Hypoglycemia in Adults

Diabetes Canada Clinical Practice Guidelines Expert Working Group:
Iliana C. Lega MD, MSc, FRCPC; Jean-François Yale MD, CSPQ, FRCPC;
Ayush Chadha PharmD; Breay Paty MD, FRCPC; Rob Roscoe BSc Pharm, ACPR, CDE;
Melanie Snider MN, NP; Jennifer Steier RN, BN, CDE

On behalf of the Diabetes Canada Clinical Practice Guidelines Steering Committee:
Harpreet S. Bajaj MD, MPH, ECNU, FACE; Tracy Barnes MA, MJ; Jeremy Gilbert MD, FRCPC;
Kristin Honshorst MSc; James Kim MBBCh PgDip; Joanne Lewis RD;
Barbara MacDonald RN, MS-DEDM, CDE; Dylan MacKay PhD; Kerry Mansell BSP, PharmD;
Peter Senior MBBS, PhD, FRCP, FRCP(E); Doreen Rabi MD, MSc, FRCPC;
Diana Sherifali RN, PhD, CDE

Key Messages

- Hypoglycemia caused by insulin or insulin secretagogues (i.e. sulfonylureas, meglitinides) can cause distressing and potentially debilitating complications. It is therefore imperative that events are reduced in frequency and severity, recognized safely, and treated quickly.
- It is safer and more effective to prevent hypoglycemia than to treat it after it occurs. Hence, individuals with diabetes who are at high risk for hypoglycemia, and their support persons (i.e. friends, family, colleagues, etc.), should be identified and counselled about ways to prevent low blood glucose (BG).
- Individuals at risk of hypoglycemia and their support persons should be counselled about the recognition and treatment of hypoglycemia.
- For individuals at high risk for hypoglycemia who are treated with insulin or insulin secretagogues, the doses and need for these agents should be reassessed and appropriately modified at each clinic visit to reduce the risk of hypoglycemia.
- Hypoglycemia should be detected and treated promptly by using an intervention that provides the fastest rise in BG to a safe level, to reduce the risk of injury, and to relieve symptoms quickly. Once the BG reaches a safe level, the individual 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.
- Individuals with type 1 diabetes and those with type 2 diabetes treated with insulin or insulin secretagogues should be screened for impaired awareness of hypoglycemia (IAH).
- Fear of hypoglycemia (FoH) is an underestimated problem for individuals living with diabetes. FoH has negative impacts on mental health (for individuals living with diabetes, caregivers, and support persons) and can lead individuals living with diabetes to target higher BG values, to overtreat hypoglycemia, and to avoid activities and social situations that may result in hypoglycemia.
- Individuals at high risk for severe hypoglycemia, such as those treated with insulin, should be prescribed glucagon, along with provision of counselling on administration technique for their support persons.
- Continuous glucose monitoring (CGM) should be used in conjunction with a structured educational program to detect and prevent hypoglycemia for those at high risk of hypoglycemia, IAH, or FoH.

Key Messages for People With Type 1 and Type 2 Diabetes

- Know the signs and symptoms of a low BG level. Some of the more common symptoms of low BG are trembling, sweating, anxiety, confusion, difficulty concentrating, or nausea. Not all symptoms will be present and some individuals may have different symptoms or no symptoms at all.
- Talk with your health-care provider about the prevention and emergency treatment of a severe low BG, which can be associated with confusion, loss of consciousness, or seizure.
- Carry a source of fast-acting carbohydrate with you at all times, such as glucose tablets, Life Savers™, and/or a juice box, that you can take quickly if you are experiencing low BG (see Table 4).
- For individuals treated with either insulin or insulin secretagogues (i.e. sulfonylureas, meglitinides), ensure that support persons, including work colleagues, are counselled on administration of glucagon.
- Wear diabetes identification (e.g. a MedicAlert® bracelet).
- Talk with your diabetes health-care team about any fears or concerns you may have related to hypoglycemia.
Introduction

Iatrogenic hypoglycemia is a major obstacle to achieving glycemic targets in individuals with type 1 or type 2 diabetes mellitus treated with insulin and/or insulin secretagogues [1–3]. The risk of severe hypoglycemia in some individuals can necessitate less stringent glycemic goals. The frequency and severity of hypoglycemia can negatively impact quality of life [4,5] in individuals with diabetes and promote fear of future episodes of hypoglycemia [6,7]. This fear may lead some individuals to target higher BG levels in an effort to avoid hypoglycemia, thereby worsening overall glycemic management [8–10]. Consequently, preventing, recognizing, and treating hypoglycemia is an important part of diabetes management (see “Glycemic Management in Adults with Type 1 Diabetes,” p. S80, and “Pharmacologic Glycemic Management of Type 2 Diabetes in Adults,” p. S88, for further discussion of drug-induced hypoglycemia).

Definition and Frequency of Hypoglycemia

An alert value of <3.9 mmol/L can be used as a cutoff to classify hypoglycemia in individuals with diabetes treated with insulin and/or insulin secretagogues. Hypoglycemia is very common; up to 65% of individuals with either type 1 or type 2 diabetes (treated with insulin or insulin secretagogues) self-report at least 1 episode of hypoglycemia in a given year, with a higher incidence in people with type 1 diabetes [11]. Hypoglycemia is rare in individuals with type 2 diabetes who are not using insulin or insulin secretagogues, although it may still occur [12,13]. The initial symptoms of hypoglycemia are usually adrenergic, followed by neuroglycopenic symptoms (Table 1), though individuals with impaired counter-regulatory responses to hypoglycemia and IAH may not exhibit adrenergic symptoms prior to neuroglycopenic symptoms, even with low glucose levels.

The severity of hypoglycemia is not strictly defined by glucose levels, but is characterized by the severity of the associated symptoms of hypoglycemia and risks, as defined by the International Hypoglycemia Study Group [14] (Tables 2 and 3). The adoption of a 3-tiered, numbered classification system helps standardize the diagnosis and treatment response according to the severity of symptoms [14,15]. While levels 1 and 2 may be recognized and treated by the individual experiencing hypoglycemia, level 3 is defined by the presence of neuroglycopenic symptoms and the necessity of external assistance (from either a friend, colleague, significant other, caregiver, support person, or health-care professional) to treat low BG.

Risk Factors for Severe Hypoglycemia and IAH

Hypoglycemia is often the primary barrier to achieving glycemic targets in individuals with type 1 diabetes [16]. The major risk factors for level 3 hypoglycemia include a prior episode of severe hypoglycemia [17–19], advancing age [20], low or high glycated hemoglobin (A1C) [18,20–24], IAH [25,26], long duration of diabetes [22,27], autonomic neuropathy [28], adolescents [29] and preschool-aged children unable to detect and/or treat mild hypoglycemia on their own, severe cognitive impairment [30,31], reduced health literacy [32], food insecurity [33], long duration of insulin therapy [34], renal impairment, and neuropathy [24] (Table 3). The choice and dose of antihyperglycemic therapy is also an important and potentially modifiable risk factor for level 3 hypoglycemia. Insulin and insulin secretagogue therapy confer the highest risk of hypoglycemia compared to other antihyperglycemic agents [1,3,35,36], especially among high-risk groups, such as older adults, those with cognitive impairment, and individuals treated to intensive glycemic targets (see “Blood Glucose Monitoring in Adults and Children with Diabetes: Update 2021,” p. 588–590).

Frequent, even mild, hypoglycemia can reduce normal responses to hypoglycemia [12] and lead to defective glucose counter-regulation and IAH. Glucose counter-regulation refers to the normal rise in glucagon, growth hormone, sympathetic (epinephrine, norepinephrine), and adrenal (cortisol) hormones in response to low BG, which counteracts the glucose-lowering effects of insulin and tends to increase BG. IAH 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. Risk factors for IAH include recurrent hypoglycemia, long duration of diabetes, genetic factors, and diabetic neuropathy [37,38]. IAH is a significant risk factor for severe hypoglycemia in individuals with type 1 and type 2 diabetes. Individuals at risk of IAH can be screened with careful history inquiring about symptoms of hypoglycemia, as well as either the Gold or Clarke scores, both validated measures of IAH [25,39].

The sympathoadrenal response to hypoglycemia is reduced during sleep, and following exercise or alcohol consumption [40,41]. Asymptomatic nocturnal hypoglycemia is common and often lasts greater than 4 hours [21,42–45]. Level 3 hypoglycemia, resulting in seizures, is more likely to occur at night than during the day [22].

Physical and Psychosocial Complications of Hypoglycemia

Neurologic complications

Cells in the brain, such as neurons and glia, rely on a constant supply of glucose from the bloodstream. When BG levels decline, as in the case of hypoglycemia, there is marked impairment in cognition, which can ultimately lead to coma and death [46]. Short-term risks of hypoglycemia include impaired cognition during dangerous situations, whether at home or at work (e.g. driving, operating machinery), which can lead to personal injury (i.e. falls with fractures, joint injuries, or head trauma).

The potential long-term complications of level 3 hypoglycemia are mild intellectual impairment and permanent neurologic sequelae, such as hemiparesis and pontine dysfunction, a neurologic condition that can lead to permanent brain damage. The latter are rare and have been reported only in case studies. There is also increasing evidence of an association between hypoglycemia—both level 3 and recurrent episodes of level 1 and 2 hypoglycemia—and cognitive disorders [47,48], but the nature of this relationship remains uncertain. Episodes of hypoglycemia may, in part, explain the higher risk of dementia in individuals with diabetes. Alternatively, hypoglycemia may be a marker for undiagnosed cognitive impairment, as individuals with cognitive disorders are at high risk of future hypoglycemic episodes.

Table 1

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<th>Symptoms of hypoglycemia</th>
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<tr>
<td>Adrenergic (autonomic)</td>
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<tr>
<td>Trembling</td>
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<tr>
<td>Palpitations</td>
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<tr>
<td>Sweating</td>
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<tr>
<td>Anxiety</td>
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<td>Hunger</td>
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<tr>
<td>Nausea</td>
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<td>Tingling</td>
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including level 3 hypoglycemia, possibly because of medication errors and irregular eating patterns [30,49,50] (see “Diabetes in Older People” chapter, p. S283).

Prospective studies have not found an association between intensive insulin therapy and cognitive function [51–53], or between level 3 hypoglycemia and future cognitive function [49,50]. In the long-term follow-up of the Diabetes Complications and Control Trial (DCCT), exposure to higher A1C levels, more episodes of severe hypoglycemia, and elevated systolic blood pressure (BP) were associated with greater decrements in psycho-motor and mental efficiency that were most notable by year 32 (p<0.0001) [54].

Cardiovascular complications

In individuals with type 2 diabetes and established, or very high, risk for cardiovascular disease (CVD), there is a clear association between increased mortality, level 3 hypoglycemia [47,55,56], and symptomatic hypoglycemia, though the mechanism for this association is not certain [57]. However, severe hypoglycemia may also be a marker of vulnerability, without a direct causal contribution to the increased mortality [58]. Acute hypoglycemia is proinflammatory, increases platelet activation, and decreases fibrinolysis, leading to a prothrombotic state [59,60]. Hypoglycemia is associated with increased heart rate, systolic BP, myocardial contractility, stroke volume, and cardiac output, and can induce ST- and T-wave changes with a lengthening of the QT interval (slower repolarization). Level 3 hypoglycemia may also increase the risk of heart block and fatal cardiac arrhythmias [61–66].

Musculoskeletal complications

There is also an association between hypoglycemia and falls and fractures [47]. The fall/fracture may, in some cases, be an immediate consequence of an acute hypoglycemic event or hypoglycemia may be a marker of frailty/vulnerability.

Despite the uncertainty that persists on the causality of severe hypoglycemia for these complications, the finding of frequent or level 3 hypoglycemia in an individual should increase awareness of their risk for future cardiovascular events, cognitive decline, and/or falls and fractures, and, in the frail individual with cognitive decline or multiple comorbidities, prevention of hypoglycemia should be prioritized.

Psychosocial complications

Individuals with type 1 diabetes describe numerous consequences of hypoglycemia on their quality of life [67]. They report worrying about burdening others because of the need for help, interruptions in activities, inappropriate behaviour, and lack of energy. This may lead to hiding hypoglycemia, reducing social activities, maintaining higher glucose levels, and lower work productivity due to interruptions at work due to diabetes and absenteeism while recuperating from a hypoglycemic episode [68]. These impacts on quality of life may also lead to anxiety, depression, and FoH (see “Diabetes and Mental Health” chapter) [69–72]. Hypoglycemia also places burden and stress on the family members and support persons of individuals living with diabetes [73]. They feel responsible for the management of hypoglycemic episodes of their loved ones, which may disrupt their own activities. Sleep may often be affected in bed partners, as well as in parents of youths with type 1 diabetes, due to concerns with nocturnal hypoglycemia [74,75].

Fear of hypoglycemia

FoH is a specific and extreme fear evoked by the risk and/or occurrence of hypoglycemia. The prevalence of FoH may be as high as 30% among individuals living with type 1 and type 2 diabetes treated with insulin and/or insulin secretagogues [6,9,76,77]. FoH occurs more frequently in women than in men [6,9] (see “Diabetes and Mental Health” chapter, p. S131).

While adaptive FoH may allow individuals to respond appropriately to the risk of hypoglycemia, FoH that is excessive may cause excess anxiety, stress, and, as a result, a reduction in function and quality of life [78,79]. Conversely, low levels of fear may increase risk of further episodes of hypoglycemia and complications of severe hypoglycemia. Additional complications from FoH may include interference with behavioural adherence to diabetes management, as individuals may intentionally target a higher BG value in order to avoid hypoglycemia in situations where it may be socially “inappropriate” to treat hypoglycemia (meetings, performances, etc) [9]. Avoidance behaviours may include things such as underdosing insulin, limiting exercise, or overeating.

Validated questionnaires for measuring FoH include the Hypoglycaemia Fear Survey (HFS-II), Quick Screening for Fear of Hypoglycaemia (QSFH), the Fear of Hypoglycemia 15-Item Scale (FH-15), and the Children’s Hypoglycemia Index (CHI) [78]. HFS-II is the most validated questionnaire, but given the large

### Table 2
Classification of hypoglycemia

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
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<tbody>
<tr>
<td>• Glucose level below normal (often between 3.0 and 3.9 mmol/L)</td>
<td>• Glucose level below normal (often &lt;3.0 mmol/L)</td>
<td>• Glucose level below normal (regardless of glucose reading)</td>
</tr>
<tr>
<td>• Associated with autonomic symptoms</td>
<td>• Associated with autoglycopenic symptoms</td>
<td>• Associated with autoglycopenic symptoms resulting in significantly altered mental/physical status</td>
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<tr>
<td>• Without neuroglycopenic symptoms or changes to mental status</td>
<td>• Without significant impact on mental status</td>
<td>• Requires assistance to treat</td>
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### Table 3
Risk factors for hypoglycemia in individuals treated with sulfonylureas or insulin

- Prior episode of severe hypoglycemia
- Current low A1C (<7.0%)
- Hypoglycemia unawareness
- Long duration of insulin therapy
- Autonomic neuropathy
- CKD
- Low economic status, food insecurity
- Low health literacy
- Preschool-aged children unable to detect and/or treat mild hypoglycemia on their own
- Adolescents
- Pregnancy
- Frailty and advanced age
- Cognitive impairment

A1C, glycated hemoglobin; CKD, chronic kidney disease.
number of questions, it may not be feasible to use it in a busy clinic setting. The QSFH shows promise for clinical relevance as it consists of only 2 questions (How worried are you about severe hypoglycemia? and How much do your worries about hypoglycemia hinder you in daily life?). However, it requires further validation before it can be widely used. Identification of individuals with FoH would allow clinicians to implement strategies targeted at addressing it.

Prevention

Prevention of hypoglycemia is safer and more effective than addressing the many short-term and long-term consequences. Choice of dose of antihyperglycemic agent and use of CGM technologies can reduce episodes of hypoglycemia (see “Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update,” p. 589; see “Blood Glucose Monitoring in Adults and Children With Diabetes: Update 2021,” p. 584–585). Structured educational and psychosocial programs (e.g., BG awareness training) may help improve detection of hypoglycemia and reduce the frequency of level 3 hypoglycemia [80–83]. The following are the prevention strategies for hypoglycemia.

Pharmacotherapy: Type and regimen

Insulin and/or insulin secretagogue therapy increases the risk of hypoglycemia. In general, basal insulin analogues are associated with a lower risk of hypoglycemia compared to NPH insulin, including among individuals with stage 3 or 4 chronic kidney disease (CKD) [84]. Among analogue insulins, degludec and glargine-300 are associated with less hypoglycemic episodes compared to glargine-100 and detemir across many populations, including older adults, individuals with obesity, renal impairment, and among those with a history of CVD and with long duration of insulin use (85–87). In addition, insulin degludec is associated with less nocturnal hypoglycemia than insulin glargine-100 [85] in both type 1 and type 2 diabetes [85,88,89]. Studies comparing insulin glargine-300 to insulin degludec show similar rates of hypoglycemia [90,91]. Switching to analogue insulins with the lowest risk of hypoglycemia (i.e. glargine-300, degludec) should be considered, especially among those at high risk of, or with a history of, hypoglycemia.

In adults with type 2 diabetes who require treatment advancement or adjustment, the use of antihyperglycemic agents that do not increase the risk or minimize the risk of hypoglycemia (i.e. glucagon-like peptide-1 receptor agonists [GLP-1RA], dipeptidylpeptidase 4 [DPP4] inhibitors, sodium-glucose cotransporter-2 [SGLT2] inhibitors, acarbose, and/or pioglitazone) should be considered (see “Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update,” p. 589) [92].

There is evidence that continuous subcutaneous insulin infusion (CSII) vs multiple daily injections (MDIs) reduces recurrent severe hypoglycemia in adults with type 1 diabetes [82,93]. Closed-loop insulin delivery has also been associated with a decrease in the number of hypoglycemic events in adults with type 1 diabetes [94].

Glucose monitoring

For individuals with type 1 diabetes or type 2 diabetes, the use of real-time CGM (rtCGM) and intermittently scanned CGM (isCGM) may be a helpful tool in reducing hypoglycemia, as well as the time spent in a hypoglycemic state (see “Blood Glucose Monitoring in Adults and Children With Diabetes: Update 2021,” p. 584–585). In individuals with type 1 diabetes, both isCGM and rtCGM have also been associated with a reduction in hypoglycemia compared to capillary blood glucose (CBG) testing [95], though CGM may not reduce episodes of level 3 hypoglycemia [96,97]. In addition, the use of CGM identifies more episodes of hypoglycemia than CBG monitoring, even among those with normal hypoglycemia awareness [98].

While both rtCGM and isCGM have been shown to improve glycemic management in individuals with type 2 diabetes, there is also evidence that these CGM technologies are associated with a reduction in hypoglycemia in adults with type 2 diabetes treated with either insulin and/or insulin secretagogues [99,100].

To reduce the risk of asymptomatic nocturnal hypoglycemia, individuals using insulin therapy can periodically monitor overnight BG levels, using either CBG monitoring or CGM.

Individualized glycemic targets and time in range

While targeting an A1C<7% is recommended for most individuals with diabetes to prevent long-term complications, those with recurrent and severe hypoglycemia, in particular older adults with frailty treated with insulin or insulin secretagogues, may benefit from individualized A1C targets to reduce the risk of hypoglycemia [101,102] (see “Targets for Glycemic Control,” p. S42, and “Diabetes in Older People,” p. S283). In addition, shorter-term relaxation of glycemic targets, especially in individuals with level 3 hypoglycemia or a clinically significant hypoglycemia, may be appropriate.

Time in range (TIR), which is derived from CGM data and summarizes the time spent within predetermined glycemic ranges, has become a novel way for individuals with diabetes and clinicians to monitor glycemic variability and frequency of hyper- and hypoglycemia [103]. Monitoring TIR in hypoglycemia is an alternative way that clinicians can monitor for hypoglycemia and adjust treatments accordingly (see “Blood Glucose Monitoring in Adults and Children With Diabetes: Update 2021,” p. S84–85).

Structured psychoeducational programs

Both impaired glucose counter-regulation and IAH 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 hypoglycemia, the counter-regulatory hormone responses, or both [104–111].

Numerous psychoeducational programs have been shown to reduce the prevalence of IAH and related frequency of hypoglycemia (i.e. HypoCOMPAss, BGAT, HAATT, and DAFNE-HART) [82,93,112–114]. Such programs focus on improving the detection of hypoglycemia through enhanced awareness of internal and external cues, education on the basics of insulin pharmacodynamics and insulin dose adjustments, as well as psychological support. Though some of these programs utilize technological components (i.e. CSII or CGM), the main benefit appears to be related to close, frequent contact between diabetesthe health-care providers and individuals living with diabetes, along with the structured education.

Counselling on exercise-induced hypoglycemia

Preparing for exercise by reducing insulin doses or increasing carbohydrate intake is essential to prevent exercise-induced hypoglycemia. Individuals with diabetes, support persons, and caregivers should be counselled on the importance of reducing pre-exercise boluses or short-term basal reduction programs on their pump, particularly in those who are reluctant to increase carbohydrate intake. Certain technologies allow for an “exercise announcement” at mealtime using a closed-loop system, allowing for a one-third reduction in meal bolus or targeting a higher BG
Treatment of hypoglycemia

Table 4

<table>
<thead>
<tr>
<th>Treatment of hypoglycemia</th>
<th>Levels 1, 2</th>
<th>Level 1, conscious</th>
<th>Level 1, unconscious</th>
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<tr>
<td></td>
<td>15 g oral carbohydrates</td>
<td>4 × 4 g glucose tablets</td>
<td>3 mg IN or 1 mg SC/IM glucagon</td>
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<td></td>
<td></td>
<td>15 mL (3 teaspoons) or 3 packets of table sugar dissolved in water</td>
<td>3 mg IN or 1 mg SC/IM glucagon</td>
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<td></td>
<td></td>
<td>5 cubes of sugar</td>
<td>25 g IV dextrose or 3 mg IN or 1 mg SC/IM glucagon</td>
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<tr>
<td></td>
<td></td>
<td>150 mL juice or regular soft drink</td>
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<td></td>
<td></td>
<td>6 Life Savers™</td>
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<tr>
<td></td>
<td></td>
<td>15 mL (1 tablespoon) honey</td>
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<td></td>
<td>20 g oral carbohydrates</td>
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Other choices, such as milk and orange juice, are slower to increase glucose levels and provide symptom relief [126,127]. Glucose gel is quite slow (<1.0 mmol/L increase at 20 minutes) and must be swallowed to have a significant effect [125–130]. In all these cases, the affected individual needs to be able to swallow to benefit from the intervention. BG should be retested 15 minutes after initial treatment and, if BG is still in the hypoglycemia range, retreatment is required. If a meal is >1 hour away, a snack (including 15 g of carbohydrate and a protein source) should be consumed.

Level 3 hypoglycemia

In the case of level 3 hypoglycemia, the affected individual is unable to self-treat and, therefore, requires the assistance of another person for recovery. Oral glucose (as above) may be administered if the affected individual is still able to swallow. However, when oral ingestion is unsafe or if the affected individual cannot swallow, the standard of care is to treat with glucagon. Glucagon is the only non-oral rescue therapy administrable outside of professional care contexts (e.g. by family, friends, or colleagues). For affected individuals with level 3 hypoglycemia who are/were unconscious, caregivers or support persons should call for emergency services after administering glucagon, and the episode should be discussed with the diabetes health-care team as soon as possible.

Glucagon 1 mg given subcutaneously (SC) or intramuscularly (IM) produces a significant increase in BG (from 3.0 to 12.0 mmol/L) within 60 minutes [7,131]. More recently, intranasal (IN) glucagon (3 mg) has been shown to be as effective as injectable (both SC and IM) glucagon in both individuals with type 1 diabetes and individuals with insulin-treated type 2 diabetes [132,133]. There have even been case reports from real-world studies where IN glucagon has been successfully used in unconscious individuals with level 3 hypoglycemia. The main advantage of IN glucagon is the ease of administration. In addition, the use of a single dose of IN glucagon has been shown to result in more complete dosing (93% IN vs 13% IM) and faster administration (16 seconds IN vs 113 seconds IM) in instructed caregivers [134]. IN glucagon has not been studied in individuals with type 2 diabetes treated with insulin secretagogues and should be used cautiously in these individuals. In individuals on a low-carbohydrate diet, the treatment effect of glucagon may be reduced [135].

Intravenous or IM glucose—administrable only by medically trained professionals in prehospital or hospital settings—is the third-line treatment option after oral glucose and glucagon. It may also be required when glucagon is unavailable, contraindicated, ineffectively administered, or unsuccessful.

The effectiveness of glucagon is reduced in individuals who have consumed more than 2 standard alcoholic drinks in the previous
few hours, after prolonged fasting, or in those who have advanced hepatic disease [136,137]. Among individuals taking secretagogues (without insulin), glucagon is less useful, as it stimulates insulin secretion through glycogenolysis [138].

**Recommendations** (Figure 1)

**Counselling and screening**

1. All individuals with diabetes currently using or starting therapy with insulin or insulin secretagogues, and their support persons, should be counselled about the risk, prevention, recognition, and treatment of hypoglycemia. Risk factors for severe hypoglycemia should be identified and addressed [Grade D, Consensus].

2. At every visit, for all individuals with diabetes, the diabetes health-care team should review the recent history of hypoglycemic episodes, including, but not limited to, identification of contributing factors, frequency, symptoms, recognition, severity, and treatment approach, as well as the risk of driving with hypoglycemia [Grade D, Consensus] (Note: For recommendations about diabetes and driving, refer to “Diabetes and Driving” chapter: https://guidelines.diabetes.ca/cpg/chapter21.).

3. All individuals at risk for severe hypoglycemia and IAH should be screened with a careful history or using a validated measure of hypoglycemia awareness at each clinic visit to identify those who may need support [Grade D, Consensus].

4. All individuals with diabetes treated with insulin and/or insulin secretagogues should be screened for FoH with a careful history or using a validated measure to identify those who may need interventions, like advanced therapeutic technologies and psychoeducational training. In addition, referrals to mental health-care professionals for those with persistent FoH can be considered [Grade D, Consensus] (see “Diabetes and Mental Health” chapter, p. 137).

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**Figure 1.** An approach/summary to preventing and treating hypoglycemia in adults with diabetes. IM, intramuscular; SC, subcutaneous.
Prevention of hypoglycemia

5. In individuals with diabetes at increased risk of hypoglycemia, the following strategies may be used to reduce the risk of hypoglycemia:
   a. use of CGM and/or increased frequency of CGM monitoring, including during sleeping hours, to identify episodes of unrecognized hypoglycemia [Grade B, Level 2 for type 2 diabetes [99]; Grade A, Level 1A for type 1 diabetes; Grade D, Consensus for CBG recommendation] (see “Blood Glucose Monitoring in Adults and Children with Diabetes: Update 2021,” p. S80).
   b. avoidance, reduction in dose, or discontinuation of pharmacotherapies associated with increased risk of hypoglycemia (i.e., insulin and insulin secretagogues), where appropriate [Grade D, Consensus] (see “Pharmacologic Glycemic Management of Type 1 Diabetes,” p. S80, and “Pharmacologic Glycemic Management of Type 2 Diabetes in Adults,” p. S88, for further discussion of drug-induced hypoglycemia).
   c. long-acting analogues (i.e., insulin glargine-U100, glargine U-300, detemir, degludec) should be considered over NPH insulin to reduce the risk of hypoglycemia, including nocturnal hypoglycemia [Grade A, Level 1A] [139–144].
   d. second-generation basal insulin analogues (i.e., insulin glargine U-300, insulin degludec) should be considered over first-generation basal insulin analogues (i.e., insulin glargine-U100, insulin detemir) to reduce the risk of hypoglycemia, including nocturnal hypoglycemia [Grade B, Level 2 for insulin glargine U-300 in insulin-naïve individuals with type 2 diabetes and ≥1 risk factor for hypoglycemia [86,87]; Grade A, Level 1A for insulin degludec for type 1 and type 2 diabetes [85]] (see “Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update,” p. 589, and “Glycemic Management of Adults with Type 1 Diabetes,” p. S84) [91].
   e. a structured diabetes education program, where available, with frequent follow-up targeting enhanced awareness of cues for hypoglycemia, education on insulin pharmacodynamics, and dose adjustments to reduce frequency and severity of hypoglycemia [Grade B, Level 1 [112] for type 1 diabetes; Grade D, Consensus for type 2 diabetes].
   f. a psychosocial intervention program (BG awareness training) [Grade C, Level 3 [80], see “Diabetes and Mental Health” chapter, p. S131].

6. In individuals with diabetes with recurrent hypoglycemia or level 3 hypoglycemia, or IAH, the following additional strategies may be considered to reduce or eliminate the risk of hypoglycemia:
   a. CSII or CGM or sensor-augmented pump with education and follow-up for type 1 diabetes [Grade B, Level 2 [82,145–147].
   b. avoidance of hypoglycemia, with individualized glycemic targets, and, where appropriate, dose reduction or cessation of antihyperglycemic agent(s) that increase the risk of hypoglycemia (i.e., insulin and insulin secretagogues) for up to 3 months [Grade D, Level 4] [109,110].
   c. islet transplantation for type 1 diabetes [Grade C, Level 3] [119].

7. In individuals with type 1 diabetes exhibiting FoH, CGM should be used to enhance glycemic awareness, reduce FoH, and minimize behaviours that lead to above-target BG trends [Grade A, Level 1A] [117].

Treatment of hypoglycemia

8. Individuals with diabetes experiencing level 1 and 2 hypoglycemia should ingest 15 g of fast-acting carbohydrate, preferably as glucose or sucrose (i.e., tablets or solution) [Grade B, Level 2 [125]]. BG should be retested after 15 minutes and retreated with 15 g of carbohydrate if BG remains <3.9 mmol/L [Grade D, Consensus].

9. Individuals with diabetes experiencing level 3 hypoglycemia who are conscious and:
   a. capable of swallowing: i) should be treated by oral ingestion of 20 g carbohydrate, preferably as glucose tablets or equivalent; ii) 3 mg glucagon IN or glucagon 1 mg SC/IM can also be used. BG should be retested in 15 minutes and then retreated with 15 g carbohydrate if it remains <3.9 mmol/L [Grade C, Level 3 for type 2 diabetes; Grade A, Level 1 for glucagon use in type 1 diabetes [132,133]; Grade D, Consensus for carbohydrate]
   b. unable to swallow: can be treated with glucagon 1 mg SC/IM or 3 mg IN [Grade D, Consensus].

10. Individuals with diabetes experiencing level 3 hypoglycemia who are unconscious with:
    a. no intravenous access: can be treated with glucagon 1 mg SC/IM or 3 mg IN. Caregivers or support persons should call for emergency services and the episode should be discussed with a health-care provider as soon as possible [Grade D, Consensus]
    b. intravenous access: can be treated with administration of 10 to 25 g (20 to 50 mL of D50W) of glucose intravenously over 1 to 3 minutes [Grade D, Consensus].

11. For individuals with diabetes at risk of level 3 hypoglycemia, support persons should be taught how to administer SC/IM or IN glucagon [Grade D, Consensus].

12. Once any level of hypoglycemia has been treated, the individual 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 of carbohydrate and a protein source) should be consumed [Grade D, Consensus].

Abbreviations

BG, blood glucose; CBC, capillary blood glucose; CGM, continuous glucose monitoring; CVD, cardiovascular disease; CSII, continuous subcutaneous insulin infusion; FoH, fear of hypoglycemia; IAH, impaired awareness of hypoglycemia; IM, intramuscular; IN, intranasal; SC, subcutaneous.

Author Disclosures

J.-F.Y. reports grants and personal fees from Eli Lilly Canada, Sanofi, Merck, AstraZeneca, Boehringer Ingelheim, Janssen, and Medtronic; personal fees from Novo Nordisk, Takeda, Abbott, and Bayer; and grants from Mylan. B.P. reports clinical trial funding from Vertex Pharmaceuticals and ViaCyte, Inc, for stem cell trials for type 1 diabetes. R.R. reports personal fees from Eli Lilly Canada, AstraZeneca, Boehringer Ingelheim, NovoNordisk, Abbott Diabetes, Dexcom, mBriefCase, BD Canada, Roche Diabetes Care, and HLS Therapeutics.

External Reviewers

Thank you to our external reviewers for their insightful feedback and the lending of their time and expertise: Professor Pratik Choudhary MBBS, MD, FRCP; Stewart Harris CM, MD, MPh, FCFP, FACP; Simon Heller DM FRCP; and Alexandria Ratzki-Leewing PhD.
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Literature Review Flow Diagram: Hypoglycemia in Adults

Identification

Records identified through database searchings N=1,487
Additional records identified through other sources N=51

Records after duplicates removed N=1,046

Screening

Records screened N=1,046
Records excluded N=955

Eligibility

Full-text articles assessed for eligibility N=91
Full-text articles excluded* N=82

Included

Studies for new or revised recommendations N=9

*Based on Population, Intervention, Comparison or Outcomes (PICO)