggestive of CAD, an abnormal resting ECG or clustering of cardiac risk factors yielding an intermediate or high global risk estimate, acknowledging that risk scores are more or less accurate in type 1 diabetes, should have additional testing for CAD (54,55). For patients able to walk on a treadmill without significant baseline ST segment abnormality (see discussion for type 2 diabetes), exercise treadmill testing remains the first-line diagnostic test due to the high cost efficacy and widespread availability. However, treadmill testing may not be possible due to the burden of peripheral neuropathy, foot pathology, lower extremity amputation and ECG abnormalities

RECOMMENDATIONS

1. A baseline resting ECG should be performed in individuals with any of the following [Grade D, Consensus]:
 - Age >40 years
 - Duration of diabetes >15 years and age >30 years
 - End organ damage (microvascular, macrovascular)
 - Cardiac risk factors
2. A repeat resting ECG should be performed every 2 years in patients with diabetes [Grade D, Consensus].
3. People with diabetes should undergo investigation for CAD by exercise ECG stress testing as the initial test [Grade D, Consensus] in the presence of the following:
 - Typical or atypical cardiac symptoms (e.g. unexplained dyspnea, chest discomfort) [Grade C, Level 3 (4)]
 - Signs or symptoms of associated diseases
 - Peripheral arterial disease (abnormal ankle-brachial index) [Grade D, Level 4 (9)]
 - Carotid bruits [Grade D, Consensus]
 - Transient ischemic attack [Grade D, Consensus]
 - Stroke [Grade D, Consensus]
 - Resting abnormalities on ECG (e.g. Q waves) [Grade D, Consensus]
4. Pharmacological stress echocardiography or nuclear imaging should be used in individuals with diabetes in whom resting ECG abnormalities preclude the use of exercise ECG stress testing (e.g. left bundle branch block or ST-T abnormalities) [Grade D, Consensus]. In addition, individuals who require stress testing and are unable to exercise should undergo pharmacological stress echocardiography or nuclear imaging [Grade C, Level 3 (22)].
5. Individuals with diabetes who demonstrate ischemia at low exercise capacity (<5 metabolic equivalents [METs]) on stress testing should be referred to a cardiac specialist [Grade D, Consensus].

Abbreviations:

CAD, coronary artery disease; ECG, electrocardiogram.

as left ventricular hypertrophy in the patient population with type 1 diabetes. Pharmacological stress imaging studies, such as nuclear myocardial perfusion imaging or pharmacological stress echocardiography may be required. Sophisticated testing has been reported in patients with type 1 diabetes. Coronary artery calcium, assessed by CT imaging, is common (56,57) and more frequent in patients with type 1 diabetes than in those without, and is seen at higher rates than in those without diabetes. Progression of coronary artery calcium is reduced by intensive glycemic control (57). The presence of coronary artery calcium is independently associated with increased prevalence of CAD, even after adjustment for traditional risk factors (56), and test performance in patients with type 1 diabetes is comparable to that of the general population. In the Pittsburgh EDC longitudinal study, 302 adults with type 1 diabetes, with a mean age of 38 years, underwent coronary artery calcium screening. The prevalence of coronary artery calcium was 11% in patients <30 years of age and as high as 88% among those 50 to 55 years. Coronary artery calcium was independently associated with prevalent CAD across the entire cohort, with a stronger graded association in men than in women. While coronary artery calcium assessment has proven to predict subsequent cardiovascular risk in the general population and in cohorts of patients with type 2 diabetes (58), no data are yet available to determine the utility of coronary artery calcium assessment for risk prediction in type 1 diabetes. Women with type 1 diabetes had just as much coronary artery calcification as men; women without diabetes have less coronary calcium than men (50).

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Clinical Practice Guidelines

Dyslipidemia

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- The beneficial effects of lowering low-density lipoprotein cholesterol (LDL-C) with statin therapy apply equally well to people with diabetes as to those without the disease.
- The primary treatment goal for people with diabetes is LDL-C ≤ 2.0 mmol/L, which is generally achievable with statin monotherapy.
- Achievement of the primary goal may require intensification of lifestyle changes and/or statin therapy and, on occasion, the addition of other lipid-lowering medications.

Dyslipidemia in Diabetes

Diabetes is associated with a high risk of vascular disease (i.e. 2- to 4-fold greater risk than that of individuals without diabetes). In fact, cardiovascular disease (CVD) is the primary cause of death among people with type 1 and type 2 diabetes (1–3). Aggressive management of all CVD risk factors, including dyslipidemia, is, therefore, generally necessary in individuals with diabetes (4). The most common lipid pattern in people with type 2 diabetes consists of hypertriglyceridemia (hyper-TG), low high-density lipoprotein cholesterol (HDL-C), and relatively normal plasma concentrations of low-density lipoprotein cholesterol (LDL-C). However, in the presence of even mild hyper-TG, LDL-C particles are typically small and dense and may be more susceptible to oxidation. In addition, chronic hyperglycemia promotes the glycation of LDL-C, and both glycation and oxidation are believed to increase the atherogenicity of LDL-C. Both of these processes may impair function and/or enhance atherogenicity even in those with type 1 diabetes with a normal lipid profile. Table 1 lists the components of dyslipidemia associated with diabetes (5,6). Many of these abnormalities also are seen in patients with metabolic syndrome (7,8).

Risk Assessment of Individuals with Diabetes

A detailed overview of risk assessment deciding in whom to use statin therapy is provided in the Vascular Protection chapter (p. S100). Principles of risk assessment also are discussed in the 2012 Canadian Cardiovascular Society (CCS) Guidelines for the Management of Dyslipidemia (9), and efforts were made to ensure consistency between the guidelines.

Screening

The burden of dyslipidemia is high in people with diabetes. A national cross-sectional chart audit study of 2473 Canadians with type 2 diabetes revealed that 55% of individuals with a diabetes diagnosis of ≤ 2 years' duration also had dyslipidemia. This proportion rose to 66% in those with diabetes for ≥ 15 years (10). Therefore, a fasting lipid profile (total cholesterol [TC], HDL-C, TG and calculated LDL-C) should be conducted at the time of diagnosis of diabetes, and, if the results are initially normal, the assessment should be repeated annually or as clinically indicated. If treatment for dyslipidemia is initiated, more frequent testing is warranted. A fast of > 8 hours may be inappropriate for individuals with diabetes, especially if long-acting basal insulin is part of their treatment regimen. Under these circumstances, non-HDL cholesterol (TC minus HDL-C) or apolipoprotein B (apo B) measurements (see below), which are valid, even in the nonfasting state, may be used. For screening in children and adolescents, please refer to the chapters dedicated to diabetes in children and adolescents, p. S153 and S163.

Lifestyle Modification

Lifestyle interventions remain a key component of CVD prevention strategies and of diabetes management in general. Achievement of ideal weight and aerobic activity level, adoption of an energy-restricted, compositionally well-balanced diet that is low in cholesterol, saturated and trans fatty acids and refined carbohydrates, inclusion of viscous fibres, plant sterols, nuts and soy proteins, use of alcohol in moderation and smoking cessation all are fundamental considerations to improve glycemic control, the overall lipid profile and, most importantly, to reduce CVD risk (11–22). Each of these is discussed in more detail in accompanying chapters (Physical Activity and Diabetes, p. S40; Nutrition Therapy, p. S45; Weight Management in Diabetes, p. S82).

LDL-C

A number of studies and meta-analyses have shown that the degree of LDL-C lowering with statins and the beneficial effects of lowering LDL-C apply equally well to people with and without diabetes (23–34). Large, published trials have demonstrated the benefits of statin therapy in both the primary and secondary prevention of vascular disease, and subgroup analyses of these

Table 1

Dyslipidemia components associated with type 2 diabetes and metabolic syndrome (5)

- Increased TG and TG-rich lipoproteins
- Increased postprandial TG
- Low HDL-C
- Low apo AI
- Small HDL, prebeta-1 HDL, alpha-3 HDL
- Increased apo B
- Increased LDL particle number
- Small, dense LDL
- Increased apo C-III
- Increased non-HDL-C
- Increased oxidized and glycated lipids

Apo, apolipoprotein; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; TG, triglyceride.

studies have shown similar benefits in subsets of participants with diabetes (23–25). Across all subgroups, statin therapy provides the same relative risk reduction in terms of outcomes, but the absolute benefit depends on the baseline level of absolute risk, which is typically increased in people with diabetes. Subgroup analyses from statin trials also have shown similar benefits of LDL-C lowering, regardless of baseline LDL-C (26,28). Therefore, statin use should be considered for any person with diabetes at risk of a vascular event. In the very small group of lower-risk individuals with type 2 diabetes, the relative reduction in CVD risk with statin therapy is likely to be similar to that seen in those at higher global risk for CVD, but the absolute benefit from statin therapy is predicted to be smaller. However, the global CVD risk of these individuals will increase with age and in the presence of additional CVD risk factors. Therefore, repeated monitoring of the CVD risk status of patients with diabetes (as outlined in the Screening section above) is recommended.

The results of the Heart Protection Study (HPS), which compared simvastatin 40 mg daily to placebo, provide considerable insight into the importance of LDL-C lowering in the general population and, in particular, patients with diabetes (27). In the overall study involving >20 000 subjects, similar risk-ratio reductions were observed in subjects with baseline LDL-C >3.5 mmol/L, 3.0 to 3.5 mmol/L and <3.0 mmol/L. In the subgroup with diabetes (n=5963, including 615 people with type 1 diabetes), treatment with 40 mg simvastatin daily resulted in a 27% reduction in cardiovascular (CV) events and a 25% reduction in stroke relative to treatment with placebo. The risk reduction was similar in the cohorts with and without diabetes, and the treatment benefit was independent of baseline HDL-C and LDL-C levels (LDL-C <3.0 mmol/L or ≥3.0 mmol/L), sex, vascular disease, type of diabetes (type 1 vs. type 2) and glycated hemoglobin (A1C) (26). These results emphasized the benefits of statin treatment irrespective of the pre-existing serum LDL-C level. However, HPS did not demonstrate the effect of treating LDL-C to any particular preset target level. In a post hoc analysis of the entire study sample, the investigators found similar event reductions in individuals with baseline LDL-C values <2.6 mmol/L. However, this analysis was not performed in the subgroup of people with diabetes who had baseline LDL-C values <2.6 mmol/L because of insufficient power. These analyses also have implications for patients with diabetes whose spontaneous LDL-C may already be below treatment goals. In this setting, treatment with a moderate dose of statin, such as simvastatin 40 mg, or equivalent doses of other statins (average LDL-C reduction of approximately 30% to 40%), would be expected to provide comparable relative risk reductions to those seen with statin treatment initiated at higher baseline levels of LDL-C.

The Collaborative Atorvastatin Diabetes Study (CARDS) was the first completed statin trial to be conducted exclusively in people with type 2 diabetes without known vascular disease (28). The mean baseline LDL-C of the study population was 3.1 mmol/L, and

all subjects had at least 1 CVD risk factor in addition to diabetes. CARDS demonstrated that treatment with atorvastatin 10 mg daily was safe and highly efficacious in reducing the risk of a first CV event, including stroke. Treatment resulted in a mean LDL-C of 2.0 mmol/L and was associated with a reduced risk for CV events and stroke of 37% and 48%, respectively. These study findings support the value of treating even so-called “normal” LDL-C levels in people with type 2 diabetes and no known vascular disease. As mentioned previously, all CARDS subjects had at least 1 additional CVD risk factor (i.e. history of hypertension, retinopathy, microalbuminuria or macroalbuminuria, or current smoking), a profile that applies to an estimated 70% to 80% of people with type 2 diabetes (28,35). Results from the United States (US) Third National Health and Nutrition Examination Survey (NHANES III) indicate that 82% of people with diabetes and no clinically evident coronary artery disease (CAD) have at least 1 of the CARDS entry criteria risk factors (28). The CARDS investigators concluded that the study findings “challenge the use of a particular threshold level of LDL-C as the sole arbiter of which individuals with type 2 diabetes should receive statin therapy.... The absolute risk, determined by other risk factors in addition to LDL-C, should drive the target levels” (28,37). Indeed, the investigators questioned whether any individual with type 2 diabetes can be considered at sufficiently low risk for statin therapy to be withheld (28). A subanalysis of the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA) revealed similar benefits of atorvastatin 10 mg vs. placebo in people with type 2 diabetes, hypertension and at least 3 additional risk factors (36).

The Atorvastatin Study for the Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) assessed the effect of atorvastatin 10 mg daily vs. placebo on CVD prevention in 2410 people with type 2 diabetes (38). Although originally designed as a secondary prevention trial, the protocol underwent several changes, including the addition of subjects without known CAD and the eventual conversion of all patients with known CAD to open-label, lipid-lowering medication. Over the 4-year study period, mean LDL-C was reduced by 29% in the atorvastatin group compared to placebo ($p<0.0001$). The composite primary endpoint was reduced by 13.7%; however, this finding was not statistically significant and was generally considered to be related to the methodological limitations of the study design and the protocol changes.

In the subgroup with diabetes (n=1051) of the Treating to New Targets (TNT) trial conducted in individuals with stable CAD, those subjects treated with atorvastatin 80 mg daily who achieved a mean LDL-C of 2.0 mmol/L had 25% fewer major CVD events than did those treated with atorvastatin 10 mg daily who achieved a mean LDL-C of 2.5 mmol/L ($p=0.026$) (30). Intensive therapy with atorvastatin 80 mg daily also reduced the rate of all CVD and cerebrovascular events compared to atorvastatin 10 mg daily. Notably, an increased event rate for all primary and secondary efficacy outcomes was noted in the diabetes subgroup compared to the overall study population. This finding provides yet further evidence that people with diabetes and CAD are at extremely high risk of subsequent CVD events.

The Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis of >170 000 statin-treated subjects found that for every 1.0 mmol/L reduction in LDL-C there was an approximate 20% reduction in CVD events, regardless of baseline LDL-C (39). The proportional reductions were very similar in all subgroups, including those with diabetes without pre-existing vascular disease (39). In fact, the CTT meta-analysis of >18 000 subjects with diabetes from 14 randomized statin trials found that the effects of statins on all fatal and nonfatal CV outcomes were similar for participants with or without diabetes (40). The updated CTT meta-analysis of 170 000 subjects showed that additional reductions in

LDL-C (down to approximately 1.0 to 2.0 mmol/L) with more intensive therapy further reduced the incidence of major vascular events and that these reductions could be achieved safely, even in individuals with lower baseline LDL-C levels (41).

Although the linear relationship between the proportional CVD risk reduction and LDL-C lowering would suggest that there is no lower limit of LDL-C or specified LDL-C target (as the CTT authors suggest), the clinical trial evidence summarized above would suggest that LDL-C ≤ 2.0 mmol/L is currently the most appropriate target for high-risk individuals. In the vast majority of people, this target can be achieved with either a statin alone or a statin in combination with another lipid-lowering agent. However, there is presently less support for the latter recommendation. For example, there are currently no completed clinical outcome trials using ezetimibe solely in patients with diabetes; however, a mechanistic trial using carotid intima-medial thickness (CIMT) as a surrogate endpoint has been reported in adult native North American subjects with diabetes (42,43). In this study, reducing LDL-C to aggressive targets resulted in a similar regression of CIMT in patients who attained equivalent LDL-C reductions from a statin alone or a statin plus ezetimibe. Patients with diabetes and renal dysfunction or those requiring dialysis constituted 23% of the study population of the recently reported Study of Heart and Renal Protection (SHARP) trial. The study showed that LDL-C reductions with simvastatin plus ezetimibe were associated with reductions in the incidence of major atherosclerotic events vs. placebo. Subgroup and heterogeneity analysis revealed no difference in risk reduction between patients with or without diabetes using the statin/ezetimibe combination (44).

Tables 2A and 2B summarize considerations that should guide the choice of pharmacological agent(s) for the treatment of dyslipidemia. Colesevelam, a bile acid sequestrant now approved in Canada, appears to have an ancillary effect on lowering A1C (45,46). People with impaired glucose tolerance (IGT) (particularly in the context of metabolic syndrome) are at significant risk for the development of CVD. Indeed, some studies suggest that their vascular risk is almost as high as individuals with existing type 2 diabetes (47,48). No clinical trials of lipid-lowering agents have been conducted exclusively in people with IGT; however, given their increased CVD risk, it is reasonable to consider treating this population to the same targets as people with diabetes (49). To reduce the CVD morbidity and mortality associated with prediabetes and metabolic syndrome, an aggressive approach aimed at associated CVD risk factors, including dyslipidemia, is warranted. Lifestyle interventions aimed at reducing the risk of developing both type 2 diabetes and CAD are essential.

Additional lipid markers of CVD risk

The TC/HDL-C ratio is a sensitive and specific index of CVD risk (53) and is considered to be an important determinant of the need for lipid-lowering therapy. An elevated TC/HDL-C ratio is usually associated with a low HDL-C and/or elevated TG, both of which are commonly seen in individuals with diabetes and often in individuals without diabetes, even in the face of an optimal LDL-C of ≤ 2.0 mmol/L. The elevated TC/HDL-C ratio is considered to represent a source of lipid-derived, residual risk in treated patients. This form of dyslipidemia is considered more responsive to lifestyle modification (e.g. an increase in physical activity and weight reduction) and improvements in glycemic control than is an isolated LDL-C elevation. Accordingly, initial treatment should consist of intensifying lifestyle modification strategies and improving glycemic control through the use of glucose-lowering therapies as needed.

To reduce the residual CVD risk despite statin therapy, the potential benefit of additional lipid-lowering efforts with adjuvant pharmacotherapy has garnered tremendous interest. However,

Table 2A

First-line therapy to achieve a primary lipid target of LDL-C ≤ 2.0 mmol/L

Statins*		
Generic name [†]	Trade name	Considerations
Atorvastatin	Lipitor and generics	Statins are drugs of choice to lower LDL-C and have modest TG-lowering and HDL-C raising effects at higher doses
Fluvastatin	Lescol	
Lovastatin	Mevacor and generics	
Pravastatin	Pravachol and generics	
Rosuvastatin	Crestor and generics	
Simvastatin	Zocor and generics	

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

Note: Physicians should refer to the most current edition of the *Compendium of Pharmaceuticals and Specialties* (Ottawa, ON: Canadian Pharmacists Association) for product monographs and complete prescribing information.

* Prevention of statin-induced myopathy requires attention to factors that increase risk, such as age >80 years (especially women); small body frame and frailty; higher dose of statin; multisystem diseases (e.g. chronic renal insufficiency due to diabetes); multiple medications; hypothyroidism; perioperative periods; alcohol abuse; excessive grapefruit juice consumption; and specific concomitant medications, such as fibrates (especially gemfibrozil) (refer to specific statin package inserts for others) (50).

[†] Listed in alphabetical order.

2 recent studies, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (cohort consisted exclusively of patients with diabetes) and the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) trial (34% of this study cohort had diabetes), highlight the importance of maintaining LDL-C lowering as the primary focus of treatment, particularly with statins (54,55). The goal of both trials was to optimize the residual dyslipidemic profile of statin-treated patients with LDL-C at or near target levels through the use of agents known to lower TG and raise HDL. Fenofibrate was used in ACCORD and niacin was used in AIM-HIGH. Both of these second-line adjunctive therapies failed to show any added clinical benefit compared to statin therapy alone. Therefore, neither niacin nor fibrates can be recommended as routine adjunctive therapy in patients already meeting LDL-C targets with statins since these agents appear to have no additional impact on macrovascular disease endpoints. In some patients, however, these agents may be required to help achieve LDL-C targets. The results of 4 recent meta-analyses examining the effects of fibrate therapy on CV outcomes found that fibrates may be particularly beneficial in patients with atherogenic dyslipidemia, which is characterized by elevated TG, small LDL particles and reduced HDL-C (56–59).

Also, recent evidence suggests that fibrate therapy may help reduce the microvascular complications associated with diabetes (i.e. retinopathy and nephropathy), and it appears as if these beneficial effects are not solely due to the lipid changes induced by this drug class (51,60,61). For example, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study found that long-term treatment with fenofibrate reduced albuminuria and slowed estimated glomerular filtration rate loss over 5 years, despite initially and reversibly increasing plasma creatinine (51). Furthermore, if residual hyper-TG is high enough to impart a risk of pancreatitis, fibrates or niacin may be warranted. If HDL-C is low and LDL-C is not at target, niacin in either the immediate-release or extended-release formulation may be effective and is generally safe (62–65). Although niacin can cause deterioration of glycemic control (62), there is now evidence that this particular adverse effect may have been overemphasized (63,66).

Specific TG targets are not provided in these guidelines because there are very few clinical trial data to support recommendations based on any specific plasma TG level. Nonetheless, a TG level <1.5 mmol/L is considered optimal since, below this level, there are fewer associated metabolic abnormalities, such as low HDL-C, small dense LDL particles and postprandial lipemia (32,67–70).

Table 2B

Other lipid-modifying medications

Drug class* Generic name* (trade name)	Principal effects	Other considerations
Bile acid sequestrants	• Lowers LDL-C	• GI intolerance, which worsens with increasing doses
• Cholestyramine resin (Questran)		• May elevate TG
• Colesevelam (Lodalis)		• Colesevelam has A1C-lowering effect
• Colestipol HCl (Colestid)		
Cholesterol absorption inhibitor	• Lowers LDL-C	• Less effective than statins as monotherapy
• Ezetimibe (Ezetrol)		• Effective when used in combination with a statin to further lower LDL-C (34)
Fibrates	• Lowers TG	• May increase creatinine and homocysteine levels; however, favourable effects on renal function have been noted with long-term fenofibrate treatment (51)
• Bezafibrate (Bezalip SR and generic 200 mg)	• Variable effect on LDL-C	• Do not use gemfibrozil in combination with a statin due to increased risk of myopathy and rhabdomyolysis†
• Fenofibrate (micronized/microcoated/nano crystals) (Lipidil Supra, Lipidil EZ, and generics)	• Highly variable effect on HDL-C (more effective at raising HDL-C when baseline TG is high)	
• Gemfibrozil (Lopid)		
Nicotinic acid	• Raises HDL-C	• Can cause dose-related deterioration of glycemic control
• Extended-release niacin (Niaspan, Niaspan FCT)	• Lowers TG	• Extended-release niacin has similar efficacy and better tolerability than immediate-release niacin
• Immediate-release niacin (generic, nonprescription)	• Lowers LDL-C	• Long-acting niacin should not be used due to increased hepatotoxicity and decreased efficacy (52)
• Long-acting (e.g. "no-flush") niacin (generic, nonprescription)		
not recommended		

A1C, glycated hemoglobin; GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

Note: Physicians should refer to the most current edition of the *Compendium of Pharmaceuticals and Specialties* (Ottawa, ON: Canadian Pharmacists Association) for product monographs and complete prescribing information.

* Listed in alphabetical order.

† See Table 2A footnote for prevention of myopathy.

While several studies have shown that fibrate therapy is associated with CVD prevention, there is much less evidence for CVD risk reduction with fibrates relative to statins, specifically in people with diabetes (71–75). In some studies, no statistically significant reduction in the primary endpoint was demonstrated with fibrate therapy (76,77). Combination therapy with fenofibrate (78,79) or bezafibrate plus a statin appears to be relatively safe if appropriate precautions are taken (Tables 2A and 2B), but, as discussed above, the efficacy of these approaches in improving patient outcomes has not been established (54). Although combination treatment with fenofibrate appears to be safe (54,76), statins should not be used in combination with gemfibrozil due to an increased risk of myopathy and rhabdomyolysis (80).

To reduce the risk of pancreatitis and to do so rapidly, a fibrate is recommended for individuals with fasting TG levels >10.0 mmol/L who do not respond to other measures, such as intensified glycemic control, weight loss and restriction of refined carbohydrates and alcohol. When there is no overriding concern for acute pancreatitis and when there is evidence of hyper-TG in association with an elevated apo B or high non-HDL-C, it would be reasonable to consider a statin as first-line therapy with the subsequent addition of a fibrate or niacin as needed.

As discussed above, evidence has emerged to support the use of apo B in the management of patients with dyslipidemia (9,37). Mechanistically, it is important to consider that there is one apo B molecule per LDL, lipoprotein (a) [Lp(a)], very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) particle, all of which are atherogenic. Apo B has repeatedly been shown to be a better risk marker for CVD events than LDL-C. Consequently, the measurement of apo B and its monitoring in response to lipid-lowering therapy have been advocated by some authors (9,37,81). The measurement of apo B is most clinically useful in the individual with hyper-TG since it provides an indication of the total number of atherogenic lipoprotein particles in the circulation. Because hyper-TG is commonly seen in people with diabetes, knowledge of the apo B level may guide the aggressiveness with which lipid-lowering therapy is pursued (i.e. more aggressive therapy in individuals with an elevated apo B level). Based on available evidence, an optimal level of apo B can be considered to be at least ~<0.9 g/L (82) or, as supported by the CARDS study in subjects with diabetes, ≤0.8 g/L (37).

Further important information has emerged from CARDS with respect to alternative targets and therapeutic goals (28). In an extensive analysis of both spontaneous and statin-induced changes in LDL-C, apo B concentrations and non-HDL-C, apo B was found to be a more consistent goal for statin treatment than LDL-C or non-HDL-C (37). In statin-treated patients, the average apo B concentration in the subgroup with concomitant LDL-C ≤2 mmol/L was 0.708 g/L with an upper 95% confidence limit of 0.720 g/L.

The calculated non-HDL cholesterol (TC minus HDL-C) has features similar to apo B: the calculation is valid in the nonfasting state, and it relates mainly to cholesterol contained in atherogenic particles, each of which has an apo B [atherogenic triglyceride-rich elements, such as VLDL and IDL, LDL-C, and Lp(a)]. A linear relationship between apo B and non-HDL exists over a broad range (83). A non-HDL-C level of 2.6 mmol/L is approximately equal to an apo B of 0.8 g/L and may be considered alternate goals of therapy. Although there is general agreement that non-HDL and apo B are more predictive of CV risk than LDL-C, controversy exists regarding the superiority of either apo B or non-HDL, presumably because they are so closely correlated. Since non-HDL is available without further cost or separate assay, it is attractive to consider it as supported by several analyses (84–86).

Apo AI is a surrogate marker of the number of HDL particles in the circulation. The relationship between apo AI and HDL is more complicated than the 1:1 relationship of the number of apo B molecules and atherogenic particles because there may be 2 to 4 apo AI molecules per HDL particle. The apo B/apo AI ratio has been proposed to be the best single predictor of CVD risk, accounting for 50% of population-attributable events in an ethnically diverse population without diabetes (although its comparison to the TC/HDL-C ratio as a risk predictor was not reported in this study) (87). Currently, in Canada, however, the measurement of apo AI is even less widely available than apo B, thus limiting the practical value of both this measurement and the apo B/apo AI ratio for clinical decision making.

In summary, in order to reduce CVD risk among individuals with diabetes, it is important to understand the atherogenicity of small, dense LDL particles, remnant lipoproteins, TG-rich particles and the antiatherogenic role of HDL particles. It is also important to improve these metabolic parameters through lifestyle

modifications, improvements in glycemic control and, perhaps, pharmacotherapy, when indicated. Despite academic interest in various lipid parameters, it is of paramount importance to realize that the current best outcome evidence for minimizing the atherogenic impact of lipid abnormalities in patients with diabetes is to remain focused on achieving very low plasma concentrations of LDL-C, typically with statin-centred therapy, as this conclusion is based on the most extensive clinical trial evidence. For patients who are not at goal, despite maximally tolerated statin therapy or in the case of statin intolerance, the use of second-line LDL-C-lowering therapies (Table 2A) can be considered, including ezetimibe, bile acid sequestrants or niacin.

Statin Therapy and Incident Diabetes

Although statins are the cornerstone of lipid-altering therapy for CVD risk reduction in people with or without diabetes, recent evidence has suggested that chronic statin use is associated with an increased risk of incident diabetes. The interplay between statin therapy and incident diabetes was highlighted in a prespecified analysis of the West of Scotland Coronary Prevention Study (WOSCOPS), which actually showed a decrease in the incidence of new-onset diabetes with statin therapy (88). In contrast, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) showed an increase in incident diabetes (89). Several meta-analyses suggest that there is indeed a small overall increase in diabetes with chronic statin use (90,91) and that this risk may be related to the statin dose (92).

Although this finding is of little relevance to patients with established diabetes, it may be of relevance to patients who are at risk for developing diabetes irrespective of statin treatment, such as those who are obese and/or who manifest metabolic syndrome. However, as discussed earlier, even these patients with risk factors for the development of diabetes enjoy a marked benefit in CVD risk reduction through the LDL-C-lowering effects of statins,

which appears to far outweigh any small risk of new-onset diabetes (47,48). Accordingly, these recent analyses do not affect the recommendation that statins are the preferred agents for lowering LDL-C in most instances, including in patients with established diabetes or in those with risk factors for developing the disease.

Other Relevant Guidelines

Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome, p. S8
Physical Activity and Diabetes, p. S40
Nutrition Therapy, p. S45
Weight Management in Diabetes, p. S82
Vascular Protection in People with Diabetes, p. S100
Screening for the Presence of Coronary Artery Disease, p. S105
Treatment of Hypertension, p. S117
Management of Acute Coronary Syndromes, p. S119
Treatment of Diabetes in People with Heart Failure, p. S126
Type 1 Diabetes in Children and Adolescents, p. S153
Type 2 Diabetes in Children and Adolescents, p. S163

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RECOMMENDATIONS

- A fasting (8-hour fast) lipid profile (TC, HDL-C, TG, and calculated LDL-C) or nonfasting lipid profile (apo B, non-HDL-C calculation) should be measured at the time of diagnosis of diabetes. If lipid-lowering treatment is not initiated, (see Vascular Protection chapter, p. S100, for indications) repeat testing is recommended yearly. More frequent testing (every 3–6 months) should be performed after treatment for dyslipidemia is initiated [Grade D, Consensus].
- For patients with indications for lipid-lowering therapy (see Vascular Protection chapter, p. S100), treatment should be initiated with a statin [Grade A, Level 1 (26,28), to achieve LDL-C \leq 2.0 mmol/L [Grade C, Level 3 (40)].
- In patients achieving goal LDL-C with statin therapy, the routine addition of fibrates or niacin for the sole purpose of further reducing CV risk should not be used [Grade A, Level 1 (54,55)].
- For individuals not at LDL-C target despite statin therapy as described above, a combination of statin therapy with second-line agents may be used to achieve the LDL-C goal [Grade D, Consensus].
- For those who have serum TG $>$ 10.0 mmol/L, a fibrate should be used to reduce the risk of pancreatitis (Grade D, Consensus) while also optimizing glycemic control and implementing lifestyle interventions (e.g. weight loss, optimal dietary strategies, reduction of alcohol).

Abbreviations:

apo B, apolipoprotein B; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

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Clinical Practice Guidelines

Treatment of Hypertension

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- People with diabetes should be treated to achieve a blood pressure (BP) <130/80 mm Hg.

Introduction

Hypertension affects the vast majority of individuals with type 2 diabetes and many of those with type 1 diabetes also. Its pathogenesis is complex, involving interactions between genetic predisposition and a range of environmental factors that include sodium retention, obesity, premature arterial stiffening and endothelial dysfunction (1). Not only are patients with diabetes more likely to have coexistent hypertension, but, for any given systolic pressure, diabetes also is associated with an increase in the age-adjusted cardiovascular death rate.

Fortunately, several, large-scale, multicentre clinical trials have shown that antihypertensive therapy is highly effective at reducing death and disability in people with diabetes (1). These clinical trials also have provided some guidance in the choice of antihypertensive therapy, particularly among those with nephropathy or at high cardiovascular risk. Most recently, much discussion has focused on selecting an appropriate, evidence-based target for systolic blood pressure (SBP). These discussions have, to a large extent, been precipitated by the findings of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which compared the effects of targeting SBP <140 mm Hg with that <120 mm Hg (2). While the primary outcome (a composite of myocardial infarction, stroke, and cardiovascular death) was not significantly different between the 2 groups, stroke, a prespecified outcome, was reduced by 41% in the group targeted to achieve the <120 mm Hg systolic target. The findings of ACCORD are further supported by 2 meta-analyses, which similarly show that (3,4):

1. Little, if any, additional reduction in cardiac events is achieved by lowering SBP to <140 mm Hg.
2. Additional reduction in stroke can be achieved by lowering SBP to <120 mm Hg.

RECOMMENDATIONS

1. Persons with diabetes mellitus should be treated to attain SBP <130 mm Hg [Grade C, Level 3 (6,7)] and DBP <80 mm Hg [Grade B, Level 1 (8)]. (These target BP levels are the same as the BP treatment thresholds). Combination therapy using 2 first-line agents may also be considered as initial treatment of hypertension [Grade C, Level 3 (9,10)] if SBP is 20 mm Hg above target or if DBP is 10 mm Hg above target. However, caution should be exercised in patients in whom a substantial fall in BP is more likely or poorly tolerated (e.g. elderly patients, patients with autonomic neuropathy).
2. For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy [Grade A, Level 1A (11–14)].
3. For persons with diabetes and hypertension not included in the above recommendation, appropriate choices include (in alphabetical order): ACE inhibitors [Grade A, Level 1A (15)], ARBs [Grade A, Level 1A (12)], dihydropyridine CCBs [Grade A, Level 1A (15)], and thiazide/thiazide-like diuretics [Grade A, Level 1A (15)].
4. If target BP levels are not achieved with standard dose monotherapy, additional antihypertensive therapy should be used [Grade D, Consensus]. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to hydrochlorothiazide [Grade A, Level 1A (16)].

Abbreviations:

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

3. Lowering SBP is associated with an increased risk of adverse events, such as hypotension and hyperkalemia. However, the majority of these are associated with SBP <120 mm Hg.

Together, these findings provide the rationale for the current Canadian Hypertension Education Program (CHEP) and the Canadian Diabetes Association harmonized clinical practice recommendations, which continue to recommend blood pressure targets of <130/80 mm Hg in hypertensive patients with diabetes (5).

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Clinical Practice Guidelines

Management of Acute Coronary Syndromes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Jean-Claude Tardif MD, FRCPC, FACC, FCAHS, Phillipe L. L'Allier MD, David H. Fitchett MD, FRCPC

KEY MESSAGES

- Diabetes is an independent predictor of increased short- and long-term mortality, recurrent myocardial infarction (MI) and the development of heart failure in patients with acute MI (AMI).
- Patients with an AMI and hyperglycemia should receive insulin-glucose infusion therapy to maintain blood glucose between 7.0 and 10.0 mmol/L for at least 24 hours, followed by strategies to achieve recommended glucose targets long term.
- People with diabetes are less likely to receive recommended treatment, such as revascularization, thrombolysis, beta blockers or acetylsalicylic acid than people without diabetes. Efforts should be directed at promoting adherence to existing proven therapies in the high-risk patient with MI and diabetes.

Incidence and Prognosis

Diabetes (together with lipid abnormalities, smoking and hypertension) is 1 of the top 4 independent risk factors for myocardial infarction (MI) (1). Today, approximately 15% to 35% of patients admitted with an acute coronary syndrome (ACS) have known diabetes (2), and as many as another 15% have undiagnosed diabetes (3).

Compared to individuals without diabetes, patients with diabetes have:

1. A 3-fold increased risk of ACS (4),
2. Occurrence of acute coronary events 15 years earlier (4).
3. A 2-fold increased short- (5,6) and long-term mortality (5,7,8).
4. An increased incidence of post-infarction recurrent ischemic events, heart failure and cardiogenic shock (3,9).
5. A similar benefit from guideline recommended management strategies (see below.)
6. Less utilization of guideline recommended care (10–13), which may contribute to adverse outcomes in the patient with diabetes (14).

Identification of Diabetes in Patients with ACS

Although the absolute number of patients with MI has fallen in the United States, the prevalence of diabetes in this population has

steadily increased from 18% in 1997 to 30% in 2006 (2). More than two-thirds of patients with MI have either diabetes or impaired glucose regulation (impaired glucose tolerance and impaired fasting glucose) (15). Abnormal glucose regulation is almost twice as prevalent in patients with MI compared to a matched control population and is a marker for adverse outcomes (16). The frequency of previously unrecognized diabetes in the ACS population is reported to be between 4% and 22% depending on the test used for the diagnosis of diabetes (3,17). If fasting glucose criteria is used alone in the ACS population, diabetes is underdiagnosed in 39% compared to when the diagnosis is made from an oral glucose tolerance test (OGTT) (18). Glycated hemoglobin (A1C) at or above 6.5% is currently a diagnostic criterion for diabetes as it captures long-term glucose exposure, does not require fasting or timed samples and is currently used to guide management decisions. A1C has been validated in an acute care population (19). Using the OGTT as a gold standard for the diagnosis of diabetes and an A1C threshold of 6.0%, A1C had a sensitivity of 77% and a specificity of 87%. It is accepted that some patients with diabetes will be missed by screening with fasting blood glucose and A1C compared to the universal use of an OGTT. However, it is likely that the patients most in need of glycemic control will be detected with these simple tests, which can be widely applied. It has been suggested that individuals with A1C of 6.0% to 6.4% should have an OGTT 6 to 8 weeks after discharge (20).

Management of ACS in the Patient with Diabetes

Guidelines for the management of patients with ACS have been developed by the American College of Cardiology (ACC)/American Heart Association (AHA) (21–23) and the European Society of Cardiology (24,25). In most situations, there are no clinical trials that specifically address management of the patient with diabetes and ACS. However, subgroup analyses in patients with diabetes and ACS show either a similar or an enhanced benefit from treatment compared to the overall group for a) reperfusion with fibrinolysis (26) or primary angioplasty (27) for ST-segment elevation ACS; and b) an early invasive strategy (28), the use of dual antiplatelet therapy with acetylsalicylic acid (ASA) and clopidogrel (29), and glycoprotein (GP) IIb/IIIa inhibitors in patients with non-ST-segment elevation ACS (NSTEMI ACS) at high risk of recurrent ischemic events (30).

A significant care gap exists for patients with diabetes not receiving guideline-recommended treatment compared to patients

without diabetes (12–14,31). It is possible that underutilization of recommended treatment is 1 factor contributing to the adverse outcome of the ACS patient with diabetes.

Antiplatelet Therapy

Platelet aggregation plays a central role in the development of the occlusive thrombus responsible for acute coronary occlusion in patients with ACS. Patients with diabetes have a prothrombotic state due to dysfunctional and hyperactive platelets, endothelial dysfunction, elevated coagulation factors and decreased fibrinolysis (32). Increased platelet activity is due to multiple metabolic and cellular factors associated with diabetes that include endothelial dysfunction, the impact of hyperglycemia and deficient insulin action (32).

Diabetes is associated with an increased incidence of recurrent atherothrombotic events (8), including stent thrombosis (33). Antiplatelet therapy has been shown to reduce atherothrombotic events in patients with ACS, both during the acute phase and in the longer term. The beneficial effect of ASA has been shown in multiple clinical trials in patients with NSTEMI and ST-elevation MI (STEMI). The Antithrombotic Trialists' Collaboration meta-analysis of antiplatelet therapy (mainly ASA) included 212 000 high-risk patients (with acute or previous vascular disease) and showed the incidence of vascular events to be reduced in both the overall population (16.8% to 12.8%; $p < 0.00001$) and in patients with diabetes (22.3% to 18.5%; $p < 0.002$) (34). Low-dose ASA (75 to 150 mg) was as effective as higher doses (> 150 mg) with a lower incidence of bleeding complications. The CURRENT/OASIS 7 trial also was unable to show any benefit from higher-dose compared to low-dose (75 to 100 mg) ASA in patients with and without diabetes (35). The use of low-dose ASA is recommended to minimize gastrointestinal bleeding in patients with and without diabetes.

Dual antiplatelet therapy with ASA and clopidogrel, administered from the time of presentation, has been the recommended standard of care for patients with NSTEMI. Patients with diabetes in the CURE trial had a similar benefit with clopidogrel vs. placebo (14.2% vs. 17.7%, relative risk [RR] 0.84, 95% confidence interval [CI] 0.70–1.02) as the overall population (9.3% vs. 11.4%, RR 0.80, 95% CI 0.72–0.90) (29).

Despite dual antiplatelet therapy with ASA and clopidogrel, recurrent atherothrombotic events continue to occur, especially in patient with diabetes. Clopidogrel is a relatively weak inhibitor of platelet aggregation with a wide variation of inhibition of *in vitro* platelet aggregation. There is a higher incidence of events in patients with residual platelet activity, and patients with diabetes have higher residual platelet activity despite ASA and clopidogrel treatment. Two new antiplatelet agents, prasugrel and ticagrelor, which are more effective and predictable inhibitors of platelet aggregation, have recently become available in Canada.

In the TRITON study, prasugrel administered at the time of coronary angioplasty in patients with ACS reduced recurrent ischemic events, including stent thrombosis, compared to patients receiving clopidogrel (36). In subjects with diabetes, prasugrel treatment was associated with greater platelet inhibition and fewer poor responders (37). Prasugrel resulted in an important net clinical benefit in patients with diabetes (14.6% vs. 19.2%, hazard ratio [HR] 0.74; $p = 0.001$) due to a 30% reduction of the primary endpoint (cardiovascular [CV] death, nonfatal MI, or stroke) over the 14.4 months of the study (38). In this subgroup with diabetes, there was no significant increase in major bleeding. There was no statistical interaction between the subgroups with and without diabetes, indicating that the enhanced absolute benefit was the result of higher event rates in patients with diabetes.

In the Platelet Inhibition and Patient Outcomes (PLATO) study, the P2Y₁₂ receptor antagonist, ticagrelor, when compared with

clopidogrel and administered early after presentation in patients with NSTEMI or STEMI, reduced CV death, nonfatal MI and stroke (10.2% vs. 12.3%, HR 0.84; $p = 0.0001$), as well as CV death (4.0% vs. 5.1%, HR 0.49; $p = 0.001$) and stent thrombosis (2.2% vs. 2.9%, HR 0.75; $p = 0.02$), with a modest increase in bleeding in patients not undergoing coronary bypass surgery (39). In the diabetic cohort of the PLATO study, similar benefits were observed as in the overall group (40).

The availability of more potent and reliable antiplatelet agents for the management of patients with ACS provides an opportunity to further reduce recurrent ACS and mortality. High-risk patients with diabetes with either STEMI or NSTEMI ACS should be considered for treatment with either prasugrel (after the coronary disease anatomy has been defined) or ticagrelor.

Platelet aggregation is largely mediated by the GPIIb/IIIa receptor through its binding to fibrinogen. The GPIIb/IIIa receptor inhibitors abciximab, eptifibatide and tirofiban were shown to be effective for the management of ACS in patients with diabetes in a meta-analysis of 6 clinical trials. GPIIb/IIIa inhibitors were shown to reduce 30-day mortality by 26% (4.6% vs. 2.6%; $p = 0.007$) (30). In contrast, patients without diabetes had no mortality benefit. Although these trials were performed in an era before dual antiplatelet therapy with ASA and clopidogrel was used, recent studies indicate an additional benefit from a GPIIb/IIIa inhibitor for patients with high risk ACS, such as those with diabetes who are undergoing percutaneous coronary intervention (PCI) (41,42).

Glycemic Control

Hyperglycemia during the first 24 to 48 hours after admission for ACS is associated with increased early mortality, whether or not the patient has diabetes (43,44). Furthermore, in-hospital mortality has a closer relationship to hyperglycemia than to diabetic status (45,46). Higher baseline glucose and a failure of glucose to decrease are independent predictors of mortality (47). For patients undergoing primary angioplasty, mortality increases when the plasma glucose is > 10.0 mmol/L (48).

Although elevated mean blood glucose level in the first 24 hours after onset of ACS is associated with adverse outcomes (46), evidence to support reducing blood glucose levels (especially to levels close to the normal range) after ACS remains inconclusive. The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) study indicated that tight glycemic control with the use of intravenous insulin in the early hours after presentation, followed by multidose subcutaneous insulin treatment over the subsequent months, resulted in a 30% reduction in 1-year mortality (49–53). The DIGAMI 2 study failed to achieve the study goals, both in the number of patients recruited and in glycemic targets (54). However, despite these limitations, it did demonstrate that outcomes were closely related to glycemic control, however achieved. Studies have shown that glucose-insulin-potassium infusion in patients with AMI do not improve outcomes (55,56). However, these protocols often resulted in increased blood glucose levels and, therefore, cannot be used as evidence for outcomes associated with glycemic control. In the Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study of glucose and insulin in patients with AMI, patients with a blood glucose maintained at < 8.0 mmol/L had lower mortality than did subjects with higher levels (57).

The AHA Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism issued a scientific statement in 2008 on hyperglycemia and ACS (58). They recommended blood glucose targets of 5.0 to 7.7 mmol/L in the intensive care unit (ICU) setting or < 10.0 mmol/L in the non-ICU setting during hospitalization for ACS. More recent ACC/AHA guidelines for the management of patients with STEMI concluded that it was prudent to

change the recommendation for the use of insulin to control blood glucose in STEMI from a Class I to a Class II recommendation (*Level of Evidence: B*) and recommended treatment for hyperglycemia >10.0 mmol/L while avoiding hypoglycemia (59). The Canadian Diabetes Association recommends glucose targets of 8.0 to 10.0 mmol/L in the critically ill and premeal glucose of 5.0 to 8.0 mmol/L and random glucose levels <10.0 mmol/L (See In-hospital Management of Diabetes chapter, page S77).

Post-ACS long-term glycemic control trials using agents from newer drug classes, such as dual peroxisome proliferator-activated receptor agonist, glucagon-like peptide-1 (GLP-1) receptor agonists, and acarbose, are currently under way (e.g. A Study of Aleglitazar in Patients With Type 2 Diabetes [ALECARDIO], Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 [Lixisenatide] [ELIXA], Acarbose Cardiovascular Evaluation Trial). Until results from dedicated post-ACS studies become available, results from 5 large-scale clinical trials of stable patients with type 2 diabetes, and either known or at high risk of CAD, are helpful (60–64). A recent meta-analysis of these trials suggested a 17% relative reduction in nonfatal MI (10.0 vs. 12.3 per 1000 person-years) in subjects included in the intensive glucose control group (target A1C ≤6.0% to 6.5%; median A1C during follow-up 6.6%), yet there was no reduction of all-cause mortality (65,66). The same

meta-analysis indicated the possibility that a greater benefit could be derived from treating patients with recently diagnosed diabetes more intensively.

Revascularization

ACS practice guidelines promote the same treatment strategies in patients with diabetes as for those without diabetes (67). An early invasive strategy with revascularization when possible in NSTEMI ACS provides a similar or greater reduction in death and MI (up to 5 years of follow-up) in the subset of patients with diabetes compared to the overall population (28,68,69). The 2011 ACC AHA non-STEMI ACS guidelines recommend that NSTEMI ACS should be considered for an early invasive, rather than a selective invasive (conservative), strategy.

In patients with diabetes and NSTEMI ACS and multivessel disease, CABG with the use of internal mammary artery may provide benefit over PCI when revascularization is indicated (70). However, PCI (with drug-eluting stents whenever possible) is acceptable for patients with less extensive disease (i.e. single-vessel disease) (59). For patients with ST-elevation ACS, immediate reperfusion strategies with either fibrinolysis or primary PCI result in similar benefits for patients with and without diabetes. The benefits of primary PCI over fibrinolysis in patients with diabetes are similar to those without diabetes (mortality with primary PCI vs. fibrinolysis in patients with diabetes, odds ratio (OR) 0.49, 95% CI 0.31–0.79) (27). However, fibrinolysis should be administered when primary PCI is not available within acceptable timeframes. Ocular hemorrhage in patients with diabetic retinopathy is extremely rare and should not limit the use of fibrinolysis when it is indicated (71).

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RECOMMENDATIONS

1. Patients with ACS should be screened for diabetes with a fasting blood glucose, A1C or 75 g OGTT prior to discharge from hospital [Grade D, Consensus].
2. All patients with diabetes and ACS should receive the same treatments that are recommended for patients with ACS without diabetes since they benefit equally [Grade D, Consensus].
3. Patients with diabetes and ACS undergoing PCI should receive antiplatelet therapy with prasugrel (if clopidogrel naïve, <75 years of age, weight >65 kg, and no history of stroke) [Grade A, Level 1 (36,38)] or ticagrelor [Grade B, Level 1 (39,40)], rather than clopidogrel, to further reduce recurrent ischemic events. Patients with diabetes and non-STEMI ACS and higher-risk features destined for a selective invasive strategy should receive ticagrelor rather than clopidogrel [Grade B, Level 2 (39,40)].
4. Patients with diabetes and non-STEMI ACS and high-risk features should receive an early invasive strategy rather than a selective invasive approach to revascularization to reduce recurrent coronary events, unless contraindicated [Grade B, Level 2 (28)].
5. In patients with diabetes and STEMI ACS, the presence of retinopathy should not be a contraindication to fibrinolysis [Grade B, Level 2 (71)].
6. In-hospital management of diabetes in ACS should include strategies to avoid both hyperglycemia and hypoglycemia:
 - Blood glucose should be measured on admission and monitored throughout the hospitalization [Grade D, Consensus]
 - Patients with acute MI and blood glucose >11.0 mmol/L on admission may receive glycemic control in the range of 7.0 to 10.0 mmol/L, followed by strategies to achieve recommended glucose targets long term [Grade C, Level 2 (52,54)]. Insulin therapy may be required to achieve these targets [Grade D, Consensus]. A similar approach may be taken in those with diabetes and admission blood glucose ≤11.0 mmol/L [Grade D, Consensus] (see In-hospital chapter, p. S77).
 - An appropriate protocol should be developed and staff trained to ensure the safe and effective implementation of this therapy and to minimize the likelihood of hypoglycemia [Grade D, Consensus].

Abbreviations:

A1C, glycated hemoglobin; ACS, acute coronary syndrome; OGTT, oral glucose tolerance test; PCI, percutaneous coronary intervention; STE, ST elevation.

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Clinical Practice Guidelines

Management of Stroke in Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- The assessment and general management of persons with diabetes who experience a stroke, and of persons with a new diagnosis of diabetes after experiencing a stroke, are the same as those without a stroke.
- A comprehensive, regularly updated, evidence-based approach to the assessment and management of all patients (including those with diabetes) with stroke across the continuum of care is available on the Canadian Stroke Strategy (CSS) Best Practices Recommendations website (1) (<http://www.strokebestpractices.ca>).

Introduction

Diabetes is an important modifiable risk factor for a first ischemic stroke, and the combination of diabetes and stroke is a major cause of morbidity and mortality worldwide (2). Evidence from large clinical trials performed in patients with diabetes supports the need for aggressive and early intervention to target the cardiovascular (CV) risks of patients to prevent the onset, recurrence and progression of acute stroke (2). Estimates of risk of ischemic stroke in people with diabetes range from a 2- to 3-fold increase in men and a 2- to 5-fold increase in women (3,4). Diabetes also doubles the risk of stroke recurrence, and stroke outcomes are significantly worse among patients with diabetes, with increased hospital and long-term stroke mortality, more residual neurological and functional disability, and longer hospital stays (2). From a clinical perspective, diabetes increases the risk of ischemic stroke more than hemorrhagic stroke, resulting in a greater ischemic to hemorrhagic stroke ratio in people with diabetes compared with the general population. The high stroke risk in diabetes may be due to the complex interplay between the various hemodynamic and metabolic components of the diabetes syndrome. Other than the many recognized risk factors associated with acute stroke (e.g. hypertension, dyslipidemia, atrial fibrillation), specific risk factors attributable to diabetes also have been reported, such as insulin resistance, central obesity, impaired glucose tolerance and hyperinsulinemia. Both individually and collectively, these factors are associated with an excess risk of stroke disease (2). Therefore, the comprehensive, multifactorial strategy addressing healthy behaviours, blood pressure, lipids, glucose and the possible use of vascular protective medications to reduce overall CV morbidity and mortality among people with diabetes (see Vascular Protection in People with Diabetes chapter, p. S100) is imperative to reduce the risk of this potentially devastating complication.

Diabetes Management in the Acute Period

The management of hyperglycemia in acute stroke (generally defined as within the first 24 hours of stroke symptom onset) remains controversial; the evidence to support tight glucose control immediately following acute ischemic stroke has not been supportive. A Cochrane Systematic Review evaluated randomized controlled trials comparing intensively monitored insulin therapy (target blood glucose range 4.0 to 7.5 mmol/L) vs. usual care in adult patients with acute ischemic stroke, with or without diabetes (5). The systematic review included 7 trials involving 1296 participants (639 participants in the intervention group and 657 in the control group). There was no difference between treatment and control groups in the outcome of death or disability and dependence (odds ratio [OR] 1.00, 95% confidence interval [CI] 0.78–1.28) or final neurological deficit (Standardized Mean Difference –0.12, 95% CI –0.23 to 0.00). The rate of symptomatic hypoglycemia was higher in the intervention group (OR 25.9, 95% CI 9.2–72.7). In the subgroup analysis of those with diabetes vs. those with no diabetes, no difference was found for the outcomes of death and dependency or neurological deficit. Of note, the control groups within the 7 studies achieved mean glucose levels of <10.5 mmol/L (6–12). It was concluded, by the authors, that the use of insulin to maintain a glucose of 4.0 to 7.5 mmol/L in the first 24 hours after stroke symptom onset is not beneficial compared to usual care and may, in fact, be harmful with increased hypoglycemia. Therefore, there is no glucose target specific to patients presenting with stroke. However, the recommendation for the majority of noncritically ill hospitalized patients to have their glucose levels maintained below 10.0 mmol/L (see In-hospital Management of Diabetes chapter, p. S77) remains applicable to those admitted with acute stroke.

RECOMMENDATIONS

1. Patients with ischemic stroke or transient ischemic attack (TIA) should be screened for diabetes with a fasting plasma glucose, glycated hemoglobin (A1C) or 75 g oral glucose tolerance test soon after admission to hospital [Grade D, Consensus].
2. All patients with diabetes and ischemic stroke or TIA should receive the same treatments that are recommended for patients with ischemic stroke or TIA without diabetes since they benefit equally [Grade D, Consensus].

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Clinical Practice Guidelines

Treatment of Diabetes in People with Heart Failure

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Jonathan G. Howlett MD, FRCPC, FACC, FSCAI, John C. MacFadyen MD, FRCPC

KEY MESSAGES

- Heart failure is still under-recognized and misdiagnosed. This has significant clinical implications as the prognosis of untreated or undertreated heart failure is poor, and yet very effective proven therapies are widely available to most physicians.
- Diabetes can cause heart failure independently of ischemic heart disease by causing a diabetic cardiomyopathy that may manifest in the setting of normal or reduced left ventricular ejection fraction. The incidence of heart failure is 2- to 4-fold higher in people with diabetes compared to those without and, when present, occurs at an earlier age.
- Even though heart failure in people with diabetes should be treated similarly to heart failure in those without diabetes, they are less likely to receive appropriate therapies. The presence of diabetes should not affect the decision for treatment of heart failure.
- Comorbidities, such as renal dysfunction and propensity for hyperkalemia, are more prevalent in people with diabetes and may influence heart failure drug doses and monitoring of therapy but not therapeutic targets.

Introduction

Type 2 diabetes often occurs in association with other cardiovascular risk factors, such as hypertension, dyslipidemia, smoking and obesity, which together are strongly associated with atherosclerosis, ischemic heart disease and left ventricular (LV) dysfunction. LV dysfunction can be clinically silent or associated with the typical clinical signs and symptoms of heart failure (e.g. peripheral edema, shortness of breath, fatigue), although the elderly may have atypical symptoms (1). These symptoms need to be differentiated from other conditions that may have similar presentations, such as chronic obstructive pulmonary disease, pneumonia, anemia, varicose veins, depression, etc.

Heart Failure in People with Diabetes

The diagnosis of heart failure is made by association of typical clinical signs and symptoms with objective evidence, such as that obtained from a chest x-ray, an echocardiogram or plasma natriuretic peptide testing (brain natriuretic peptide [BNP] and pro-hormone of BNP [NT-pro-BNP]) (1). Documentation of systolic and diastolic myocardial function is recommended at the time of diagnosis of heart failure or with any significant change in clinical stability. Heart failure can occur over the entire range of LV ejection

fractions (LVEFs), from <10% to >60%. The measurement of plasma BNP and NT-pro-BNP, which are acutely released by ventricular myocytes when the myocardium is stretched due to increased filling pressures, may help make an accurate diagnosis where clinical uncertainty exists (2). However, the practising physician may still under-recognize and misdiagnose heart failure. This has significant clinical implications as the prognosis of untreated or undertreated heart failure is poor, yet very effective proven therapies are widely available to most physicians. Because of this, many studies have explored the clinical utility of screening patients with diabetes for the presence of reduced LV function with BNP/NT-pro-BNP testing. The results to date are mixed, with no clear consensus to institute this strategy. Diabetes is associated with increased prevalence of heart failure, both systolic (commonly defined as LVEF <40%) and diastolic (commonly defined as LVEF >50%, but also referred to as preserved systolic function or preserved EF). However, the overlap between systolic and diastolic heart failure is considerable, and many people have a combination of systolic and diastolic dysfunction, although 1 is often reported to be predominant. Current tests, such as echocardiography, do usually fully characterize all aspects of systolic and diastolic dysfunction in individuals.

It is recognized that diabetes can cause heart failure independently of ischemic heart disease by causing a diabetic cardiomyopathy (3). Epidemiological studies have shown that the incidence of heart failure is 2- to 4-fold higher in people with diabetes compared to those without diabetes (4,5). Additionally, studies have shown the occurrence of asymptomatic abnormalities of ventricular systolic and diastolic function, independently from ischemic heart disease or systemic hypertension. While an increase in glycated hemoglobin (A1C) among individuals with diabetes is a recognized risk factor for heart failure (6–10), no prospective study to date has demonstrated that improved glycemic control significantly reduces the incidence of heart failure (11). Micro-albuminuria is also an independent risk factor for heart failure, especially in people with diabetes. In individuals with and without diabetes, increasing urinary albumin-to-creatinine ratio is associated with a stepwise increase (2- to 4-fold) in the risk of heart failure development (8,12). Angiotensin-converting enzyme (ACE) inhibitors significantly reduce urinary albumin excretion, and, in large clinical trials of subjects with cardiovascular disease or diabetes, they have been shown to lower the risk of new-onset heart failure (13–15).

Treatment of Individuals with Both Diabetes and Heart Failure

In nearly every clinical trial involving patients with heart failure, diabetes is present in over one-third of subjects. In the large landmark clinical trials of heart failure, subgroup analysis of diabetic populations has shown that, despite their increased risk of morbidity and mortality, they derive greater absolute benefit from efficacious therapies as compared to patients without diabetes (15–17). As such, heart failure in people with diabetes should be treated similarly to those without diabetes, although comorbidities, such as renal dysfunction and hyperkalemia, may be more prevalent in people with diabetes (<http://www.ccsguidelineprograms.ca>).

In particular, patients with diabetes are at increased risk for development of hyperkalemia and worsening renal dysfunction in the setting of renin-angiotensin-aldosterone (RAAS) blocking agents (18–23). Clinicians should be aware of this potential complication, especially in view of current guidelines advocating the expanded use of combined RAAS blockade in patients with mild-to-moderate heart failure and low EF.

Three beta blockers have been shown to reduce morbidity and mortality for patients with heart failure and diabetes: carvedilol, bisoprolol and metoprolol. Data to date suggest overall glycemic control for these patients improves as their heart failure syndrome improves on therapy (24–26). Carvedilol, in comparison to other beta blockers, has been shown to be associated with improved glycemic control. In addition, some data suggest the improvement in LVEF is also greater with carvedilol (17,27). For this reason, some clinicians prefer carvedilol as the beta blocker of choice in such patients. While there is a theoretical concern for the occurrence of severe hypoglycemia without awareness associated with the use of nonselective beta blockers, this has not been reported in clinical trials.

Numerous registries and reports indicate that persons with diabetes are less likely than those without diabetes to receive efficacious and evidence-based therapies for systolic heart failure. Perhaps this is due, in part, to the increased incidence of side effects and/or intolerance to RAAS blockade and the increased prevalence of renal disease in patients with diabetes. However, even when controlled for these conditions, the differences persist. This is particularly concerning considering the increased absolute benefit

the agents confer to patients with heart failure and diabetes in comparison to unselected heart failure populations. As such, prescribers must be diligent in providing these therapies.

Metformin

Metformin is an effective oral antihyperglycemic agent, but, based on isolated case reports and a biochemical rationale for a risk of lactic acidosis, it is approved for use under a warning in the setting of several conditions, including heart failure. Meta-analyses have evaluated the occurrence of lactic acidosis with the use of metformin (over 70 000 patient-years) or other antihyperglycemic agents (over 55 000 patient-years) and they have consistently shown no increase in lactic acidosis in the metformin group (28,29). In fact, cardiovascular outcomes in heart failure patients taking metformin were better than in those taking other antihyperglycemic agents (30). The current evidence suggests that patients with heart failure fare at least as well, if not better, with metformin than with other antihyperglycemic agents if they have only mild-to-moderate renal dysfunction (estimated glomerular filtration rate >30 mL/min) (30). As such, metformin should still be considered as first-line therapy in heart failure patients with mild-to-moderate renal dysfunction.

A detailed discussion of the rationale and evidence for the treatment approach to heart failure patients is available in the Canadian Cardiovascular Society consensus recommendations (<http://www.ccsguidelineprograms.ca>) (31).

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RECOMMENDATIONS

- Individuals with diabetes and heart failure should receive the same heart failure therapies as those identified in the evidence-based Canadian Cardiovascular Society heart failure recommendations (<http://www.ccsguidelineprograms.ca>) [Grade D, Consensus].
- In people with diabetes and heart failure and an estimated glomerular filtration rate <60 mL/min, or if combined renin-angiotensin-aldosterone blockade is employed:
 - Starting doses of angiotensin-converting enzyme inhibitors or angiotensin receptor II antagonists (angiotensin receptor blockers) should be halved [Grade D, Consensus].
 - Serum electrolytes and creatinine, blood pressure and body weight, as well as heart failure symptoms and signs, should be monitored within 7–10 days of any initiation or titration of therapy [Grade D, Consensus].
 - Dose-up titration should be more gradual (with monitoring of blood pressure, serum potassium and creatinine) [Grade D, Consensus].
 - The target drug doses should be the same as those identified in the evidence-based Canadian Cardiovascular Society recommendations on heart failure (<http://www.ccsguidelineprograms.ca>), if well tolerated [Grade D, Consensus].
- Beta blockers should be prescribed when indicated for systolic heart failure, as they provide similar benefits in people with diabetes compared with people without diabetes [Grade B, Level 2 (17,27)].

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Clinical Practice Guidelines

Chronic Kidney Disease in Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Philip McFarlane MD, FRCPC, Richard E. Gilbert MBBS, PhD, FACP, FRACP, FRCPC, Lori MacCallum BScPhm, PharmD, Peter Senior MBBS, PhD, MRCP

KEY MESSAGES

- Identification of chronic kidney disease (CKD) in diabetes requires screening for proteinuria, as well as an assessment of renal function.
- All individuals with CKD should be considered at high risk for cardiovascular events and should be treated to reduce these risks.
- The progression of renal damage in diabetes can be slowed through intensive glycemic control and optimization of blood pressure. Progression of diabetic nephropathy can be slowed through the use of medications that disrupt the renin-angiotensin-aldosterone system.

PRACTICAL TIPS

Management of Potassium and Creatinine During the Use of Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin II Receptor Blocker (ARB) or Direct Renin Inhibitor (DRI)

- Check serum **potassium** and **creatinine** at baseline and within 1 to 2 weeks of initiation or titration of therapy AND during times of acute illness.
- If potassium becomes elevated or creatinine increases by more than 30% from baseline, therapy should be reviewed and serum creatinine and potassium levels should be rechecked.
- Mild-to-moderate stable hyperkalemia:
 - Counsel on a low-potassium diet.
 - If persistent, non-potassium-sparing diuretics and/or oral sodium bicarbonate (in those with a metabolic acidosis) should be considered.
 - Consider temporarily holding renin-angiotensin-aldosterone system (RAAS) blockade (i.e. ACE inhibitor, ARB or DRI).
- Severe hyperkalemia:
 - In addition to emergency management strategies, RAAS blockade should be held or discontinued.

Introduction

Diseases of the kidney are a common finding in people with diabetes, with up to half demonstrating signs of kidney damage in their lifetime (1–3). Diabetes is the leading cause of kidney disease in Canada (4). Kidney disease can be a particularly devastating complication, as it is associated with significant reductions in both

length and quality of life (5,6). A variety of forms of kidney disease can be seen in people with diabetes, including diabetic nephropathy, ischemic damage related to vascular disease and hypertension, as well as other renal diseases that are unrelated to diabetes (Figure 1) (7,8). In this chapter, we will discuss how to screen for and diagnose chronic kidney disease (CKD) in people with diabetes, how to treat them with an aim to slow progression of CKD and discuss the impact of CKD on other aspects of diabetes management.

Diabetic Nephropathy

The classic description of diabetic nephropathy is of a progressive increase in proteinuria in people with longstanding diabetes followed by declining function that eventually can lead to end stage renal disease (ESRD) (Figure 2) (1,9,10). Key risk factors for diabetic nephropathy include long duration of diabetes, poor glycemic control, hypertension, male gender, obesity and cigarette smoking. Many of these factors are modifiable.

The earliest stage of diabetic nephropathy is hyperfiltration, where the glomerular filtration rate (GFR) is significantly higher than normal. Identification of hyperfiltration is not clinically useful, as it is difficult to determine from routine testing. Persistent albuminuria is considered the earliest clinical sign of diabetic nephropathy (Table 1). Initially, small amounts of albumin are leaked, below the detection threshold of a urine dipstick. This stage is referred to as “microalbuminuria.” This can worsen so that the urinary albumin excretion is sufficiently high to be detectable by a urine dipstick, a stage known as “overt nephropathy.” The rate of progression from normoalbuminuria to microalbuminuria then to overt nephropathy usually is slow, typically taking 5 years or longer to progress through each stage (11,12). During the early stages of diabetic nephropathy, the rate of loss of renal function is relatively slow (1 to 2 mL/min/1.73 m² per year) and not impressively higher than what is seen in the general population (0.5 to 1 mL/min/1.73 m² per year). However, late in the overt nephropathy phase, the rate of decline of renal function can accelerate (5 to 10 mL/min/1.73 m² per year). Thus, significant renal dysfunction is not usually seen until late in the course of diabetic nephropathy (13).

It is important to note that the rate of progression can vary between individuals, and that the clinical markers of the disease (i.e. estimated glomerular filtration rate [eGFR], urinary albumin

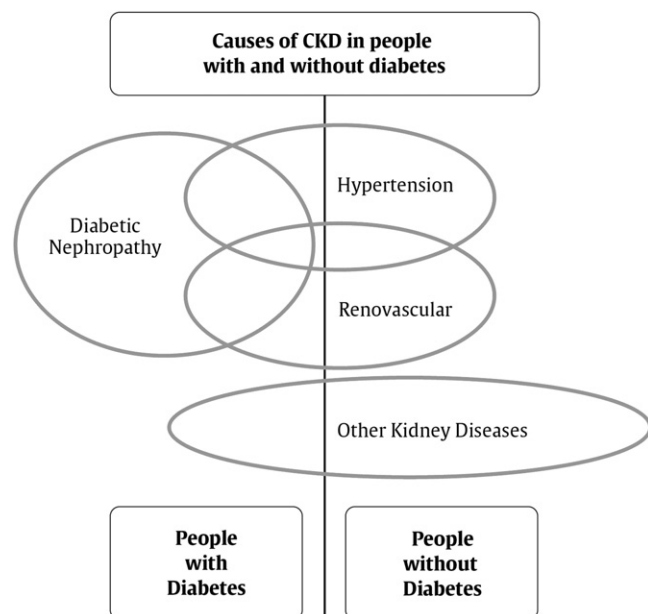


Figure 1. Causes of chronic kidney disease (CKD) in people with and without diabetes.

levels) do not always correlate well with the severity of renal disease seen on biopsy (14). Additionally, aggressive control of blood pressure (BP) and glycemia, and the use of renal protective drugs can slow or stop progression of diabetic nephropathy.

Other Kidney Diseases in People with Diabetes

People with diabetes (particularly type 2 diabetes) often develop kidney diseases other than diabetic nephropathy. Kidney biopsy series in type 2 diabetes have found that nondiabetic glomerular disease, particularly hypertensive or ischemic nephropathy, is as common as diabetic nephropathy in people with diabetes (7). In addition, there can be significant overlap (Figure 1). While these biopsy series are biased (biopsies are usually done in people with diabetes when nondiabetic renal disease is suspected), other studies have suggested that half of everyone with diabetes and significant kidney function impairment do not have albuminuria (15). These studies suggest that testing for albuminuria may be insufficient in identifying all patients with diabetes who have renal disease. In addition to measurements of urinary albumin excretion, estimations of the level of kidney function and urinalyses are required to identify patients with kidney disease other than diabetic nephropathy. In most cases, the risk of ESRD in diabetes does not appear to matter whether the renal diagnosis is one of diabetic nephropathy or an alternative diagnosis as management is the same (16). However, Table 2 lists some concerning clinical and laboratory features that would lead to suspicion of a kidney disease unrelated to diabetes, requiring such a person to undergo additional testing or referral (17–20).

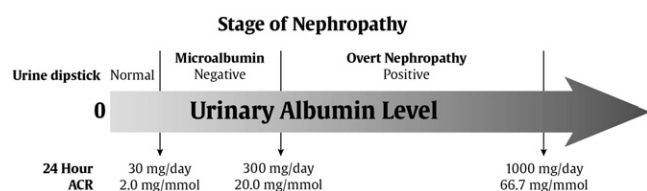


Figure 2. Level of urinary albumin by various test methods and stage of diabetic nephropathy. ACR, albumin-to-creatinine ratio.

Screening for Kidney Disease in People with Diabetes

Screening for kidney disease in people with diabetes involves an assessment of urinary albumin excretion and a measurement of the overall level of kidney function through an estimation of the GFR. Persistent abnormalities of either urinary albumin excretion or GFR, or significant urinalysis abnormalities, lead to the diagnosis of kidney disease in people with diabetes. People with type 1 diabetes are not expected to have kidney disease at the time of onset of diabetes, so screening can be delayed until the duration of diabetes exceeds 5 years. As the delay between onset and diagnosis of type 2 diabetes can be many years and as nondiabetic kidney disease is common, significant renal disease can be present at the time of diagnosis of type 2 diabetes (21,22), so screening should be initiated immediately at the time of diagnosis in this group.

Screening for Albuminuria

When screening for albuminuria, the test of choice is the random urine albumin-to-creatinine ratio (urinary ACR). The 24-hour urine collection for protein/albumin remains the gold standard; however, it is cumbersome to implement on a large scale and is often performed incorrectly (23–27). The random urine for albumin is insufficient, as the urinary albumin concentration can vary due to urine concentration (24). A random urine ACR predicts 24-hour urinary albumin excretion sufficiently well and is the test of choice for screening for albuminuria (23,25–27).

There is substantial day-to-day variability in albuminuria. In addition, transient increases in albuminuria can be provoked by a number of factors (Table 3) (28–32). When such conditions are present, screening for kidney disease should be delayed to avoid false positives. Furthermore, diagnosing a person as having albuminuria requires the elevated urinary albumin level to be persistent. At least 2 of 3 urine samples over time exhibiting elevations in urinary albumin levels are required before it is considered to be abnormal.

Estimation of GFR

The serum creatinine is the most common measurement of kidney function; however, it can inaccurately reflect renal function in many scenarios, particularly in extremes of patient age or size (33,34). Indeed, in people with diabetes, the GFR usually will be less than half of normal before the serum creatinine exceeds the lab normal range (35).

As mentioned, the 24-hour urine collection can be difficult to perform accurately. For this reason, a variety of methods have been developed to better estimate the level of glomerular filtration by combining the patient's serum creatinine with factors such as age, weight, and gender. The most common method of estimating renal function in Canada currently is the eGFR, using the 4-variable MDRD ("Modification of Diet in Renal Disease") equation (36). This equation requires knowledge of the patient's age, sex, serum creatinine and race and is automatically computed and reported by many labs whenever a serum creatinine is ordered. The MDRD eGFR performs well when the GFR is <60 mL/min (37) and despite its flaws is generally a better estimate of glomerular filtration than the serum creatinine value. Kidney diseases of all forms can be staged based on the degree of impairment of eGFR (Table 4).

The eGFR is useful for assessing chronic changes in renal function but should not be used in situations where kidney function is changing rapidly. Dehydration and other conditions that lead to intravascular volume contraction can lead to a transient decline in renal function. When such conditions are present, assessment of the level of kidney function may be clinically necessary but should

Table 1

Stages of diabetic nephropathy by level of urinary albumin level

Stages of Diabetic Nephropathy by Level of Urinary Albumin Level			
Stage of nephropathy	Urine dipstick for protein	Urine ACR (mg/mmol)	24 hour urine collection for albumin
Normal	Negative	<2	<30 mg/day
Microalbuminuria	Negative	2–20	30–300 mg/day
Overt nephropathy	Positive	>20	>300 mg/day
		>67	>1000 mg/day
Values are for urinary albumin, not total urinary protein, which will be higher than urinary albumin levels. ACR results may be elevated with conditions other than diabetic nephropathy (see text and Table 4)			

not be used to assess the stage of CKD. Because renal function can be transiently depressed, a persistent reduction in eGFR is required before it is considered to be abnormal.

Other Clinical Features and Urinary Abnormalities: When to Consider Additional Testing or Referral

Urinalysis findings of red blood cell casts are not a common finding in renal disease due to diabetes, and white blood cell casts or heme-granular casts are not compatible with a diagnosis of kidney disease due to diabetes. Although persistent microscopic hematuria can occur in about 20% of people with diabetic nephropathy, its presence should lead to the consideration of other urological or nephrological conditions. Table 2 lists other clinical clues that may point to a renal diagnosis other than kidney disease due to diabetes. Such patients should undergo an appropriate assessment for the cause of their disease. A rapid decline in eGFR or development of severe hypertension would suggest prompt referral to a specialist.

Although 24-hour collections are not needed for routine screening in diabetes, they can be useful when there is doubt about the accuracy of an eGFR, when screening for nonalbumin urinary proteins (e.g. multiple myeloma) or when estimating daily sodium intake in an individual with refractory edema or hypertension. Individuals should be counseled to discard the first morning urine on the day of collection and then collect all subsequent urine for a 24-hour period, including the first morning urine of the next day.

Screening Recommendations

People with diabetes should undergo annual screening for the presence of kidney disease when they are clinically stable and not

suspected of having acute kidney injury or nondiabetic renal disease. Screening should be delayed in the presence of conditions that can cause transient albuminuria (Table 3) or a transient fall in eGFR.

Screening for CKD in people with diabetes should be performed with a random urine ACR and a serum creatinine that is then converted into an eGFR (Figure 3). This can be delayed 5 years from the onset of type 1 diabetes but should begin immediately at the time of diagnosis of type 2 diabetes. An abnormal screening test should be confirmed by repeat testing of the eGFR within 3 months, and 2 more random urine ACRs ordered during that interval. If either the eGFR remains low or at least 2 of the 3 random urine ACRs are abnormal, then a diagnosis of CKD is confirmed. The exception to this approach is when the random urine ACR indicates albuminuria in the overt nephropathy range, as this level of proteinuria rarely resolves spontaneously, so confirmatory testing is usually unnecessary.

Once a diagnosis of CKD has been made, a urine sample for dipstick and microscopy should be ordered. In the absence of any significant abnormalities other than proteinuria, then a presumptive diagnosis of kidney disease due to diabetes is made. The presence of clinical or laboratory abnormalities suggesting nondiabetic kidney disease indicates the need for appropriate workup or referral.

Prevention, Treatment and Follow Up

Optimal glycemic control established as soon as possible after diagnosis will reduce the risk of development of diabetic nephropathy (38–42). Optimal BP control also appears to be important in the prevention of diabetic nephropathy, although the results have been less consistent (41,43–45). Blockade of the renin-angiotensin-aldosterone system (RAAS) with either an

Table 2

Factors favouring the diagnosis of classical diabetic nephropathy or alternative renal diagnoses

Factors Favouring Classical Diabetic Nephropathy vs. Alternate Diagnoses (17–20)	
Favours Diabetic Nephropathy	Favours Alternate Renal Diagnosis
Persistent albuminuria	Extreme proteinuria (>6 g/d)
Bland urine sediment	Persistent hematuria (micro- or macroscopic) or active urinary sediment
Slow progression of disease	Rapidly falling eGFR
Low eGFR associated with overt proteinuria	Low eGFR with little or no proteinuria
Other complications of diabetes present	Other complications of diabetes not present or relatively not as severe
Known duration of DM >5 years	Known duration of diabetes <5 years
	Family history or nondiabetic renal disease (e.g. polycystic kidney disease)
	Signs or symptoms of systemic disease

Table 3
Conditions that can cause transient albuminuria

Potential Causes for Transient Albuminuria
Recent major exercise
Urinary tract infection
Febrile illness
Decompensated congestive heart failure
Menstruation
Acute severe elevation in blood glucose
Acute severe elevation in blood pressure

angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) can reduce the risk of diabetic nephropathy independent of their effect on BP. This protective effect has been demonstrated in people with diabetes and hypertension (46) but not in normotensive people with diabetes (47–49).

All people with CKD are at risk for cardiovascular (CV) events and should be treated to reduce these risks (see Vascular Protection chapter, p. S100) (50–52). The degree of risk of CV events or progression to ESRD increases as albuminuria levels rise, and as eGFR falls, with the combination of albuminuria and low eGFR predicting a very high level of risk (Figure 4) (53,54).

The progression of renal damage in diabetes can be slowed through intensive glycemic control (38) and optimization of BP (55). Progression of diabetic nephropathy can be slowed through the use of an ACE inhibitor or ARB (56), independent of their effect on BP, and these 2 medication classes appear to be equally effective for cardiorenal protection (57,58). In type 1 diabetes, ACE inhibitors have been shown to decrease albuminuria and prevent worsening of nephropathy (59), and ARBs have been shown to reduce proteinuria (60). In type 2 diabetes, ACE inhibitors and ARBs have been shown to decrease albuminuria and prevent worsening of nephropathy, and ARBs have been shown to delay the time to dialysis in those with renal dysfunction at baseline (61–64). In type 2 diabetes, ACE inhibitors have also been shown to reduce the chance of developing new nephropathy (46,61). These renal-protective effects also appear to be present in proteinuric individuals with diabetes and normal or near-normal BP. ACE inhibitors have been shown to reduce progression of diabetic nephropathy in albuminuric normotensive individuals with both type 1 (65–68) and type 2 diabetes (69).

Table 4
Stages of chronic kidney disease

Stages of Chronic Kidney Disease of all Types		
Stage	Qualitative Description	Renal Function (mL/min/1.73 m ²)
1	Kidney damage-normal GFR	≥90
2	Kidney damage-mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	End-stage renal disease	<15 (or dialysis)

In CKD from causes other than diabetic nephropathy, ACE inhibition has been shown to reduce proteinuria, slow progressive loss of glomerular filtration rate and delay the need for dialysis (70,71). The issue of whether ARBs and ACE inhibitors are similarly effective in CKD that is not caused by diabetic nephropathy remains controversial (72,73).

A variety of strategies to more aggressively block the RAAS have been studied in kidney disease, including combining RAAS blockers or using very high doses of a single RAAS blocker. These strategies reduce proteinuria but have not been proven to improve patient outcomes in diabetic nephropathy (74–77) and come at a risk of increased acute renal failure, typically when a patient develops intravascular volume contraction (78). Aggressive RAAS blockade strategies should be restricted to specialized clinics.

Treating Kidney Disease Safely

The “sick day” medication list (see Appendix 7)

Several classes of medications used commonly in people with diabetes can reduce kidney function during periods of intercurrent illness and should be discontinued when patients are unwell, in particular when they develop significant intravascular volume contraction due to reduced oral intake or excessive losses due to vomiting or diarrhea. Diuretics can exacerbate intravascular volume contraction during periods of intercurrent illness. Blockers of the RAAS interfere with the kidney’s response to intravascular volume contraction, namely, the ability of angiotensin II to contract the efferent arteriole to support glomerular filtration during these periods. Nonsteroidal anti-inflammatory drugs cause constriction of the afferent arterioles, which can further reduce blood flow into the glomerulus in patients who are volume contracted. For these reasons, all of these drugs can reduce kidney function during times of intercurrent illness. Consideration should be given to providing patients with a “sick day” medication list, instructing the patient to hold these medications if they feel that they are becoming dehydrated for any reason. A number of additional medications need to be dose adjusted in patients with renal dysfunction, so their usage and dosage should be reevaluated during periods where kidney function changes.

The safe use of RAAS blockers (ACE inhibitors, ARBs, and direct renin inhibitors [DRIs])

Drugs that block the RAAS reduce intraglomerular pressure, which, in turn, leads to a rise in serum creatinine of up to 30%, which then stabilizes (79). Although these drugs can be used safely in patients with renovascular disease, these patients may have an even larger rise in serum creatinine when these drugs are used (80–82). In the case of severe renovascular disease that is bilateral (or unilateral in a person with a single functioning kidney), RAAS blockade can precipitate renal failure. In addition, RAAS blockade can lead to hyperkalemia. For these reasons, the serum creatinine and potassium should be checked between 1 and 2 weeks after initiation or titration of a RAAS blocker (82). In patients in whom a significant change in creatinine or potassium is seen, further testing should be performed to ensure that these results have stabilized.

Mild-to-moderate hyperkalemia can be managed through dietary counselling. Diuretics, in particular furosemide, can increase urinary potassium excretion. Sodium bicarbonate (500 to 1300 mg orally twice a day) can also increase urinary potassium excretion, especially amongst individuals with a metabolic acidosis as demonstrated by a low serum bicarbonate level. If hyperkalemia is severe, RAAS blockade would need to be held or discontinued (83).

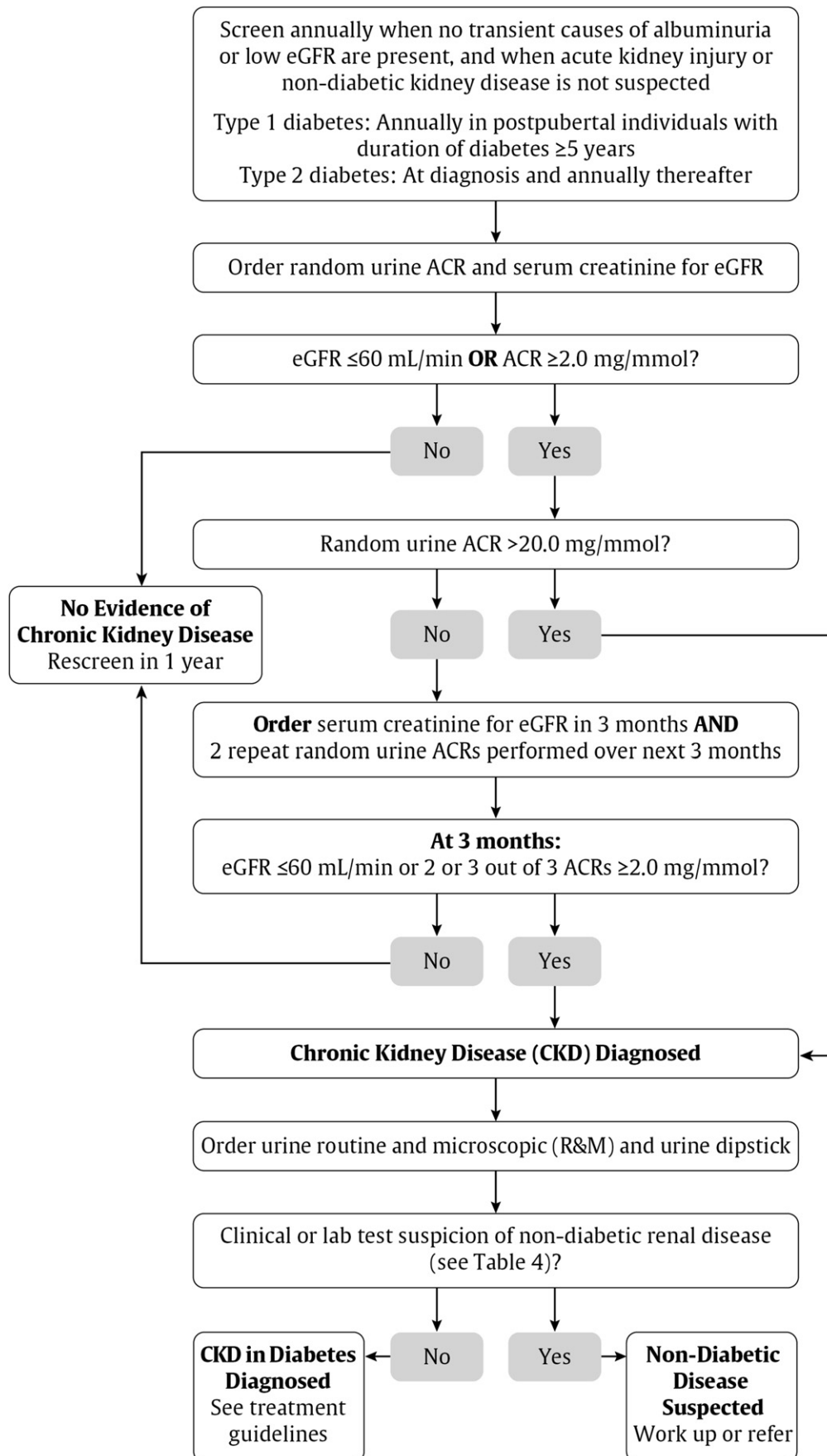


Figure 3. Screening for chronic kidney disease (CKD) in people with diabetes. ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate.

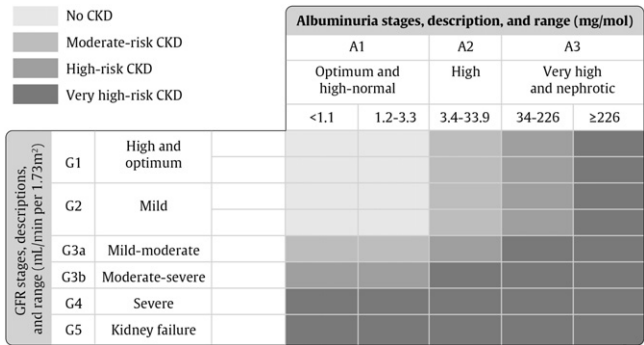


Figure 4. Relative risk of chronic kidney disease (CKD). Shading shows how adjusted relative risk is ranked for 5 outcomes from a meta-analysis of general population cohorts: all-cause mortality, cardiovascular mortality, kidney failure treated by dialysis and transplantation, acute kidney injury, and progression of kidney disease. *GFR*, glomerular filtration rate.

As the use of RAAS blockers during pregnancy has been associated with congenital malformations, women with diabetes of childbearing age should avoid pregnancy if drugs from these classes are required (84). If a woman with diabetes receiving such

medications wishes to become pregnant, consideration should be given to their discontinuation prior to conception.

Medication selection and dosing in CKD

Many medications need to have their dose adjusted in the presence of low kidney function, and some are contraindicated in people with significant disease. Appendix 6 lists some medications commonly used in people with diabetes and how they should be used if kidney dysfunction is present.

Referral to a specialized renal clinic

Most people with CKD and diabetes will not require referral to a specialist in renal disease. However, specialist care may be necessary when renal dysfunction is severe, when there are difficulties implementing renal-protective strategies or when there are problems managing the sequelae of renal disease (85).

Other Relevant Guidelines

- Targets for Glycemic Control, p. S31
- Monitoring Glycemic Control, p. S35
- Pharmacotherapy in Type 1 Diabetes, p. S56
- Pharmacologic Management of Type 2 Diabetes, p. S61
- Type 1 Diabetes in Children and Adolescents, p. S153
- Type 2 Diabetes in Children and Adolescents, p. S163
- Diabetes and Pregnancy, p. S168
- Diabetes in the Elderly, p. S184

Relevant Appendices

- Appendix 6: Therapeutic Considerations for Renal Impairment
- Appendix 7: Sick Day Medication List

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RECOMMENDATIONS

1. In adults, screening for CKD in diabetes should be conducted using a random urine ACR and a serum creatinine converted into an eGFR [Grade D, Consensus]. Screening should commence at diagnosis of diabetes in individuals with type 2 diabetes and 5 years after diagnosis in adults with type 1 diabetes and repeated yearly thereafter. A diagnosis of CKD should be made in patients with a random urine ACR ≥ 2.0 mg/mmol and/or an eGFR < 60 mL/min on at least 2 of 3 samples over a 3-month period [Grade D, Consensus].
2. All patients with diabetes and CKD should receive a comprehensive, multifaceted approach to reduce cardiovascular risk (see Vascular Protection, p. S100) [Grade A, Level 1A (51,86)].
3. Adults with diabetes and CKD with either hypertension or albuminuria should receive an ACE inhibitor or an ARB to delay progression of CKD [Grade A, Level 1A for ACE inhibitor use in type 1 and type 2 diabetes, and for ARB use in type 2 diabetes; Grade D, Consensus, for ARB use in type 1 diabetes (59,61–65,68,69,87,88)].
4. People with diabetes on an ACE inhibitor or an ARB should have their serum creatinine and potassium levels checked at baseline and within 1 to 2 weeks of initiation or titration of therapy and during times of acute illness [Grade D, Consensus].
5. Adults with diabetes and CKD should be given a “sick day” medication list that outlines which medications should be held during times of acute illness (see Appendix, 7) [Grade D, Consensus].
6. Combination of agents that block the renin-angiotensin-aldosterone system (ACE inhibitor, ARB, DRI) should not be routinely used in the management of diabetes and CKD [Grade A, Level 1(89,90)].
7. People with diabetes should be referred to a nephrologist or internist with an expertise in CKD in the following situations:
 - a. Chronic, progressive loss of kidney function
 - b. ACR persistently > 60 mg/mmol
 - c. eGFR < 30 mL/min
 - d. Unable to remain on renal-protective therapies due to adverse effects such as hyperkalemia or $> 30\%$ increase in serum creatinine within 3 months of starting an ACE inhibitor or ARB
 - e. Unable to achieve target BP (could be referred to any specialist in hypertension) [Grade D, Consensus]

Abbreviations:

ACE, angiotensin-converting enzyme; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor block; CKD, chronic kidney disease; DRI, direct renin inhibitor.

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Clinical Practice Guidelines

Retinopathy

Canadian Diabetes Association Clinical Practice Guideline Expert Committee

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KEY MESSAGES

- Screening is important for early detection of treatable disease. Screening intervals for diabetic retinopathy vary according to the individual's age and type of diabetes.
- Tight glycemic control reduces the onset and progression of sight-threatening diabetic retinopathy.
- Laser therapy, local intraocular pharmacological therapy and surgery reduce the risk of significant visual loss.

Introduction

Diabetic retinopathy is the most common cause of new cases of legal blindness in people of working age (1). The Eye Diseases Prevalence Research Group determined the crude prevalence rate of retinopathy in the adult population with diabetes of the United States to be 40.3%; sight-threatening retinopathy occurred at a rate of 8.2% (1). Previous data showed the prevalence rate of proliferative retinopathy to be 23% in people with type 1 diabetes, 14% in people with type 2 diabetes and on insulin therapy, and 3% in people receiving oral antihyperglycemic therapies (2). Macular edema occurs in 11%, 15% and 4% of these groups, respectively (3). Higher prevalence rates were noted in First Nations populations in Canada (4,5).

Visual loss is associated with significant morbidity, including increased falls, hip fracture and a 4-fold increase in mortality (6). Among individuals with type 1 diabetes, limb amputation and visual loss due to diabetic retinopathy are the independent predictors of early death (7).

Definition and Pathogenesis

Diabetic retinopathy is clinically defined, diagnosed and treated based on the extent of retinal vascular disease exclusively. Three distinct forms of diabetic retinopathy are described: 1) macular edema, which includes diffuse or focal vascular leakage at the macula; 2) progressive accumulation of blood vessel change that includes microaneurysms, intraretinal hemorrhage, vascular tortuosity and vascular malformation (together known as non-proliferative diabetic retinopathy) that ultimately leads to abnormal vessel growth (proliferative diabetic retinopathy); and 3) retinal capillary closure, a form of vascular change detected on

fluorescein angiography, which is also well recognized as a potentially blinding complication of diabetes but currently has no treatment options.

Screening

Because laser therapy for sight-threatening diabetic retinopathy reduces the risk of blindness, ophthalmic screening strategies are intended to detect disease treatable by this modality (8–11). Sight-threatening diabetic retinopathy includes severe nonproliferative diabetic retinopathy, proliferative diabetic retinopathy or clinically significant macular edema (CSME) (8), a strictly defined form of diabetic macular edema (DME) that relies on the clinical assessment of retinal thickening based on subjective assessment of area and distance from the fovea (the centre of the macula responsible for high-acuity vision), with or without so-called hard exudates. Since the introduction of new treatments based on intravitreal (intraocular) injection of pharmacological agents and use of Optical Coherence Tomography (OCT) to quantify macular thickness, the more general term DME, or “centre-involving” DME has come to describe patients who could benefit from this treatment over laser, the latter of which cannot be applied to the fovea. Despite the change in treatment modalities, screening programs remain unchanged and consider the differences in incidence and prevalence of retinopathy observed in type 1 and type 2 diabetes, and distinguish between children and adults (Table 1) (12–17).

Diabetic retinopathy rarely develops in children with type 1 diabetes <10 years of age regardless of the duration of diabetes (16). Among patients <15 years of age, irrespective of age of onset of diabetes, the prevalence of mild nonproliferative retinopathy was 2%, and none had sight-threatening diabetic retinopathy (9,16). However, the prevalence rate increases sharply after 5 years' duration of diabetes in postpubertal individuals with type 1 diabetes (16). In the Wisconsin Epidemiology Study of Diabetic Retinopathy 4-year incidence study, no person <17 years of age developed proliferative retinopathy or macular edema (14,18,19). Conversely, in people with type 2 diabetes, retinopathy may be present in 21% to 39% of patients soon after clinical diagnosis but is sight-threatening in only about 3% (3,15,17,20). In the United Kingdom Prospective Diabetes Study (UKPDS), few patients without retinopathy at diagnosis of diabetes had disease progression to the point of requiring retinal photocoagulation (laser treatment) in the following 3 to 6 years (21). More recently,

Table 1
Screening for retinopathy

When to initiate screening
<ul style="list-style-type: none"> • Five years after diagnosis of type 1 diabetes in all individuals ≥ 15 years • In all individuals at diagnosis of type 2 diabetes
Screening methods
<ul style="list-style-type: none"> • Seven-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard) • Direct ophthalmoscopy or indirect slit-lamp funduscopy through dilated pupil • Digital fundus photography
If retinopathy is present
<ul style="list-style-type: none"> • Diagnose retinopathy severity and establish appropriate monitoring intervals (≤ 1 year) • Treat sight-threatening retinopathy with laser, pharmacological or surgical therapy • Review glycemic, BP and lipid control, and adjust therapy to reach targets per guidelines* • Screen for other diabetes complications
If retinopathy is not present
<ul style="list-style-type: none"> • Type 1 diabetes: rescreen annually • Type 2 diabetes: rescreen every 1–2 years • Review glycemic, BP and lipid control, and adjust therapy to reach targets per guidelines* • Screen for other diabetes complications

BP, blood pressure.

* See "Other Relevant Guidelines".

progression rates of diabetic retinopathy were prospectively evaluated (12,13,22). The Liverpool Diabetic Eye Study reported the 1-year cumulative incidence of sight-threatening diabetic retinopathy in individuals with type 1 or type 2 diabetes who, at baseline, had no diabetic retinopathy, had background retinopathy or had mild preproliferative retinopathy. In people with type 1 diabetes, the incidence in these groups was 0.3%, 3.6% and 13.5%, respectively (12), and in type 2 diabetes individuals it was 0.3%, 5.0% and 15.0%, respectively (13). Although the incidence of sight-threatening diabetic retinopathy in the group without baseline diabetic retinopathy is low (12,13,21,22), there have been no studies comparing various screening intervals in their effectiveness to reduce the risk of vision loss (23).

Telemedicine programs relying on fundus photography are widely used in Canada and internationally for the identification and triage of patients with diabetic retinopathy (24). Programs relying on OCT to evaluate macular edema are under investigation.

Delay of Onset and Progression

Risk factors for the development or progression of diabetic retinopathy are longer duration of diabetes, elevated glycated hemoglobin (A1C), increased blood pressure (BP), dyslipidemia, low hemoglobin level, pregnancy (with type 1 diabetes), proteinuria and severe retinopathy itself (14–17,19,25–31).

Glycemic control

Tight glycemic control, targeting an A1C $\leq 7\%$, is recommended to slow the development and progression of diabetic retinopathy. The Diabetes Control and Complications Trial (DCCT) and the UKPDS demonstrated that intensive glycemic control (A1C $\leq 7\%$) reduced both the development and progression of retinopathy (32–34), with the beneficial effects of intensive glycemic control persisting for up to 10 years after completion of the initial trials (35,36). Two studies examined the effect of more aggressive blood glucose lowering (A1C $\leq 6.5\%$) in patients with established type 2 diabetes (duration 6 to 10 years). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study, intensive glycemic control was associated with a lower rate of retinopathy progression than standard therapy (37), while in the Action in Diabetes and

Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) Retinal Measurements study (AdRem), intensive glycemic control did not significantly reduce development or progression of retinopathy (38). In type 1 diabetes, rapid improvement of glycemia may be associated with transient early worsening of retinopathy, but this effect is offset by long-term benefits (39).

Blood pressure control

BP control is an important component of risk factor modification in diabetes and reduces the risk of retinopathy progression. The UKPDS showed that, among patients with newly diagnosed type 2 diabetes, BP control (target BP $<150/85$ mm Hg, actual BP $144/82$ mm Hg) resulted in a significant reduction in retinopathy progression as well as a decrease in significant visual loss and requirement for laser therapy compared to less control (target BP $<180/105$ mm Hg, actual mean BP $154/87$ mm Hg) (40). The ACCORD and ADVANCE studies examined more aggressive BP lowering in patients with established type 2 diabetes. In both these studies, where mean BP was $<140/80$ mm Hg in both the active intervention and control groups, active treatment did not show additional benefit vs. standard therapy.

Although a number of trials have examined the effect of renin-angiotensin system (RAS) blockade on retinopathy progression or development among normotensive patients with diabetes, the results generally have been conflicting or inconclusive. In the Renin-Angiotensin System Study (RASS), involving 223 normotensive, normoalbuminuric participants with type 1 diabetes, neither the angiotensin-converting enzyme (ACE) inhibitor, enalapril, nor the angiotensin receptor blocker (ARB), losartan, reduced retinopathy progression independent of BP change (41). The Diabetic Retinopathy Candesartan Trials (DIRECT) program, involving 5231 participants, evaluated the effect of the angiotensin II type 1 ARB candesartan 32 mg daily on the incidence of new retinopathy in patients with type 1 diabetes (DIRECT-Prevent 1) (42) and on the progression of retinopathy in patients with either type 1 diabetes (DIRECT-Protect 1) (42) or type 2 diabetes (DIRECT-Protect 2) (43). The DIRECT studies did not meet their primary endpoints, although there was an overall change toward less severe retinopathy with candesartan (42,43). Thus, while BP lowering (including use of RAS blockers) reduces retinopathy rates and is an important component of vascular protection, there is insufficient evidence to recommend RAS blockade as primary prevention for retinopathy for all normotensive patients with diabetes.

Lipid-lowering therapy

Dyslipidemia is an independent risk factor for retinal hard exudates and CSME in type 1 diabetes (28,44). While statin-based lipid-lowering therapies are an integral part of vascular protection in diabetes, the role of these agents in preventing the development or progression of retinopathy has not been established (34,45). The role of the peroxisome proliferator-activated receptor- α agonist, fenofibrate, has been assessed in 2 large-scale randomized controlled trials. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate 200 mg daily reduced both the requirement for laser therapy (a pre-specified tertiary endpoint) and retinopathy progression among patients with pre-existing retinopathy (46). In the ACCORD Eye study, the addition of fenofibrate 160 mg daily to simvastatin was associated with a 40% reduction in the primary outcome of retinopathy progression over 4 years (37). From the study's control and event rates, the number of patients needed to treat with combination statin and fenofibrate therapy to prevent 1 retinopathy progression event is estimated at 27 over the 4-year period. The

mechanism for any beneficial effect of fenofibrate in diabetic retinopathy has not been established, with active treatment being associated with an increase in high-density lipoprotein-cholesterol and decrease in serum triglycerides in ACCORD Eye (37) but appearing to be independent of plasma lipid concentrations in FIELD (46). Thus, the addition of fenofibrate to statin therapy could be considered in patients with type 2 diabetes to slow the progression of established retinopathy.

Antiplatelet therapy

Systematic review suggests that acetylsalicylic acid (ASA) therapy neither decreases nor increases the incidence or progression of diabetic retinopathy (47). Correspondingly, ASA use does not appear to be associated with an increase in risk of vitreous hemorrhage or DME (48,49).

Treatment

Treatment modalities for diabetic retinopathy include retinal photocoagulation, intraocular injection of pharmacological agents and vitreoretinal surgery.

Laser therapy

As determined in the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS), laser therapy by panretinal photocoagulation to the retinal periphery reduces severe visual loss and reduces legal blindness by 90% in people with severe nonproliferative or proliferative retinopathy (9–11). As determined by the ETDRS, focal and/or grid laser treatment to the macula for CSME reduces the incidence of moderate visual loss by 50% (8). Long-term follow-up studies to the original laser photocoagulation trials confirm its benefit over several decades (50).

Local (intraocular) pharmacological intervention

In the treatment of DME with centre-involving disease, as defined by OCT or clinical examination, intraocular pharmacotherapy is now available. With the knowledge that the cytokine vascular endothelial growth factor (VEGF) plays a primary role in the development of DME, 2 anti-VEGF drugs are now widely used. Two masked phase III clinical trials, RISE and RIDE, using monthly ranibizumab, a humanized recombinant anti-VEGF antibody fragment, with or without prompt laser, improved visual acuity compared against sham over the 2 years of study (51). In the RISE trial, 44% and 39% of patients receiving 0.3 or 0.5 mg ranibizumab, respectively, gained 15 letters or more (3 lines) of acuity vs. 18% of those in the control arm. In the RIDE study, 33% or 45% of patients gained 15 letters or more at doses of 0.3 or 0.5 mg, respectively. Furthermore, 1-year results of a phase III clinical trial, RESTORE, using an initial loading dose of 3 monthly injections of 0.5 mg ranibizumab, and as-needed treatment thereafter, likewise showed improvement in the primary and secondary outcome measures of best correct visual acuity and reduction in central macular thickness. In all studies, this was true when ranibizumab was used as monotherapy or in conjunction with macular photocoagulation. In the RESTORE study, 37% to 43% of ranibizumab-treated patients improved vision by 10 letters or more compared to 16% with standard laser therapy (52). Two-year results are pending. Similar results were obtained by the Diabetic Retinopathy Clinical Research Network using physician-based flexible treatment algorithms rather than a strict prescribed injection schedule (53). Intravitreal injection with ranibizumab is approved by Health Canada.

A similar outcome was noted when comparing intraocular injection of bevacizumab (a full-length antibody against VEGF) to

macular laser. Two-year results of a phase III clinical trial, the BOLT trial, demonstrated a gain of at least 15 letters or more in 32% of patients receiving 1.25 mg bevacizumab compared to 4% in the control arm (54). However, unlike ranibizumab, intraocular injection of bevacizumab in diabetic retinopathy constitutes off-label use of the drug in Canada.

Steroids are an alternate class of drug evaluated in the treatment of DME. Intraocular injection of steroid combined with prompt macular laser was as effective as ranibizumab in a single subgroup of patients characterized by previous cataract surgery (53). However, treatment with intraocular steroid was associated with increased rates of glaucoma. Two phase III clinical trials investigating the implantation of a long-term drug delivery device containing fluocinolone acetonide met their primary and secondary outcomes (visual acuity and OCT) but showed increased rates of glaucoma and cataract progression compared to sham (55,56). The risk-to-benefit ratio was considered unacceptable to the United States Food and Drug Administration (FDA) where the treatment was not approved. By contrast, the fluocinolone insert has received approval in several European countries.

Surgical intervention

The Diabetic Retinopathy Vitrectomy Study (DRVS) Group evaluated the benefit of early vitrectomy (<6 months) in the treatment of severe vitreous hemorrhage (57) and very severe proliferative diabetic retinopathy (58). People with type 1 diabetes of <20 years' duration and severe vitreous hemorrhage were more likely to achieve good vision with early vitrectomy compared to conventional management (57). Similarly, early vitrectomy was

RECOMMENDATIONS

1. In individuals ≥ 15 years of age with type 1 diabetes, screening and evaluation for retinopathy by an expert professional should be performed annually starting 5 years after the onset of diabetes [Grade A, Level 1 (14,16)].
2. In individuals with type 2 diabetes, screening and evaluation for diabetic retinopathy by an expert professional should be performed at the time of diagnosis of diabetes [Grade A, Level 1 (15,18)] and annually thereafter. The interval for follow-up assessments should be tailored to the severity of the retinopathy. In those with no or minimal retinopathy, the recommended interval is 1–2 years [Grade A, Level 1 (15,18)].
3. Screening for diabetic retinopathy should be performed by experienced professionals, either in person or through interpretation of retinal photographs taken through dilated pupils [Grade A, Level 1 (66)].
4. To prevent the onset and delay the progression of diabetic retinopathy, people with diabetes should be treated to achieve optimal control of blood glucose [Grade A, Level 1A (32,33)] and BP [Grade A, Level 1A (40), for type 2 diabetes].
5. Though not recommended for CVD prevention or treatment, fenofibrate, in addition to statin therapy, may be used in patients with type 2 diabetes to slow the progression of established retinopathy [Grade A, Level 1A (37,46)].
6. Patients with sight-threatening diabetic retinopathy should be assessed by a general ophthalmologist or retina specialist [Grade D, Consensus]. Laser therapy and/or vitrectomy [Grade A, Level 1A (8,10,57,58)] and/or pharmacological intervention [Grade A, Level 1A (51,52,55,56)] should be used.
7. Visually disabled people should be referred for low-vision evaluation and rehabilitation [Grade D, Consensus].

Abbreviations:

BP, blood pressure; CVD, cardiovascular disease.

associated with higher chance of visual recovery in people with either type 1 or 2 diabetes with very severe proliferative diabetic retinopathy (58). Surgical advances in vitrectomy since the DRVS trials have demonstrated reduced side effects with more consistent favourable visual outcomes, thus supporting vitrectomy in advanced proliferative diabetic retinopathy (59). Furthermore, these advances have expanded surgical indications to include vitrectomy for diffuse macular edema with or without vitreomacular traction (60). It is worth noting that the use of peri-operative ASA (49,61,62) and warfarin therapy (63) for persons undergoing ophthalmic surgery does not appear to raise the risk of hemorrhagic complications.

Overall, the last few years have seen significant advances in systemic, local and surgical treatments of diabetic eye disease, with significantly improved visual outcome. Most notably, long-term follow-up to early laser studies confirm their sustained efficacy in preserving vision (50). New therapies, such as intraocular pharmacological treatment, await long-term follow-up but already demonstrate both preservation and recovery of vision in persons with DME. Despite these successes, it is important to encourage patients with even moderate visual loss to seek assistance from community services that provide spectacle correction, enhanced magnification, vision aids and measures to encourage independence and ongoing quality of life (64,65).

Other Relevant Guidelines

Targets for Glycemic Control, p. S31

Dyslipidemia, p. S110

Treatment of Hypertension, p. S117

Type 1 Diabetes in Children and Adolescents, p. S153

Type 2 Diabetes in Children and Adolescents, p. S163

Diabetes and Pregnancy, p. S168

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Clinical Practice Guidelines

Neuropathy

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Elevated blood glucose levels, elevated triglycerides, high body mass index, smoking and hypertension are risk factors for neuropathy.
- Intensive glycemic control is effective for the primary prevention or secondary intervention of neuropathy in people with type 1 diabetes.
- In people with type 2 diabetes, lower blood glucose levels are associated with a reduced frequency of neuropathy.
- Simple physical examination screening tests, such as the monofilament and vibration perception tests for neuropathy, perform reasonably well for the identification of neuropathy and prediction of its future onset.

Introduction

Detectable sensorimotor polyneuropathy will develop within 10 years of the onset of diabetes in 40% to 50% of people with type 1 or type 2 diabetes (1). Furthermore, up to 50% of children with type 1 diabetes will have subclinical polyneuropathy (2). While clinical neuropathy is uncommon in people with type 1 diabetes within the first 5 years after the onset of diabetes, people with type 2 diabetes may have neuropathy at the time of diagnosis (3). Risk factors for neuropathy include elevated blood glucose levels, elevated triglycerides, high body mass index, smoking and hypertension (4). Foot ulceration, which depends on the degree of foot insensitivity (5), and amputation are important and costly sequelae of diabetic neuropathy (6). Although not all patients with neuropathy have motor or sensory symptoms, the neuropathic pain associated with symptomatic disease is frequently bothersome and often limits physical activity, quality of life and work productivity (7,8). Additionally, patients with neuropathy utilize more health resources than those without this complication (9). Both somatic and autonomic neuropathies may occur and may require referral to a specialist experienced in managing the affected body system. Mononeuropathy, particularly carpal tunnel syndrome, is common in people with diabetes and can be difficult to diagnose (10). The underdiagnosis of neuropathy is a fundamental problem in the primary care of people with diabetes and impedes the benefits of early identification, the management necessary to achieve improved glycemic control and the prevention of neuropathy-related sequelae (11).

Screening for Peripheral Neuropathy

Screening for neuropathy can be performed rapidly and reliably using the 10-g Semmes-Weinstein monofilament or the 128-Hz tuning fork (12–16). Methods for using the monofilament or tuning fork to detect diabetic neuropathy are explained in Appendix 8 (12,13,16). In individuals with significant early progressive symptoms of neuropathy or in whom a clinical suspicion of nondiabetic neuropathy exists, referral for additional neurological evaluation is indicated.

Management of Neuropathy

Intensive glycemic control is effective for the primary prevention and secondary intervention of neuropathy in people with type 1 diabetes (8,17,18). In fact, the benefits of intensive insulin treatment persist for over a decade for the primary prevention of neuropathy (19). In those with type 2 diabetes, lower blood glucose levels are associated with a reduced frequency of neuropathy (7,20). No other disease-modifying treatments are currently available. Multiple treatments are available for the management of neuropathic pain, and detailed evidence-based guidelines on the treatment of painful diabetic neuropathy (PDN) have been published (21). An important observation is that few patients have complete relief of painful symptoms with any treatment, and that a 30% to 50% reduction in baseline pain is considered to be a clinically meaningful response. There are insufficient comparative studies to recommend which oral medication should be used first, although most practitioners advise against the use of opioids for PDN due to the potential for dependency, tolerance, dose escalation and diversion (21). Anticonvulsants (22–30) and antidepressants (31–40) are most often used as first-line therapy. Details are listed in Table 1. Opioids are effective for PDN (41–45) and are used mostly when other treatments fail. Other effective therapeutic options include topical nitrate sprays (46,47), topical capsaicin (48–52) and transcutaneous electrical nerve stimulation (52,53). However, effective treatment with capsaicin involves short-term pain that limits its acceptability and generalizability in clinical practice. The surgical release of distal lower limb nerves is not recommended due to lack of evidence supporting efficacy (54) and the possible complications of foot and ankle surgery in patients with diabetes.

Table 1

Treatment options for the management of painful diabetic peripheral neuropathy

	Suggested starting dose	Suggested titration if tolerated	Suggested maximal tolerated dose	Estimated monthly cost for starting dose
Anticonvulsants				
Gabapentin [†] (23,55)	300 mg bid	May titrate slowly up to 600 mg po qid	3,600 mg/day	\$36.55
Pregabalin (24–26,30)	75 mg bid	May titrate slowly up to 300 mg po bid	600 mg/day	\$101.84
Valproate [†] (27,28)	250 mg bid	May titrate slowly up to 500 mg po bid	1500 mg/day	\$12.37
Antidepressants				
Amitriptyline [†] (31,32)	10 mg qhs	May titrate slowly up to 100 mg po qhs	150 mg/day	\$19.92
Duloxetine (35,40)	30 mg OD	May titrate to 60 mg po OD	120 mg/day	\$138.81
Venlafaxine [†] (37)	37.5 mg bid	May titrate slowly up to 150 mg po bid	300 mg/day	\$8.16
Opioids				
Dextromethorphan (41)	100 mg qid	May titrate slowly up to 200 mg po qid	960 mg/day	\$4.08
Morphine sustained release (55)	15 mg bid	May titrate slowly up to 60 mg po bid	180 mg/day	\$62.05
Oxycodone ER (43)	10 mg bid	May titrate slowly up to 40 mg po bid	160 mg/day	\$56.90
Tapentadol ER	100 mg bid	May titrate slowly up to 250 mg po bid	500 mg/day	
Tramadol (44)	50 mg qid	May titrate slowly up to 50 mg po qid	400 mg/day	\$132.30
Others				
Topical nitrate sprays (46,47,51)	30 mg spray to legs qhs	May titrate slowly up to 30 mg spray to legs bid	60 mg/day	\$1.36
Capsaicin cream (48,49)	0.075% cream applied 3–4 times per day	May titrate to 5–6 times per day	5–6 applications per day	\$14.14
Transcutaneous electrical nerve stimulation (53,56)	—	—	—	—

bid, 2 times a day; OD, once daily; qhs, every bedtime; qid, 4 times a day.

Dose ranges are for adults and are taken from published trials; smaller starting doses and slower titration schedules may be indicated. Optimal doses are the lowest doses required for maximum efficacy without significant side effects. Although required for some agents, dose adjustments for renal and hepatic dysfunction are not shown here. Physicians should refer to the most current edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.

[†] Denotes that this drug is not currently approved by Health Canada for the management of neuropathic pain associated with diabetic peripheral neuropathy.

Although subclinical autonomic neuropathic manifestations are common, symptomatic involvement is infrequent. The diagnosis of symptomatic autonomic neuropathy is based on the exclusion of specific cardiovascular, gastrointestinal or genitourinary manifestations through assessment by a specialist in the affected system. The treatment of autonomic neuropathy is based primarily on expert opinion, but research in this field remains active.

Other Relevant Guidelines

Targets for Glycemic Control, p. S31

RECOMMENDATIONS

- In people with type 2 diabetes, screening for peripheral neuropathy should begin at diagnosis of diabetes and occur annually thereafter. In people with type 1 diabetes, annual screening should commence after 5 years' post-pubertal duration of diabetes [Grade D, Consensus].
- Screening for peripheral neuropathy should be conducted by assessing loss of sensitivity to the 10-g monofilament or loss of sensitivity to vibration at the dorsum of the great toe [Grade A, Level 1 (13,16)].
- People with diabetes should be treated with intensified glycemic control to prevent the onset and progression of neuropathy [Grade A, Level 1A (8,17), for type 1 diabetes; Grade B, Level 2 (20), for type 2 diabetes].
- The following agents may be used alone or in combination for relief of painful peripheral neuropathy:
 - Anticonvulsants (pregabalin [Grade A, Level 1 (24,29)], gabapentin,[†] valproate[†] [Grade B, Level 2 (23,27,28,55)])
 - Antidepressants (amitriptyline,[†] duloxetine, venlafaxine[†]) [Grade B, Level 2 (31,32,35,37,39)]
 - Opioid analgesics (tapentadol ER, oxycodone ER, tramadol) [Grade B, Level 2 (41,43–45,55)]
 - Topical nitrate spray [Grade B, Level 2 (46,47,51)]

Footnote:

[†] Denotes that this drug is not currently approved by Health Canada for the management of neuropathic pain associated with diabetic peripheral neuropathy. Most studies failed to achieve Grade A, Level 1, due to a <80% completion rate (21).

Foot Care, p. S145

Type 1 Diabetes in Children and Adolescents, p. S153

Type 2 Diabetes in Children and Adolescents, p. S163

Relevant Appendix

Appendix 8: Rapid Screening for Diabetic Neuropathy

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Clinical Practice Guidelines

Foot Care

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Foot problems are a major cause of morbidity and mortality in people with diabetes and contribute to increased healthcare costs.
- The management of foot ulceration in people with diabetes requires an interdisciplinary approach that addresses glycemic control, infection, off-loading of high-pressure areas, lower-extremity vascular status and local wound care.
- Antibiotic therapy is not generally required for neuropathic foot ulcerations that show no evidence of infection.

Introduction

Foot complications are a major cause of morbidity and mortality in persons with diabetes and contribute to increased healthcare utilization and costs (1–3). In populations with diabetes, individuals with peripheral neuropathy and peripheral arterial disease (PAD) are predisposed to foot ulceration and infection, which ultimately may lead to lower-extremity amputation (4–6). Although amputation rates for people with diabetes have decreased in the past decade, they remain exceedingly high compared to nondiabetic populations (7,8). Therefore, it is essential that every effort possible be made to prevent foot problems, and, if they do occur, that early and aggressive treatment be undertaken.

Risk Assessment

Characteristics that have been shown to confer a risk of foot ulceration in persons with diabetes include peripheral neuropathy, previous ulceration or amputation, structural deformity, limited joint mobility, PAD, microvascular complications, high glycated hemoglobin (A1C) levels and onychomycosis (9–11). Loss of sensation over the distal plantar surface to the 10-g Semmes Weinstein monofilament is a significant and independent predictor of future foot ulceration and the possibility of lower-extremity amputation (12).

In those persons with diabetes with foot ulcers, a number of wound classification systems have been developed to provide objective assessment of severity. Of these, the University of Texas Diabetic Wound Classification System has been validated as a predictor of serious outcomes in patients with diabetes with foot ulcers (Table 1) (13,14).

In persons with diabetes with underlying ischemia, the distribution of PAD is greater in the arterial tree below the knee than is seen in those without diabetes (15). Noninvasive assessments for PAD in diabetes include the use of the ankle-brachial blood pressure index (ABI), determination of systolic toe pressure by photoplethysmography (PPG) (PPG assesses the intensity of light reflected from the skin surface and the red cells below, which is indicative of arterial pulse flow in the arterioles of the respective area), transcutaneous oximetry (tcPO₂) and Doppler arterial flow studies (16,17). Although the ABI is a readily available and easy-to-perform technique, it may underestimate the degree of peripheral arterial obstruction in some individuals with diabetes partly due to medial arterial wall calcification in lower-extremity arteries (18). Measurement of systolic toe pressure by PPG may be more accurate in determining the presence of arterial disease in this population (19).

For those persons in whom lower-limb ischemia is suspected, intra-arterial digital subtraction contrast arteriography has provided the most definitive assessment of PAD but may precipitate renal failure in individuals with higher degrees of renal insufficiency. Advanced magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) do not require arterial access and, therefore, have gained popularity as reliable alternatives to iodinated contrast studies due to their less invasive approaches (20–22). However, caution is still necessary with MRA and CTA in persons with renal dysfunction. The injection of intravenous radiocontrast dye also must be used in CTA; therefore, caution should be exercised (as with the use of intra-arterial iodinated contrast) in persons with renal insufficiency so as to avoid precipitating acute renal failure. Gadolinium-based contrast agents used in MRA have been associated with the development of nephrogenic systemic fibrosis in individuals with poor renal function (23,24).

The foot examination should include the assessment of skin temperature since increased warmth is the first indicator of inflammation in an insensate foot and also may be the first sign of acute Charcot neuroarthropathy resulting from the loss of protective sensation in the foot (25–27). In addition, an acute Charcot foot may be associated with erythema and swelling, with overall clinical characteristics very similar to cellulitis (28,29). The clinical and radiological differentiation between an acute Charcot foot and a foot infection can be very challenging (30). Plain radiographs have low sensitivity and specificity in differentiating osteomyelitis from Charcot changes. Magnetic resonance imaging (MRI) of the foot may help clarify this differential diagnosis, although no single

Table 1
University of Texas Diabetic Wound Classification System (13)

University of Texas Diabetic Wound Classification System				
Stage	Grade			
	0	I	II	III
A (no infection or ischemia)	Pre- or post-ulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischemia	Ischemia	Ischemia	Ischemia
D	Infection and ischemia	Infection and ischemia	Infection and ischemia	Infection and ischemia

radiological investigation to date has proven to be completely definitive (31).

Management and Preventative Care

The prevention of amputations has involved the use of various preventative measures, including regular foot examination and evaluation of amputation risk, regular callus debridement, patient education, professionally fitted therapeutic footwear to reduce plantar pressure and accommodate foot deformities, and early detection and treatment of diabetic foot ulcers (32). Many of the studies conducted to assess interventions designed to reduce the occurrence of and heal diabetic foot ulcers have, unfortunately, suffered from methodological problems, thereby reducing the quality of the evidence to support their use (33,34).

Generally, the management of foot ulceration should address glycemic control, pressure relief/offloading, infection, lower-extremity vascular status and local wound care (35). This is best achieved with an interdisciplinary approach (36,37).

Specific recommendations about dressing types cannot be made as there is insufficient evidence to support the use of one variety versus another; however, the concepts that are generally accepted as the essentials of good wound care include the provision of an optimal wound environment, pressure offloading from the ulcer site and, in nonischemic wounds, regular debridement of nonviable tissue (38,39). In general, wound dressings that maintain a moist wound environment should be selected. There are insufficient data to support the use of specific dressing types or antimicrobial dressings in the routine management of diabetic foot wounds (40–48). There is also insufficient evidence to make any recommendation about the role of negative pressure wound therapy (NPWT) in the routine management of neuropathic wounds. There is, however, some evidence to support NPWT as a postoperative intervention after extensive debridement (49–52). Other adjunctive measures for wound healing, such as topical growth factors and dermal substitutes, have been studied in diabetic foot ulcer management, but these studies have been limited in sample size, duration and follow-up. These therapies may be considered if other conventional options already have been explored (53).

Pressure offloading may be achieved with temporary footwear until the ulcer heals and the character of the foot stabilizes. Removable and irremovable cast walkers and total contact casting have demonstrated efficacy as pressure-reducing devices in plantar surface ulcers (54–56). Although very effective in healing noninfected, nonischemic plantar surface neuropathic ulcers, total contact casting requires careful individual selection and personnel trained specifically in its application due to its potential for complications (57). Where bony foot deformities prevent the fitting

of appropriate footwear and/or offloading of pressure-related ulcers, consultation with a surgeon skilled in foot surgery may be considered to address the deformity (58–60).

Treatment of the acute Charcot foot requires immobilization of the foot, typically for several months, in a total contact cast or removable walker device until excessive foot temperatures return to normal (61). Although bisphosphonate therapy has been considered for the management of Charcot arthropathy, further studies are necessary to fully evaluate the use of these agents and other medical therapies in the routine treatment of Charcot arthropathy (62–64).

Infection may complicate foot ulcers and may progress rapidly to become limb and/or life threatening (65). When infections first begin, the most frequently encountered pathogens include *Staphylococcus aureus*, *Streptococcus pyogenes* (group A streptococcus) and *Streptococcus agalactiae* (group B streptococcus). With time and the presence of devitalized tissue, gram-negative and anaerobic pathogens also can play a role in the process, leading to polymicrobial infections (66,67). Specimens for culture from the surface of wounds, as opposed to deeper tissues obtained by debridement, are unreliable in determining the bacterial pathogens involved (68–70). Initial antibiotic therapy is typically empiric and may be broad spectrum, with subsequent antibiotic selection tailored to the sensitivity results of cultured specimens. With the exception of only a small number of antimicrobial agents that do have a specific indication for the treatment of diabetic foot infections, the majority of the agents available for use are selected for their antibacterial spectrum (66,71). Table 2 summarizes the different antimicrobial choices for the empiric management of foot infections in persons with diabetes. Uncontrolled diabetes can result in immunopathy with a blunted cellular response to infection. Up to 50% of patients with diabetes who have a significant limb infection may not have systemic signs of fever or leukocytosis at presentation (72). Deep infections require prompt surgical debridement in addition to appropriate antibiotic therapy (73). Granulocyte colony-stimulating factors have been used as adjunctive therapy in infected diabetic wounds and, in some studies, were found to reduce the need for surgical intervention. Data are limited and caution is advised in interpreting these findings (74).

In medically suitable individuals with PAD, distal limb revascularization has potential benefit in long-term limb salvage. Certain subpopulations with diabetes on insulin therapy have poorer outcomes after revascularization than those on oral antihyperglycemic therapy, perhaps reflecting a greater association of comorbidities (75,76). Endovascular techniques with angioplasty and stenting in infrainguinal arteries are also effective in limb salvage, although the long-term results are inferior in the population with diabetes compared to those without diabetes (77,78).

Table 2

Empiric antimicrobial therapy for infection in the diabetic foot

Empiric therapy for infection in the diabetic foot*	
Infection severity	Antimicrobial agent (1,2,3,4)
Localized infections: <ul style="list-style-type: none"> • Neither limb- nor life-threatening • Usually associated with cellulitis surrounding an ulcer • Purulent debris may be present at the base of the ulcer • Usual organisms: aerobic Gram-positive cocci (<i>S. aureus</i>) and beta-hemolytic streptococci • Frequently treated with outpatient oral antimicrobial therapy 	<ul style="list-style-type: none"> • cloxacillin • cephalexin • TMP-SMX • clindamycin • amoxicillin-clavulanic acid • linezolid • doxycycline
More extensive infections: <ul style="list-style-type: none"> • Includes more severe infections than those classified as localized infections, including more extensive cellulitis, plantar abscess, and deep-space infections • The choice of oral or parenteral therapy should be guided by the extent of the infection and the patient's overall clinical status • Initial antimicrobial therapy against staphylococci, streptococci, anaerobes, and common Enterobacteriaceae species • Patients who are not toxic may be treated with debridement and oral antimicrobial therapy • Patients who are ill or toxic despite moderate local signs are treated as having a severe infection <ul style="list-style-type: none"> - Limb- or life-threatening - Patients may be critically ill or toxic and usually are treated with initial parenteral therapy until stable, then oral therapy - Frequently polymicrobial - Immediate hospitalization, early surgical debridement, and parenteral antimicrobial therapy - If MRSA is present or suspected, the addition of vancomycin, or linezolid, may be considered 	Oral Options <ul style="list-style-type: none"> • TMP-SMX plus metronidazole or clindamycin • ciprofloxacin (or levofloxacin) plus clindamycin or metronidazole • amoxicillin-clavulanic acid • moxifloxacin • linezolid Parenteral Options <ul style="list-style-type: none"> • cefoxitin • first (cefazolin), second (cefuroxime), or third (ceftriaxone or cefotaxime) generation cephalosporin plus metronidazole • combination of beta-lactam antibiotic and beta-lactamase inhibitor (piperacillin/tazobactam) • clindamycin plus third generation cephalosporin (cefotaxime, ceftriaxone or ceftazidime) • carbapenem (imipenem/cilastatin, meropenem or ertapenem)
Osteomyelitis: <ul style="list-style-type: none"> • Treat with parenteral therapy or long-term oral antimicrobial therapy with agents that are well absorbed from the gastrointestinal tract and have good distribution to bone and tissue • Surgical debridement is indicated to remove necrotic debris, abscess, or sequestrum • Therapy should be based on culture results whenever possible • If MRSA is present or suspected, addition of vancomycin, or linezolid, may be considered 	Oral Options <ul style="list-style-type: none"> • cloxacillin • cephalexin • TMP-SMX • clindamycin • amoxicillin-clavulanic acid • linezolid • doxycycline • TMP-SMX plus metronidazole or clindamycin • levofloxacin or ciprofloxacin plus metronidazole or clindamycin Parenteral Options <ul style="list-style-type: none"> • combination of beta-lactam antibiotic and beta-lactamase inhibitor (piperacillin/tazobactam) • clindamycin (oral or parenteral) plus third generation cephalosporin (cefotaxime, ceftriaxone, or ceftazidime) • carbapenem (imipenem/cilastatin, meropenem, ertapenem)
<ol style="list-style-type: none"> 1. The agents suggested in this section are for empiric therapy prior to the availability of final culture and susceptibility results. Dosages must be adjusted based upon the creatinine clearance. 2. Knowledge of local epidemiology must also guide therapeutic choices, as some agents (beta-lactams) are ineffective against MRSA. 3. Antibacterial therapy should be guided by available culture results. If culture results are unavailable to guide therapy or there is any doubt about the most appropriate antimicrobial regimen, discussion with an infectious diseases consultant may be prudent. 4. Duration of therapy is based on clinical response. However, typical treatment courses for skin and soft tissue infections range from seven (mild) to 21 (severe) days, and the treatment of osteomyelitis may require four to six weeks of parenteral or several months of oral antimicrobial therapy. Whenever possible, it is desirable to switch to oral antimicrobial therapy to avoid complications from parenteral administration. 	

MRSA, methicillin-resistant *Staphylococcus aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.*Modified and used with permission from Embil JM, Trepman E. Diabetic foot infections. In: *Principles and Practice of Hospital Medicine*. Editors: Sylvia C. McKean, John J. Ross, Daniel D. Dressler, Daniel J. Brotman, Jeffrey S. Ginsberg. Printed in China: McGraw-Hill; 2012.

Hyperbaric oxygen therapy (HBOT) is not considered part of the routine management of persons with neuropathic/neuroischemic foot ulcerations with or without underlying infection. In carefully selected persons with nonhealing foot ulcerations for whom all possible interventions have been attempted, HBOT may be considered as an adjunctive therapy (79–81). Currently, evidence-based criteria for the selection of persons with diabetes who have foot problems and who may benefit from HBOT do not exist.

RECOMMENDATIONS

1. In people with diabetes, foot examinations by healthcare providers should be an integral component of diabetes management to identify persons at risk for ulceration and lower-extremity amputation [Grade C, Level 3 (5,12)] and should be performed at least annually and at more frequent intervals in those at high risk [Grade D, Level 4 (1)]. Assessment by healthcare providers should include the assessment of skin changes, structural abnormalities (e.g. range of motion of ankles and toe joints, callus pattern, bony deformities), skin temperature, evaluation for neuropathy and PAD, ulcerations and evidence of infection [Grade D, Level 4 (1)].
2. People at high risk of foot ulceration and amputation should receive foot care education (including counselling to avoid foot trauma), professionally fitted footwear and early referrals to a healthcare professional trained in foot care management if foot complications occur [Grade C, Level 3 (33,82,83)].
3. Individuals who develop a foot ulcer should be managed by a multidisciplinary healthcare team with expertise in the management of foot ulcers to prevent recurrent foot ulcers and amputation [Grade C, Level 3 (36)].
4. There is currently insufficient evidence to recommend any specific dressing type for diabetic foot ulcers [Grade C, Level 3 (40)]. General principles of wound management involve the provision of a moist wound environment, debridement of nonviable tissue (nonischemic wounds) and offloading of pressure areas [Grade B, Level 3 (38)].
5. Evidence is currently lacking to support the routine use of adjunctive wound-healing therapies, such as topical growth factors, granulocyte colony-stimulating factors, dermal substitutes or HBOT in diabetic foot ulcers, but they may be considered in nonhealing, nonischemic wounds when all other options have been exhausted [Grade D, Level 4 (53,74,80)].

Abbreviations:

HBOT, hyperbaric oxygen therapy; PAD, peripheral arterial disease.

Other Relevant Guidelines

Targets for Glycemic Control, p. S31
Neuropathy, p. S142

Relevant Appendices

Appendix 9: Diabetes and Foot Care: A Patient's Checklist
Appendix 10: Diabetic Foot Ulcers: Essentials of Management

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Clinical Practice Guidelines

Erectile Dysfunction

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Gerald Brock MD, FRCSC, William Harper MD, FRCPC

KEY MESSAGES

- Erectile dysfunction (ED) affects approximately 34% to 45% of adult men with diabetes, has been demonstrated to negatively impact quality of life among those affected across all age strata and may be the earliest sign of cardiovascular disease.
- All adult men with diabetes should be regularly screened for ED with a sexual function history. Those with ED should be investigated for hypogonadism.
- The current mainstay of therapy is phosphodiesterase type 5 inhibitors. They have been shown to have major impacts on erectile function and quality of life, with a low reported side effect profile, and should be offered as first-line therapy to men with diabetes wishing treatment for ED.

Introduction

Erectile dysfunction (ED) affects approximately 34% to 45% of men with diabetes and has been demonstrated to negatively impact quality of life among those affected across all age strata, with a greater likelihood among men with diabetes that their ED is permanent (1). Recent reports describe up to one-third of newly diagnosed men with diabetes have ED at presentation (2), with upward of 50% of men having ED by year 6 after diagnosis (3). Furthermore, studies indicate that 40% of men with diabetes >60 years of age have complete ED (4–12). Recent studies have reported that alteration of the cyclic guanosine monophosphate (cGMP)/nitric acid (NO) pathway among men with diabetes with impaired vascular relaxation is related to endothelial dysfunction (13–15). Among the population with diabetes, risk factors include increasing age, duration of diabetes, poor glycemic control, cigarette smoking, hypertension, dyslipidemia, androgen deficiency states (16) and cardiovascular (CV) disease (8,10,17,18). ED as a marker of potential CV events has been reported by numerous investigators (19–26). In fact, ED has been shown to be significantly associated with all-cause mortality and CV events (27,28). Diabetic retinopathy has been shown to correlate with the presence of ED (8,10,29). Organic causes of ED include microvascular and macrovascular disease, and neuropathy. In addition, psychological or situational factors may cause or contribute to ED.

In spite of the overwhelming amount of data linking ED and diabetes, this remains a subject often neglected by clinicians treating the population with diabetes (30).

Compared with the general population, multiple studies have reported men with diabetes having higher rates of hypogonadism (16,31–34). Interestingly, a recent report describes

a correlation between glycemic control and testosterone levels (35). Importantly, phosphodiesterase type 5 (PDE5) inhibitors appear to be less effective in hypogonadal states (32,34,36), where treatment of nonresponders to PDE5 inhibitors with testosterone replacement is successful in roughly 50% of individuals. In addition, ED is a side effect of many drugs commonly prescribed to men with diabetes, such as some antihypertensives and antidepressants.

Screening

All adult men with diabetes should be regularly screened for ED with a sexual function history. Screening for ED in men with type 2 diabetes should begin at diagnosis of diabetes. Validated questionnaires (e.g. International Index of Erectile Function (37,38) or Sexual Health Inventory for Men (39)) have been shown to be both sensitive and specific in determining the presence of ED and providing a means of assessing response to therapy. Men with diabetes and ED should be further investigated for hypogonadism. The Androgen Deficiency in Aging Males (ADAM) instrument is the most widely accepted screening questionnaire, and, while bioavailable testosterone is recognized as the gold standard for biochemistry confirmation, total testosterone is an acceptable alternative if bioavailable testosterone is unavailable or unaffordable (40).

Treatment

While no randomized clinical trials have demonstrated that interventions that improve glycemic control also reduce the incidence and progression of ED, the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive glycemic control was effective for primary prevention of and secondary intervention for neuropathy, a condition that can impair sensory feedback from the penis, leading to reduced erectile function (41–43). The current data are controversial as it relates to diet, glycemic control and ED, with both positive and negative studies (28,44–46). Based on these conflicting data, a prudent physician should encourage tight glycemic control as a potential factor in maintaining erectile function (28).

The current mainstay of treatment for ED is therapy with PDE5 inhibitors. They have been reported to have a major impact on erectile function and quality of life, and should be

offered as first-line therapy to men with diabetes wishing treatment for ED (47–52). Evidence for scheduled daily therapy is effective within the population with diabetes and ED (53,54), and may improve efficacy with lower rates of side effects, may impact lower urinary tract symptoms and has the potential for endothelial benefits (55). Additionally, among PDE5 inhibitor failure patients, use of a vacuum constriction device may salvage a significant percentage of erectile function and should be considered (56).

Contraindications for the use of PDE5 inhibitors include unstable angina or untreated cardiac ischemia and concomitant use of nitrates (3,57,58). Interestingly, men with diabetes appear to have lower rates of side effects with PDE5 inhibitors than the general population. This is believed to be a result of altered vaso-motor tone or other factors (59).

Referral to a specialist in ED should be offered to men who do not respond to PDE5 inhibitors or for whom the use of PDE5 inhibitors is contraindicated. Second-line therapies (e.g. vacuum constriction devices, intracorporal injection therapy with prostaglandin E1 [PGE1] alone or in combination with papaverine and phentolamine [triple therapy], or intraurethral therapy using PGE1) or third-line therapy (penile prosthesis) may be considered for these men (60).

Ejaculatory Disorders

Ejaculatory disorders are a common disorder of sexual function in men with diabetes, occurring in 32–67% of that population (61). They range in scope from retrograde ejaculation, usually secondary to autonomic neuropathy with incomplete closure of the bladder neck during ejaculation, to premature or retarded ejaculation. Their recognition as an important component in sexual quality of life makes inquiry about ejaculatory function important.

RECOMMENDATIONS

1. All adult men with diabetes should be regularly screened for ED with a sexual function history [Grade D, Consensus].
2. Men with diabetes and ED should be investigated for hypogonadism [Grade D, Level 4 (16,31,32,34)].
3. A PDE5 inhibitor, if there are no contraindications to its use, should be offered as first-line therapy to men with diabetes and ED in either an on-demand [Grade A, Level 1A (47–53)] or scheduled-use [Grade B, Level 2 (53,54)] dosing regimen.
4. Referral to a specialist in ED should be considered for eugonadal men who do not respond to PDE5 inhibitors or for whom the use of PDE5 inhibitors is contraindicated [Grade D, Consensus].
5. Men with diabetes and ejaculatory dysfunction who are interested in fertility should be referred to a healthcare professional experienced in the treatment of ejaculatory dysfunction [Grade D, Consensus].

Abbreviations:

ED, erectile dysfunction; PDE5, phosphodiesterase type 5.

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Other Relevant Guidelines

Screening for the Presence of Coronary Artery Disease, p. S105
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Clinical Practice Guidelines

Type 1 Diabetes in Children and Adolescents

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Suspicion of diabetes in a child should lead to immediate confirmation of the diagnosis and initiation of treatment to reduce the likelihood of diabetic ketoacidosis (DKA).
- Management of pediatric DKA differs from DKA in adults because of the increased risk for cerebral edema. Pediatric protocols should be used.
- Children should be referred for diabetes education, ongoing care and psychosocial support to a diabetes team with pediatric expertise.

Note: Unless otherwise specified, the term “child” or “children” is used for individuals 0 to 18 years of age, and the term “adolescent” for those 13 to 18 years of age.

Introduction

Diabetes mellitus is the most common endocrine disease and one of the most common chronic conditions in children. Type 2 diabetes and other types of diabetes, including genetic defects of beta cell function, such as maturity-onset diabetes of the young, are being increasingly recognized in children and should be considered when clinical presentation is atypical for type 1 diabetes. This section addresses those areas of type 1 diabetes management that are specific to children.

Education

Children with new-onset type 1 diabetes and their families require intensive diabetes education by an interdisciplinary pediatric diabetes healthcare (DHC) team to provide them with the necessary skills and knowledge to manage this disease. The complex physical, developmental and emotional needs of children and their families necessitate specialized care to ensure the best long-term outcomes (1,2). Education topics must include insulin action and administration, dosage adjustment, blood glucose (BG) and ketone testing, sick-day management and prevention of diabetic ketoacidosis (DKA), nutrition therapy, exercise, and prevention, detection, and treatment of hypoglycemia. Anticipatory guidance and lifestyle counselling should be part of routine care, especially during critical developmental transitions (e.g. upon school entry, beginning high school). Healthcare providers should regularly initiate discussions with children and their families about

school, diabetes camp, psychological issues, substance use, obtaining a driver's license and career choices.

Children with new-onset diabetes who present with DKA require a short period of hospitalization to stabilize the associated metabolic derangements and to initiate insulin therapy. Outpatient education for children with new-onset diabetes has been shown to be less expensive than inpatient education and associated with similar or slightly better outcomes when appropriate resources are available (3).

Glycemic Targets

As improved metabolic control reduces both the onset and progression of diabetes-related complications in adults and adolescents with type 1 diabetes (4,5), aggressive attempts should be made to reach the recommended glycemic targets outlined in Table 1. However, clinical judgement is required to determine which children can reasonably and safely achieve these targets. Treatment goals and strategies must be tailored to each child, with consideration given to individual risk factors. Young age at diabetes onset (<7 years of age) has been associated with poorer cognitive function in many studies (6). Episodes of severe hypoglycemia have been associated with poorer cognitive function in some follow-up studies, while other studies have found chronic hyperglycemia in young children to be associated with poorer cognitive performance (7–10). Analysis from a large multicentre observational study found that knowledge of glycemic targets by patients and parents, and consistent target setting by the diabetes team, was associated with improved metabolic control (11).

Insulin Therapy

Insulin therapy is the mainstay of medical management of type 1 diabetes. A variety of insulin regimens can be used, but few have been studied specifically in children with new-onset diabetes. The choice of insulin regimen depends on many factors, including the child's age, duration of diabetes, family lifestyle, socioeconomic factors, and family, patient, and physician preferences. Regardless of the insulin regimen used, all children should be treated to meet glycemic targets.

The honeymoon period, which can last up to 2 years after diagnosis, is characterized by good glycemic control and low insulin requirements (<0.5 units/kg/day). At the end of this period, more

Table 1
Recommended glycemic targets for children and adolescents with type 1 diabetes

Age (years)	A1C (%)	Fasting/preprandial PG (mmol/L)	Two-hour postprandial PG* (mmol/L)	Considerations
<6	<8.0	6.0–10.0	—	Caution is required to minimize hypoglycemia because of the potential association between severe hypoglycemia and later cognitive impairment. Consider target of <8.5% if excessive hypoglycemia occurs
6–12	≤7.5	4.0–10.0	—	Targets should be graduated to the child's age. Consider target of <8.0% if excessive hypoglycemia occurs.
13–18	≤7.0	4.0–7.0	5.0–10.0	Appropriate for most adolescents. [†]

A1C, glycated hemoglobin; PG, plasma glucose.

* Postprandial monitoring is rarely done in young children except for those on pump therapy for whom targets are not available.

[†] In adolescents in whom it can be safely achieved, consider aiming toward normal PG range (i.e. A1C ≤6.0%, fasting/preprandial PG 4.0–6.0 mmol/L and 2-hour postprandial PG 5.0–8.0 mmol/L).

intensive management may be required to continue meeting glycemic targets. Two methods of intensive diabetes management have been used: basal-bolus regimens (long-acting basal insulin analogues and rapid-acting bolus insulin analogues) and continuous subcutaneous insulin infusion (CSII; insulin pump therapy). Basal-bolus therapy has resulted in improved control over traditional twice daily NPH and rapid-acting bolus analogue therapy in some but not all studies (12,13). CSII is safe and effective and can be initiated at any age (14). A Cochrane review found that CSII gave slightly improved metabolic control over basal-bolus therapy (15). Some clinic-based studies of CSII in school-aged children and adolescents have shown a significant reduction in glycated hemoglobin (A1C) with reduced hypoglycemia 12 to 24 months after initiation of CSII when compared to pre-CSII levels (16). CSII, with use of a continuous glucose sensor, resulted in improved control over basal-bolus therapy alone (17). Most, but not all, pediatric studies of the long-acting basal insulin analogues, detemir and glargine, have demonstrated improved fasting BG levels and fewer episodes of nocturnal hypoglycemia with a reduction in A1C (12,18–20). Two large population-based observational studies have not found improved A1C in patients using basal-bolus therapy or CSII when compared to those using NPH and rapid-acting bolus analogues (21,22). Individualization of insulin therapy to reach A1C targets, minimize hypoglycemia and optimize quality of life is indicated.

Glucose Monitoring

Self-monitoring of BG is an essential part of management of type 1 diabetes (23). Subcutaneous continuous glucose sensors allow detection of asymptomatic hypoglycemia and hyperglycemia. Use has resulted in improved diabetes control with less hypoglycemia in some studies. A randomized controlled trial did not show improved control in children and adolescents but did in adults (24). Benefit correlated with duration of sensor use, which was much lower in children and adolescents.

Nutrition

All children with type 1 diabetes should receive counselling from a registered dietitian experienced in pediatric diabetes. Children with diabetes should follow a healthy diet as recommended for children without diabetes in *Eating Well with Canada's Food Guide* (25). This involves consuming a variety of foods from the 4 food groups (grain products, vegetables and fruits, milk and alternatives, and meat and alternatives). There is no evidence that 1 form of nutrition therapy is superior to another in attaining age-appropriate glycemic targets. Appropriate matching of insulin to carbohydrate content may allow increased flexibility and improved glycemic control (26,27), but the use of insulin to carbohydrate ratios is not required. The effect of protein and fat on glucose

absorption must also be considered. Nutrition therapy should be individualized (based on the child's nutritional needs, eating habits, lifestyle, ability and interest) and must ensure normal growth and development without compromising glycemic control. This plan should be evaluated regularly and at least annually. Features suggestive of eating disorders and of celiac disease should be systematically sought out (28).

Hypoglycemia

Hypoglycemia is a major obstacle for children with type 1 diabetes and can affect their ability to achieve glycemic targets. Children with early-onset diabetes are at greatest risk for disruption of cognitive function and neuropsychological skills, but the respective roles of hypoglycemia and hyperglycemia in their development are still questioned (6,29). Significant risk of hypoglycemia often necessitates less stringent glycemic goals, particularly for younger children. There is no evidence in children that 1 insulin regimen or mode of administration is superior to another for resolving non-severe hypoglycemia. As such, treatment must be individualized (30). Frequent use of continuous glucose monitoring in a clinical care setting may reduce episodes of hypoglycemia (31). Severe hypoglycemia should be treated with pediatric doses of intravenous (IV) dextrose in the hospital setting or glucagon in the home setting. In children, the use of mini-doses of glucagon has been shown to be useful in the home management of mild or impending hypoglycemia associated with inability or refusal to take oral carbohydrate. A dose of 10 µg per year of age (minimum dose 20 µg, maximum dose 150 µg) is effective at treating and preventing hypoglycemia, with an additional doubled dose given if the BG has not increased in 20 minutes (32,33). See Table 2 for treatment of mild-to-moderate hypoglycemia.

Chronic Poor Metabolic Control

Diabetes control may worsen during adolescence. Factors responsible for this deterioration include adolescent adjustment issues, psychosocial distress, intentional insulin omission and physiological insulin resistance. A careful multidisciplinary assessment should be undertaken for every child with chronic poor metabolic control (e.g. A1C >10.0%) to identify potential causative

Table 2
Examples of carbohydrate for treatment of mild-to-moderate hypoglycemia

Patient weight	<15 kg	15–30 kg	>30 kg
Amount of carbohydrate	5 g	10 g	15 g
Carbohydrate source			
Glucose tablet (4 g)	1	2 or 3	4
Dextrose tablet (3 g)	2	3	5
Apple or orange juice, regular soft drink, sweet beverage (cocktails)	40 mL	85 mL	125 mL

factors, such as depression and eating disorders, and to identify and address barriers to improved control. Multipronged interventions that target emotional, family and coping issues show a modest reduction in A1C with reduced rates of hospital admission (34,35).

DKA

DKA occurs in 15% to 67% of children with new-onset diabetes and at a frequency of 1 to 10 episodes per 100 patient years in those with established diabetes (36). As DKA is the leading cause of morbidity and mortality in children with diabetes, strategies are required to prevent the development of DKA (37). In new-onset diabetes, DKA can be prevented through earlier recognition and initiation of insulin therapy. Public awareness campaigns about the early signs of diabetes have significantly reduced the frequency of DKA in new-onset diabetes (38). In children with established diabetes, DKA results from failing to take insulin or poor sick-day management. Risk is increased in children with poor metabolic control or previous episodes of DKA, peripubertal and adolescent girls, children on insulin pumps or long-acting basal insulin analogues, children with psychiatric disorders and those with difficult family circumstances (39–41). The frequency of DKA in established diabetes can be decreased with education, behavioural intervention and family support (42,43), as well as access to 24-hour telephone services for parents of children with diabetes (44,45).

Management of DKA

While most cases of DKA are corrected without event, 0.7% to 3.0% of pediatric cases are complicated by cerebral edema (CE) (46), which is associated with significant morbidity (21% to 35%) and mortality (21% to 24%) (47). In contrast, CE has rarely been reported in adults (39,47). Although the cause of CE is still unknown, several factors are associated with increased risk (Table 3) (48–52). A bolus of insulin prior to infusion is not recommended since it does not offer faster resolution of acidosis (53,54) and may contribute to CE (55). Recent evidence suggests early insulin administration (within the first hour of fluid replacement) may increase the risk for CE (52). Special caution should be exercised in young children with DKA and new-onset diabetes or a greater degree of acidosis and extracellular fluid volume depletion because of the increased risk of CE. Use of bedside criteria may allow earlier identification of patients who require treatment for CE (56). DKA should be managed according to published protocols for management of pediatric DKA (Figure 1) (57).

Immunization

Historically, national guidelines have recommended influenza and pneumococcal immunization for children with type 1 diabetes (58–60). Currently, there is no evidence supporting increased morbidity or mortality from influenza or pneumococcus in children with type 1 diabetes (61,62). However, the management of type 1 diabetes can be complicated by illness, requiring parental knowledge of sick-day management and increased attention during periods of illness. For this reason, parents may choose to immunize their children. Long-lasting immunogenicity to influenza vaccination has been shown to be adequate in these children (63).

Smoking Prevention and Cessation

Smoking is a significant risk factor for both macrovascular and microvascular complications of diabetes (64) and, in adolescents, is associated with worse metabolic control (65). Smoking prevention should be emphasized throughout childhood and adolescence.

Table 3

Risk factors for cerebral edema

- Younger age (<5 years)
- New-onset diabetes
- High initial serum urea
- Low initial partial pressure of arterial carbon dioxide (pCO₂)
- Rapid administration of hypotonic fluids
- IV bolus of insulin
- Early IV insulin infusion (within first hour of administration of fluids)
- Failure of serum sodium to rise during treatment
- Use of bicarbonate

IV, intravenous.

Contraception and Sexual Health Counselling

Adolescents with diabetes should receive regular counselling about sexual health and contraception. Unplanned pregnancies should be avoided, as pregnancy in adolescent females with type 1 diabetes with suboptimal metabolic control may result in higher risks of maternal and fetal complications than in older women with type 1 diabetes who are already at increased risk compared to the general population (66).

Psychological Issues

For children, and particularly adolescents, there is a need to identify psychological disorders associated with diabetes and to intervene early to minimize the impact over the course of development.

Psychological/psychiatric risks

Children and adolescents with diabetes have significant risks for psychological problems, including depression, anxiety, eating disorders and externalizing disorders (67–69). The risks increase exponentially during adolescence (70,71). Studies have shown that psychological disorders predict poor diabetes management and control (72–75) and, consequently, negative medical outcomes (76–79). Conversely, as glycemic control worsens, the probability of psychological problems increases (80).

The presence of psychological symptoms and diabetes problems in children and adolescents are often strongly affected by caregiver/family distress. Research has demonstrated that while parental psychological issues may distort perceptions of the child's diabetes control (81), often, they are related to poor psychological adjustment and diabetes control (82–85). Maternal anxiety and depression are associated with poor diabetes control in younger adolescents and with reduced positive effect and motivation in older teens (86).

Eating disorders

Ten percent of adolescent females with type 1 diabetes meet the *Diagnostic and Statistical Manual of Mental Disorders* (4th Edition) criteria for eating disorders compared to 4% of their age-matched peers without diabetes (87). Furthermore, eating disorders are associated with poor metabolic control and earlier onset and more rapid progression of microvascular complications (88). Eating disorders should be suspected in those adolescent and young adult females who are unable to achieve and maintain metabolic targets, especially when insulin omission is suspected. It is important to identify individuals with eating disorders because different management strategies are required to optimize metabolic control and prevent microvascular complications (87–89).

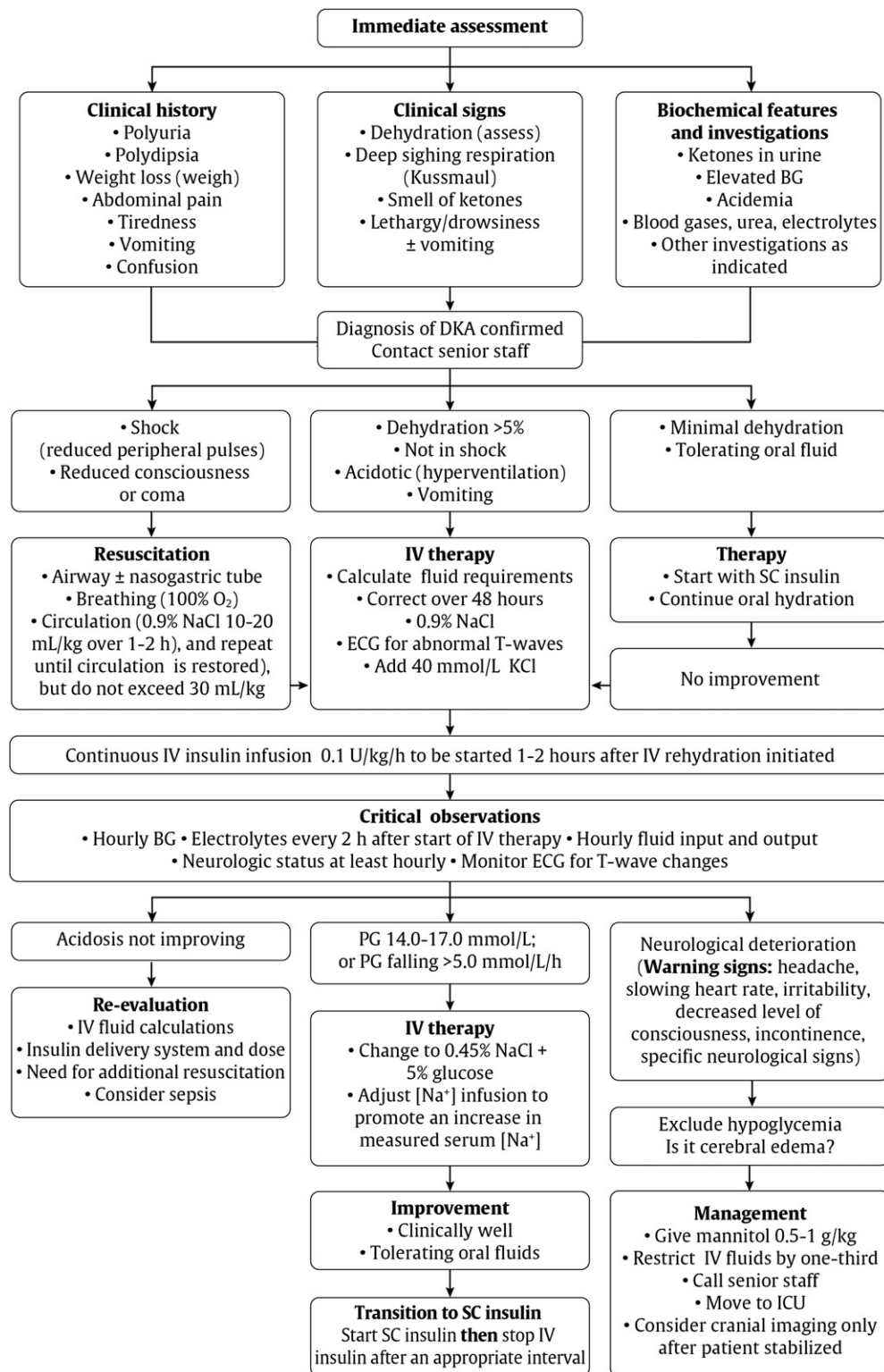


Figure 1. Immediate assessment and management of diabetic ketoacidosis (DKA) in children. BG, blood glucose; ECG, electrocardiogram; ICU, intensive care unit; IV, intravenous; PG, plasma glucose; SC, subcutaneous. Adapted with permission from 57. Wolfsdorf J, Craig ME, Daneman D, et al; for the International Society for Pediatric and Adolescent Diabetes. Diabetic ketoacidosis. *Pediatr Diabetes*. 2007;8:28-43.

Prevention and intervention

Children and adolescents with diabetes, along with their families, should be screened throughout their development for psychological disorders (90). Given the prevalence of psychological issues, screening in this area can be seen as equally important as

screening for microvascular complications in children and adolescents with diabetes (91).

Psychological interventions with children and adolescents, as well as families, have been shown to improve mental health (67,92), including overall well-being and perceived quality of life (93), along with depressive symptoms (94,95). In addition, there is

Table 4

Recommendations for screening for comorbid conditions in children with type 1 diabetes

Condition	Indications for screening	Screening test	Frequency
Autoimmune thyroid disease	All children with type 1 diabetes	Serum TSH level + thyroperoxidase antibodies	At diagnosis and every 2 years thereafter
Addison's disease	Positive thyroid antibodies, thyroid symptoms or goiter Unexplained recurrent hypoglycemia and decreasing insulin requirements	Serum TSH level + thyroperoxidase antibodies 8 AM serum cortisol + serum sodium and potassium	Every 6–12 months As clinically indicated
Celiac disease	Recurrent gastrointestinal symptoms, poor linear growth, poor weight gain, fatigue, anemia, unexplained frequent hypoglycemia or poor metabolic control	Tissue transglutaminase + immunoglobulin A levels	As clinically indicated

TSH, thyroid-stimulating hormone.

some evidence that psychosocial interventions can positively affect glycemic control (34,92,96). Most importantly, some studies have demonstrated that psychological interventions can increase both diabetes treatment adherence and glycemic control, as well as psychosocial functioning (97,98).

Comorbid Conditions

Autoimmune thyroid disease

Clinical autoimmune thyroid disease (AITD) occurs in 15% to 30% of individuals with type 1 diabetes (99). The risk for AITD during the first decade of diabetes is directly related to the presence or absence of thyroid antibodies at diabetes diagnosis (100). Hypothyroidism is most likely to develop in girls at puberty (101). Early detection and treatment of hypothyroidism will prevent growth failure and symptoms of hypothyroidism (Table 4). Hyperthyroidism also occurs more frequently in association with type 1 diabetes than in the general population.

Addison's disease

Addison's disease is rare, even in those with type 1 diabetes (102). Targeted screening is required in those with unexplained recurrent hypoglycemia and decreasing insulin requirements (Table 4).

Celiac disease

Celiac disease can be identified in 4% to 9% of children with type 1 diabetes (99), but in 60% to 70% of these children the disease is

asymptomatic (silent celiac disease). Children with type 1 diabetes are at increased risk for classic or atypical celiac disease during the first 10 years of diabetes (103). There is good evidence that treatment of classic or atypical celiac disease with a gluten-free diet improves intestinal and extraintestinal symptoms (104) and prevents the long-term sequelae of untreated classic celiac disease (105). However, there is no evidence that untreated asymptomatic celiac disease is associated with short- or long-term health risks (106) or that a gluten-free diet improves health in these individuals (107). Thus, universal screening for and treatment of asymptomatic celiac disease remains controversial (Table 4).

Diabetes Complications

There are important age-related considerations regarding surveillance for diabetes complications and interpretation of investigations (Table 5).

Nephropathy

Prepubertal children and those in the first five years of diabetes should be considered at very low risk for microalbuminuria (108,109). A first morning urine albumin to creatinine ratio (ACR) has high sensitivity and specificity for the detection of microalbuminuria (110,111). Although screening with a random ACR is associated with greater compliance than with a first morning sample, its specificity may be compromised in adolescents due to their higher frequency of exercise-induced proteinuria and benign postural proteinuria. Abnormal random ACRs (>2.5 mg/mmol)

Table 5

Screening for diabetes complications, dyslipidemia and hypertension in children with type 1 diabetes

Complication	Indications and intervals for screening	Screening method
Nephropathy	<ul style="list-style-type: none"> Yearly screening commencing at 12 years of age in those with duration of type 1 diabetes >5 years 	<ul style="list-style-type: none"> First morning (preferred) or random ACR Abnormal ACR requires confirmation at least 1 month later with a first morning ACR and, if abnormal, followed by timed, overnight or 24-hour split urine collections for albumin excretion rate Repeated sampling should be done every 3–4 months over a 12-month period to demonstrate persistence
Retinopathy	<ul style="list-style-type: none"> Yearly screening commencing at 15 years of age with duration of type 1 diabetes >5 years Screening interval can increase to 2 years if good glycemic control, duration of diabetes <10 years and no retinopathy at initial assessment 	<ul style="list-style-type: none"> Standard field, stereoscopic colour fundus photography with interpretation by a trained reader (gold standard), or Direct ophthalmoscopy or indirect slit-lamp funduscopy through dilated pupil, or Digital fundus photography
Neuropathy	<ul style="list-style-type: none"> Postpubertal adolescents with poor metabolic control should be screened yearly after 5 years' duration of type 1 diabetes 	<ul style="list-style-type: none"> Question and examine for symptoms of numbness, pain, cramps and paraesthesia, as well as skin sensation, vibration sense, light touch and ankle reflexes
Dyslipidemia	<ul style="list-style-type: none"> Delay screening after diabetes diagnosis until metabolic control has stabilized Screen at 12 and 17 years of age <12 years of age: screen only those with body mass index >95th percentile, family history of hyperlipidemia or premature cardiovascular disease 	<ul style="list-style-type: none"> Fasting total cholesterol, high-density lipoprotein cholesterol, triglycerides, calculated low-density lipoprotein cholesterol
Hypertension	<ul style="list-style-type: none"> Screen all children with type 1 diabetes at least twice a year 	<ul style="list-style-type: none"> Use appropriate cuff size

ACR, albumin to creatinine ratio.

require confirmation with a first morning ACR or timed urine overnight collection (112).

Microalbuminuria is rare in prepubertal children, regardless of the duration of diabetes or metabolic control (108). Furthermore, the likelihood of transient or intermittent microalbuminuria is higher during the early peripubertal years (109). Individuals with transient or intermittent microalbuminuria may be at increased risk of progression to overt nephropathy (113). Abnormal screening results require confirmation and follow-up to demonstrate persistent abnormalities.

Treatment is indicated only for those adolescents with persistent microalbuminuria. One short-term randomized controlled trial in adolescents demonstrated that angiotensin-converting enzyme (ACE) inhibitors were effective in reducing microalbuminuria compared to placebo (114). However, there are no long-term intervention studies assessing the effectiveness of ACE inhibitors or angiotensin II receptor antagonists in delaying progression to overt nephropathy in adolescents with microalbuminuria. Therefore, treatment of adolescents with persistent microalbuminuria is based on the effectiveness of treatments in adults with type 1 diabetes (115).

Retinopathy

Retinopathy is rare in prepubertal children with type 1 diabetes and in postpubertal adolescents with good metabolic control (116,117).

Neuropathy

When present, neuropathy is mostly subclinical in children (118). While prospective nerve conduction studies and autonomic neuropathy assessment studies have demonstrated increased prevalence of abnormalities over time (119), persistence of abnormalities is an inconsistent finding (120). Vibration and monofilament testing have suboptimal sensitivity and specificity in adolescents (121). With the exception of intensifying diabetes management to achieve and maintain glycemic targets, no other treatment modality has been studied in children and adolescents.

Dyslipidemia

Most children with type 1 diabetes should be considered at low risk for vascular disease associated with dyslipidemia (122,123). The exceptions are those with longer duration of disease, microvascular complications or other cardiovascular disease (CVD) risk factors, including smoking, hypertension, obesity and/or family history of premature CVD (124). Dyslipidemia screening should be targeted at those >12 years of age and younger children with specific risk factors for dyslipidemia. Statin therapy has only rarely been studied specifically in children with diabetes, and there is no evidence linking specific low-density lipoprotein cholesterol (LDL-C) cutoffs in children with diabetes with long-term outcomes. In pubertal children without diabetes but with familial hypercholesterolemia, statin therapy is safe and effective at lowering LDL-C levels and attenuating progression of surrogate markers for future vascular disease (125).

Hypertension

Up to 16% of adolescents with type 1 diabetes have hypertension (126). Twenty-four-hour ambulatory blood pressure (BP) monitoring has been used to exclude white coat hypertension and to identify loss of diurnal systolic rhythm (nondippers) with nocturnal hypertension in some normotensive adolescents with type 1

diabetes (127). These abnormalities may be predictive of future microalbuminuria (127). However, the role of ambulatory BP monitoring in routine care remains uncertain. Children with type 1 diabetes and confirmed hypertension should be treated according to the guidelines for children without diabetes (128).

Transition to Adult Care

The change of physician or DHC team can have a major impact on disease management and metabolic control in the person with diabetes (129). Between 25% and 65% of young adults have no medical follow-up during the transition from pediatric to adult diabetes care services (130,131). Those with no follow-up are more likely to experience hospitalization for DKA during this period. Organized transition services may decrease the rate of loss of follow-up (132,133).

RECOMMENDATIONS

Delivery of care

1. All children with diabetes should have access to an experienced pediatric DHC team and specialized care starting at diagnosis [Grade D, Level 4 (1)].
2. Children with new-onset type 1 diabetes who are medically stable should receive their initial education and management in an outpatient setting, provided that appropriate personnel and daily communication with the DHC are available [Grade B, Level 1A (3)].
3. To ensure ongoing and adequate diabetes care, adolescents should receive care from a specialized program aimed at creating a well-prepared and supported transition to adult care that includes a transition coordinator, patient reminders, and support and education, with or without a joint pediatric and adult clinic [Grade C, Level 3 (132,133)].

Glycemic targets

4. Glycemic targets should be graduated with age (see Table 1):
 - Children <6 years of age should aim for an A1C <8.0% [Grade D, Consensus]. Caution should be used to minimize hypoglycemia because of the potential association in this age group between severe hypoglycemia and later cognitive impairment [Grade D, Level 4 (134)].
 - Children 6–12 years of age should aim for a target A1C ≤7.5% [Grade D, Consensus].
 - Adolescents should aim for the same glycemic targets as adults [Grade A, Level 1A (5)].
5. Children with persistently poor glycemic control (e.g. A1C >10%) should be assessed by a specialized pediatric diabetes team for a comprehensive interdisciplinary assessment and referred for psychosocial support as indicated [Grade D, Consensus]. Intensive family and individualized psychological interventions aimed at improving glycemic control should be considered to improve chronically poor metabolic control [Grade A, Level 1A (34,35,135)].

Insulin therapy

6. Children with new-onset diabetes should be started on at least 2 daily injections of bolus insulin (e.g. short-acting bolus insulin or rapid-acting bolus insulin analogues) combined with basal insulin (e.g. intermediate-acting insulin or long-acting basal insulin analogue) [Grade D, Consensus].
7. Insulin therapy should be assessed at each clinical encounter to ensure it still enables the child to meet A1C targets, minimizes the risk of hypoglycemia and allows flexibility in carbohydrate intake, daily schedule and activities [Grade D, Consensus]. If these goals are not being met, an intensified diabetes management approach (including increased education, monitoring and contact with diabetes team) should be used [Grade A, Level 1(4) for adolescents; Grade D, Consensus for younger children], and treatment options may include the following:
 - Increased frequency of injections [Grade D, Consensus].
 - Change in the type of basal and/or bolus insulin [Grade B, Level 2 (19), for adolescents; Grade D, Consensus, for younger children].
 - Change to continuous subcutaneous insulin infusion therapy [Grade C, Level 3 (136)].

Hypoglycemia

8. In children, the use of mini-doses of glucagon (10 µg per year of age with minimum dose 20 µg and maximum dose 150 µg) should be considered in the home management of mild or impending hypoglycemia associated with inability or refusal to take oral carbohydrate [Grade D, Level 4 (32)].
9. In the home situation, severe hypoglycemia in an unconscious child >5 years of age should be treated with 1 mg glucagon subcutaneously or intramuscularly. In children ≤5 years of age, a dose of 0.5 mg glucagon should be given. The episode should be discussed with the diabetes healthcare team as soon as possible and consideration given to reducing insulin doses for the next 24 hours to prevent further severe hypoglycemia [Grade D, Consensus].
10. Dextrose 0.5–1 g/kg should be given over 1–3 minutes to treat severe hypoglycemia with unconsciousness when IV access is available [Grade D, Consensus].

Diabetic ketoacidosis (DKA)

11. To prevent DKA in children with diabetes:
 - Targeted public awareness campaigns should be considered to educate parents and other caregivers (e.g. teachers) about the early symptoms of diabetes [Grade C, Level 3 (42)].
 - Comprehensive education and support services [Grade C, Level 3 (43)], as well as 24-hour telephone services [Grade C, Level 3 (44)], should be available for families of children with diabetes.
12. DKA in children should be treated according to pediatric-specific protocols [Grade D, Consensus]. If appropriate expertise/facilities are not available locally, there should be immediate consultation with a centre with expertise in pediatric diabetes [Grade D, Consensus].
13. In children in DKA, rapid administration of hypotonic fluids should be avoided [Grade D, Level 4 (49)]. Circulatory compromise should be treated with only enough isotonic fluids to correct circulatory inadequacy [Grade D, Consensus]. Restoration of extracellular fluid volume should be extended over a 48-hour period with regular reassessments of fluid deficits [Grade D, Level 4 (49)].
14. In children in DKA, IV insulin bolus should not be given; an IV infusion of short-acting insulin should be used at an initial dose of 0.1 units/kg/h [Grade D, Level 4 (53)]. The insulin infusion should not be started until 1 hour after starting fluid replacement therapy [Grade D, Level 4 (52)].
15. In children in DKA, the insulin infusion rate should be maintained until the plasma anion gap normalizes. Once plasma glucose reaches 14.0–17.0 mmol/L, IV glucose should be started to prevent hypoglycemia [Grade D, Consensus].
16. In children in DKA, administration of sodium bicarbonate should be avoided except in extreme circulatory compromise, as this may contribute to cerebral edema [Grade D, Level 4 (48)].

Microvascular complications

17. Screening for microalbuminuria should be performed annually, commencing at 12 years of age in children with type 1 diabetes >5 years' duration [Grade D, Consensus].
18. Children ≥12 years should be screened for microalbuminuria with a first morning urine ACR (preferred) [Grade B, Level 2 (111)] or a random ACR [Grade D, Consensus]. Abnormal results should be confirmed [Grade B, Level 2 (137)] at least 1 month later with a first morning ACR or timed, overnight urine collection for albumin excretion rate [Grade D, Consensus]. Microalbuminuria (ACR >2.5 mg/mmol) should not be diagnosed in children ≥12 years unless it is persistent, as demonstrated by 2 consecutive first morning ACR or timed collections obtained at 3- to 4-month intervals over a 6- to 12-month period [Grade D, Consensus].
19. Children ≥12 years with persistent microalbuminuria should be treated per adult guidelines (see Chronic Kidney Disease chapter, p. S129) [Grade D, Consensus].
20. In children ≥15 years of age with type 1 diabetes, screening and evaluation for retinopathy by an expert professional should be performed annually, starting 5 years after the onset of diabetes [Grade D, Consensus]. The screening interval can be increased to every 2 years in children with type 1 diabetes who have good glycemic control, duration of diabetes <10 years and no significant retinopathy (as determined by an expert professional) [Grade D, Consensus].

21. Postpubertal children with type 1 diabetes of >5 years' duration and poor metabolic control should be questioned about symptoms of numbness, pain, cramps and paresthesia, and examined for skin sensation, vibration sense, light touch and ankle reflexes [Grade D, Consensus].

Comorbid conditions and other complications

22. Children and adolescents with diabetes, along with their families, should be screened regularly for psychosocial or psychological disorders [Grade D, Level 4 (108,109)] and should be referred to an expert in mental health and/or psychosocial issues for intervention when required (Grade D, Consensus).
23. Adolescent females with type 1 diabetes should be regularly screened using nonjudgemental questions about weight and body image concerns, dieting, binge eating and insulin omission for weight loss [Grade D, Consensus].
24. Children with type 1 diabetes who are <12 years of age should be screened for dyslipidemia if they have other risk factors, such as obesity (body mass index >95th percentile for age and gender) and/or a family history of dyslipidemia or premature cardiovascular disease. Routine screening for dyslipidemia should begin at 12 years of age, with repeat screening after 5 years [Grade D, Consensus].
25. Once dyslipidemia is diagnosed in children with type 1 diabetes, the dyslipidemia should be treated per lipid guidelines for adults with diabetes [Grade D, Consensus].
26. All children with type 1 diabetes should be screened for hypertension at least twice annually [Grade D, Consensus].
27. Children with type 1 diabetes and BP readings persistently above the 95th percentile for age should receive lifestyle counselling, including weight loss if overweight [Grade D, Level 4 (138)]. If BP remains elevated, treatment should be initiated based on recommendations for children without diabetes [Grade D, Consensus].
28. Influenza immunization should be offered to children with diabetes as a way to prevent an intercurrent illness that could complicate diabetes management [Grade D, Consensus].
29. Formal smoking prevention and cessation counselling should be part of diabetes management for children with diabetes [Grade D, Consensus].
30. Adolescent females with type 1 diabetes should receive counselling on contraception and sexual health in order to prevent unplanned pregnancy [Grade D, Level 4 (139)].
31. Children with type 1 diabetes who have thyroid antibodies should be considered high risk for autoimmune thyroid disease [Grade C, Level 3 (100)]. Children with type 1 diabetes should be screened at diabetes diagnosis with repeat screening every 2 years using a serum thyroid-stimulating hormone and thyroid peroxidase antibodies [Grade D, Consensus]. More frequent screening is indicated in the presence of positive thyroid antibodies, thyroid symptoms or goiter [Grade D, Consensus].
32. Children with type 1 diabetes and symptoms of classic or atypical celiac disease (see Table 4) should undergo celiac screening [Grade D, Consensus] and, if confirmed, be treated with a gluten-free diet to improve symptoms [Grade D, Level 4 (104)] and prevent the long-term sequelae of untreated classic celiac disease [Grade D, Level 4 (105)]. Parents should be informed that the need for screening and treatment of asymptomatic (silent) celiac disease is controversial [Grade D, Consensus].

Abbreviations:

A1C, glycated hemoglobin; ACR, albumin to creatinine ratio; BP, blood pressure; DHC, diabetes healthcare; IV, intravenous.

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Clinical Practice Guidelines

Type 2 Diabetes in Children and Adolescents

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Anticipatory guidance regarding healthy eating and active lifestyle is recommended to prevent obesity.
- Regular targeted screening for type 2 diabetes is recommended in children at risk.
- Children with type 2 diabetes should receive care in consultation with an interdisciplinary pediatric diabetes healthcare team.
- Early screening, intervention and optimization of glycemic control are essential, as the onset of type 2 diabetes during childhood is associated with severe and early onset of microvascular complications.

Note: Unless otherwise specified, the term “child” is used for individuals 0 to 18 years of age, and the term “adolescent” for those 13 to 18 years of age.

Introduction

Type 2 diabetes in children has increased in frequency around the world over the past 2 decades (1). Children from ethnic groups at high risk for type 2 diabetes in their adult populations, namely, those of Aboriginal, African, Arabic, Hispanic or Asian descent, are disproportionately affected. A recent Canadian national surveillance study demonstrated a minimum incidence of type 2 diabetes in children and adolescents <18 years of age of 1.54 per 100 000 children per year (2). Significant regional variation was observed with the highest minimum incidence seen in Manitoba of 12.45 per 100 000 children per year. In this study, 44% of children with new onset type 2 diabetes were of Aboriginal heritage, 25% Caucasian, 10.1% Asian, 10.1% African/Caribbean and the remaining of other or mixed ethnic origin (2). Recent data from the United States (US) demonstrated an incidence of 8.1 per 100 000 person years in the 10- to 14-year age group and 11.8 per 100 000 person years in the 15- to 19-year group. In this study, the highest rates were found in American Indian, African American, Asian/Pacific Islander and Hispanic youth (in descending order), and the lowest incidence occurred in non-Hispanic white youth (3).

Prevention

Breastfeeding has been shown to reduce the risk of youth-onset type 2 diabetes in some populations (4).

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Obesity is a major modifiable risk factor for the development of type 2 diabetes (2). In 2004, 18% of Canadian children and adolescents were overweight and 8% were obese (5). Studies on the prevention of obesity in children are limited and have generally not been demonstrated to be successful (6). In obese children, standard lifestyle interventions in the form of dietary recommendations and regular clinic visits have been shown to have little benefit for weight reduction (6). While data are limited, family-based lifestyle interventions with a behavioural component aimed at changes in diet and physical activity patterns have been shown to result in significant weight reduction in both children and adolescents (6). Health Canada—endorsed recommendations for physical activity and nutrition in children can be accessed on the Canadian Society for Exercise Physiology (<http://www.csep.ca/english/view.asp?x=804>) and Health Canada (<http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/chose-choix/advice-conseil/child-enfant-eng.php>) websites (7,8).

The role of pharmacotherapy in the treatment of childhood obesity is controversial, as there are few controlled trials and no long-term safety or efficacy data (9). Several studies suggest that lifestyle changes plus pharmacotherapy may act synergistically when lifestyle intervention is aggressively pursued (10). Orlistat may be considered to aid in weight reduction and weight maintenance when added to a regimen of lifestyle intervention in adolescents (11–13). Metformin has been observed to promote modest weight loss in small, short-term trials in children and adolescents (9). However, while both metformin and orlistat have potential for short-term positive effects on weight, glycemic control, insulin sensitivity and/or lipids, no pediatric studies have been performed to assess the prevention of diabetes or long-term complications. In obese adolescents with evidence of severe insulin resistance, pharmacological therapy with metformin or orlistat should only be considered after a comprehensive evaluation of the child's metabolic status, family history and review of lifestyle interventions. Due to a lack of data in prepubertal children, the use of antiobesity drugs should only be considered in this population within the context of a supervised clinical trial. Bariatric surgery in adolescents should be limited to exceptional cases and be performed only by experienced teams (14).

Screening and Diagnosis

The microvascular complications of type 2 diabetes have been identified at diagnosis, implying long-term, unrecognized

hyperglycemia (15). Children may also present with acute decompensation in diabetic ketoacidosis (DKA) and/or hyperosmolar coma. This argues for a systematic screening program aimed to identify children with type 2 diabetes in order to prevent acute, life-threatening presentation and to decrease the development of chronic complications. Although not proven in children, it is generally assumed that earlier diagnosis of diabetes will lead to interventions that will improve glycemic control and reduce the related short- and long-term complications (15).

Risk factors for the development of type 2 diabetes in children include a history of type 2 diabetes in a first- or second-degree relative (16), being a member of a high-risk population (e.g. people of Aboriginal, Hispanic, South Asian, Asian or African descent) (1), obesity (2), impaired glucose tolerance (17), polycystic ovary syndrome (PCOS) (18), exposure to diabetes in utero (19–21), acanthosis nigricans (22), hypertension and dyslipidemia (23), and nonalcoholic fatty liver disease (NAFLD) (24). Atypical antipsychotic medications are associated with significant weight gain, insulin resistance and impaired fasting glucose/type 2 diabetes in children (25). Neuropsychiatric disorders and the use of neuropsychiatric medications are more common in obese children at diagnosis of type 2 diabetes compared to the general pediatric population (26). In the recent national Canadian incidence study, the mean age of diagnosis of type 2 diabetes in youth was 13.7 years (2). However, 8% of all newly diagnosed children with type 2 diabetes were <10 years of age. In children of Aboriginal, Caucasian and Asian origin, 11%, 8.8% and 8.7%, respectively, presented at <10 years of age. Thus, consideration should be given for screening at a younger age in high-risk individuals (2). A fasting plasma glucose (FPG) is the recommended routine screening test for children, although ensuring a fasting state may be a challenge. The reproducibility of the FPG is high (27). The oral glucose tolerance test may have a higher detection rate (28,29) in children who are very obese (body mass index [BMI] \geq 99th percentile for age and gender) and who have multiple risk factors for type 2 diabetes, but it has poor reproducibility (27). Glycated hemoglobin (A1C) is not recommended as a method to diagnose type 2 diabetes in children. Otherwise, the diagnostic criteria for diabetes in children are the same as for adults.

Classification

In most children, the presence of clinical risk factors, mode of presentation and early course of the disease indicate whether the child has type 1 or type 2 diabetes. However, differentiation may be difficult in some. Children with type 2 diabetes can present with DKA (30,31). Testing for the absence of islet autoantibodies may be useful (32–34). Fasting insulin levels are not helpful at diagnosis, as levels may be low due to glucose toxicity (35). DNA diagnostic testing for genetic defects in beta cell function should be considered in children who have a strong family history suggestive of autosomal dominant inheritance and who are lacking features of insulin resistance. This may be helpful when diabetes classification is unclear and may lead to more appropriate management (36,37).

Management

Children with type 2 diabetes should receive care in conjunction or consultation with an interdisciplinary pediatric diabetes healthcare team. The target glycated hemoglobin (A1C) for most children with type 2 diabetes should be \leq 7.0%. To be effective, treatment programs for adolescents with type 2 diabetes need to address the lifestyle and health habits of the entire family, emphasizing healthy eating and physical activity (38). While a recent systematic review found no good-quality studies directly assessing the effects of physical activity in youth with type 2 diabetes, it is reasonable to recommend (in the absence of direct evidence for this population) that children with type 2 diabetes strive to achieve the same activity level recommended for children in general: 60 minutes daily of moderate-to-vigorous physical activity and limiting sedentary screen time to no more than 2 hours per day (39). Canadian physical activity guidelines for children and youth are available from the Canadian Society for Exercise Physiology (www.csep.ca). In a retrospective review of a predominantly First Nations population of youth with type 2 diabetes, target A1C (\leq 7%) was achieved and maintained on lifestyle monotherapy for 12 months after diagnosis in 54% of individuals who had presented with an A1C $<$ 9%

Table 1
Screening for diabetes complications and comorbidities in children with type 2 diabetes

Complication/comorbid condition	Indications and intervals for screening	Screening test
Dyslipidemia	Screening should commence at diagnosis of diabetes and every 1–3 years thereafter as clinically indicated	Fasting TC, HDL-C, TG, calculated LDL-C
Hypertension	At diagnosis of diabetes and every diabetes-related clinical encounter thereafter (at least twice annually).	BP measurement using appropriately sized cuff
NAFLD	Yearly screening commencing at diagnosis of diabetes	ALT <ul style="list-style-type: none"> First morning (preferred) or random ACR Abnormal ACR requires confirmation at least 1 month later with either a first morning ACR or timed overnight urine collection for ACR Repeated sampling should be done every 3 to 4 months over a 6- to 12-month period to demonstrate persistence
Nephropathy	Yearly screening commencing at diagnosis of diabetes	
Neuropathy	Yearly screening commencing at diagnosis of diabetes	Questioned and examined for: <ul style="list-style-type: none"> Symptoms of numbness, pain, cramps and paresthesia Vibration sense Light touch and ankle reflexes
PCOS	Yearly clinical screening commencing at diagnosis of diabetes in pubertal females	Clinical assessment on history and physical exam for oligo/amenorrhea, acne and/or hirsutism
Retinopathy	Yearly screening commencing at diagnosis of diabetes	<ul style="list-style-type: none"> Seven-standard field, stereoscopic colour fundus photography with interpretation by a trained reader (gold standard); or Direct ophthalmoscopy or indirect slit-lamp funduscopy through dilated pupil; or Digital fundus photography

ACR, albumin to creatinine ratio; ALT, alanine aminotransferase; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome; TC, total cholesterol; TG, triglycerides.

at diagnosis (40). In addition, psychological issues, such as depression, binge eating (41) and smoking cessation, need to be addressed and interventions offered as required. In 1 retrospective cohort of pediatric patients, the prevalence of neuropsychiatric disorders at presentation of type 2 diabetes was 19.4% (26).

Insulin is required in those with severe metabolic decompensation at diagnosis (e.g. DKA, glycated hemoglobin [A1C] $\geq 9.0\%$, symptoms of severe hyperglycemia) but may be successfully weaned once glycemic targets are achieved, particularly if lifestyle changes are effectively adopted (42). There are limited data about the safety or efficacy of oral antihyperglycemic agents in the pediatric population, and none of the oral antidiabetic agents have been approved by Health Canada for use in children. Metformin has been shown to be safe in adolescents for up to 16 weeks, reducing A1C by 1.0% to 2.0% and lowering FPG with similar side effects as seen in adults (43). Glimepiride has also been shown to be safe and effective in adolescents for up to 24 weeks, reducing A1C (-0.54%) to a similar extent as metformin (-0.71%) but resulting in a significant weight increase of 1.3 kg (44). The Treatment Options for Type 2 Diabetes in Youth (TODAY) study was a multicentre trial that randomized youth with type 2 diabetes to metformin alone, metformin plus a lifestyle intervention, or metformin plus rosiglitazone (45). The study population included youth 10 to 17 years of age with a mean diabetes duration of 7.8 months and A1C $< 8\%$. In the entire study population, treatment failure (defined as A1C $\geq 8\%$ over 6 months or sustained metabolic decompensation requiring insulin therapy) occurred in 51.7% of the metformin group, 46.6% of the metformin plus lifestyle group, and 38.6% of the metformin plus rosiglitazone group (metformin-rosiglitazone vs. metformin alone; $p=0.006$). However, there were important differences in response between genders and ethnic groups. This study demonstrated that a significant proportion of youth with type 2 diabetes requires aggressive intervention early in the course of the disease, and treatment failure is common. Serious adverse events thought to be related to study medication were uncommon over mean follow-up of 3.9 years. Given the concerns raised around the long-term safety of rosiglitazone since the start of this trial, it is premature to recommend its routine use in children on the basis of this study. A pharmacokinetic and safety study of a single injection of exenatide in 13 adolescents being treated with metformin demonstrated good tolerability and improved postprandial glucose levels (46).

The experience of bariatric surgery in adolescents with type 2 diabetes is very limited with specific eligibility criteria (BMI > 35 kg/m², Tanner stage IV or V, and skeletal maturity). A single retrospective case series of 11 postpubertal adolescents with type 2 diabetes who underwent roux-en-Y gastric bypass demonstrated significant improvements in BMI, glycemic control, serum lipid levels and blood pressure (BP) compared to 67 adolescents who were medically managed over 1 year (47). Notably, 10 of the 11 surgically treated youth experienced remission of their diabetes without the need for medication.

Immunization

The recommendations for influenza and pneumococcal immunization in Canada do not address the issue of type 2 diabetes in children, and there are no studies evaluating the usefulness of the influenza or pneumococcal vaccine in this population. There is no reason not to manage these children in a similar fashion to those with type 1 diabetes in whom influenza immunization is recommended to be offered as a way to avoid an intercurrent illness that could complicate diabetes management.

Some children with type 2 diabetes may also have other factors (e.g. Aboriginal heritage) that may place them at higher risk of increased influenza- and pneumococcal-related morbidity (48–50).

Complications

Short-term complications of type 2 diabetes in children include DKA and hyperglycemic hyperosmolar state (HHS); 10% of Canadian youth present with DKA at the time of diagnosis (2). High mortality rates (up to 37% in 1 series) have been reported in youth presenting with combined DKA and HHS at onset of type 2 diabetes (51–53). Evidence suggests that early-onset type 2 diabetes in adolescence is associated with severe and early-onset microvascular complications, including retinopathy, neuropathy and nephropathy (54–56). Although neither retinopathy nor neuropathy has been described in adolescents with type 2 diabetes at diagnosis, 1 study found that 1 in 5 youth with type 2 diabetes had peripheral nerve abnormalities, and more than half had autonomic neuropathy after a median duration of diabetes of 1.3 years (56). Micro- or macroalbuminuria has been noted in 14.2% of Canadian youth at diagnosis (2) and in up to 22.2% of US youth with a mean diabetes duration of 1.9 years (57). Therefore, it is prudent to consider screening for these complications at diagnosis and yearly thereafter until the natural history is better understood (Table 1). Furthermore, Aboriginal youth in Canada are at increased risk of renal diseases that are not associated with diabetes (58). Given that the documentation of persistent albuminuria may indicate one of several possible diagnoses, including underlying primary renal disease, diabetic nephropathy or focal sclerosing glomerulosclerosis (a comorbid condition associated with obesity), referral to a pediatric nephrologist for assessment of etiology and treatment is recommended (58).

Comorbid Conditions

Children with type 2 diabetes have an increased prevalence of dyslipidemia (56,57,59,60), with 44.8% of Canadian children reported to have dyslipidemia at the time of diagnosis (2). Thus, screening for dyslipidemia at diagnosis and every 1 to 3 years as clinically indicated thereafter is recommended. In children with familial dyslipidemia and a positive family history of early cardiovascular events, a statin should be started if the low-density lipoprotein cholesterol level remains > 4.1 mmol/L after a 3- to 6-month trial of dietary intervention (61). A similar approach seems reasonable in the absence of evidence to recommend a specific intervention in children with type 2 diabetes.

Similarly, screening for high BP should begin at diagnosis of diabetes and continue at every diabetes-related clinical encounter thereafter (62), since up to 36% of adolescents with type 2 diabetes have hypertension (56) (see Type 1 Diabetes in Children and Adolescents chapter, p. S153, for additional discussion on the treatment of dyslipidemia and hypertension).

Since 95% of adolescents with type 2 diabetes present with obesity and 73% have clinical evidence of insulin resistance as manifested by acanthosis nigricans (2), surveillance should occur for comorbid conditions associated with insulin resistance, including PCOS (63) and NAFLD (64) (Table 1). PCOS was reported in 12.1% and NAFLD (defined as alanine aminotransferase [ALT] $> 3\times$ the upper limit of normal or fatty liver on ultrasound) in 22.2% of children and youth at diagnosis of type 2 diabetes (2).

RECOMMENDATIONS

- Anticipatory guidance promoting healthy eating, maintenance of a healthy weight and regular physical activity is recommended as part of routine pediatric care [Grade D, Consensus].
- Intensive lifestyle intervention, including dietary and exercise interventions, family counselling and family-oriented behaviour therapy, should be undertaken for obese children in order to achieve and maintain a healthy body weight [Grade D, Consensus].
- Screening for type 2 diabetes should be performed every 2 years using an FPG test in children with any of the following:
 - ≥ 3 risk factors in nonpubertal or ≥ 2 risk factors in pubertal children [Grade D, Consensus]
 - Obesity (BMI ≥ 95 th percentile for age and gender) [Grade D, Level 4 (2)]
 - Member of a high-risk ethnic group (e.g. Aboriginal, African, Asian, Hispanic or South Asian descent) [Grade D, Level 4 (2)]
 - Family history of type 2 diabetes and/or exposure to hyperglycemia in utero [Grade D, Level 4 (2)]
 - Signs or symptoms of insulin resistance (including acanthosis nigricans, hypertension, dyslipidemia, NAFLD [ALT $>3\times$ upper limit of normal or fatty liver on ultrasound], PCOS) [Grade D, Level 4 (2)]
 - Impaired fasting glucose or impaired glucose tolerance [Grade D, Consensus]
 - Use of atypical antipsychotic medications [Grade D, Consensus]
- An oral glucose tolerance test (1.75 g/kg; maximum 75 g) may be used as a screening test in very obese children (BMI ≥ 99 th percentile for age and gender) or those with multiple risk factors who meet the criteria in recommendation 3 [Grade D, Consensus].
- Commencing at the time of diagnosis of type 2 diabetes, all children should receive ongoing intensive counselling, including lifestyle modification, from an interdisciplinary pediatric healthcare team [Grade D, Level 4 (40)].
- The target A1C for most children with type 2 diabetes should be $\leq 7.0\%$ [Grade D, Consensus].
- In children with type 2 diabetes and A1C $\geq 9.0\%$ and in those with severe metabolic decompensation (e.g. DKA), insulin therapy should be initiated but may be successfully weaned once glycemic targets are achieved, particularly if lifestyle changes are effectively adopted [Grade D, Level 4 (42)].
- In children with type 2 diabetes, if glycemic targets are not achieved within 3–6 months using lifestyle modifications alone, one of the following should be initiated:
 - Metformin [Grade B, Level 2 (43)] OR
 - Glimepiride [Grade B, Level 2 (44)] OR
 - Insulin [Grade D, Consensus]
 If the decision is made to use an oral antihyperglycemic agent, metformin should be used over glimepiride [Grade D, Consensus]. Metformin may be used at diagnosis in those children presenting with A1C $>7.0\%$ [Grade B, Level 2 (43)].
- Children with type 2 diabetes should be screened annually for microvascular complications (nephropathy, neuropathy, retinopathy) beginning at diagnosis of diabetes [Grade D, Level 4 (56)].
- Children with type 2 diabetes should be screened for microalbuminuria with a first morning urine ACR (preferred) [Grade B, Level 2 (65)] or a random ACR [Grade D, Consensus]. Abnormal results should be confirmed [Grade B, Level 2 (66)] at least 1 month later with a first morning ACR and, if abnormal, followed by timed, overnight urine collection for albumin excretion rate [Grade D, Consensus]. Microalbuminuria [ACR > 2.5 mg/mmol (67)] should not be diagnosed in adolescents unless it is persistent as demonstrated by 2 consecutive first morning ACR or timed collections obtained at 3- to 4-month intervals over a 6- to 12-month period [Grade D, Consensus]. Those with persistent albuminuria should be referred to a pediatric nephrologist for assessment of etiology and treatment [Grade D, Level 4 (58)].
- Children with type 2 diabetes should have a fasting lipid profile measured at diagnosis of diabetes and every 1–3 years thereafter, as clinically indicated [Grade D, Consensus].

- Children with type 2 diabetes should be screened for hypertension beginning at diagnosis of diabetes and at every diabetes-related clinical encounter thereafter (at least biannually) [Grade D, Consensus].
- Children with type 2 diabetes should be screened at diagnosis for comorbid conditions associated with insulin resistance, including NAFLD [Grade D, Level 4 (2,64)] and PCOS in pubertal females [Grade D, Level 4 (2)], and yearly thereafter as clinically indicated [Grade D, Consensus].

Abbreviations:

A1C, glycated hemoglobin; ACR, albumin to creatinine ratio; ALT, alanine aminotransferase; BMI, body mass index; DKA, diabetic ketoacidosis; FPG, fasting plasma glucose; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome.

Other Relevant Guidelines

Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome, p. S8

Reducing the Risk of Developing Diabetes, p. S16

Hyperglycemic Emergencies in Adults, p. S72

Dyslipidemia, p. S110

Treatment of Hypertension, p. S117

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Clinical Practice Guidelines

Diabetes and Pregnancy

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

Pregestational Diabetes

- All women with pre-existing type 1 or type 2 diabetes should receive preconception care to optimize glycemic control, assess complications, review medications and begin folate supplementation.
- Care by an interdisciplinary diabetes healthcare team composed of diabetes nurse educators, dietitians, obstetricians and diabetologists, both prior to conception and during pregnancy, has been shown to minimize maternal and fetal risks in women with pre-existing type 1 or type 2 diabetes.

Gestational Diabetes Mellitus

- The diagnostic criteria for gestational diabetes mellitus (GDM) remain controversial; however, the committee has chosen a preferred approach and an alternate approach. The preferred approach is to begin with a 50 g glucose challenge test and, if appropriate, proceed with a 75 g oral glucose tolerance test, making the diagnosis of GDM if ≥ 1 value is abnormal (fasting ≥ 5.3 mmol/L, 1 hour ≥ 10.6 mmol/L, 2 hours ≥ 9.0 mmol/L). The alternate approach is a 1-step approach of a 75 g oral glucose tolerance test, making the diagnosis of GDM if ≥ 1 value is abnormal (fasting ≥ 5.1 mmol/L, 1 hour ≥ 10.0 mmol/L, 2 hours ≥ 8.5 mmol/L).
- Untreated GDM leads to increased maternal and perinatal morbidity, while treatment is associated with outcomes similar to control populations.

Introduction

This chapter discusses pregnancy in both pre-existing diabetes (pregestational diabetes) as well as gestational diabetes (GDM; diabetes diagnosed in pregnancy). Some of the management principles are common to both types of diabetes. These recommendations have been created in collaboration with the Society of Obstetricians and Gynaecologists of Canada (SOGC).

Glucose Levels in Pregnancy

Elevated glucose levels have adverse effects on the fetus throughout pregnancy. At conception and during the first trimester, hyperglycemia increases the risk of fetal malformations. Later in pregnancy, it increases the risk of macrosomia and metabolic complications at birth (1,2). As a result, meticulous glycemic control is required for optimal maternal and fetal outcomes. Based on a systematic review of reports of glucose levels in non-GDM pregnancies, normal glucose levels during later pregnancy (mean

and 1 SD above mean) were fasting 3.9 ± 0.4 mmol/L, 1 hour postprandial 6.1 ± 0.7 mmol/L, and 2 hours postprandial 5.5 ± 0.6 mmol/L with a mean glucose of 4.9 ± 0.6 mmol/L (3). The peak postprandial glucose occurred at 69 ± 24 minutes (3). However, it should be noted that the mean fasting glucose derived from the total of 255 subjects in this report was 0.6 mmol/L lower than that reported in the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study (4). The HAPO study was the largest prospective study of glycemia in pregnancy and reported a mean fasting glucose of 4.5 ± 0.4 mmol/L, derived from 23 316 pregnant women (4). Finally, glucose levels in obese, nondiabetic pregnant women were slightly higher than their lean counterparts (5).

Pregestational Diabetes (Type 1 and Type 2)

The term “pregestational diabetes” refers to diabetes that was present before pregnancy. The prevalence of pregestational diabetes has increased in the past decade, primarily as a result of the increase in type 2 diabetes (6). Recent large studies of women with pregestational diabetes continue to show higher rates of complications compared to the general population, including perinatal mortality, congenital malformations, hypertension, preterm delivery, large-for-gestational-age (LGA) infants, caesarean delivery and neonatal morbidities (7–9).

Preconception care

Preconception care for women with pregestational diabetes is associated with better outcomes (10,11). Although multidisciplinary clinics improve outcomes, <50% of women receive such care. Women who are heavier, younger and smokers, and who have a lower socioeconomic status, lower health literacy and a poor relationship with their healthcare provider, are less likely to receive preconception care (11–14). Some, but not all, have shown that women with type 2 diabetes are also less likely to receive preconception care (7,15). Higher glycated hemoglobin (A1C) levels are associated with poorer outcomes, but even women who achieve tight glycemic control (A1C <7.0%) have an increased risk of complications, which may be caused, in part, by maternal obesity (16,17). By discussing pregnancy prior to conception, healthcare providers may be able to improve outcomes by educating women

about the importance of strict glycemic control, encouraging folic acid supplementation, discontinuing potentially harmful medications and reducing body weight. Although there are no intervention trials to support larger doses of folic acid for women with diabetes, several factors favour recommending a larger dose. Obesity, which is more common in women with type 2 diabetes, is associated with lower serum folate levels for the same intake, lower intake of folate rich foods and increased risk of neural tube defects independent of glucose (18,19,20). Using a mathematical model, a 5 mg intake will be more effective in reducing neural tube defects in this vulnerable population (21).

Assessment and management of complications

Women with pre-existing vascular complications are more likely to have poor pregnancy outcomes, and there may be progression in the degree of vascular damage (7).

Retinopathy. Women with type 1 (22,23) and type 2 diabetes (24) should have ophthalmological assessments before conception, during the first trimester, as needed during pregnancy and within the first year postpartum (25,26). The risk of progression of retinopathy is increased with poor glycemic control during pregnancy, and such progression may occur up to 1 year postpartum (23,25). Additional risk factors for retinopathy progression include chronic and pregnancy-induced hypertension, preeclampsia and more severe pre-existing retinopathy (22,27–29). Laser photocoagulation for severe nonproliferative or proliferative retinopathy prior to pregnancy reduces the risk of visual impairment in pregnancy (30). Pregnancy does not affect the long-term outcome of mild-to-moderate retinopathy (25).

Hypertension. The incidence of hypertension complicating pregnancy is 40% to 45% in women with type 1 and type 2 diabetes (29). Type 1 diabetes is more often associated with preeclampsia and type 2 diabetes with chronic hypertension. Other risk factors for hypertension, such as poor glycemic control in early pregnancy, are potentially modifiable. Some (31,32), but not all (33), studies have found that increased urinary protein excretion in early pregnancy raises the risk of developing hypertension. Any type of hypertension is strongly associated with adverse outcomes. A number of antihypertensive medications are known to be safe and effective in pregnancy, including calcium channel blockers, labetalol and methyldopa.

Chronic kidney disease. Prior to conception, women should be screened for chronic kidney disease. Microalbuminuria and overt nephropathy are associated with increased risk of maternal and fetal complications (34–39). An estimated glomerular filtration rate (eGFR) should be used prior to pregnancy to determine risk (40). However, during pregnancy, serum creatinine and not eGFR should be used, as eGFR will underestimate GFR in pregnancy (41,42). A random albumin to creatinine ratio and serum creatinine should be measured each trimester. Proteinuria increases during pregnancy, but, in women with a normal GFR, pregnancy has no adverse effects on long-term renal function as long as blood pressure and blood glucose are well controlled (34–37,43–45). In women with elevated serum creatinine, however, pregnancy can lead to a permanent deterioration in renal function (46).

There is conflicting information on whether first-trimester exposure to angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) is associated with an increased risk of congenital malformations. Some (47), but not all (48), cohort studies have demonstrated an increased risk of malformations. A meta-analysis, limited by small study size (786 exposed infants), demonstrated a significant risk ratio (relative risk [RR] 1.78, 95% confidence interval [CI] 1.07–2.94) of increased

anomalies in infants exposed to first-trimester ACE inhibitors and ARBs compared to the normal population (49). However, when the group exposed to ACE inhibitor/ARB exposed was compared to a group of other antihypertensive pregnancies, there was no statistically significant difference (RR 1.41, 95% confidence interval [CI] 0.66–3.04). Thus, the increased risk of malformations may be more related to the hypertension itself rather than a direct effect of ACE inhibitors and ARBs. Fetal exposure in the second and third trimesters is clearly associated with a fetal renin-angiotensin system blockade syndrome, which includes renal failure, oligohydramnios, hypotension, intrauterine growth restriction and death (50). The decision to discontinue an ACE inhibitor or ARB prior to pregnancy should be discussed with the patient and may depend on the indication for use/availability of an effective alternative medication. Once a woman is pregnant, all ACE inhibitors and ARBs should be discontinued.

Cardiovascular disease. Although rare, cardiovascular disease (CVD) can occur in women of reproductive age with diabetes. Myocardial infarction in pregnancy is associated with poor maternal and fetal outcomes (51,52). Women with known CVD should be evaluated and counselled about the significant risks associated with pregnancy.

Management

Care by an interdisciplinary diabetes healthcare (DHC) team composed of diabetes nurse educators, dietitians, obstetricians and diabetologists both prior to conception and during pregnancy, has been shown to minimize maternal and fetal risks in women with diabetes (53–56). An early working relationship should be established between the woman and the DHC team to optimize care, facilitate the planning of pregnancy, ensure adequate self-care practices and discuss the need for social support during pregnancy.

Glycemic control

An important first step in achieving good glycemic control is to set target glucose levels (2,54). Older studies confirm that the lower the mean glucose the better the outcome, with some suggesting a target mean glucose <6.7 mmol/L and others a mean <6.9 mmol/L, while a fasting target <5.9 was still associated with a 29% macrosomia rate (54,57,58). A prospective study in pregnant women with type 1 diabetes showed less preeclampsia with glucose targets of fasting <5.1 mmol/L, preprandial <6.0 mmol/L and 1 hour postprandial <7.8 mmol/L (59). In the absence of specific treatment studies addressing this issue, use of the mean plus 2 SD glucose values of nondiabetic pregnant women appears appropriate giving targets of fasting <5.3 mmol/L, 1 hour postprandial <7.5 and 2 hours postprandial <6.7 mmol/L. Studies in GDM indicate a 1-hour postprandial target <7.8 mmol/L is associated with good outcomes (see below); thus, harmonizing the 1-hour target <7.8 mmol/L is reasonable.

The limiting factor when seeking euglycemia in women with pregestational diabetes is the increased risk of hypoglycemia during pregnancy, particularly in the first trimester (60–64). The risk of severe hypoglycemia ranged from 22% to 71%, with the likely predictors being a history of severe hypoglycemia and hypoglycemic unawareness. The latter may relate, in part, to the loss of counterregulatory hormones reported in women with pregestational diabetes during pregnancy, particularly growth hormone and epinephrine (65–68). This risk of hypoglycemia may be ameliorated if efforts are made to achieve good glycemic control preconception and by the use of analogue insulins (64,69,70). The risk of hypoglycemia is also present in pregnant women with type 2 diabetes (2). Maternal hypoglycemia does not increase the risk of congenital malformations in the offspring (53,71,72) or other adverse outcomes (2). In later pregnancy, maternal hypoglycemia

was associated with a nonsignificant increase in fetal movements (73) and had no impact on fetal heart rate (74) and no long-term consequences for the infant (75), although repeated hypoglycemia and associated loss of glycemic control were associated with macrosomia (68).

Monitoring

Frequent self-monitoring of blood glucose (SMBG) in pregnant women with type 1 diabetes is essential during pregnancy in order to obtain the level of glycemic control associated with better outcomes (57). Preprandial determinations, which are needed to guide the meal-time insulin dose adjustment and, postprandial testing to achieve targets are associated with less macrosomia and preeclampsia (58,59,76). Due to the increased risk of nocturnal hypoglycemia with any intensive insulin therapy, glucose monitoring during the night is often necessary in patients receiving insulin (77). Continuous glucose monitoring systems may help identify periods of hyper- or hypoglycemia (78,79) and certainly confirm glycemic variability (80). Whether closed loop systems will become practical for use in pregnancy remains to be seen (81). Monitoring glucose 4 to 7 times per day is also needed in managing type 2 diabetes (i.e. fasting, preprandially and 1 or 2 hours postprandially to achieve good glycemic control).

Pharmacological therapy

Insulin. Insulin therapy must be individualized and regularly adapted to the changing needs of pregnancy (82–85). Intensive insulin therapy with basal-bolus therapy or continuous subcutaneous insulin infusion (CSII or the insulin pump) is recommended to achieve glycemic targets prior to pregnancy. Women using CSII should be educated about the increased risk of diabetic ketoacidosis (DKA) in the event of insulin pump failure because DKA is a potentially fatal complication for the fetus (86).

Rapid-acting bolus analogues (e.g. aspart, lispro) appear safe for use in pregnancy and show some improvement in postprandial glycemia with reduced hypoglycemia. Lispro does not cross the placenta except at very high doses (>50 units), similar to human insulin (87). There is, as yet, no evidence regarding placental transfer of aspart. Cohort studies have shown improved A1C levels and less hypoglycemia in women with pregestational diabetes in pregnancy taking lispro compared with human insulin, while fetal outcomes were similar (88–90). A randomized trial of 322 women with type 1 diabetes, randomized to insulin aspart vs. human insulin, showed a trend toward reduced episodes of major hypoglycemia, with improved postprandial glucose increments but similar overall glycemic control (91). Perinatal outcomes were similar using insulin aspart and human insulin; however, the study was not powered to show differences in these outcomes (91). Insulin antibodies were low in both groups, in both mother and baby (cord blood) (92). There are no published data on the use of glulisine in pregnancy.

Glargine does not cross the placenta except at very high doses (93). There have been no studies looking at detemir placental transfer. A recent meta-analysis of observational studies showed no adverse fetal outcomes in women taking glargine in pregnancy, while maternal outcomes were similar (94). A randomized trial of detemir use compared with NPH in women with type 1 diabetes has recently been completed, with similar maternal and fetal outcomes in both groups (95). Detemir appears safe in pregnancy. Data on glargine are more limited (cohort and case control studies), and theoretical considerations make it less desirable; however, no adverse maternal or fetal effects have been found to date.

CSII. While use of CSII may be preferred by some women with type 1 diabetes, studies have not demonstrated superiority over basal-bolus regimen (89,96–99), and, in some studies, there have been more adverse outcomes with CSII (89,99).

Oral antihyperglycemic agents and type 2 diabetes. A meta-analysis of first-trimester use of either glyburide or metformin and 1 meta-analysis of metformin alone did not show an increased incidence of congenital anomalies (100,101). Therefore, women with type 2 diabetes who find themselves on metformin or glyburide when they conceive should continue these agents until insulin is started. One cohort study of women with type 2 diabetes found an increase in perinatal mortality in women taking metformin compared with insulin; however, the circumstances surrounding these deaths suggest other confounding factors played a role (102). In another cohort study, there was an increase in perinatal mortality in women taking sulphonylureas, or sulphonylureas plus metformin compared to insulin, but not in those taking metformin alone (103). The reason for this is not known. Currently, a large randomized trial is underway to see if adding metformin to insulin will benefit mothers with type 2 diabetes and their infants (MiTy trial). In the meantime, the use of oral agents is not recommended for glycemic control in women with type 2 diabetes during pregnancy.

Metformin and polycystic ovary syndrome. Considerable research has been done on the use of metformin in women with polycystic ovary syndrome (PCOS) around the time of conception and during pregnancy. A number of these studies have evaluated metformin for use in ovulation induction and infertility in this population; however, there are conflicting data regarding the benefits of metformin use in this population. Several observational studies have suggested that metformin may decrease the rate of spontaneous abortions in women with PCOS, prompting many to advocate the use of metformin up to the end of the first trimester or throughout pregnancy in these women (104,105). However, in a meta-analysis of 17 randomized controlled trials (RCTs), metformin use, either alone or with other fertility drugs, had no significant effect on the abortion risk when used preconception (106). In each of the trials in this meta-analysis, metformin was discontinued at the time of diagnosis of pregnancy. Other nonrandomized studies have noted benefit in women who used metformin throughout pregnancy (107). Further data are needed to clarify this issue. A recent Cochrane review of randomized trials found that although metformin was effective in improving ovulation rates and pregnancy rates in women with PCOS, both alone and in combination with clomiphene, this did not translate into a significant increase in live births (108). The reason for this is not known. Metformin also has been associated with improvement in other pregnancy outcomes, including prevention of GDM, in observational studies (109). However, in a recent, randomized, placebo-controlled trial of metformin treatment started in the first trimester of pregnancy in women with PCOS, metformin failed to reduce the rates of preeclampsia, GDM, preterm delivery or a composite of the 3 outcomes (110). Only 1 study to date has looked at longer-term outcomes in women with PCOS taking metformin in pregnancy. This small study found no increase in the rate of abnormal growth and motor development in infants at 18 months of age (111).

In summary, higher-level evidence has not shown metformin to be of benefit in women with PCOS in pregnancy. The evidence, therefore, does not support the practice of continuing metformin after conception in women with PCOS and normal glucose tolerance. However, the considerable data available help to confirm the safety of metformin given during pregnancy.

Postpartum

Few studies have examined breastfeeding and the use of oral agents. Three case series found metformin in the milk and plasma of breastfeeding women who were taking metformin 500 mg bid or tid, but infant exposure was well below the 10% “level of concern” (0.182% to 0.65%) (112–114). A study looking at weight, height and motor-social development up to 6 months of age in children of mothers taking metformin while breastfeeding showed normal development and no difference from formula-fed infants (111). One of the case series that looked at women taking glyburide or glipizide while breastfeeding found neither drug in the breast milk, and the maximum theoretical infant dose again was well below 10% (<1.5%), with no hypoglycemia found in the 3 infants tested (115). There are no studies to date looking at thiazolidinedione use, glucagon-like peptide-1 agonist or dipeptidyl peptidase-4 (DPP-4) inhibitor use while breastfeeding; therefore, they should not be taken during breastfeeding. In conclusion, metformin and glyburide can be considered for use during breastfeeding, although further long-term studies are needed to better clarify the safety of these drugs.

GDM

Screening and diagnosis

Background

In order to justify mass screening for a medical disorder, a set of criteria needs to be met (Table 1). For GDM, screening programs became widespread despite not meeting many of these traditional criteria and, thus, have led to numerous debates regarding the utility and methodology of GDM screening (116,117). Recent studies and the publication of new guidelines by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus panel have given us the opportunity to revisit the evidence on screening for GDM (118).

Up until the publication of the 2 large-scale RCTs, the benefit of treatment of varying degrees of hyperglycemia in pregnancy was unclear (119,120). The results of these 2 trials, despite some methodological differences, show a benefit to treatment over no treatment of diagnosed GDM with regard to select perinatal outcomes. These findings support the need for a screening strategy for GDM, a largely asymptomatic condition, as there appears to be a beneficial intervention for patients with the disease. Worldwide, there is currently no agreement regarding the optimal screening strategy for GDM. Universal and selective (risk factor based) screening are the most common methods used, but only 1 randomized trial has compared these 2 strategies (121). The most common method of screening is with the stepwise 50 g oral glucose challenge test (OGCT) at 24 to 28 weeks of gestation, followed by an

oral glucose tolerance test (OGTT) as the diagnostic test if a certain threshold has been surpassed. The diagnostic test is either the 75 g OGTT or the 100 g OGTT, and for each of these tests different thresholds are recommended by different professional organizations (122–125) (see Table 2).

The HAPO study, published in 2008, was a prospective observational study designed to determine if hyperglycemia during pregnancy was associated with an increased risk of maternal or fetal complications, and whether a diagnostic threshold value based on adverse perinatal outcomes could be calculated (4). This large study (n=23 316) confirmed the findings from 2 previous large-scale, prospective, observational studies (126,127) that the incidence of select adverse maternal and fetal outcomes increases along a continuum of increasing maternal hyperglycemia. Unfortunately, no outcome-associated glycemic thresholds were identified that could be used to define internationally accepted criteria for the diagnosis of GDM. Despite this, in 2010, the IADPSG consensus panel decided to use the HAPO data to create new diagnostic thresholds for GDM. These recommendations are summarized in Table 2. The thresholds for the 75 g OGTT used were calculated by defining glucose concentrations at which the odds ratio of the 4 HAPO primary outcomes (birthweight >90%, primary caesarean section rate, neonatal hypoglycemia and cord C-peptide levels >90%) reached 1.75. These arbitrary thresholds, when applied to the HAPO cohort, led to a GDM incidence of 17.8%.

Obviously, adopting these recommendations in Canada will profoundly impact the healthcare system, healthcare providers and our pregnant patients. We will address the issue of whether to change the Canadian Diabetes Association (CDA) guidelines by answering the following questions:

- Is there a need to screen for GDM?
- What is the optimal method of screening?
- What should the diagnostic threshold for GDM be?

Is there a need to screen for GDM?

In two large RCTs comparing treatment vs. nontreatment of pregnant women with glucose intolerance that did not meet the criteria for overt diabetes, the incidence of select adverse perinatal outcomes was lower in the treatment group (119,120). In the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) study (119), there was a reduction in the composite outcome of severe perinatal complications (death, shoulder dystocia, bone fracture, nerve palsy; adjusted RR 0.33, 95% CI 0.14 to 0.75), while in the National Institute of Child Health and Human Development (NICHD) study (120), there was no reduction in the composite primary outcome (perinatal mortality, birth trauma and neonatal hypoglycemia, hyperbilirubinemia, or hyperinsulinemia), but reductions were found in fetal overgrowth, shoulder dystocia, caesarean delivery and preeclampsia. One cannot directly infer from these studies that there is utility to screening for GDM as they were not designed to assess screening vs. nonscreening. The utility of screening will vary based on the baseline characteristics of the screened population and the country-specific health economics evaluation. We can, therefore, infer from the results of these management studies, along with the data confirming that the incidence of adverse perinatal outcomes increases as glucose intolerance increases, that identification of women with hyperglycemia in pregnancy has clinical significance. As hyperglycemia in pregnancy is an asymptomatic condition, diagnosis is dependent on some form of screening. Until a large-scale, randomized trial of screening vs. nonscreening for hyperglycemia in pregnancy is performed, the recommendation to perform screening for GDM will remain in place.

Table 1
Criteria for mass screening

1. The condition sought should be a health problem for the individual and community.
2. There should be an accepted treatment or useful intervention for patients with the disease.
3. The natural history of the disease should be adequately understood.
4. There should be a latent or early symptomatic stage.
5. There should be a suitable and acceptable screening test or examination.
6. Facilities for diagnosis and treatment should be available.
7. There should be an agreed policy on whom to treat as patients.
8. Treatment started at an early stage should be of more benefit than treatment started later.
9. The cost should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a once and for all project.

Table 2
Screening and diagnosis guidelines from different associations

Organization	Who is screened?	Method of screening	Screen positive threshold	Diagnostic test	Diagnostic threshold for GDM
CDA 2013 (Canadian Diabetes Association)	All women	50 g GCT (preferred) Alternative = “1-step” 75 g OGTT (see IADPSG below)	≥7.8 mmol/L	75 g OGTT	1. ≥11.1 mmol/L on 50 g GCT 2. 75 g OGTT Fasting ≥5.3 1 hour ≥10.6 2 hours ≥9.0 One abnormal value needed for diagnosis
ADA 2013 (American Diabetes Association) (122)	All women	“One-step” 75 g OGTT	N/A	N/A	Fasting ≥5.1 1 hour ≥10.0 2 hours ≥8.5 One abnormal value needed for diagnosis
ADIPS 1998 (Australasia) (124)	1. All women 2. Only “high risk”*	50 g or 75 g GCT (nonfasting)	1. 50 g GCT: ≥7.8 mmol/L 2. 75 g GCT: ≥8.0 mmol/L	75 g OGTT	Fasting ≥5.5 2 hours ≥8.0 One abnormal value needed for diagnosis
IADPSG 2010 (118)	All women	“One-step” 75 g OGTT	N/A	N/A	Fasting ≥5.1 1 hour ≥10.0 2 hours ≥8.5 One abnormal value needed for diagnosis
NICE 2008 (United Kingdom) (82)	Women with risk factors	Risk factors†	N/A	75 g OGTT	Fasting ≥7.0 2 hours ≥7.8 One abnormal value needed for diagnosis
WHO 1999(World Health Organization) (125)	1. Women with risk factors 2. All women	1. Risk factors‡ 2. “One-step” with 75 g OGTT	N/A	75 g OGTT	Fasting ≥7.0 2 hours ≥7.8 One abnormal value needed for diagnosis

GCT, Glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

* Glycosuria, age >30 years, obesity, family history of diabetes, past history of GDM or glucose intolerance, previous adverse pregnancy outcome and belonging to a high-risk ethnic group.

† Body mass index >30 kg/m², previous macrosomic baby weighing ≥4.5 kg, previous GDM, family history of diabetes (first-degree relative with diabetes), family origin with a high prevalence of diabetes, such as South Asian (specifically women whose country of family origin is India, Pakistan or Bangladesh), black Caribbean, Middle Eastern (specifically women whose country of family origin is Saudi Arabia, United Arab Emirates, Iraq, Jordan, Syria, Oman, Qatar, Kuwait, Lebanon or Egypt).

‡ Older women; obese women; those with previous history of glucose intolerance; any pregnant woman who has elevated fasting, or casual, blood glucose levels; those with a history of GDM; those with a history of large-for-gestational-age babies; women from certain high-risk ethnic groups; strong family history of diabetes mellitus.

What is the optimal method of screening?

Screening can be universal or risk factor based. The goal of risk factor–based screening would be to ideally identify through historical and clinical risk factors those patients who would benefit most from biochemical screening while allowing those at lower risk to avoid the screening process. Unfortunately, traditional risk factor–based screening has low sensitivity and specificity for identification of GDM (128–130), and the presence of risk factors does not necessarily identify those with the highest risk of adverse outcomes (131). In populations that are older and have increased body mass index (BMI), selective screening ultimately leads to a majority of the pregnant population being screened; thus, universal screening is the pragmatic approach accepted in most North American centers. It is possible that future analysis of the HAPO data based on GDM risk factors might allow modification of this recommendation (132).

Assuming universal screening, the method of screening can be either a sequential or a 1-step process. Methods for sequential screening include the use of glycosuria, A1C, fasting plasma glucose (FPG), random plasma glucose and a glucose load. Aside from the glucose load, all the other methods mentioned have not been adopted due to their poor performance as screening tests in most populations (133–138).

The most common glucose test used in sequential screening is the 50 g GCT performed between 24 to 28 weeks of gestation, and it is the screening test recommended by the CDA in the 2008 guidelines. The performance of the GCT as a screening test depends on the cutoff values used, the criteria for diagnosis of GDM and the prevalence of GDM in the screened population.

The best data regarding the GCT as a screening test come from the Toronto Tri-Hospital study, as all participants had both a 50 g GCT and a 100 g OGTT regardless of the GCT results (127). The threshold for the GCT was 7.8 mmol/L, and GDM was diagnosed according to the National Diabetes Data Group criteria. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the GCT in this study were 76.6%, 82.2%, 14.4% and 98.9% respectively. Using the data from this study, we need to understand that, by using the sequential 50 g GCT followed by a glucose tolerance test, some 20% of the population will screen positive, of whom 16% will not have GDM. Due to the low sensitivity, almost one-fourth of the patients with GDM will not be diagnosed using this strategy; specifically, the test will not identify those women whose only abnormality is elevated FPG. The performance of the 50 g GCT can be improved when slightly more complicated strategies are used, such as factoring in certain risk factors, ethnic background or time from last meal (139–141).

An additional question is whether there is a GCT threshold above which GDM can be reliably diagnosed. The 2008 CDA guidelines recommend diagnosing GDM if the glucose level 1 hour after the 50 g GCT is 10.3 mmol/L. This recommendation is based on a retrospective cohort study in 514 women with a positive 50 g GCT who went on to have a 100 g OGTT (142). Using receiver operating curve analysis, the optimal cutoff point for the upper limit of the GCT was found to be 186 mg/dL (10.3 mmol/L). Using a 2.7% prevalence of GDM, this cutoff point had 36.1% sensitivity, 95.9% specificity, 19.6% PPV and 98.2% NPV. Approximately 21% of those with values >10.3 mmol/L had normal GTT results and, thus, would be wrongly classified as

having GDM. More recent studies do not support this cutoff value and, in fact, suggested that only cutoff values >12.2 mmol/L can reliably diagnose an abnormal GTT (143–146). As with all aspects of hyperglycemia in pregnancy, there is evidence that along a continuum of GCT results without a diagnosis of GDM, there is an increase in certain adverse perinatal outcomes (146). At this point, there is no evidence supporting a specific cutoff value of the 50 g GCT to diagnose GDM.

One-step approach

Those who subscribe to the notion that all cases of hyperglycemia in pregnancy need to be diagnosed and treated (i.e. increased sensitivity over specificity) will support the use of 1-step screening. The use of the term screening is misleading in this context as this strategy entails performing the diagnostic test on the entire population at risk. The 1-step approach includes a 75 g OGTT performed in the fasting state at 24 to 28 weeks of gestation with plasma glucose measured at fasting and 1 and 2 hours after the glucose load. The IADPSG and the American Diabetes Association (ADA) have supported this option (118,122), while some European guidelines recommend the 75 g OGTT only to women with risk factors but use the IADPSG thresholds for diagnosis of GDM (147–149). In March 2013, the National Institutes of Health (NIH) held a consensus development conference to discuss the diagnosis of GDM. As of March 6, 2013, a draft statement was published online (150). This draft statement stated that, as of that time, the NIH panel did not find sufficient evidence to support adopting a 1-step approach, such as that proposed by IADPSG (150). Since this is only a draft NIH statement, the final statement may differ. As mentioned above, adopting 1-stage “screening” using the IADPSG thresholds will lead to almost 18% of pregnant patients being diagnosed with GDM. There are no data regarding the performance of combinations of risk factor–based screening and a 75 g OGTT or sequential 50 g GCT followed by a 75 g OGTT using the new IADPSG criteria.

Given this lack of evidence, it is possible that the decision regarding the recommended screening method will be determined by the economic implications on the healthcare resources. An excellent review of the literature on cost effectiveness of different screening strategies for GDM can be found in Health Technology Assessment 2010. Canadian economic data from a prospective, randomized trial of 3 different screening strategies offers relevant information for the Canadian population (151). One thousand five hundred ninety four women were randomized to 1 of 3 groups: sequential screening with the 50 g GCT (cutoff 7.8 mmol/L) followed by the 100 g OGTT as the diagnostic test (group 1) or the 75-g OGTT (group 2); group 3 underwent a 1-step 75 g OGTT. The sequential screening strategy was found to be less expensive while having the same diagnostic power as there was no difference in the incidence of GDM in all 3 groups. This, in itself, is surprising as one would expect the incidence of GDM to be higher in the universally tested group. The authors also indicate that these results might not be applicable to higher-risk ethnic populations (151).

There are no economic analyses of the impact of the newly proposed IADPSG guidelines, although the impact on workload is expected to be substantial (152). In summary, most cost analysis evaluations support a sequential screening approach to GDM; thus, our preferred approach is to continue with this strategy.

What should be the diagnostic threshold for GDM?

GDM has classically been in the unusual situation of having no true “gold standard” for its diagnosis. Thus, all of the recent diagnostic thresholds for GDM have been determined by consensus agreement of various national and international professional organizations (see Table 2).

The original criteria for diagnosis of GDM were defined solely on the basis of their ability to identify a prediabetic state in the mother (153). Ideally, the diagnostic thresholds would be based on their ability to predict clinically relevant perinatal outcomes, such as perinatal mortality, birth trauma or birth asphyxia. The HAPO trial was supposed to provide this missing link (4). Unfortunately, in this study, no single threshold could be identified that predicted the primary outcome. The continuous association between increasing glucose intolerance and the risk of caesarean section, birth weight $>90\%$, neonatal hypoglycemia and cord C-peptide levels did not permit the determination of new diagnostic criteria. The new IADPSG criteria are the result of yet another expert consensus statement (118). Use of these new thresholds without subjecting them to rigorous clinical evaluation will lead to a significant increase in the number of women labeled as having GDM. This might prove to have a clinical benefit, but there is also the possibility of causing harm through unnecessary interventions, increased anxiety and an effect on women's perceptions of their health.

2013 CDA diagnostic criteria for GDM

Given the controversy that persists in the international community about the diagnosis of gestational diabetes, there is no clear answer as to what is ideal. In the absence of a single threshold to predict adverse outcomes in pregnancy, one can justifiably select thresholds for the 75 g OGTT that result in an odds ratio (OR) of 1.75 for development of the 4 primary outcomes in HAPO (4) or an odds ratio of 2.00 (Table 3). The IADPSG consensus committee selected the thresholds of OR 1.75; however, this may have implications on cost and workload. Therefore, the 2013 CDA expert committee acknowledges the controversy and has chosen the *preferred* approach of sequential screening with a 50 g GCT followed by a 75 g OGTT using the glucose thresholds that result in an OR of 2.00 (fasting ≥ 5.3 mmol/L, 1 hour ≥ 10.6 mmol/L, 2 hours ≥ 9.0 mmol/L). This represents minimal change from 2008. However, it is recognized that the IADPSG consensus group selected a different approach. Therefore, an alternative approach would be 1-step 75 g OGTT using the glucose thresholds that result in an OR of 1.75 (IADPSG recommended criteria) (Figures 1 and 2).

Management

Lifestyle

During pregnancy, women should be evaluated and followed by a registered dietitian to ensure that nutrition therapy promotes euglycemia, appropriate weight gain and adequate nutritional intake (154–157). Meal planning should emphasize moderate carbohydrate restriction and distribution over 3 meals and 3 snacks, one of which should be at bedtime. Hypocaloric diets are not recommended, as they result in weight loss and significant ketosis and are likely inadequate in required nutrients, such as protein and calcium. Prepregnancy body mass is a potent predictor of birth weight and should be considered when making recommendations about energy intake and rate of weight gain (158).

Table 3

Differences between selecting an OR of 1.75 vs. 2.0 for the primary outcome in the HAPO cohort (4,118)

	OR 1.75	OR 2.0
Threshold glucose levels (mmol/L)		
Fasting	5.1	5.3
1 hour	10.0	10.6
2 hours	8.5	9.0
% of HAPO cohort that met ≥ 1 glucose threshold	16.1%	8.8%

HAPO, Hyperglycemia and Adverse Pregnancy Outcomes; OR, odds ratio.

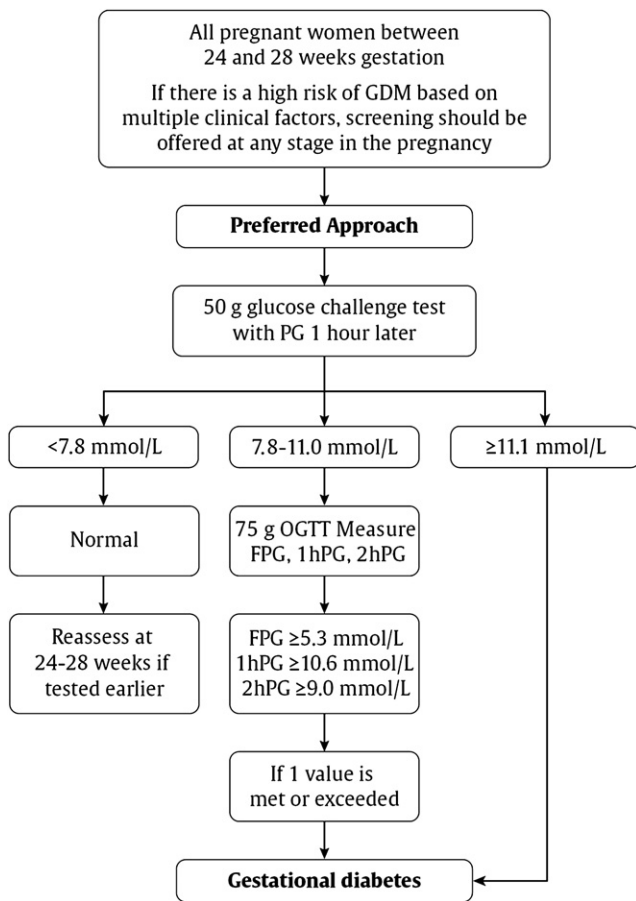


Figure 1. Preferred approach for the screening and diagnosis of gestational diabetes. 1hPG, 1-hour plasma glucose; 2hPG, 2-hour plasma glucose; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PG, plasma glucose.

Detailed recommendations for nutritional management of GDM are available (157). Physical activity should be encouraged unless obstetrical contraindications exist or glycemic control is worsened by the activity (159,160).

Glycemic control

For GDM, good outcomes have been reported using targets of fasting <5.3 mmol/L, 1 hour postprandial <7.8 and 2 hours postprandial <6.7 mmol/L (161–164) and are close to the targets of the 2 RCTs showing benefit for the treatment of GDM (119,120). The upper therapeutic target for 1- and 2-hour postprandial, if based on 2 SD above normal, would be 7.5 and 6.7 mmol/L (3), but, as noted above, the veracity of the numbers from this systematic analysis are suspect. Thus, until prospective studies of precise targets are available, using the targets in the Maternal-Fetal-Medicine-Unit Network study that were associated with achieving good glycemic control and outcomes appears reasonable (120).

Monitoring

Frequent SMBG is essential to guide therapy of GDM (165,166). Both fasting and postprandial testing are recommended to guide therapy in order to achieve glycemic targets (164,165). Studies support the use of a 1-hour postprandial target, typically 7.8 mmol/L (164,167–169) or a 2-hour postprandial target, typically 6.7 mmol/L (120,170,171). Although the peak for postprandial glycemia occurs at 69 ± 24 minutes (3) and hence may lend support to a 1-hour target being used, in obesity, this peak appears delayed (172). Continuous glucose monitoring systems have been useful in picking up previously undetected hyperglycemia, but it is unproven

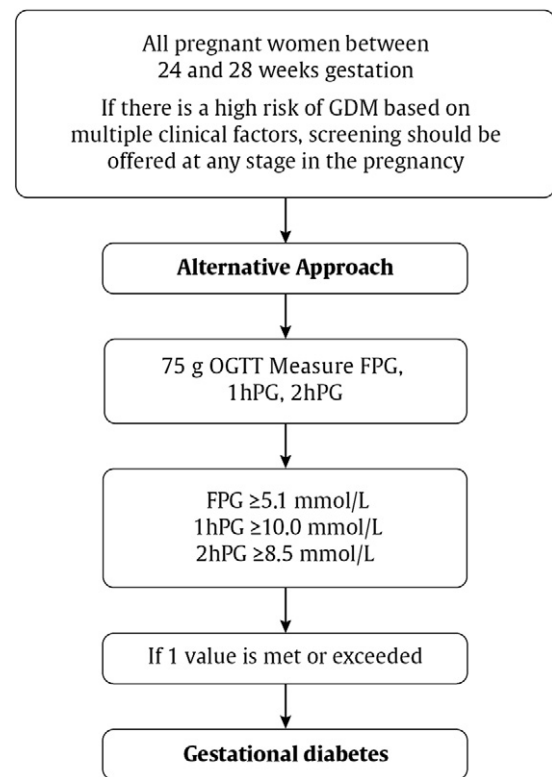


Figure 2. Alternative approach for the screening and diagnosis of gestational diabetes. 1hPG, 1-hour plasma glucose; 2hPG, 2-hour plasma glucose; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PG, plasma glucose.

if they are cost effective (173–175). Women with GDM, in an effort to control their glucose by diet, may put themselves and their baby at risk for starvation ketosis. Older studies raised the possibility that elevated ketoacids may be detrimental to the baby (75,176). While the clinical significance of these findings are doubtful, it appears prudent to check that urine ketones are negative when focusing on diet therapy for GDM.

Pharmacological therapy

Insulin. If women with GDM do not achieve glycemic targets within 2 weeks from nutritional therapy alone, insulin therapy should be initiated (177,178). In some cases, assessment of fetal growth by early third-trimester ultrasound can be used to guide therapy (179,180). The use of insulin to achieve glycemic targets has been shown to reduce fetal and maternal morbidity (178,181). A variety of protocols have been used, with multiple injections being the most effective (182). Insulin usually needs to be continuously adjusted to achieve glycemic targets. Although the rapid-acting bolus analogues aspart and lispro can help achieve postprandial targets without causing severe hypoglycemia (181–183), improvements in fetal outcomes have not been demonstrated with the use of aspart or lispro compared to regular insulin (181,182). A recent analysis reveals that glargine is safe in pregnancy and can be considered an option for pregnant patients (184). A recent Canadian review of rapid and long-acting basal analogues in GDM for glycemic control and hypoglycemia did not shown superiority (185).

Oral antihyperglycemic agents. Glyburide is safe and effective in controlling glucose levels in >80% of patients with GDM (186–188) and does not cross the placenta (189). Women who are older, are diagnosed earlier than 25 weeks and have higher fasting and postprandial glucose values on their OGTT are less likely to respond

to glyburide (187,190). Despite the glucose levels, some earlier studies report more adverse outcomes in women treated with glyburide compared to insulin (191,192). More recent studies have shown glyburide to be a safe alternative with no dose-related increment in neonatal hypoglycemia (193).

In 2008, Rowan et al (194) studied 751 women with GDM who were randomly assigned to open treatment with metformin (with supplemental insulin if required) or insulin. Of the women assigned to metformin, 46.3% received supplemental insulin. Metformin (alone or with supplemental insulin) was not associated with increased perinatal complications compared with insulin. There was less severe hypoglycemia in neonates receiving metformin but more spontaneous preterm delivery (i.e. <37 weeks' gestation). Other studies have confirmed the safety of metformin with less neonatal hypoglycemia (195). While metformin appears to be a safe alternative to insulin therapy, it does cross the placenta, plus metformin clearance is increased in pregnancy (196). Results of the offspring follow-up of the Metformin in Gestational diabetes trial (Mig TOFU), expected in several years, will provide more data on the long-term safety of metformin.

When comparing metformin to glyburide, there is a 2:1 failure of control of patients on metformin vs. glyburide (197). There is less hypoglycemia with metformin and less weight gain with metformin (198). Ongoing safety data show glyburide is safe (199,200). A recent systematic review of the literature has shown glyburide and metformin have similar outcomes when compared to insulin therapy (201).

Intrapartum glucose management

The primary goal of intrapartum management is to prevent neonatal hypoglycemia, which is thought to occur from the fetal hyperinsulinism caused by maternal hyperglycemia (202).

Neonatal hypoglycemia. There has been much disagreement over the definition of neonatal hypoglycemia because of the lack of rigorous scientific studies. However, recognizing that some guidelines must be provided for use in practice, the Canadian and American Pediatric Associations suggest that plasma glucose <2.6 mmol/L can result in adverse outcomes and, therefore, should be treated in symptomatic infants (203,204). Mild neonatal hypoglycemia has been found to be associated with transient abnormalities on physical examination (205), neurophysiological testing (206) and brain imaging (207).

Longer term follow-up found that infants with neonatal hypoglycemia had increased rates of neurological abnormalities at 18 months (208,209) and 8 years of age (210).

Risk of neonatal hypoglycemia is related to maternal glucose levels. Maternal hyperglycemia during labour, even when produced for a few hours by intravenous fluids in mothers without diabetes, can cause neonatal hypoglycemia (205,211). Studies have generally been performed in mothers with pregestational diabetes or insulin-treated GDM. These have been observational with no randomized trials deliberately targeting different levels of maternal glycemia during labour. Most have found that there is a continuous relationship between mean maternal glucose levels during labour and the risk of neonatal hypoglycemia with no obvious threshold. Authors have often chosen 2 levels within the range and shown that there is more hypoglycemia with the higher value, but the studies do not arrive at a common value. For example, Miodovnik et al (212) found the lowest risk if maternal glucose was <5.0 mmol/L, while Andersen et al (213) reported <7.1 mmol/L. Curet et al (214) found there was less hypoglycemia if the mean glucose was 4.6 mmol/L compared to 5.9 mmol/L (and recommended <5.6 mmol/L), while Lean et al (215) found that a mean of 7.6 mmol/L resulted in more hypoglycemia than 4.1 mmol/L, and Feldberg et al (216) found the same result, comparing values of

7.6 mmol/L and 4.8 mmol/L. Stenninger et al (217) reported 7.8 and 5.3 mmol/L, and Balsells et al (218) recommend keeping the level <7.0 mmol/L. Some authors advocate less stringent targets as being able to prevent neonatal hypoglycemia if the maternal glucose is kept 4.0 to 8.0 mmol/L (219–221).

Intrapartum insulin management. Insulin requirements decrease in-trapartum, and some patients with type 1 diabetes even do not require exogenous insulin to maintain good glucose control during labour (219,220). There are very few studies (although many published protocols) as to the best method of managing glycemia during labour (221,222). Rotating intravenous fluids compared with intravenous insulin were no different in controlling maternal glycemia in GDM (223). Adequate glucose must be provided during labour to meet the high glucose requirements. Given the lack of studies, there are no specific protocols that can be recommended to achieve the desired maternal glucose levels during labour.

Postpartum

Breastfeeding. Women with GDM may have more difficulty breastfeeding due to increased operative deliveries and obesity. Women with GDM should be encouraged to breastfeed immediately after delivery and for at least 3 months postpartum, as this may reduce neonatal hypoglycemia and offspring obesity, and prevent the development of metabolic syndrome and type 2 diabetes in the mother (224–230).

Long-term maternal risks. With the diagnosis of GDM, there is evidence of impairment of both insulin secretion and action (231,232). These defects persist postpartum and increase the risk of impaired fasting glucose, IGT and type 2 diabetes (233,234). The cumulative risk increases markedly in the first 5 years and more slowly after 10 years (235,236). At 3 to 6 months postpartum, risks of dysglycemia are in the 16% to 20% range. While elevated FPG during pregnancy is a strong predictor of early development of diabetes (237,238), other predictors include age at diagnosis, use of insulin, especially bedtime insulin or oral agents, and more than 2 pregnancies (239,240). A1C at diagnosis of GDM is also a predictor of postpartum diabetes (241). Any degree of dysglycemia is associated with increased risk of postpartum diabetes (242). After 9 years, 20% of women with prior GDM will develop type 2 diabetes (243). Some women with GDM, especially lean women <30 years of age who require insulin during pregnancy, progress to type 1 diabetes (244,245). Women with positive antibodies (anti-glutamic acid decarboxylase (anti-GAD), anti-insulinoma antigen 2 (anti-IA2)) are more likely to have diabetes by 6 months postpartum (246). Postpartum testing is essential to identify women who continue to have diabetes, those who developed diabetes after temporary normalization and those at risk, including those with IGT. However, many women do not receive adequate postpartum follow-up, and many believe they are not at high risk for diabetes (247–249). Only 50% return for postpartum testing (249–252). It is essential that the importance of follow-up be explicitly communicated with women and their caregivers who are responsible for postpartum testing. Telephone and e-mail reminders are helpful at increasing follow-up rates (253). Women should be screened postpartum to determine their glucose status. Postnatal fasting blood glucose has been the most consistently found variable in determining women at high risk for early postpartum diabetes (254). FPG alone, however, will miss many women with some degree of abnormal glucose tolerance (255–257); therefore, a 75 g OGTT should be done between 6 weeks and 6 months postpartum. Women should be counselled that the recurrence rate of GDM is high, from 30% to 84%, in subsequent pregnancies (258,259).

Metabolic syndrome has been shown to be more prevalent in women with GDM (260–262). Given the increased risk of CVD with metabolic syndrome, consideration should be given for screening for all components of metabolic syndrome in the postpartum care of women with GDM, specifically if there is a family history (263,264). High C-reactive protein, high low-density lipoprotein, fibrinogen and uric acid have been described postpartum in women with a history of GDM (265). Education on lifestyle modification to prevent diabetes and CVD should begin in pregnancy and continue postpartum. Awareness of exercise for prevention of diabetes is low (266), and emphasis on targeted strategies that incorporate women's exercise beliefs may increase participation rates (267).

Long-term fetal risks. There is increasing interest in determining how long the adverse effects of diabetes on pregnancy persist. Freinkel (268) extended the original Pedersen hypothesis of fuel-mediated teratogenesis to suggest that abnormal metabolism during pregnancy could have long-term effects on the offspring of diabetic mothers (ODM) (269). Two groups pioneered work in this area with careful prospective studies.

Information has been collected from the Pima Indians since 1965 examining the impact of maternal diabetes on children and adolescents (270). Children whose mothers had diabetes during pregnancy had a significantly higher incidence of obesity and type 2 diabetes that was detectable by age 9 and persisted into adulthood. Northwestern University enrolled women with both GDM and pregestational diabetes from 1977 to 1983 and followed their offspring until adolescence. Most women had good control of their diabetes during pregnancy. They found that aberrant maternal metabolism in the second and third trimesters (most often beta-hydroxybutyrate levels) was associated with reduced intellectual and psychomotor development on a number of tests performed up to age 11. With respect to growth, neonatal macrosomia had resolved by age 1, and weight was not different from controls until age 5. From age 5 through 16, the BMI of ODM (both GDM and pregestational diabetes) was significantly higher than in control subjects (271).

Since that time, the great majority of studies (270) continue to show an increased risk of obesity and metabolic abnormalities in childhood extending into adolescence and early adulthood (273–275). Some suggest GDM carries greater risk than type 1 for obesity in the offspring (276,277). Obesity in adolescence results in an increased risk of metabolic syndrome (277) and coronary artery disease (278).

How are the long-term consequences of maternal diabetes caused and could they be prevented? Genetics, exposure to abnormal intrauterine metabolism or the family environment all could potentially be involved. The issue was addressed in the Pima

by studying nuclear families with siblings born within 3 years of each other, before and after the mother developed diabetes. The fact that the risk of the child developing diabetes was significantly higher (OR 3.7) in siblings born after the mother developed diabetes demonstrated that intrauterine exposure per se conveyed the increased risk (279). A similar study was done in Sweden and looked at BMI at age 18 years. After examining multiple factors, they found that increased BMI was mediated through an intrauterine mechanism (280). Studies have looked at factors that potentially could be modified to reduce risk. Elevated maternal prepregnancy weight and excessive weight gain during pregnancy have been found by many studies to be independent risk factors for childhood obesity and metabolic abnormalities (271–283).

LGA infants of diabetic mothers and accelerated third-trimester growth have widely been found to be independent risk factors for offspring obesity and metabolic syndrome (272–283). Similarly, risk has been shown to be related to maternal glucose levels during pregnancy (281,284,285). In a detailed study, Chandler-Laney et al (286) were able to show that the relationship between maternal glucose and childhood obesity was independent of a child's resting energy expenditure, time spent physically active and energy intake. Studies also have found that adequate breastfeeding is associated with a significant decrease in the risk of childhood obesity (223,283,287).

Firm conclusions about the benefits of modifying these risk factors are limited by the lack of intervention studies. One study found that treatment of GDM did not affect obesity at age 2 (288); however, in view of the study by Silverman et al (271) and other data, this follow-up is too short to draw conclusions about childhood and adolescence. In view of the known benefits of breastfeeding and of preventing maternal obesity and LGA infants, it would not be ethical to conduct randomized trials deliberately exposing 1 group to suboptimal levels of 1 of these risk factors. However, it seems reasonable to assume that our current efforts at tight control of maternal nutrition and diabetes during pregnancy and promoting breastfeeding will provide benefits throughout childhood and adolescence.

Planning future pregnancies

Women with previous GDM should plan future pregnancies in consultation with their healthcare providers (289,290). Glucose tolerance should be assessed prior to conception to assure normoglycemia at the time of conception, and any glucose abnormality should be treated. In an effort to reduce the risk of congenital anomalies and optimize pregnancy outcomes, all women should take a folic acid supplement of 0.4 to 1.0 mg (291).

RECOMMENDATIONS

Pregestational Diabetes

Preconception care

- All women of reproductive age with type 1 or type 2 diabetes should receive advice on reliable birth control, the importance of glycemic control prior to pregnancy, the impact of BMI on pregnancy outcomes, the need for folic acid and the need to stop potentially embryopathic drugs prior to pregnancy [Grade D, Level 4 (11)].
- Women with type 2 diabetes and irregular menses/PCOS who are started on metformin or a thiazolidinedione should be advised that fertility may improve and be warned about possible pregnancy [Grade D, Consensus].
- Before attempting to become pregnant, women with type 1 or type 2 diabetes should:
 - Receive preconception counselling that includes optimal diabetes management and nutrition, preferably in consultation with an interdisciplinary pregnancy team to optimize maternal and neonatal outcomes [Grade C, Level 3 (10,56)]
 - Strive to attain a preconception A1C $\leq 7.0\%$ (or A1C as close to normal as can safely be achieved) to decrease the risk of:
 - Spontaneous abortion [Grade C, Level 3 (292)]
 - Congenital anomalies [Grade C, Level 3 (56,292–294)]

- Preeclampsia [Grade C, Level 3 (295,296)]
 - Progression of retinopathy in pregnancy [Grade A, Level 1, for type 1 diabetes (23); Grade D, Consensus, for type 2 diabetes]
 - c. Supplement their diet with multivitamins containing 5 mg folic acid at least 3 months preconception and continuing until at least 12 weeks postconception [Grade D, Level 4 (291)]. Supplementation should continue with a multivitamin containing 0.4–1.0 mg folic acid from 12 weeks postconception to 6 weeks postpartum or as long as breastfeeding continues [Grade D, Consensus].
 - d. Discontinue medications that are potentially embryopathic, including any from the following classes:
 - ACE inhibitors and ARBs prior to conception or upon detection of pregnancy [Grade C, Level 3 (47–49)]
 - Statins [Grade D, Level 4 (297)]
4. Women with type 2 diabetes who are planning a pregnancy should switch from noninsulin antihyperglycemic agents to insulin for glycemic control [Grade D, Consensus]. Women with pregestational diabetes who also have PCOS may continue metformin for ovulation induction [Grade D, Consensus].

Assessment and management of complications

5. Women should undergo an ophthalmological evaluation by an eye care specialist [Grade A, Level 1, for type 1 (23,298); Grade D, Level 4, for type 2 (26)].
6. Women should be screened for chronic kidney disease prior to pregnancy (see Chronic Kidney Disease chapter, p. S129) [Grade D, Level 4, for type 1 diabetes (39); Grade D, Consensus, for type 2 diabetes]. Women with microalbuminuria or overt nephropathy are at increased risk for development of hypertension and preeclampsia [Grade A, Level 1 (39,44)] and should be followed closely for these conditions [Grade D, Consensus].

Management in pregnancy

7. Pregnant women with type 1 or type 2 diabetes should:
- a. Receive an individualized insulin regimen and glycemic targets typically using intensive insulin therapy [Grade A, Level 1B, for type 1 (53,85); Grade A, Level 1, (85) for type 2]
 - b. Strive for target glucose values:
 - Fasting PG <5.3 mmol/L
 - 1-hour postprandial <7.8 mmol/L
 - 2-hour postprandial <6.7 mmol/L [Grade D, Consensus]
 - c. Be prepared to raise these targets if needed because of the increased risk of severe hypoglycemia during pregnancy [Grade D, Consensus]
 - d. Perform SMBG, both pre- and postprandially, to achieve glycemic targets and improve pregnancy outcomes [Grade C, Level 3 (56)]
8. Women with pregestational diabetes may use aspart or lispro in pregnancy instead of regular insulin to improve glycemic control and reduce hypoglycemia [Grade C, Level 2, for aspart (69); Grade C, Level 3, for lispro (89,90)].
9. Detemir [Grade C, Level 2 (95)] or glargine [Grade C, Level 3 (94)] may be used in women with pregestational diabetes as an alternative to NPH.

Intrapartum glucose management

10. Women should be closely monitored during labour and delivery, and maternal blood glucose levels should be kept between 4.0 and 7.0 mmol/L in order to minimize the risk of neonatal hypoglycemia [Grade D, Consensus].
11. Women should receive adequate glucose during labour in order to meet their high-energy requirements [Grade D, Consensus].

Postpartum

12. Women with pregestational diabetes should be carefully monitored postpartum as they have a high risk of hypoglycemia [Grade D, Consensus].
13. Metformin and glyburide may be used during breastfeeding [Grade C, Level 3 (109) for metformin; Grade D, Level 4, for glyburide (115)].
14. Women with type 1 diabetes in pregnancy should be screened for postpartum thyroiditis with a TSH test at 6–8 weeks postpartum [Grade D, Consensus].
15. All women should be encouraged to breastfeed since this may reduce offspring obesity, especially in the setting of maternal obesity [Grade C, Level 3 (224)].

Gestational Diabetes

Diagnosis

16. All pregnant women should be screened for GDM at 24–28 weeks of gestation [Grade C, Level 3 (121)].
17. If there is a high risk of GDM based on multiple clinical factors, screening should be offered at any stage in the pregnancy [Grade D, Consensus]. If the initial screening is performed before 24 weeks of gestation and is negative, rescreen between 24 and 28 weeks of gestation. Risk factors include:
- Previous diagnosis of GDM
 - Prediabetes
 - Member of a high-risk population (Aboriginal, Hispanic, South Asian, Asian, African)
 - Age ≥35 years
 - BMI ≥30 kg/m²
 - PCOS, acanthosis nigricans
 - Corticosteroid use
 - History of macrosomic infant
 - Current fetal macrosomia or polyhydramnios [Grade D, Consensus]

18. The preferred approach for the screening and diagnosis of GDM is the following [Grade D, Consensus]:
 - a. Screening for GDM should be conducted using the 50 g GCT administered in the nonfasting state with PG glucose measured 1 hour later [Grade D, Level 4 (299)]. PG ≥ 7.8 mmol/L at 1 hour will be considered a positive screen and will be an indication to proceed to the 75 g OGTT [Grade C, Level 2 (127)]. PG ≥ 11.1 mmol/L can be considered diagnostic of gestational diabetes and does not require a 75 g OGTT for confirmation [Grade C, Level 3 (145)].
 - b. If the GCT screen is positive, a 75 g OGTT should be performed as the diagnostic test for GDM using the following criteria:
 - ≥ 1 of the following values:
 - Fasting ≥ 5.3 mmol/L
 - 1 hour ≥ 10.6 mmol/L
 - 2 hours ≥ 9.0 mmol/L [Grade B, Level 1 (4)]
19. An alternative approach that may be used to screen and diagnose GDM is the 1-step approach [Grade D, Consensus]:
 - a. A 75 g OGTT should be performed (with no prior screening 50 g GCT) as the diagnostic test for GDM using the following criteria [Grade D, Consensus]:
 - ≥ 1 of the following values:
 - Fasting ≥ 5.1 mmol/L
 - 1 hour ≥ 10.0 mmol/L
 - 2 hours ≥ 8.5 mmol/L [Grade B, Level 1 (4)]

Management during pregnancy

20. Women with GDM should:
 - a. Strive for target glucose values:
 - i. Fasting PG < 5.3 mmol/L [Grade B, Level 2 (164)]
 - ii. 1-hour postprandial < 7.8 mmol/L [Grade B, Level 2 (163)]
 - iii. 2-hour postprandial < 6.7 mmol/L [Grade B, Level 2 (164)]
 - b. Perform SMBG, both fasting and postprandially, to achieve glycemic targets and improve pregnancy outcomes [Grade B, Level 2 (163)].
 - c. Avoid ketosis during pregnancy [Grade C, Level 3 (300)].
21. Receive nutrition counselling from a registered dietitian during pregnancy [Grade C, Level 3 (157)] and postpartum [Grade D, Consensus]. Recommendations for weight gain during pregnancy should be based on pregravid BMI [Grade D, Consensus].
22. If women with GDM do not achieve glycemic targets within 2 weeks from nutritional therapy alone, insulin therapy should be initiated [Grade D, Consensus].
23. Insulin therapy in the form of multiple injections should be used [Grade A, Level 1 (85)].
24. Rapid-acting bolus analogue insulin may be used over regular insulin for postprandial glucose control, although perinatal outcomes are similar [Grade B, Level 2 (181,182)].
25. For women who are nonadherent to or who refuse insulin, glyburide [Grade B, Level 2 (187–192)] or metformin [Grade B, Level 2 (194)] may be used as alternative agents for glycemic control. Use of oral agents in pregnancy is off-label and should be discussed with the patient [Grade D, Consensus].

Intrapartum glucose management

26. Women should be closely monitored during labour and delivery, and maternal blood glucose levels should be kept between 4.0 and 7.0 mmol/L in order to minimize the risk of neonatal hypoglycemia [Grade D, Consensus].
27. Women should receive adequate glucose during labour in order to meet their high-energy requirements [Grade D, Consensus].

Postpartum

28. Women with GDM should be encouraged to breastfeed immediately after delivery in order to avoid neonatal hypoglycemia [Grade D, Level 4 (227)] and to continue for at least 3 months postpartum in order to prevent childhood obesity [Grade C, Level 3 (225)] and reduce risk of maternal hyperglycemia [Grade C, Level 3 (301)].
29. Women should be screened with a 75 g OGTT between 6 weeks and 6 months postpartum to detect prediabetes and diabetes [Grade D, Consensus].

Abbreviations:

A1C, glycated hemoglobin; ACE, angiotension-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; GCT, glucose challenge test; OGTT, oral glucose tolerance test; PCOS, polycystic ovarian syndrome; PG, plasma glucose; SMBG, self-monitoring of blood glucose; TSH, thyroid-stimulating syndrome.

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Clinical Practice Guidelines

Diabetes in the Elderly

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetes in the elderly is metabolically distinct from diabetes in younger people and the approach to therapy should be different.
- Sulphonylureas should be used with caution because the risk of hypoglycemia increases exponentially with age.
- Long-acting basal analogues are associated with a lower frequency of hypoglycemia than conventional insulins in this age group.
- In elderly people, if mixture of insulin is required, the use of premixed insulins as an alternative to mixing insulins minimizes dose errors.

Introduction

The definition of “elderly” varies, with some studies defining the elderly population as ≥ 60 years of age. Administrative guidelines frequently classify people >65 years of age as elderly. Although there is no uniformly agreed-upon definition of elderly, it is generally accepted that this is a concept that reflects an age continuum starting sometime after age 65 and is characterized by a slow, progressive impairment in function that continues until the end of life (1).

Diagnosis

As noted in the Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter (p. S8), glycated hemoglobin (A1C) can be used as 1 of the diagnostic tests for type 2 diabetes in adults. Unfortunately, normal aging is associated with a progressive increase in A1C, and there is a significant discordance between fasting plasma glucose–based and A1C-based diagnosis of diabetes in this age group, a difference that is accentuated by race and gender (2). Pending further studies to define the role of A1C in the diagnosis of diabetes in the elderly, other screening tests may need to be considered in some patients. Screening for diabetes may be warranted in select individuals. In the absence of positive intervention studies on morbidity or mortality in this population, the decision about screening for diabetes should be made on an individual basis.

Reducing the Risk of Developing Diabetes

Lifestyle interventions are effective in reducing the risk of developing diabetes in elderly people at high risk for the

development of the disease (3). Acarbose (4), rosiglitazone (5) and pioglitazone (6) also are effective in preventing diabetes in elderly people at high risk. Metformin may not be effective (3).

Management

Glycemic control

As interdisciplinary interventions, especially those that have been specifically designed for this age group, have been shown to improve glycemic control in elderly individuals with diabetes, these people should be referred to a diabetes healthcare team (7–9). Pay-for-performance programs improve a number of quality indicators in this age group (10,11). Telemedicine case management and web-based interventions can improve glycemic control, lipids, blood pressure (BP), psychosocial well-being and physical activity; reduce hypoglycemia and ethnic disparities in care; and allow for detection and remediation of medically urgent situations, as well as reduce hospitalizations (12–21). A pharmaceutical care program can significantly improve medication compliance, as well as the control of diabetes and its associated risk factors (22).

The same glycemic targets apply to otherwise healthy elderly as to younger people with diabetes. In older patients with diabetes of several years' duration and established complications, intensive control reduces the risk of microvascular events but does not reduce macrovascular events or mortality (23–25). However, better glycemic control appears to be associated with less disability and better function (26,27). It is known that postprandial glucose values are a better predictor of outcome in elderly patients with diabetes than A1C or preprandial glucose values. Recently, it has been demonstrated that older patients with type 2 diabetes who have survived an acute myocardial infarction may have a lower risk for a subsequent cardiovascular (CV) event with targeting of postprandial vs. fasting/preprandial glycemia (28). In patients with equivalent glycemic control, greater variability of glucose values is associated with worse cognition (29).

Unfortunately, aging is a risk factor for severe hypoglycemia with efforts to intensify therapy (30). Asymptomatic hypoglycemia, as assessed by continuous glucose monitoring, is frequent in this population (31). This increased risk of hypoglycemia appears to be due to an age-related reduction in glucagon secretion, impaired awareness of hypoglycemic warning symptoms and altered psychomotor performance, which prevents the patient from

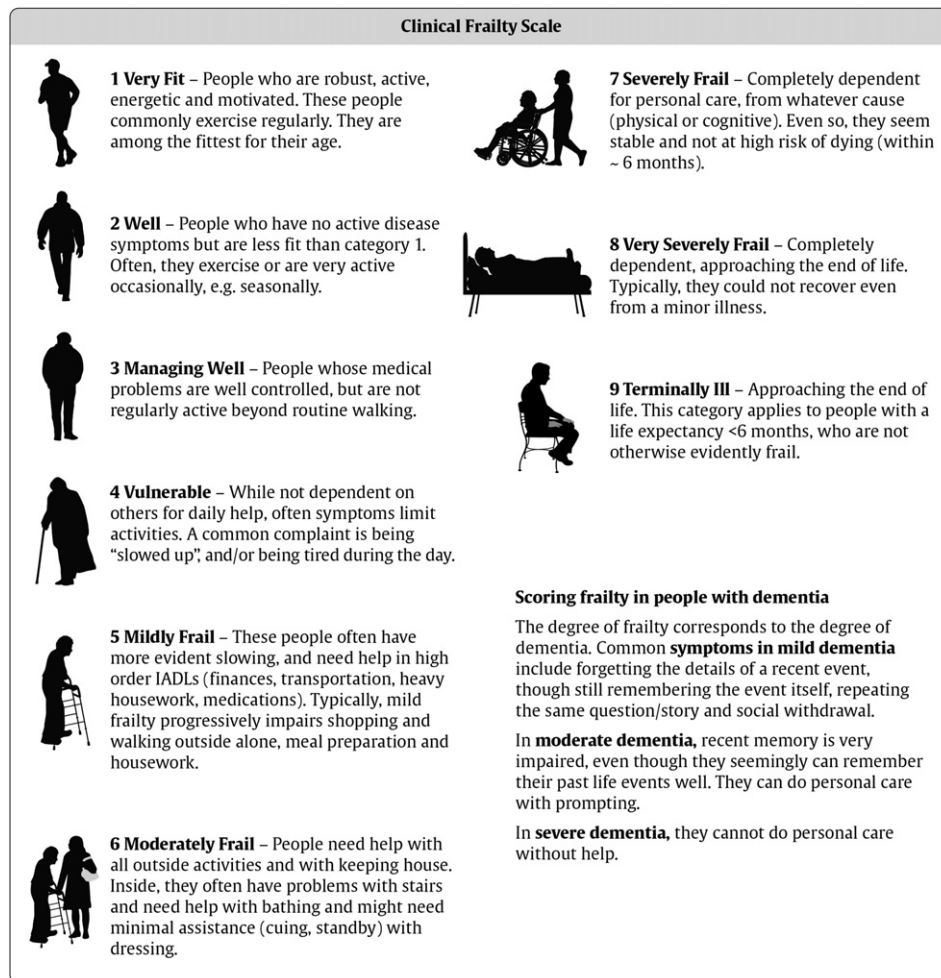


Figure 1. Clinical frailty scale. Adapted with permission from Moorhouse P, Rockwood K. Frailty and its quantitative clinical evaluation. J R Coll Physicians Edinb. 2012;42:333–340.

taking steps to treat hypoglycemia (32,33). Episodes of severe hypoglycemia may increase the risk of dementia (34), although this is controversial. Cognitive dysfunction in elderly subjects has been identified as a significant risk factor for the development of severe hypoglycemia (35,36). Therefore, the most important issue to address when attempting to achieve treatment guidelines in elderly patients is to prevent hypoglycemia as much as possible, even if that means that higher glycemic targets must be used.

“Frailty” is a widely used term associated with aging that denotes a multidimensional syndrome that gives rise to increased vulnerability. Frailty may have a biological basis and appears to be a distinct clinical syndrome. Many definitions of frailty have been proposed. The most commonly applied definition (Fried’s Frailty Phenotype) suggests that a patient is frail when 3 or more of the following criteria are present: unintentional weight loss (>10 pounds in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity (37). Progressive frailty has been associated with reduced function and increased mortality, and older patients with diabetes are more likely to be frail (38). When frailty occurs, it is a better predictor of complications and death in elderly patients with diabetes than is chronological age or burden of comorbidity (39). The Clinical Frailty Scale, developed by Rockwood et al (40), has demonstrated validity as a 7-point frailty scale that has since been modified to a 9-point frailty scale from 1 (very fit) to 9 (terminally ill), which can help to determine which subjects are frail (41) (Figure 1). In people with multiple comorbidities, a high level of functional dependency and

limited life expectancy (i.e. frail patients), decision analysis suggests that the benefit of intensive control is likely to be minimal (42). From a clinical perspective, the decision to offer more or less stringent glycemic control should be based on the degree of frailty. Patients with moderate or more advanced frailty (Figure 1) have a reduced life expectancy and should not undergo stringent glycemic control. When attempts are made to improve glycemic control in these patients, there are fewer episodes of significant hyperglycemia but also more episodes of severe hypoglycemia (43).

Nutrition and physical activity

Nutrition education programs can improve metabolic control in ambulatory older people with diabetes (44). Amino acid supplementation may improve glycemic control and insulin sensitivity in these patients, although this is controversial (45,46). Physical training programs can be successfully implemented in older people with diabetes, although comorbid conditions may prevent aerobic physical training in many patients, and increased activity levels may be difficult to sustain. Prior to instituting an exercise program, elderly subjects should be carefully evaluated for underlying CV or musculoskeletal problems that may preclude such programs. Aerobic exercise improves arterial stiffness and baroreflex sensitivity, both surrogate markers of increased CV morbidity and mortality (47,48). While the effects of aerobic exercise programs on glucose and lipid metabolism are inconsistent (49–51), resistance training has been shown to result in modest improvements in

glycemic control, as well as improvements in strength, body composition, and mobility (52–56). Exercise programs may reduce the risk of falls and improve balance in patients with neuropathy (57,58). However, it appears difficult to maintain these lifestyle changes outside of a supervised setting (59).

Oral antihyperglycemic agents

In lean elderly people with type 2 diabetes, the principal metabolic defect is impairment in glucose-induced insulin secretion (60). Therefore, initial therapy for these individuals should involve agents that stimulate insulin secretion. In obese elderly people with type 2 diabetes, the principal metabolic defect is resistance to insulin-mediated glucose disposal, with insulin secretion being relatively preserved (61–63). Initial therapy for obese older people with diabetes should involve agents that improve insulin resistance. There have been no randomized trials of metformin in the elderly, although clinical experience suggests it is an effective agent. Metformin may reduce the risk of cancer in elderly patients with diabetes (64,65). Alpha-glucosidase inhibitors are modestly effective in older people with diabetes, but a substantial percentage of individuals cannot tolerate them because of gastrointestinal side effects (66–69). Thiazolidinediones are effective agents but are associated with an increased incidence of edema and congestive heart failure (CHF) in older people (70–73). Rosiglitazone, but not pioglitazone, may increase the risk of CV events and death (74–77). These agents also increase the risk of fractures in women (77,78). When used as monotherapy, they are less likely to fail than metformin or glyburide (73). Interestingly, drugs that increase insulin sensitivity, such as thiazolidinediones and metformin, may attenuate the progressive loss in muscle mass that occurs in older people with diabetes and contributes to frailty (79).

Sulphonylureas should be used with caution because the risk of severe or fatal hypoglycemia increases exponentially with age (80,81) and appears to be higher with glyburide (82–84). Glimepiride and glipizide are preferred over glyburide in the elderly because they are associated with a lower frequency of hypoglycemia and CV events (85–90). A long-acting formulation of glimepiride resulted in equivalent glycemic control and the same frequency of hypoglycemic events as regular glimepiride in the elderly (87), and appears to result in a lower frequency of hypoglycemic events than glimepiride (88). Meglitinides (repaglinide and nateglinide) are associated with a lower frequency of hypoglycemia in the elderly compared to glyburide (91–93) and would be preferred in individuals with irregular eating habits.

Dipeptidyl peptidase (DPP)-4 inhibitors (linagliptin, saxagliptin and sitagliptin) are similarly effective in young and old patients, cause minimal hypoglycemia when used alone and do not result in weight gain (94–97). The efficacy of liraglutide with respect to A1C and weight is independent of age and is well tolerated in the elderly with a low risk of hypoglycemia (98).

Insulin therapy

Insulin regimens in the elderly should be individualized and selected to promote patient safety. The clock drawing test can be used to predict which elderly subjects are likely to have problems with insulin therapy (99). In elderly people, the use of premixed insulins as an alternative to mixing insulins (100) and prefilled insulin pens as an alternative to conventional syringes (101,102) minimizes dose errors and may improve glycemic control. Premixed insulin analogues can be administered after meals (103–105) and may be associated with better control than basal insulins, but at the expense of more hypoglycemia and greater

weight gain (106). Basal-bolus regimens may be associated with greater improvements in glycemic control, health status and mood than twice-daily injections of long-acting insulin (107), although premixed insulin analogues can result in equivalent glycemic control to basal-bolus regimens (108). In older people with poorly controlled type 2 diabetes requiring insulin, both continuous subcutaneous insulin infusion and basal-bolus regimens can result in excellent glycemic control with reduced glycemic variability, as well as good safety and patient satisfaction (109,110). One study demonstrated equivalent glycemic control in older people treated with either twice-daily insulin injections or a combination of a single injection of NPH insulin with an oral antihyperglycemic agent (111). The addition of glargine to oral agents results in improved control and a reduced frequency of hypoglycemia when compared to escalation of oral agents (112). Both detemir and glargine resulted in a reduced rate of hypoglycemia when compared to 30/70 insulin or NPH (113,114). Finally, elderly patients with diabetes are at increased risk for falls and fractures, and insulin therapy increases this risk, although the mechanism for this effect is unclear (115).

Prevention and Treatment of Complications

Hypertension

Treatment of isolated systolic hypertension or combined systolic and diastolic hypertension in elderly people with diabetes is associated with a significant reduction in CV morbidity and mortality and microvascular events. Also, the number needed to treat (NNT) reduces with increasing age (116–120). Treatment of isolated systolic hypertension may also preserve renal function in elderly people with diabetes (121). Several different classes of antihypertensive agents have been shown to be effective in reducing the risk of CV events and end stage renal disease, including thiazide-like diuretics, long-acting calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (116–126). Any of these agents is a reasonable first choice (122–124). Although the calcium channel blocker amlodipine may be associated with an increased risk of CHF (124), the combination of ACE inhibitor and amlodipine appears to reduce CV events more than the combination of an ACE inhibitor and hydrochlorothiazide (127). Cardioselective beta blockers and alpha-adrenergic blockers are less likely to reduce CV risk than the above agents (122–125). ACE inhibitors may be particularly valuable for people with diabetes and ≥ 1 other CV risk factor (128). More intensive control of BP (systolic <140 vs. <120) does not improve outcomes and results in more side effects (129). As a result, there has been discussion about altering the systolic BP target for the elderly to 140 mm Hg; however, the Canadian Hypertension Education Panel (CHEP), in collaboration with the Canadian Diabetes Association, have maintained the target BP of <130/80 mm Hg in diabetes. There has been a significant improvement in the last decade in the number of older people treated for hypertension, and therapies being used are more consistent with current clinical practice guidelines (130).

Dyslipidemia

The treatment of dyslipidemia with statins for both primary and secondary prevention of CV events has been shown in most, although not all, studies to significantly reduce CV morbidity and mortality in older people with diabetes (131–139). The data on the use of fibrates in this patient population are equivocal (140,141), although they may reduce albuminuria and slow glomerular filtration rate loss (142).

Erectile dysfunction

Type 5 phosphodiesterase inhibitors appear to be effective for the treatment of erectile dysfunction in carefully selected elderly people with diabetes (143–145).

Depression

Depression is common in elderly patients with diabetes, and a systematic approach to the treatment of this illness not only improves quality of life but reduces mortality (146).

Diabetes in Nursing Homes

Diabetes is often undiagnosed in nursing home patients (147–150). The prevalence of diabetes is high in institutions, and individuals frequently have established macro- and microvascular complications, as well as substantial comorbidity (150–153). Antipsychotic drug use is a risk factor for the development of diabetes in patients in institutions (154). In observational studies, the degree of glycemic control varies widely between different centres (147,152), adherence to clinical practice guidelines is poor and insulin sliding scales are used frequently despite lack of evidence for their effectiveness (150). Undernutrition is a major problem in people with diabetes living in nursing homes (152).

There are very few intervention studies on diabetes in nursing homes. The short-term substitution of a regular diet or a standard nutritional formula for a “diabetic diet” or a diabetic nutritional formula did not modify the level of glycemic control (150,155–157). For selected nursing home residents with type 2 diabetes, substitution of regular insulin by lispro insulin (bolus analogue) may improve glycemic control and A1C levels with a reduced number of hypoglycemic episodes (158).

RECOMMENDATIONS

1. Healthy elderly people with diabetes should be treated to achieve the same glycemic, blood pressure and lipid targets as younger people with diabetes [Grade D, Consensus].
2. In the frail elderly, while avoiding symptomatic hyperglycemia, glycemic targets should be A1C \leq 8.5% and fasting plasma glucose or preprandial PG 5.0–12.0 mmol/L, depending on the level of frailty. Prevention of hypoglycemia should take priority over attainment of glycemic targets because the risks of hypoglycemia are magnified in this patient population [Grade D, Consensus].
3. In elderly people with cognitive impairment, strategies should be used to strictly prevent hypoglycemia, which include the choice of anti-hyperglycemic therapy and less stringent A1C target [Grade D, Consensus].
4. Elderly people with type 2 diabetes should perform aerobic exercise and/or resistance training, if not contraindicated, to improve glycemic control [Grade B, Level 2 (49–53)].
5. In elderly people with type 2 diabetes, sulphonylureas should be used with caution because the risk of hypoglycemia increases exponentially with age [Grade D, Level 4 (80)].
 - In general, initial doses of sulphonylureas in the elderly should be half of those used for younger people, and doses should be increased more slowly [Grade D, Consensus].
 - Gliclazide and gliclazide MR [Grade B, Level 2 (85,87)] and glimepiride [Grade C, Level 3 (86)] should be used instead of glyburide, as they are associated with a reduced frequency of hypoglycemic events.

- Meglitinides may be used instead of glyburide to reduce the risk of hypoglycemia [Grade C Level 2 (92) for repaglinide; Grade C, Level 3 (93) for nateglinide], particularly in patients with irregular eating habits [Grade D Consensus].

6. In elderly people, thiazolidinediones should be used with caution due to the increased risk of fractures and heart failure [Grade D Consensus].
7. Detemir and glargine may be used instead of NPH or human 30/70 insulin to lower the frequency of hypoglycemic events [Grade B, Level 2 (113,114)].
8. In elderly people, if insulin mixture is required, premixed insulins and prefilled insulin pens should be used instead of mixing insulins to reduce dosing errors and to potentially improve glycemic control [Grade B, Level 2 (100–102)].
9. The clock drawing test may be used to predict which elderly subjects will have difficulty learning to inject insulin [Grade D, Level 4 (99)].
10. In elderly nursing home residents, regular diets may be used instead of “diabetic diets” or nutritional formulas [Grade D, Level 4 (155–157)].

Other Relevant Guidelines

Screening for Type 1 and Type 2 Diabetes, p. S12
 Reducing the Risk of Developing Diabetes, p. S16
 Organization of Diabetes Care, p. S20
 Self-Management Education, p. S26
 Targets for Glycemic Control, p. S31
 Pharmacotherapy in Type 1 Diabetes, p. S56
 Pharmacologic Management of Type 2 Diabetes, p. S61
 Hypoglycemia, p. S69
 Screening for the Presence of Coronary Artery Disease, p. S105
 Dyslipidemia, p. S110
 Treatment of Hypertension, p. S117
 Erectile Dysfunction, p. S150

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Clinical Practice Guidelines

Type 2 Diabetes in Aboriginal Peoples

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Aboriginal peoples living in Canada are among the highest risk populations for diabetes and related complications. Community-based and culturally appropriate prevention strategies and surveillance of diabetes indicators among this high risk population are essential to reducing health disparities.
- Efforts to prevent diabetes should focus on diabetes risk factors, including prevention of childhood, adolescent, adult, and pregravid obesity; prevention and optimal management of gestational diabetes; and prevention of modifiable risk factors, such as smoking, inactivity, stress, and unhealthy eating habits.
- Screening for diabetes in adults should be considered every 1 to 2 years in Aboriginal individuals with ≥ 1 additional risk factor(s). Screening every 2 years also should be considered from age 10 years or established puberty in Aboriginal children with ≥ 1 additional risk factor(s), including exposure to diabetes in utero.
- Early identification of diabetes in pregnancy should be emphasized and post-partum screening for diabetes in those with gestational diabetes should be instituted with appropriate follow-up.
- Treatment of diabetes in Aboriginal peoples should follow current clinical practice guidelines using community-specific diabetes management programs developed and delivered in partnership with the target communities.
- Improvements in systematic care and medical management are needed to help close the substantial care gap between Aboriginal and non-Aboriginal peoples to mitigate diabetes-related morbidity and premature mortality.

Introduction

Around the globe, diabetes incidence and prevalence rates are several times higher among Indigenous peoples compared to the general population (1). In Canada, Aboriginal peoples are a heterogeneous population comprised of individuals of First Nations, Inuit, and Métis heritage living in a range of environments from large cities to small, isolated communities. National survey data have consistently shown that the national age-adjusted prevalence of diabetes is 3 to 5 times higher in First Nations than in the general population (2–5) and population screening has shown rates as high as 26% in individual communities (6). As in most populations where incidence and prevalence rates are higher, age of diagnosis is younger in First Nations peoples (7,8). These rates are similar in other countries where Indigenous populations have been subject to colonization (1). In a recent profile of health status, Métis, aged 19 years and older, in Manitoba, were found to have an age and sex

adjusted diabetes rate of 11.8% compared to the provincial rate of 8.8% (9). In 2006, 7% of Métis were reported to have been diagnosed with diabetes while the national prevalence during the same time period was reported at 4% (10). Among the Inuit and Alaska Natives, it has recently been shown that the diabetes prevalence rate has substantially increased and is now comparable with the general Canadian population (11,12).

The higher rate of adverse health outcomes in Aboriginal peoples is associated with a number of factors, including lifestyle (diet and physical activity), genetic susceptibility, and historic-political and psychosocial factors, stemming from a history of colonization that severely undermined Aboriginal values, culture, and spiritual practices (13). Barriers to care that are unique to Aboriginal settings also exacerbate the problem with fragmented healthcare, poor chronic disease management, high healthcare staff turnover, and limited or non-existent surveillance (14). In addition, social determinants of health, including low income, lack of education, high unemployment, poor living conditions, lack of social support, negative stereotyping and stigmatization, and poor access to health services compound the problem (14). Different understandings of the etiology of health and illness from the holistic, collective social experience adopted by many Indigenous peoples to the traditional biomedical model which centers the disease within the individual may also influence care (15).

Among First Nations peoples, a gender difference exists with more females impacted by type 2 diabetes than males (7,16). This is most striking during reproductive years, resulting in recent age standardized prevalence rates of over 20% among First Nations women compared to about 16% among First Nations men. In addition, diabetes prevalence rates have more than tripled from 1980 to 2005 among First Nations children (8,17). Similarly, incidence rates of type 2 diabetes among Indigenous youth in Australia have been documented to be 6.1 times that of non-Indigenous youth (18). Métis men and women are reported to have a similar prevalence of diabetes (10).

Aboriginal women in Canada also experience gestational diabetes mellitus (GDM) rates 2 to 3 times higher than others (19,20), in part related to an interaction of Aboriginal ethnicity with pregravid adiposity (19,21). High GDM rates preceded the appearance of the type 2 diabetes epidemic in remote communities surveyed in the early 1990s (22) and increasing GDM rates (20) have paralleled

increases in high birth weight rates over several decades. Both maternal GDM (23) and high birth weight (24) are predictors for type 2 diabetes in the offspring (25) and likely contribute to the higher type 2 diabetes rates in First Nations women compared to men (7).

While genetic factors are important in the epidemic of type 2 diabetes among Indigenous peoples (26), its rapid appearance over a few decades in genetically diverse populations is likely the result of an interaction of local genetic mutations with numerous social stressors and lifestyle factors (27–32). Recent research suggests that epigenetic factors play a key role in the interaction between genes and the environment, influencing the development of diabetes complications (33,34). Inequities in the social determinants of health brought about through colonization (14) contribute to the main risk factors for type 2 diabetes in Aboriginal peoples, such as decreased rates of physical activity, stress, dietary acculturation and an unhealthy diet, food insecurity, obesity/metabolic syndrome, and high rates of diabetes during pregnancy.

Complications and Mortality Due to Diabetes

Indigenous peoples with diabetes also experience disparities in diabetes-related complications and mortality. Higher prevalence rates of microvascular disease, including chronic kidney disease (CKD) (35), lower limb amputation (9,36), foot abnormalities (37,38), and more severe retinopathy (39), are found in Aboriginal peoples with diabetes than in the general population with diabetes. Aboriginal peoples also are burdened by higher rates of macrovascular disease (9,15) and exhibit higher rates of cardiometabolic risk factors, including smoking, obesity, and hypertension (9,35,40), that may indicate a future increase in cardiovascular morbidity and mortality.

As in other Indigenous populations, First Nations people with diabetes have high rates of albuminuria (41) and are more likely than others to progress to end-stage renal disease (ESRD) (42). Potentially modifiable risk factors for kidney disease progression include poor glycemic control, systolic hypertension, smoking, and insufficient use of angiotensin-converting-enzyme (ACE) inhibitors (41,43) as well as periodontal disease (44). Likely relevant for other chronic diabetic complications, longer duration of diabetes (41,45) related to younger adult onset (45) is associated with higher ESRD rates and differential mortality and highlights the urgent need for primary diabetes prevention. The provincial dialysis initiation rate is higher for Métis than other Manitobans (0.46% vs. 0.34%) (9). On a positive note, ESRD incidence among Aboriginal peoples has stabilized since the early 1990s in both the United States (46) and Canada (42), and is probably due to the introduction of ACE inhibitors and application of interdisciplinary chronic disease care models (46).

The prevalence of metabolic syndrome is elevated among both First Nations adults (47) and children (48,49) and, like type 2 diabetes, disproportionately affects females with rates as high as 45% in Oji-Cree women. Increased adiposity and dysglycemia are more common components than hypertension (47), and non-traditional risk factors, such as elevated C-reactive protein are also elevated (48). There is a strong relationship between metabolic syndrome and later type 2 diabetes (50,51). Thus, Aboriginal peoples with metabolic syndrome should be targeted by programs designed to prevent type 2 diabetes since interventions, such as increased physical activity (52) and consumption of long chain omega 3 fatty acids (53), have been shown to improve glucose tolerance in Aboriginal peoples.

A reversal in long-term trends for decreasing mortality among American Indians since the mid-1980s appears primarily due to the direct and indirect effects of type 2 diabetes (54). Surveillance

data from Alberta indicate that Aboriginal peoples with diabetes have mortality rates 2 to 3 times higher than the general population with diabetes (8). Provincially, Métis with diabetes are significantly more likely to die within a 5-year period than other Manitobans with diabetes (20.8% vs. 18.6%) (9). In British Columbia, First Nations peoples with diabetes have nearly twice the mortality rate than First Nations peoples without diabetes (55). Additionally, administrative data have demonstrated increased hospitalizations for heart disease among First Nations people in Ontario, despite decreases in the general population (56). Healthcare costs for Aboriginal peoples with diabetes have been shown to be considerably higher than costs in the general population with diabetes due to higher use of physician and hospital services (57). Increased morbidity and mortality among First Nations people are at least partly due to poorer quality of diabetes care (35,58,59).

Screening

Routine medical care for Aboriginal peoples of all ages should include identification of modifiable risk factors, such as obesity, abnormal waist circumference (WC) or body mass index (BMI), physical inactivity, smoking, and unhealthy eating habits. Screening for diabetes with a fasting plasma glucose (FPG) test, an A1C, or an oral glucose tolerance test (OGTT) should be considered every 1 to 2 years in individuals with ≥ 1 additional risk factor(s). Screening every 2 years also should be considered from age 10 or established puberty (60) in Aboriginal children with ≥ 1 additional risk factor(s), including exposure to diabetes in utero (see Screening for Type 1 and Type 2 Diabetes chapter, p. S12). Regular screening and follow-up should be done in children who are very obese (BMI ≥ 99.5 percentile) (see Type 1 Diabetes in Children and Adolescents, p. S153; Type 2 Diabetes in Children and Adolescents, p. S163). While an OGTT remains the standard for the diagnosis of diabetes, the A1C has a distinct appeal for testing in this population as it is relatively inexpensive and does not require fasting.

Systematic screening for diabetes and related complications has taken place in several Aboriginal community settings across North America. Screening has proved possible in both rural and remote communities through appropriate dialogue, respect and planning, the provision of concomitant health education and care, and the promotion of follow-up (58,61–64). In the United States, a kidney evaluation program screened 89,552 participants in 49 states, 4.5% of whom were Native Americans (63). In Alberta, substantial numbers of Aboriginal individuals with abnormalities have been identified through community-based screening (64), particularly First Nations people with documented risk factors.

Regular screening, follow-up, and surveillance in individuals with prediabetes (IFG and/or IGT), history of GDM, or polycystic ovary syndrome (PCOS) should be encouraged, as 20 to 50% of high risk individuals with IFG may have a 2-hour plasma glucose ≥ 11.1 mmol/L (65). Lifestyle or metformin should be initiated as treatment of prediabetes and ongoing monitoring should be instituted.

Primary Prevention

Efforts to prevent diabetes should focus on all diabetes risk factors, including prevention of childhood, adolescent, adult, and pregravid obesity; and prevention and optimal management of diabetes in pregnancies to reduce macrosomia and diabetes risk in offspring. Prevention strategies in communities should be implemented in collaboration with community leaders, healthcare professionals, and funding agencies to engage entire communities, promote environmental changes, and prevent increased risk of diabetes (66,67). Such partnerships are important in incorporating

traditions and local culture, building both trusting relationships and community capacity, and increasing diabetes-related knowledge (68). Programs should be developed in collaboration with communities and implemented within the framework of available health resources and infrastructure of each community and promote traditional activities and foods (provided they are safe, acceptable, and accessible).

Prevention of childhood obesity through moderate interventions, starting in infancy, has shown promise (69). In Zuni First Nations children in the United States, an educational component targeting decreased consumption of sugared beverages, knowledge of diabetes risk factors, and a youth-oriented fitness centre significantly decreased insulin resistance (70). These types of interventions aimed at decreasing childhood obesity, as well as efforts to promote breast-feeding in the first year of life (23), may help to reduce the risk for diabetes. As well, strategies aimed at the prevention of pregravid obesity prior to first conception or subsequent pregnancy may be important tools to decrease the incidence of GDM and type 2 diabetes in pregnancy, thereby potentially decreasing the incidence of diabetes in subsequent generations of Aboriginal peoples (71–73).

Management

Lifestyle intervention programs targeted towards Aboriginal people with diabetes show modest results. Targeted programs to improve diet and increase exercise have been effective in improving glycemic control (74,75), reducing caloric intake (76), reducing weight (74), reducing WC and diastolic blood pressure (77), and increasing folate intake (78). A key component to all successful programs is cultural appropriateness.

Similar to prevention strategies, treatment of diabetes in Aboriginal peoples should be in the context of local traditions, language, and culture, while also adhering to current clinical practice guidelines. While most diabetes education programs work most effectively when delivered by multidisciplinary teams, in Aboriginal communities, where access to physicians is often limited, strategies to improve care should focus on building capacity of existing front-line staff (community health care providers, nurses) to implement clinical practice guidelines (58,79,80).

Working with community healthcare providers and community leaders assures that local resources and challenges, such as access to healthy foods, geographic location, and isolation level, are acknowledged and considered and that programs developed are community-directed (81–84). A diabetes management program incorporating self-management and patient education addressing diet and exercise within a Hawaiian/Samoan Indigenous population utilized community health workers in the application of clinical practice guidelines and a chronic disease management model. The study demonstrated a significant improvement in A1C levels and important changes in patient knowledge of reducing consumption of non-healthy foods (82). Maori and Pacific Islander adults with type 2 diabetes and CKD received community care provided by local healthcare assistants to manage hypertension and demonstrated a reduction in systolic blood pressure and in 24-hour urine protein, and a greater number of prescribed antihypertensives. Left ventricular mass and left atrial volume progressed in the usual care group, but not in the intervention group (85).

Systems Intervention

Comprehensive management of diabetes in small remote communities (where many Aboriginal people live) remains difficult due to discontinuities in staffing, lack of work-practice

support, and services not adapted to individual's needs (86). Existing intervention studies have assessed impact on clinical outcomes, process measures of care, lifestyle changes, and patient satisfaction. The main types of interventions that have been tested include: expanding the scope of practice for nurses and allied care (82,87–89), increasing access to care and screening (90,91), multifaceted interventions designed to improve quality of care, and targeting patients through lifestyle programs (92).

Expanding the scope of practice for nurses and allied health professionals in diabetes care is an effective strategy, and particularly important where doctors are scarce. The DREAM 3 study used home and community care workers to implement a nurse-led algorithm-driven hypertension management program which produced sustained reductions in blood pressure in a Saskatchewan First Nations community through a randomized controlled trial (87–89). Algorithm-based screening and management of renal and cardiovascular abnormalities by local health workers supported by nurses and physicians reduced renal failure (93,94). Algorithm-based, nurse-led management showed improvement in hypertension and cholesterol (95–97). Nurse case management has shown benefit in urban and rural settings, increasing screening rates and compliance (98,99). Multidisciplinary teams, occasionally including Aboriginal health workers, also have shown benefit (100–102). The SANDS study demonstrated that aggressive lipid targets could be safely maintained in Indigenous peoples with diabetes with the help of standardized algorithms, point-of-care lipid testing, and non-physician providers (103).

For mitigation of geographic access to diabetes care, mobile screening and treatment units that target Aboriginal communities have been found to be effective in Western Canada. Mobile units equipped with staff, lab, and diagnostic equipment showed significant improvements in BMI, blood pressure, A1C, and lipid levels (90,91). An outreach team conducting small group academic detailing with clinicians improved blood pressure and client satisfaction (104). Retinal photography has been shown to be an effective strategy to increase access to screening for diabetic retinopathy in remote communities (105).

Given the multiple barriers to high quality care, multifaceted interventions also have shown benefit. These include: diabetes registries, recall systems, care plans, training for community health workers, and an outreach service. These have been found to be effective in Australia, but it is not clear which elements are key (86,106–108).

There is an urgent need for systematic and validated surveillance of prevalence, incidence, and morbidity and mortality rates due to type 2 diabetes in First Nations communities (35). Surveillance systems in Australia monitoring diabetes rates in their Aboriginal peoples have shown improvements in quality of care (109). In the United States, federally funded on-reserve programs include diabetes registries, use of flow charts, annual chart audits with continuous quality assurance, full-time dedicated diabetes clinical staff, and funding for community initiatives. These programs have been associated with consistent improvements in diabetes quality measures (110). The James Bay Cree in Quebec have instituted a regional diabetes surveillance system that tracks clinical outcomes, including complications (111,112). A registry program also has been developed for Queensland in Australia (113). Surveillance systems incorporating diabetes registries would allow organizations and providers to document clinical care, monitor trends in care, identify community needs, evaluate programs, and facilitate policy development (8,55,109,114). A national surveillance program should be considered in Canada for on- and off-reserve Aboriginal communities.

RECOMMENDATIONS

- Starting in early childhood, Aboriginal people should be evaluated for modifiable risk factors of diabetes (e.g. obesity, lack of physical activity, unhealthy eating habits), prediabetes, or metabolic syndrome [Grade D, Consensus, see Type 2 Diabetes in Children and Adolescents, p. S163].
- Screening for diabetes in Aboriginal children and adults should follow guidelines for high risk populations (i.e. earlier and at more frequent intervals depending on presence of additional risk factors) [Grade D, Consensus, see Screening for Type 1 and Type 2 Diabetes, p. S12; Type 2 Diabetes in Children and Adolescents, p. S163].
- Culturally appropriate primary prevention programs for children and adults should be initiated in and by Aboriginal communities with support from the relevant health system(s) and agencies to assess and mitigate the environmental risk factors, such as:
 - geographic and cultural barriers
 - food insecurity
 - psychological stress
 - insufficient infrastructure
 - settings that are not conducive to physical activity [Grade D, Consensus].
- Management of prediabetes and diabetes in Aboriginal peoples should follow the same clinical practice guidelines as those for the general population with respect for, and sensitivity to, particular language, cultural history, traditional beliefs and medicines, and geographic issues as they relate to diabetes care and education in Aboriginal communities across Canada. Programs should adopt a holistic approach to health that addresses a broad range of stressors shared by Aboriginal peoples [Grade D, Consensus].
- Aboriginal peoples in Canada should have access in their communities to a diabetes management program that would include an interprofessional nurse-led team, diabetes registries, and ongoing quality assurance and surveillance programs [Grade D, Level 4 (35,80,87)].
- Aboriginal women should attempt to reach a healthy body weight prior to conception to reduce their risk for gestational diabetes [Grade D, Level 4 (6,19)].
- Programs to detect pre-gestational and gestational diabetes, provide optimal management of diabetes in pregnancy, and timely post-partum follow-up should be instituted for all Aboriginal women to improve perinatal outcomes, manage persistent maternal dysglycemia, and reduce type 2 diabetes rates in their children [Grade D, Level 4 (115,116), see Diabetes and Pregnancy, p. S168].
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Other Relevant Guidelines

Screening for Type 1 and Type 2 Diabetes, p. S12
 Reducing the Risk of Developing Diabetes, p. S16
 Weight Management in Diabetes, p. S82
 Type 2 Diabetes in Children and Adolescents, p. S163

Related Websites

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Appendix 1

Etiologic Classification of Diabetes Mellitus

I. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency) A. Immune-mediated B. Idiopathic	
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)	
III. Other specific types	
IV. Gestational diabetes mellitus	
Genetic defects of betacell function <ul style="list-style-type: none"> • Chromosome 20, HNF-4alpha (MODY1) • Chromosome 7, glucokinase (MODY2) • Chromosome 12, HNF-1alpha (MODY3) • Chromosome 13, IPF-1 (MODY4) • Chromosome 17, HNF-1beta (MODY5) • Chromosome 2, NeuroD1 (MODY6) • Chromosome 2, KLF11 (MODY7) • Chromosome 9, CEL (MODY8) • Chromosome 7, PAX4 (MODY9) • Chromosome 11, INS (MODY10) • Chromosome 8, BLK (MODY11) • Mitochondrial DNA • Permanent neonatal diabetes • Transient neonatal diabetes • Others Genetic defects in insulin action <ul style="list-style-type: none"> • Leprechaunism • Lipomatrophic diabetes • Rabson-Mendenhall syndrome • Type A insulin resistance • Others Diseases of the exocrine pancreas <ul style="list-style-type: none"> • Cystic fibrosis • Fibrocalculous pancreatopathy • Hemochromatosis • Neoplasia • Pancreatitis • Trauma/pancreatectomy • Others Endocrinopathies <ul style="list-style-type: none"> • Acromegaly • Aldosteronoma • Cushing's syndrome • Glucagonoma • Hyperthyroidism • Pheochromocytoma • Somatostatinoma • Others 	Drug- or chemical-induced <ul style="list-style-type: none"> • Alpha-interferon • Atypical antipsychotics • Beta-adrenergic agonists • Diazoxide • Dilantin • Glucocorticoids • Highly Active Antiretroviral Therapy (HAART) • HMG CoA reductase inhibitors (statins) • Nicotinic acid • Pentamidine • Thiazides • Thyroid hormone • Vacor (rodenticide) • Others Infections <ul style="list-style-type: none"> • Congenital rubella • Cytomegalovirus • Others Uncommon forms of immune-mediated diabetes <ul style="list-style-type: none"> • Anti-insulin receptor antibodies • "Stiff-man" syndrome • Others Other genetic syndromes sometimes associated with diabetes <ul style="list-style-type: none"> • Down syndrome • Friedreich ataxia • Huntington chorea • Klinefelter syndrome • Laurence-Moon-Bardet-Biedl syndrome • Myotonic dystrophy • Porphyria • Prader-Willi syndrome • Turner syndrome • Wolfram syndrome • Others
Adapted and updated from: American Diabetes Association. Diagnosis and classification of diabetes mellitus. <i>Diabetes Care</i> . 2012;35(suppl 1):S64-S71.	

Appendix 2

Sample Diabetes Patient Care Flow Sheet for Adults

Name:			Type of diabetes: Type 1 <input type="checkbox"/> Type 2 <input type="checkbox"/> Other <input type="checkbox"/>			Date of birth:			Date of diagnosis:			
Risk factors, co-morbidities						Self-Management (discuss with patient; add date and location in chart)						
<input type="checkbox"/> Hypertension <input type="checkbox"/> Dyslipidemia <input type="checkbox"/> Coronary Artery Disease <input type="checkbox"/> Peripheral Artery Disease <input type="checkbox"/> Chronic Kidney Disease <input type="checkbox"/> Mental health diagnosis <input type="checkbox"/> Polycystic Ovary Syndrome <input type="checkbox"/> Foot disease <input type="checkbox"/> Erectile Dysfunction <input type="checkbox"/> Smoking _____ (Date stopped) <input type="checkbox"/> Alcohol: _____ (Assess/discussed)						Patient Goals: _____ Possible Barriers to Self-Management: _____ Diabetes Self-Management Education: _____ <input type="checkbox"/> Weight Management: Ht: _____ Target Wt: _____ Target BMI: _____ <input type="checkbox"/> Physical Activity (aerobic 150 min/week; resistance 2-3 times/week) _____ <input type="checkbox"/> Glucose Meter/lab comparison <input type="checkbox"/> Patient Care Plan (Pregnancy Planning/Driving License): _____ Date discussed						
Vaccinations												
Flu (annual) Date: _____ Date: _____												
Pneumococcus Date: _____												
Visits (Every 3 to 6 months)												
Date	BP	Weight	A1C Target $\leq 7\%$ or _____	Notes (Goals, clinical status)			Hypo- glycemia	Antihyperglycemic Agents / CV protection agents (ACEi / ARB / Statin / ASA as indicated*)				
Review SMBG records. Target: pre-prandial 4–7 mmol/L; 2-hour post-prandial 5–10 mmol/L (5–8 mmol/L if A1C not at target)												
Screen for diabetes complications annually or as indicated												
Nephropathy			Neuropathy					Retinopathy				
Date	ACR	eGFR	• Check feet for lesions and sensation (10-g monofilament or 128 Hz tuning fork) • Check for pain, ED, GI symptoms Date: _____ Findings: _____ Date: _____ Findings: _____ Date: _____ Findings: _____					Annual eye exam: Date: _____ Date: _____ Ophthalmologist/ Optometrist: _____ _____				
*For vascular protection:			Lipids Targets: If indicated to treat LDL-C ≤ 2 mmol/L					CAD Assessment				
<input type="checkbox"/> Statins if ≥ 40 yrs OR > 30 yrs and > 15 yrs duration OR end organ damage <input type="checkbox"/> ACEi/ARB if ≥ 55 yrs OR end organ damage (even in the absence of hypertension)			Date	Medication	LDL-C	HDL-C	TG	(Non-HDL-C)	(Apo B)	ECG: _____ Stress ECG: _____ Other: _____		
See reverse side for care objectives and targets												

Care	Objective	Target
Self-monitoring of Blood Glucose	Ensure patient can use glucose meter, interpret results and modify treatment as needed. Develop a blood glucose monitoring schedule with patient and review records.	Premeal (mmol/L) = 4.0-7.0 mmol/L for most patients 2hr Postmeal (mmol/L) = 5.0-10.0 mmol/L for most patients 5.0-8.0 mmol/L if not achieving A1C target
Blood Glucose Control	Measure A1C every three months for most adults. Consider testing at least every 6 months in adults during periods of treatment and lifestyle stability when glycemic targets have been consistently achieved.	A1C ≤7.0% for most patients . Individualized based on life expectancy, functional dependency, extensive coronary artery disease at high risk of ischemia, multiple comorbidities, recurrent severe hypoglycemia, hypoglycemia unawareness, longstanding diabetes unable to achieve A1C ≤7% despite best efforts (including intensified insulin).
Hypoglycemia	Enquire about hypoglycemia at each visit. Discuss recognition and treatment of hypoglycemia and risk/ benefit of hypoglycemia and pharmacologic management.	Avoidance of hypoglycemia especially in the elderly, those with hypoglycemia unawareness, and those with criteria for less stringent control.
Blood glucose meter accuracy	Meter results should be compared with laboratory measurements at least annually , and when indicators of glycemic control do not match meter.	Simultaneous fasting glucose/meter lab comparison within 20% .
Hypertension	Measure BP at diagnosis and at every diabetes clinic visit	<130/80
Waist Circumference	Measure as an indicator of abdominal fat	Central obesity defined as: WC M ≥102cm W ≥88cm (North America) WC M ≥94cm W ≥80cm (Europe; Middle-Eastern; Sub-Saharan African; Mediterranean) WC M ≥90cm W ≥80cm (Asians; Japanese; South and Central Americans)
Body Mass Index	Calculate BMI (mass in kilograms/height in metres ²)	Healthy body weight target: BMI: 18.5-24.9
Nutrition	Encourage nutritional therapy (by a registered dietitian) as an integral part of treatment and self-management.	Meet nutritional needs by following Eating Well with Canada's Food Guide
Physical Activity	Discuss and encourage aerobic and resistance exercise. Evaluate those with possible CAD or microvascular complications undertaking exercise substantially more vigorous than brisk walking.	Aerobic: ≥150 minutes/week Resistance: 3 sessions/week
Smoking	Encourage patient to stop at each visit; provide support as needed.	Smoking cessation
Chronic Kidney Disease (CKD)	Identification of CKD requires screening for proteinuria using random urine ACR (2 out of 3 samples over 3 mths) and assessment of renal function using a serum creatinine converted to eGFR . Type 1 diabetes -Screen at 5 years duration and then annually if no CKD. Type 2 diabetes -Screen at diagnosis and then yearly if no CKD.	Normal ACR <2.0 mg/mmol Normal eGFR >60 mL/min
Retinopathy	Type 1 diabetes -Screen 5 years after diagnosis, then rescreen annually Type 2 diabetes -Screen at diagnosis and 1-2 years after initial screening if no retinopathy is present. The interval for follow-up assessment should be tailored to the severity of the retinopathy. Screening should be conducted by an experienced eye care professional.	Early detection and treatment
Neuropathy/Foot Examination	Type 1 diabetes -Screen 5 years duration and annually Type 2 diabetes -Screen at diagnosis, then annually Screen for neuropathy with 10-g monofilament or 128 Hz tuning fork at dorsum of great toe. In foot exam look for: structural abnormalities, neuropathy, vascular disease, ulceration, infection.	Early detection and treatment. If neuropathy present: require foot care education, specialized footwear, smoking cessation. If ulcer present: manage by multidisciplinary team with expertise
Coronary Artery Disease (CAD)	Conduct CAD risk assessment periodically: CV history, lifestyle, duration of DM, sexual function, abdominal obesity, lipid profile, BP, reduced pulses, bruits, glycemic control, retinopathy, eGFR, ACR. Baseline ECG and every 2 years if >40 years, >30 years and duration >15 years, end organ damage, cardiac risk factors.	Vascular Protection: First priority in prevention of diabetes complications is reduction of cardiovascular risk by vascular protection through a comprehensive multifaceted approach All people with DM: optimize: BP, glycemic control and lifestyle Statin if: age ≥40 years OR macrovascular disease OR microvascular disease OR long duration of DM (DM >15 years and age >30 years) ACEi or ARB if: age ≥55 years OR macrovascular disease OR microvascular disease
Dyslipidemia	Fasting lipid levels (TC, HDL, TG and calculated LDL) at diagnosis, then yearly if treatment not initiated. More frequent testing if treatment initiated.	Lipid targets for those who need therapy: Primary target: LDL ≤2.0 mmol/L or ≥50% reduction Alternate Primary target: apo B ≤0.8 g/L or non-HDL-C ≤2.6 mmol/L
Care Objectives: People with diabetes will have better outcomes if primary care providers 1) identify patients with diabetes in their practices 2) encourage self-management and use interdisciplinary team approach to attain care objectives 3) schedule diabetes-focused visits 4) use diabetes patient care flow sheets and systematic recall.		

Appendix 3

Examples of Insulin Initiation and Titration Regimens in People with Type 2 Diabetes

All people starting insulin should be counseled about the recognition, prevention and treatment of hypoglycemia. Consider a change in type or timing of insulin administration if glycemic targets are not being reached.

Example A: Basal insulin (Humulin®-N, Lantus®, Levemir®, Novolin®ge NPH) added to oral antihyperglycemic agents

- Insulin should be titrated to achieve target fasting BG levels of 4.0 to 7.0 mmol/L.
- Individuals can be taught self-titration, or titration may be done in conjunction with a healthcare provider.
- Suggested starting dose is 10 units once daily at bedtime.
- Suggested titration is 1 unit per day until target is reached.
- A lower starting dose, slower titration and higher targets may be considered for elderly or normal weight subjects.
- In order to safely titrate insulin, patients must perform SMBG at least once a day fasting.
- Insulin dose should not be increased if the individual experiences 2 episodes of hypoglycemia (BG <4.0 mmol/L) in 1 week or any episode of nocturnal hypoglycemia.
- For fasting BG levels consistently <5.5 mmol/L, a reduction of 1 to 2 units of insulin may be considered to avoid nocturnal hypoglycemia.
- Oral antihyperglycemic agents (especially secretagogues) may need to be reduced if daytime hypoglycemia occurs.

Example B: Basal Plus Strategy - Adding bolus (prandial) insulin (Apidra®, Humalog®, NovoRapid®) once daily to optimized basal insulin therapy

- When intensification of insulin therapy is necessary, start one injection of meal time insulin to either main meal or breakfast.
- Starting dose is 2 to 4 units and patient can be taught self titration or dose increase can be done by HCP.
- To safely increase dose, glucose levels should be measured at least prior to insulin dose then titrated by 1 unit daily to either of the following targets.
 - 2 hour post meal glucose of 10.0 mmol/L (or \leq 8.0 mmol/L in certain cases)
 - pre-meal glucose of the next meal of 4.0 to 7.0 mmol/L.
- Important to keep carbohydrate intake constant. Oral antihyperglycemic agents (especially secretagogues) may need to be reduced or stopped particularly if daytime hypoglycemia occurs.

Example C: Basal-Bolus Insulin - Intensive insulin therapy

- Calculate total daily dose of 0.3 to 0.5 units/kg then distribute as follows:
 - a. 40% of total insulin dose as basal insulin (Humulin®-N, Lantus®, Levemir®, Novolin®ge NPH).
 - b. 20% of total insulin as bolus (prandial) insulin 3 times per day using either rapid-acting insulin analogue (Apidra®, Humalog®, NovoRapid®) or short-acting insulin (Humulin®, Novolin®ge Toronto).

Example D: Premixed insulin (Humulin® 30/70, Novolin® 30/70, Humalog® Mix 25 or Humalog® Mix 50, NovoMix® 30,) added to oral antihyperglycemic agents

- Suggested starting dose is 5 to 10 units once or twice daily (prebreakfast and/or presupper).
- Suggested titration is 1 to 2 units added to prebreakfast dose and/or presupper dose daily until target BG values are reached based on prebreakfast and presupper BG readings.
- Prebreakfast premixed insulin achieves presupper target BG value (4.0 to 7.0 mmol/L).
- Presupper premixed insulin achieves target fasting BG value (4.0 to 7.0 mmol/L).
- 30/70 premixed insulin should be given 30 to 45 minutes before meals.
- Humalog® Mix 25 or NovoMix® 30 premixed insulin should be given immediately before eating.
- Stop increasing insulin when both target BG levels are reached.
- If both BG targets are not reached, continue to increase the relevant dose until both targets achieved.
- The individual needs to self-monitor BG at least twice daily to safely titrate insulin.
- Insulin dose should not be increased if the individual experiences 2 or more episodes of hypoglycemia (BG <4.0 mmol/L) in 1 week or any episode of nocturnal hypoglycemia.
- Oral antihyperglycemic agents (especially secretagogues) may need to be reduced or stopped at the start of this regimen or when daytime hypoglycemia occurs.

Sample Instructions for Patients With Type 2 Diabetes Who Are Starting and Adjusting Basal Insulin

You will be taking insulin _____ at _____.

It is important that you continue to take your other diabetes medications as prescribed unless you have been told to change the dose or stop them.

How to adjust your insulin dose

- Your target fasting blood glucose level is _____ mmol/L.
- You will inject _____ units of _____ at _____.
- You will continue to increase your insulin dose by _____ unit(s) every _____ day(s) until your fasting blood glucose level is _____ mmol/L.
- Do not increase your insulin when your fasting blood glucose is _____ mmol/L.
- You should call for further instructions when your blood glucose reaches _____ mmol/L for 3 or more days: phone number _____.
- A side effect of insulin is low blood glucose (hypoglycemia); low blood glucose can occur with too much insulin, increased activity or not enough food.

Monitoring your blood glucose

- It is important to test your blood glucose while your insulin treatment is being modified.
- You should test your blood glucose and record the value every day before breakfast and _____.
- Test before each meal, unless you are instructed differently.
- It is important to record your blood glucose values and any changes in activity or food in your diary and bring this to your next appointment; this information helps us to understand your diabetes control.
- Unless otherwise instructed, you are trying to reach a target blood glucose of 4.0 to 7.0 mmol/L before meals, and 5.0 to 10.0 mmol/L after meals.
- If you think your blood glucose is low, check it and record that information in your diary.

Instructions for taking your diabetes medications

Current medications	Dose	Time of day	Special instructions

Appendix 4

Self-Monitoring of Blood Glucose (SMBG) Recommendation Tool for Healthcare Providers

Basic SMBG requirements (must be met)

The person with diabetes (or a family member/caregiver) must have the knowledge and skills to use a home blood glucose monitor and to record the results in an organized fashion.

The person with diabetes and/or members of the healthcare team must be willing to review and act upon the SMBG results in addition to the A1C results.



A. REGULAR SMBG is required if the person with diabetes is:

SITUATION	SMBG RECOMMENDATION
Using multiple daily injections of insulin (≥ 4 times per day) Using an insulin pump	SMBG ≥ 4 times per day (see page 2 – QID – [basal-bolus/MDI])
Using insulin < 4 times per day	SMBG at least as often as insulin is being given (see page 2 – premixed or basal insulin only)
Pregnant (or planning a pregnancy), whether using insulin or not Hospitalized or acutely ill	SMBG individualized and may involve SMBG ≥ 4 times per day
Starting a new medication known to cause hyperglycemia (e.g. steroids) Experiencing an illness known to cause hyperglycemia (e.g. infection)	SMBG individualized and may involve SMBG ≥ 2 times per day



B. INCREASED FREQUENCY OF SMBG may be required if the person with diabetes is:

SITUATION	SMBG RECOMMENDATION
Using drugs known to cause hypoglycemia (e.g. sulfonylureas, meglitinides)	SMBG at times when symptoms of hypoglycemia occur or at times when hypoglycemia has previously occurred
Has an occupation that requires strict avoidance of hypoglycemia	SMBG as often as is required by employer
Not meeting glycemic targets	SMBG ≥ 2 times per day, to assist in lifestyle and/or medication changes until such time as glycemic targets are met
Newly diagnosed with diabetes (< 6 months)	SMBG ≥ 1 time per day (at different times of day) to learn the effects of various meals, exercise and/or medications on blood glucose
Treated with lifestyle and oral agents and is meeting glycemic targets	Some people with diabetes might benefit from very infrequent checking (SMBG once or twice per week) to ensure that glycemic targets are being met between A1C tests



C. DAILY SMBG is not USUALLY required if the person with diabetes:

Screen for diabetes complications annually or as indicated

Is treated only with lifestyle and is meeting glycemic targets

Has pre-diabetes

Additional CDA resources

- Lows and highs: blood glucose levels
- Managing your blood glucose
- Monitoring for Glycemic Control. Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes*. 2008;32(suppl 1):S32–S36.
- Self-Monitoring of Blood Glucose in People with Type 2 Diabetes: Canadian Diabetes Association Briefing Document for Healthcare Providers. *Can J Diabetes*. 2011;35:317–319.

Suggested SMBG Patterns for Patients Using Insulin

Basal Insulin Only – NPH or long-acting insulin analog, typically given at bedtime. *SMBG at least as often as insulin is being given.* Optional, less frequent SMBG can be done at other times of day to ensure glycemic stability throughout the day.

	BREAKFAST		LUNCH		SUPPER		BEDTIME	NIGHT
	before	after	before	after	before	after		
Insulin							NPH/long (basal)	
SMBG pattern	SMBG test							
Adjustment	Basal insulin ↑ if BG high ↓ if BG low							

Premixed – typically given pre-breakfast and pre-supper. *SMBG at least as often as insulin is being given.* SMBG QID until glycemic targets are met; SMBG BID (alternating times) is usually sufficient once glycemic targets are met.

	BREAKFAST		LUNCH		SUPPER		BEDTIME	NIGHT
	before	after	before	after	before	after		
Insulin	pre-mixed				pre-mixed			
SMBG pattern 1: Starting	SMBG test		SMBG test		SMBG test		SMBG test	
SMBG pattern 2: Stable Alternating daily	SMBG test				SMBG test			
			SMBG test				SMBG test	
Adjustment	Pre-supper insulin ↑ if BG high ↓ if BG low		Pre-breakfast insulin ↑ if BG high ↓ if BG low		Pre-breakfast insulin ↑ if BG high ↓ if BG low		Pre-supper insulin ↑ if BG high ↓ if BG low	

QID (basal-bolus/MDI) – typically given as a rapid-acting analog or regular insulin (bolus) before each meal and NPH or long-acting analog (basal) typically given at bedtime. SMBG should be QID, pre-meal and bedtime, in order to assess previous dose and to adjust next dose. Some patients find that post-prandial checking can also be helpful.

	BREAKFAST		LUNCH		SUPPER		BEDTIME	NIGHT
	before	after	before	after	before	after		
Insulin	rapid/regular (bolus)		rapid/regular (bolus)		rapid/regular (bolus)		NPH/long (basal)	
SMBG pattern 1: Starting or Stable	SMBG test		SMBG test		SMBG test		SMBG test	
SMBG pattern 2: Stable, Focus on post-meal BG	SMBG test	SMBG test		SMBG test		SMBG test		
SMBG pattern 3: Intensive management	SMBG test	SMBG test	SMBG test	SMBG test	SMBG test	SMBG test	SMBG test	SMBG test
Adjustment	Basal insulin ↑ if BG high ↓ if BG low	Pre-breakfast insulin ↑ if BG high ↓ if BG low	Pre-lunch insulin ↑ if BG high ↓ if BG low		Pre-supper insulin ↑ if BG high ↓ if BG low			Basal insulin ↓ if BG low

MDI = multiple daily injections

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Appendix 5

Approximate Cost Reference List for Antihyperglycemic Agents

Antihyperglycemic Agents	Available strengths	Usual maintenance dose or usual dosage range	Approximate Wholesale cost*/unit
Alpha Glucosidase Inhibitor			
Acarbose (Glucobay®)	100 mg 50 mg	50-100 mg three times a day	\$ 0.39/Tab \$ 0.28/Tab
Biguanides			
Metformin (Glucophage®, generic)	500 mg 850 mg	500-2000 mg per day in divided doses 850-2550 mg per day in divided doses	\$ 0.09/Tab \$ 0.19/Tab
Metformin ER (Glumetza®)	500 mg 1000 mg	500-2000 mg per day 500-2000 mg per day	\$ 0.63/Tab \$ 1.29/Tab
Incretin Agents - DPP-4 inhibitors			
Linagliptin (Trajenta™)	5 mg	5 mg once daily	\$ 2.64/Tab
Saxagliptin (Onglyza®)	2.5 mg 5 mg	2.5-5 mg once daily 2.5-5 mg once daily	\$ 2.48/Tab \$ 2.72/Tab
Sitagliptin (Januvia®)	25 mg 50 mg 100 mg	25 mg once daily (depending on renal function) 50 mg once daily (depending on renal function) 100 mg once daily	\$ 2.97/Tab \$ 2.97/Tab \$ 2.97/Tab
Incretin Agents – GLP-1 receptor agonists			
Exenatide (Byetta®)	5 mcg prefilled pen (250 µg/mL) 10 mcg prefilled pen (250 µg/mL)	10 mcg twice a day 10 mcg twice a day	\$ 2.47/5 mcg dose (supplied as prefilled pen) \$ 2.47/10 mcg dose (supplied as prefilled pen)
Liraglutide (Victoza®)	6 mg/mL	1.2 -1.8 mg once daily	\$ 2.71/0.6 mg dose \$ 5.43/1.2 mg dose \$ 8.13/1.8 mg dose (supplied as prefilled pen)
Insulin Secretagogues – Sulfonylureas			
Gliclazide (Diamicon®, generic)	80 mg	80-320 mg per day (doses >160 mg should be twice a day)	\$ 0.17/Tab
Gliclazide (Diamicon MR®)	30 mg 60 mg	30-120 mg once daily 60-120 mg once daily	\$ 0.15/Tab \$ 0.28/Tab
Glimepiride (Amaryl®, generic)	1 mg 2 mg 4 mg	1-4 mg once daily (may increase to a maximum dose of 8 mg/day) 1-4 mg once daily (may increase to a maximum dose of 8 mg/day) 1-4 mg once daily (may increase to a maximum dose of 8 mg/day)	\$ 0.47/Tab \$ 0.47/Tab \$ 0.47/Tab
Glyburide (Diabeta®, generic)	2.5 mg 5 mg	1.25-20 mg once daily 1.25-20 mg once daily	\$ 0.04/Tab \$ 0.06/Tab
Note: Chlorpropamide and Tolbutamide are still available in Canada, but rarely used			

Approximate Cost Reference List ¹ for Antihyperglycemic Agents			
Antihyperglycemic Agents	Available strengths	Usual maintenance dose or usual dosage range	Approximate Wholesale cost [*] /unit
Insulin Secretagogues – Meglitinides			
Nateglinide (Starlix®) Repaglinide (GlucosNorm®, generic)	60 mg	120 mg three times a day	\$ 0.60/Tab
	120 mg	120 mg three times a day	\$ 0.63/Tab
	0.5 mg	0.5–4 mg taken with meals (max daily dose: 16 mg/day)	\$ 0.16/Tab
	1 mg	0.5–4 mg taken with meals (max daily dose: 16 mg/day)	\$ 0.16/Tab
	2 mg	0.5–4 mg taken with meals (max daily dose: 16 mg/day)	\$ 0.38/Tab
Thiazolidinediones			
Pioglitazone (Actos) generic	15 mg	15–30 mg once daily	\$ 1.28/Tab
	30 mg	15–30 mg once daily	\$ 1.94/Tab
	45 mg	Maximum daily dose	\$ 2.71/Tab
Rosiglitazone (Avandia®)	2 mg	4–8 mg daily as a single or as a divided dose	\$ 1.43/Tab
	4 mg	4–8 mg daily as a single or as a divided dose	\$ 2.25/Tab
Weight Loss Agent			
Orlistat (Xenical®)	120 mg tab	120 mg three times a day	\$ 1.78/Tab
Combination products			
Linagliptin/Metformin (Jentadueto®)	2.5 mg/500 mg	Usual dose 1 tablet twice per day	\$ 1.45/Tab
	2.5 mg/850 mg	Usual dose 1 tablet twice per day	\$ 1.45/Tab
	2.5 mg/1000 mg	Usual dose 1 tablet twice per day	\$ 1.45/Tab
Rosiglitazone/Metformin (AvandaMet®)	2 mg/500 mg	Starting dose of 2 mg/500 mg may increase to a maximum dose of 8 mg/2000 mg per day	\$ 1.23/Tab
	2 mg/1000 mg	Starting dose of 2 mg/500 mg may increase to a maximum dose of 8 mg/2000 mg per day	\$ 1.33/Tab
	4 mg/500 mg	Starting dose of 2 mg/500 mg may increase to a maximum dose of 8 mg/2000 mg per day	\$ 1.68/Tab
	4 mg/1000 mg	Starting dose of 2 mg/500 mg may increase to a maximum dose of 8 mg/2000 mg per day	\$ 1.83/Tab
Sitagliptin/Metformin (Janumet®)	50 mg/500 mg	Usual dose 1 tablet twice per day	\$ 1.58/Tab
	50 mg/850 mg	Usual dose 1 tablet twice per day	\$ 1.58/Tab
	50 mg/1000 mg	Usual dose 1 tablet twice per day	\$ 1.58/Tab

Approximate Cost Reference List for Insulins ⁱⁱ			
Antihyperglycemic Agents	Available strengths	Usual maintenance dose or usual dosage range	Approximate Wholesale cost*/unit
PRANDIAL (BOLUS) INSULINS – Rapid-Acting Insulin Analogues			
Aspart (NovoRapid®)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.038/unit
Glulisine (Apidra®)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.035/unit
Lispro (Humalog®)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.038/unit
PRANDIAL (BOLUS) INSULINS – Short-Acting			
Insulin regular (Humulin®-R)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.028/unit
Insulin regular (Novolin®ge Toronto)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.022/unit
BASAL INSULINS – Intermediate-acting			
Insulin NPH (Humulin®-N)	100 units/mL (300 units / cartridge)	N/A as dose is determined by response by patient	\$ 0.028/unit
Insulin NPH (Novolin®ge NPH)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.029/unit
BASAL INSULINS – Long-acting Basal Insulin Analogues			
Detemir (Levemir®)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.071/unit
Glargine (Lantus®)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.064/unit
PREMIXED INSULINS – Premixed Regular Insulin - NPH			
Insulin regular/NPH (Humulin® 30/70)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.028/unit
Insulin regular/NPH (Novolin®ge 30/70, 40/60, 50/50)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.028/unit
PREMIXED INSULINS – Premixed Insulin Analogues			
Aspart 30%/aspart protamine 70% (NovoMix® 30)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.038/unit
Lispro 25%/lispro protamine 75% (Humalog® Mix25)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.038/unit
Lispro 50%/lispro protamine 50% (Humalog® Mix50)	100 units/mL (300 units/cartridge)	N/A as dose is determined by response by patient	\$ 0.038/unit

*Approximate unit drug cost **not including** dispensing/professional fee and pharmacy mark-up. Approximate Canadian Cost average based on wholesale costs derived from McKesson Canada as of March 2013.

ⁱ The listed medications represent both the classes and the agents that are most commonly used in primary care practices. It is not meant to be an exhaustive list, and is intended only as a guide for the family physician.

ⁱⁱ Insulin prices are based on the pen cartridge price and corresponding vial price would be marginally less.

Appendix 6

Therapeutic Considerations for Renal Impairment

Therapeutic considerations when using common therapies in patients with diabetes with varying degrees of renal impairment						
	CKD 1 & 2 eGFR ≥60 mL/min	CKD 3 eGFR 30-59 mL/min	CKD 4 eGFR 15-29 mL/min	CKD 5 eGFR <15 mL/min or dialysis	Comments	
Antihyperglycemic Therapies	Metformin	No dose adjustment	Reduce dose	Use alternative agent		See “Sick Day Medication List” (Appendix 7). Risk of drug accumulation with declining renal function, especially if acute.
	Alpha-glucosidase Inhibitor					
	Acarbose	No dose adjustment	No dose adjustment	Use alternative agent		
	DPP4-Inhibitors					
	Linagliptin	No dose adjustment required				Experience in patients with ESRD or on dialysis is limited. Use with caution in these patients.
	Saxagliptin		Lower Dose 2.5 mg once daily (<50 mL/min)		Use alternative agent	Should not be used in patients on dialysis.
	Sitagliptin		Lower dose (50 mg daily) (30-49 mL/min)	Use lowest dose (25 mg daily)		Risk of accumulation.
	GLP-1 Receptor Agonists					
	Exenatide	No dose adjustment	Lower dose (5 mcg BID)	Use alternative agent		
	Liraglutide	No dose adjustment	Use alternative agent (<50 mL/min)			
	Insulin Secretagogues					
	Gliclazide			Risk of hypoglycemia, consider lower dose	Risk of hypoglycemia, consider alternative agent	
	Glimepiride			Risk of hypoglycemia, consider lower dose	Max 1 mg daily, consider alternative agent	Both pharmacokinetics and pharmacodynamics are altered, increasing risk of hypoglycemia.
	Glyburide		Use alternative agent			Increased risk of prolonged hypoglycemia due to accumulation of parent drug and active metabolites.
	Nateglinide	No dose adjustment required				
	Repaglinide	No dose adjustment required				
	Thiazolidinediones (TZDs)					
	Pioglitazone	No dose adjustment required				Risk of volume overload.
	Rosiglitazone	No dose adjustment required				

Lipid Lowering Therapies	Bile Acid Sequestrant					
	Cholestyramine	No dose adjustment				
	Cholesterol Absorption Inhibitor					
	Ezetimibe	No dose adjustment				
	Nicotinic Acid (niacin)	No dose adjustment	50% of total daily dose administered as divided doses	25% of total daily dose administered in divided doses		
	Fibrates	Risk of rhabdomyolysis when fibrates used in combination with statins is increased in CKD and, therefore, combination should be avoided.				
	Bezafibrate	No dose adjustment	Use alternative agent			
	Fenofibrate	No dose adjustment	Reduce dose	Use alternative agent	Fenofibrate micronized should not be used as initial treatment in CKD. Initiate with Lipidil EZ 48 mg/day.	
	Gemfibrozil	No dose adjustment	Use alternative agent		Concomitant use of gemfibrozil and repaglinide should be avoided as can result in hypoglycemia.	
	Statins					
	Atorvastatin		Manufacturer recommends lowest dose (10 mg once daily) be used		Plasma concentrations are similar to those with normal renal function, but several cases of rhabdomyolysis reported in patients with renal insufficiency.	
	Fluvastatin	No dose adjustment		Not recommended	Recommendation from manufacturer is based on lack of experience rather than renal excretion.	
	Lovastatin	No dose adjustment		Use low dose (max dose 20 mg/day)	10% renal elimination. Doubling of plasma concentration in moderate to severe renal impairment.	
	Pravastatin		Use lowest dose as precautionary measure		Lack of data. 20% renal elimination.	
	Rosuvastatin	No dose adjustment		Use low dose (max dose 10 mg/day)	10% renal elimination.	
	Simvastatin	No dose adjustment		Use low dose (max dose 10 mg/day)	13% renal elimination.	
Neuropathy Therapies	Anticonvulsants					
	Gabapentin	Max 3600 mg/day divided tid	Max 1400 mg/day divided bid	Max 700 mg/day given once daily	Max 150-300 mg/day given once daily	Hemodialysis supplemental dosing required: 125-350 mg after each 4 hours of hemodialysis.
	Pregabalin	Max 600 mg/day divided bid or tid	Max 300 mg/day divided bid or tid	Max 150 mg/day given once daily or bid	Max 75 mg/day given once daily	Hemodialysis supplemental dosing required.
Erectile Dysfunction Therapies	Phosphodiesterase-5 (PDE-5) Inhibitors					
	Sildenafil	No dose adjustment		Reduce starting dose to 25 mg		
	Tadalafil		10-20 mg (max frequency of alternate days and not more than 3 times per week)		2.5-5 mg once a day may be considered in CKD stage 3 but daily dosing is not recommended in CKD stage 4 and 5.	

Appendix 7

Sick Day Medication List

Instructions for Healthcare Professionals:

If patients become ill and are unable to maintain adequate fluid intake, or have an acute decline in renal function (e.g. due to gastrointestinal upset or dehydration), they should be instructed to hold medications which will:

A) Increase risk for a decline in kidney function:

- Angiotensin-converting enzyme inhibitor
- Angiotensin receptor blockers
- Direct renin inhibitors
- Non-steroidal anti-inflammatory drugs
- Diuretics

B) Have reduced clearance and increase risk for adverse effects:

- Metformin
- Sulfonylureas (gliclazide, glimepiride, glyburide)

S sulfonylureas

A ACE-inhibitors

D diuretics, direct renin inhibitors

M metformin

A angiotensin receptor blockers

N non-steroidal anti-inflammatory

Please complete the following card and give it to your patient.

Patients should be instructed that increased frequency of self blood glucose monitoring will be required and adjustments to their doses of insulin or oral antihyperglycemic agents may be necessary.

Instructions for Patients

When you are ill, particularly if you become dehydrated (e.g. vomiting or diarrhea), some medicines could cause your kidney function to worsen or result in side effects.

If you become sick and are unable to drink enough fluid to keep hydrated, you should **STOP** the following medications:

- Blood pressure pills
- Water pills
- Metformin
- Diabetes pills
- Pain medications
- Non-steroidal anti-inflammatory drugs (see below)

Please be careful not to take non-steroidal anti-inflammatory drugs (which are commonly found in pain medications (e.g. Advil) and cold remedies).

Please check with your pharmacist before using over-the-counter medications and discuss all changes in medication with your healthcare professional.

Please increase the number of times you check your blood glucose levels. If they run too high or too low, contact your healthcare professional.

If you have any problems, you can call:

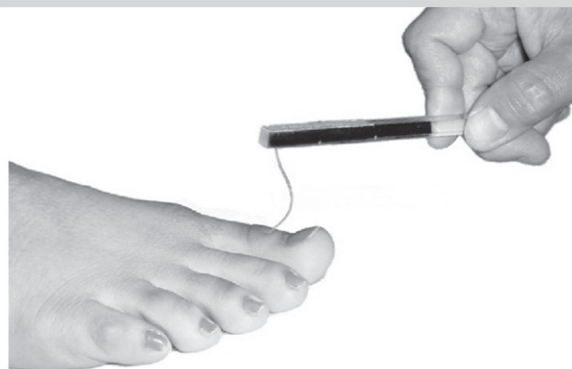
Appendix 8

Rapid Screening for Diabetic Neuropathy

Multiple screening methods are published. These methods (1) are designed to screen for the presence or absence of diabetic neuropathy, as opposed to screening for specific sites on the feet that are at risk of ulceration (multisite testing). If neuropathy is identified by either of these methods, other sites may be tested to identify high-risk areas for ulceration.

Rapid Screening for Diabetic Neuropathy Using the 10-g Semmes-Weinstein Monofilament

1. Show the 10-g Semmes-Weinstein monofilament to the patient.
2. Touch it first to the patient's forehead or sternum so that the sensation is understood.
3. Instruct the patient to say "yes" every time the monofilament stimulus is perceived.
4. With the patient's eyes closed, apply the monofilament to the dorsum of the great toe proximal to the nail bed as shown in the illustration below. Use a smooth motion—touch the skin, bend the filament for a full second, then lift from the skin.
5. Perform this stimulus 4 times per foot in an arrhythmic manner so the patient does not anticipate when the stimulus is to be applied.
6. For each of the 8 stimuli, assign a score of 0 if it is not perceived, 0.5 if it is substantially less than that perceived on the forehead or sternum, and 1 if it is perceived normally. A score of 3 out of 8 correct responses means that the presence of neuropathy is likely. A score of 3.5 to 5 means that the risk of new onset neuropathy in the next four years is high. A score of 5.5 or greater indicates that there is a low risk of neuropathy onset in the next four years.



Rapid Screening for Diabetic Neuropathy Using the 128-Hz Vibration Tuning Fork (The "On-Off" Method)

1. Strike the tuning fork against the palm of your hand hard enough that it will vibrate for approximately 40 seconds.
2. Apply the base of the tuning fork to the patient's forehead or sternum and ensure that the vibration sensation (not just the touch sensation) is understood.
3. With the patient's eyes closed, apply the tuning fork to the bony prominence situated at the dorsum of the first toe just proximal to the nail bed. Ask if the vibration sensation is perceived.
4. Ask the patient to tell you when the vibration stimulus is stopped, and then dampen the tuning fork with your other hand.
5. One point is assigned for each vibration sensation perceived (vibration "on"). Another point is assigned if the correct timing of dampening of the vibration is perceived (vibration "off").
6. Repeat this procedure again on the same foot, then twice on the other foot in an arrhythmic manner so the patient does not anticipate when the stimulus is to be applied.
7. Though this test can be used to rule out the presence of neuropathy, unlike for the monofilament described above, threshold scores do not exist to indicate the risk of future onset of neuropathy.



Appendix 9

Diabetes and Foot Care: A Patient's Checklist

Many people with diabetes have problems with their feet. You can prevent serious problems by following these basic guidelines. Ask your doctor to explain your risk factors for foot problems.

DO...

- check your feet every day for cuts, cracks, bruises, blisters, sores, infections or unusual markings.
- use a mirror to see the bottom of your feet if you can't lift them up.
- check the colour of your legs and feet. If there is swelling, warmth or redness or if you have pain, see your doctor or foot specialist right away.
- clean a cut or scratch with a mild soap and water and cover with a dry dressing for sensitive skin.
- trim your nails straight across.
- wash and dry your feet every day, especially between the toes.
- apply a good skin lotion every day on your heels and soles. Wipe off any excess lotion.
- change your socks every day.
- always wear a good supportive shoe.
- always wear professionally fitted shoes from a reputable store. Professionally fitted orthotics may help.
- choose shoes with low heels (under 5 cm high).
- buy shoes in the late afternoon (since your feet swell slightly by then).
- avoid extreme cold and heat (including the sun).
- exercise regularly.
- see a foot care specialist if you need advice or treatment.

DON'T...

- cut your own corns or calluses.
- treat your own in-growing toenails or slivers with a razor or scissors. See your doctor or foot care specialist.
- use over-the-counter medications to treat corns and warts. They are dangerous for people with diabetes.
- apply heat to your feet with a hot water bottle or electric blanket. You could burn your feet without realizing it.
- soak your feet.
- take very hot baths.
- use lotion between your toes.
- walk barefoot inside or outside.
- wear tight socks, garters or elastics, or knee highs.
- wear over-the-counter insoles – they can cause blisters if they are not right for your feet.
- sit for long periods of time.
- smoke.

Adapted with permission from: Casella A. Feeling well...diabetes and foot care, a patient's checklist. Knowing Diabetes. © Diabetes Hamilton, 2002.

Appendix 10

Diabetic Foot Ulcers: Essentials of Management

1. Assess underlying cause(s): neuropathy and/or ischemia.
 2. Ulcers should be probed with a blunt-tipped instrument to detect sinus tracks or palpable bone suggestive of deep infections.
 3. Plantar-surface ulcers require pressure relief. Individuals with plantar-surface foot ulcers should be non-weight-bearing as much as possible and utilize off-loading footwear or appliances (1).
 4. Clinically noninfected ulcers do not routinely require cultures or antibiotics (2).
 5. More serious infections in chronic foot ulcers tend to be polymicrobial and typically require empiric use of broad spectrum systemic antibiotics as soon as possible. Antibiotics can be subsequently tailored according to culture and sensitivity results. Cultures obtained by curettage or biopsy tend to be more reliable than surface swabs (3).
 6. Wound bed preparation involves debridement of necrotic tissue (neuropathic wounds and noncritical ischemic wounds only) and maintenance of adequate moist wound environment with appropriate wound dressings. Hydrogels are used to increase wound bed moisture in dry or minimally draining neuropathic ulcers.
 7. Comorbidities need to be managed (e.g. hyperglycemia).
 8. Refer to a specialized wound clinic where available.
1. Lavery LA, Baranoski S, Ayello EA. Options for off-loading the diabetic foot. *Adv Skin Wound Care*. 2004;17:181–186.
 2. Lipsky BA, Berendt AR, Deery HG, et al; for the Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2004;39:885–910.
 3. Frykberg RG, Zgonis T, Armstrong DG, et al; for the American College of Foot and Ankle Surgeons. Diabetic foot disorders. A clinical practice guideline (2006 revision). *J Foot Ankle Surg*. 2006;45(5 suppl):S1–S66.

Appendix 11

A1C Conversion Chart

National Glucose Standardization Program (NGSP) values (%) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) values (mmol/mol) based on the formula of IFCC = 10.93(NGSP)–23.50. Conversions are grouped according to each percentage point on the NGSP measurement scale. IFCC-standardised values are rounded to the nearest whole number.

5		6		7		8		9	
DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
5.0	31	6.0	42	7.0	53	8.0	64	9.0	75
5.1	32	6.1	43	7.1	54	8.1	65	9.1	76
5.2	33	6.2	44	7.2	55	8.2	66	9.2	77
5.3	34	6.3	45	7.3	56	8.3	67	9.3	78
5.4	36	6.4	46	7.4	57	8.4	68	9.4	79
5.5	37	6.5	48	7.5	58	8.5	69	9.5	80
5.6	38	6.6	49	7.6	60	8.6	70	9.6	81
5.7	39	6.7	50	7.7	61	8.7	72	9.7	83
5.8	40	6.8	51	7.8	62	8.8	73	9.8	84
5.9	41	6.9	52	7.9	63	8.9	74	9.9	85

10		11		12		13		14	
DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
10.0	86	11.0	97	12.0	108	13.0	119	14.0	130
10.1	87	11.1	98	12.1	109	13.1	120	14.1	131
10.2	88	11.2	99	12.2	110	13.2	121	14.2	132
10.3	89	11.3	100	12.3	111	13.3	122	14.3	133
10.4	90	11.4	101	12.4	112	13.4	123	14.4	134
10.5	91	11.5	102	12.5	113	13.5	124	14.5	135
10.6	92	11.6	103	12.6	114	13.6	125	14.6	136
10.7	93	11.7	104	12.7	115	13.7	126	14.7	137
10.8	95	11.8	105	12.8	116	13.8	127	14.8	138
10.9	96	11.9	107	12.9	117	13.9	128	14.9	139