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2018 Clinical Practice Guidelines

Hypoglycemia

Diabetes Canada 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.
- It is safer and more effective to prevent hypoglycemia than to treat it after it occurs, so people with diabetes who are at high risk for hypoglycemia should be identified and counselled about ways to prevent low blood glucose.
- It is important to counsel individuals who are at risk of hypoglycemia and their support persons about the recognition and treatment of hypoglycemia.
- The goals of treatment for hypoglycemia are to detect and treat a low blood glucose level promptly by using an intervention that provides the fastest rise in blood glucose to a safe level, to eliminate the risk of injury and to relieve symptoms quickly. 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.
- It is important to avoid overtreatment of hypoglycemia, since this can result in rebound hyperglycemia and weight gain.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Know the signs and symptoms of a low blood glucose level. Some of the more common symptoms of low blood glucose are trembling, sweating, anxiety, confusion, difficulty concentrating or nausea. Not all symptoms will be present and some individuals may have other or no symptoms.
- Carry a source of fast-acting carbohydrate with you at all times, such as glucose tablets, Life Savers™ and/or a juice box (see Table 4).
- Wear diabetes identification (e.g. a MedicAlert® bracelet)
- Talk with your diabetes health-care team about prevention and emergency treatment of a severe low blood glucose associated with confusion, loss of consciousness or seizure.

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). The negative social and emotional impact of hypoglycemia may make individuals reluctant to intensify therapy. As such, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin or insulin secretagogues (see Glycemic Management in Adults with Type 1 Diabetes, p. S80; Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88 for further discussion of drug-induced hypoglycemia).

Definition and Frequency of Hypoglycemia

Hypoglycemia is defined by: 1) the development of autonomic or neuroglycopenic symptoms (Table 1); 2) a low plasma glucose (PG) level (<4.0 mmol/L for people with diabetes 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). Hypoglycemia is most frequent in people with type 1 diabetes, followed by people with type 2 diabetes managed by insulin, and people with type 2 diabetes managed by sulfonylureas.

Severe Hypoglycemia and Hypoglycemia Unawareness

The major risk factors for severe hypoglycemia in people with type 1 diabetes include a prior episode of severe hypoglycemia

Table 1
Symptoms of hypoglycemia

Neurogenic (autonomic)	Neuroglycopenic
Trembling	Difficulty concentrating
Palpitations	Confusion, weakness, drowsiness, vision changes
Sweating	Difficulty speaking, headache, dizziness
Anxiety	
Hunger	
Nausea	
Tingling	

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.

Conflict of interest statements can be found on page S106.

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Table 3
Risk factors for severe hypoglycemia in people treated with sulfonylureas or insulin

- Prior episode of severe hypoglycemia
- Current low A1C (<6.0%)
- Hypoglycemia unawareness
- Long duration of insulin therapy
- Autonomic neuropathy
- Chronic kidney disease
- Low economic status, food insecurity
- Low health literacy
- Preschool-aged children unable to detect and/or treat mild hypoglycemia on their own
- Adolescence
- Pregnancy
- Elderly
- Cognitive impairment

A1C, glycated hemoglobin.

(8–10), current low glycated hemoglobin (A1C) (<6.0%) (9,11–13), hypoglycemia unawareness (14), long duration of diabetes (12,15), autonomic neuropathy (16), adolescence (17) and preschool-aged children unable to detect and/or treat mild hypoglycemia on their own. Risk factors for hypoglycemia in people with type 2 diabetes include advancing age (18), severe cognitive impairment (19), poor health literacy (20), food insecurity (21), increased A1C (18,22), hypoglycemia unawareness (23), duration of insulin therapy, renal impairment and neuropathy (22). Individuals 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 (SMBG), and taking appropriate precautions prior to the activity, and documenting blood glucose (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.

Frequent hypoglycemia can decrease normal responses to hypoglycemia (12) and lead to defective glucose counter-regulation and hypoglycemia unawareness. 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 (24) and occurs frequently during sleep or in the presence of hypoglycemia unawareness (11,25). The sympathoadrenal response to hypoglycemia is reduced during sleep, and following exercise or alcohol consumption (26,27). Asymptomatic nocturnal hypoglycemia is common and often lasts greater than 4 hours (11,28–31). Severe hypoglycemia, resulting in seizures, is more likely to occur at night than during the day (12).

Both hypoglycemia unawareness and defective glucose counter-regulation 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 counter-regulatory hormone responses or both (32–39). 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.

Structured educational and psycho-behavioural programs (e.g. BG awareness training) may help improve detection of hypoglycemia and reduce the frequency of severe hypoglycemia (40–43). People with diabetes who continue to have frequent and severe hypoglycemia and/or impaired awareness of hypoglycemia, despite educational interventions, may benefit from continuous subcutaneous insulin infusion (CSII) therapy or continuous glucose monitoring (CGM) or both (i.e. a sensor augmented pump), to reduce the risk of severe hypoglycemia (44–47). Islet cell transplantation, which has been shown to reduce hypoglycemia (48) and restore glucose counter-regulation (49), should be considered for people with type 1 diabetes who experience recurrent severe hypoglycemia (50) (see Diabetes and Transplantation chapter, p. S145). Similarly, pancreas transplantation has been shown to reduce hypoglycemia and restore glucose counter-regulation (43,51–53).

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 (54,55).

There is a clear association between severe hypoglycemia and cognitive disorders, but the nature of this relationship remains unclear. The person with cognitive disorders is at high risk of future severe hypoglycemic episodes, possibly because of medication errors (19,56,57) (see Diabetes in Older People chapter, p. S283). Prospective studies have not found an association between intensive insulin therapy and cognitive function (58–60), or between severe hypoglycemia and future cognitive function (56,57). Lowered cognitive performance appears to be more associated with the presence of microvascular complications or poor metabolic control than with the occurrence of severe hypoglycemic episodes (57,61).

In people with type 2 diabetes and established, or very high risk for, cardiovascular disease (CVD), there is a clear association between an increased mortality and severe hypoglycemia (62,63) and symptomatic hypoglycemia (64). The mechanism for this increase is not certain. Acute hypoglycemia is proinflammatory, increases platelet activation and decreases fibrinolysis, leading to a prothrombotic state (65,66). Hypoglycemia is associated with increased heart rate, systolic blood pressure (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), which may increase the risk of arrhythmias (67–71). However, severe hypoglycemia may also be a marker of vulnerability, without any direct causal contribution to the increased mortality (72).

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 overtreatment 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) (73–77). This has not been well studied in individuals with gastroparesis. A 20 g oral glucose dose will produce a BG increment of approximately 3.6 mmol/L at 45 minutes (74,75). Other choices, such as milk and orange juice, are slower to increase BG levels and provide symptom relief (74,75). Glucose gel is quite slow (<1.0 mmol/L increase at 20 minutes) and must be swallowed to have a significant effect (73–78). People taking an alpha glucosidase