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Assessment and management of hypoglycemia in children and adolescents with diabetes

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- Hypoglycemia is the commonest acute complication of type 1 diabetes. Hypoglycemia may also occur in type 2 diabetes when treatment includes, for example, insulin or sulfonylurea therapy.
- The risk of hypoglycemia presents a major physiological and psychological barrier to achieving optimal glycemic control and may result in significant emotional morbidity for patients and carers.
- Monitoring hypoglycemia is a key component of diabetes care as is education about its causes, prevention, and treatment. Parents and caregivers need to be reassured that good glycemic control can be achieved without frequent severe hypoglycemic events.
- Hypoglycemia is best defined as a fall of the blood glucose level that exposes a patient to potential harm and there can be no single numerical definition of hypoglycemia for all patients and situations.
- A blood glucose level of <3.6 mmol/L (65 mg/dL) has been often accepted as a level for defining hypoglycemia. In clinical practice, however, a glucose value of ≤ 3.9 mmol/L (70 mg/dL) is used as the threshold value for initiating treatment for hypoglycemia in diabetes because of the potential for the glucose to fall further.
- In children, severe hypoglycemia is most often defined as an event associated with a seizure or loss of consciousness. In adults, an event requiring assistance from others is defined as severe but as almost all children require assistance with treatment, these events are more difficult to determine and events associated with significant neuroglycopenia may be classified as moderate events. All other hypoglycemic events are described as mild.
- Hypoglycemia is also classified as symptomatic and asymptomatic.
- The incidence of severe hypoglycemia varies with different surveys but most careful prospective studies

suggest a rate of 5 to 20/100 patient-years. This rate has fallen over the last 10 yr, but children remain at a higher risk than adults [B (1)].
- Symptoms of hypoglycemia in the young result from *adrenergic activation* (e.g., shakiness, pounding heart, and sweatiness) and *neuroglycopenia* (e.g., headache, drowsiness, and difficulty concentrating). In young children *behavioral* changes such as irritability, agitation, quietness, and tantrums may be prominent. The dominant symptoms may change with age.
- Symptoms of hypoglycemia and physiological hormone responses may occur at a higher glucose level in children compared to adults and thresholds for activation may be altered by chronic hyperglycemia (i.e., occur at a higher blood glucose) or repeated hypoglycemia (i.e., occur at a lower blood glucose level) (B).
- In type 1 diabetes, hypoglycemia results from imperfect insulin replacement. The risk of hypoglycemia is increased further by compromised counterregulatory hormone defects, including loss of the glucagon response to hypoglycemia, which may occur soon after diagnosis (B).
- Common clinical precipitants for hypoglycemia include: excessive insulin dosing, missed meals, exercise, sleep and, in adolescents, alcohol ingestion. Risk factors include young age, previous severe hypoglycemic events, and reduced hypoglycemia awareness. Lower A1C remains a risk factor but this association is less pronounced with contemporary therapy.
- Severe hypoglycemia requires urgent treatment. In a hospital setting, this may include intravenous glucose (10% glucose, 2–3 mL/kg) (B). In the home or ambulatory setting, intramuscular (IM) or subcutaneous (SC) glucagon should be given (<12 yr 0.5 mg, >12 yr 1.0 mg). Carers should receive training in its administration and have glucagon available (E).
- Milder hypoglycemic events should be treated with oral glucose (10 to 15 g glucose). Depending on the circumstances, rapid-acting glucose should be followed by additional carbohydrates to prevent recurrence of hypoglycemia (B).
- Exercise may be associated with hypoglycemia at the time of activity and up to 8 to 12 h later (delayed hypoglycemia) (B). Carers and patients should receive education and advice as to how to exercise safely and avoid hypoglycemic events.
- Sleep is a time of particular risk for severe hypoglycemia and asymptomatic hypoglycemia is common; because of this, routine testing is recommended overnight (B).
- Impaired hypoglycemia awareness occurs in children with diabetes and when present, is associated with a significantly increased risk of severe hypoglycemia. The determination of hypoglycemia awareness should be a component of routine clinical review. Impaired awareness may be corrected by avoidance of hypoglycemia (B).
- New technologies including continuous glucose monitoring (CGM), closed-loop systems, and semi-closed loop systems offer potential to reduce the impact of hypoglycemia in the future (B).

Prevention of hypoglycemia

- Diabetes education is critical to preventing hypoglycemia.
- The aim of diabetes treatment should be to maintain blood glucose levels >3.9 mmol/L (70 mg/dL) while striving to achieve the best possible glycemic control without the occurrence of severe hypoglycemia (A).
- Education about the risk factors for hypoglycemia should be given to patients and families to alert them as to times and situations when increased glucose monitoring is required and when treatment regimens need to be changed (E).
- Hypoglycemia should be prevented because its occurrence is frequently predictable, and it is often associated with significant psychosocial dysfunction; more importantly, it can in rare cases lead to permanent long-term sequelae and may be potentially life-threatening.
- Particular attention should be given to training children, parents, schoolteachers, and other caregivers to recognize the early warning signs of hypoglycemia and treat low blood glucose immediately and appropriately (E).
- Children and adolescents with diabetes should wear some form of identification or alert of their diabetes (E).
- An immediate source of glucose must always be available to young people with diabetes (A).
- Equipment for blood glucose measurement must be available to all children with diabetes for immediate confirmation and safe management of hypoglycemia (B, E).

Treatment of hypoglycemia

- Glucagon should be readily accessible to all parents and caregivers, especially when there is a high risk of severe hypoglycemia. Education on administration of glucagon is essential (E).
- Treatment of hypoglycemia should increase the blood glucose approximately 3–4 mmol/L (54–70 mg/dL). This can be accomplished by giving glucose tablets or sweetened fluids such as juice. Approximately 9 g of glucose is needed for a 30 kg

child and 15 g for a 50 kg child (approximately 0.3 g/kg).
- Following initial hypoglycemia treatment, blood glucose should be retested in 10–15 min. If there is no response or an inadequate response, repeat hypoglycemia treatment. Retest the blood glucose in another 10–15 min to confirm that target glucose (100 mg/dL) has been reached (E).
- Blood glucose monitoring should be performed prior to exercise, and extra carbohydrates should be consumed based on the blood glucose level and the expected intensity and duration of the exercise (B).
- Patients and their parents should be trained to contact their diabetes care provider if hypoglycemia is documented without symptoms or if the symptoms are those of neuroglycopenia and not autonomic symptoms (i.e., hypoglycemia unawareness).
- Blood glucose goals may need to be adjusted upward in patients with recurrent hypoglycemia and/or hypoglycemia unawareness (B).
- If unexplained hypoglycemia is frequent, evaluation for unrecognized celiac and Addison's disease should be considered (E).

Introduction

Hypoglycemia is the most common acute complication of type 1 diabetes (2, 3). The risk of recurrent and severe hypoglycemia causes significant anxiety and emotional morbidity for patients and families and is a limiting factor in achieving optimal glycemic control (4). For the child with type 1 diabetes, hypoglycemia can have a range of adverse consequences including unpleasant or embarrassing and potentially dangerous symptoms, impaired concentration, and behavioral disturbances. Severe, prolonged hypoglycemia, in particular during sleep, can result in coma, seizures, and even death (5, 6).

It is important that hypoglycemia is recognized as a key component of diabetes care and that patients and families receive education about its causes, effects, treatment, and prevention. At the same time, patients and families need reassurance that good glycemic control can be achieved without frequent severe hypoglycemic events as fear of hypoglycemia is common and disabling for many caregivers and young people with diabetes. Rates of severe hypoglycemia should be monitored as an important outcome of clinical management.

In recent years, there have been improvements in insulin therapy, including availability of insulin analogs, insulin pump therapy, and the introduction of CGM systems. Although there are some data to suggest that severe hypoglycemia has reduced in incidence recently (7, 8), hypoglycemia remains common (3). Furthermore, despite advances in therapy, the majority of patients, particularly children, fail to achieve recommended glycemic targets in part because of the risk of hypoglycemic events (9, 10).

Definition and incidence

Definition

There is no consistent or agreed upon numerical definition of hypoglycemia for the child with diabetes.

Hypoglycemia is not defined by a single glucose value as glycemic thresholds for symptoms, central nervous system dysfunction, and hormonal counter-regulation vary both between individuals and in the same individual over time (11, 12). The American Diabetes Association and Endocrine Society work-group report (13) defines iatrogenic hypoglycemia in patients with diabetes as all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm. Blood glucose values of $<$3.3–3.9 mmol/L (60–70 mg/dL) are generally agreed to place the individual at risk of severe hypoglycemia because values in this range are associated with alterations in the counterregulatory hormones essential to the spontaneous reversal of hypoglycemia (11–13). A plasma concentration of $\leq$3.9 mmol/L (70 mg/dL) can be used as the threshold value for identifying and treating hypoglycemia in children with diabetes because of the potential for glucose levels to drop further. On the other hand, in clinical practice, the glucose value of $<$3.6 mmol/L (65 mg/dL) has been most often accepted as a level for defining hypoglycemia.

Severe hypoglycemia

In the adult population, severe hypoglycemia is defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions (13). In childhood, this definition is problematic as most young children require assistance to correct even mild hypoglycemia. As a result, in the pediatric population, severe hypoglycemia is generally defined as an event associated with severe neuroglycopenia usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose) (14).

Mild/moderate hypoglycemia

There is no clinically important reason to distinguish between mild and moderate hypoglycemia, and younger children will almost always need to be treated by a parent or caregiver. For this reason, mild and moderate hypoglycemia are considered together.

Symptomatic hypoglycemia occurs when the child or parent is aware of, responds to, and treats the hypoglycemia orally after documenting a blood glucose level of $\leq$3.9 mmol/L (70 mg/dL).

Asymptomatic hypoglycemia applies when the child is not symptomatic with hypoglycemia but the blood glucose is documented to be ≤3.9 mmol/L (70 mg/dL). It is important to consider asymptomatic hypoglycemia, especially if ≤3.6 mmol/L (65 mg/dL), in order to recognize the frequency of hypoglycemia unawareness or glucose values that place an individual at risk for hypoglycemia unawareness.

Incidence

The incidence of moderate or mild hypoglycemia is unknown. Such events occur frequently among patients treated with insulin and are quite often unrecognized or underreported. Severe hypoglycemia is more likely to be recognized. Variations in definitions, sample sizes, and retrospective surveys have made comparisons between studies difficult.

Among adolescents participating in the Diabetes Control and Complications Trial (DCCT), the incidence of hypoglycemia requiring treatment assistance was 86/100 patient-years in intensively treated vs. 28/100 patient-years in those conventionally treated (15). The incidence of coma or seizure in these adolescents was 27/100 patient-years and 10/100 patient-years, respectively.

Several studies have examined the incidence rates of severe hypoglycemia in children during post-DCCT era. Few studies used a prospective design or were population-based. The incidence of severe hypoglycemia of 19/100 patient-years was reported from a large cohort of children with type 1 diabetes aged 0–19 yr followed by the Barbara Davis Center for Childhood Diabetes, Denver, CO, USA (16).

More recently, there is emerging evidence that rates of severe hypoglycemia may be declining. Data from the T1D Exchange, a registry of >25 000 individuals with type 1 diabetes at 67 centers in the USA (17), reported a 12-month frequency of 6.2% of one or more severe hypoglycemia events with seizure or loss of consciousness in their 2 to 26-yr-old cohort. This compares to a prevalence of severe hypoglycemia of 27% over a 4 yr period in the earlier Denver cohort (16).

O'Connell et al. (7) recently reported one of the largest studies monitoring the epidemiology of severe hypoglycemia in children with type 1 diabetes in Australia. The rate of severe hypoglycemia per 100 patient-years peaked at 17.3 in 2001 and then declined from 2004 to a nadir of 5.8 in 2006. The reduction in the hypoglycemia rate may have resulted from changes in clinical practice including new insulin regimens, more intensive glucose monitoring, improved management guidelines, but this remains speculative. In contrast to previous studies from the same center (18), in this cohort, an A1C <7% was not significantly associated with higher risk of severe hypoglycemia, compared with the reference group of A1C 8–9%, which was the average level in this cohort across the decade. Children with duration of diabetes >1 yr had a significantly higher risk than those with duration of diabetes <1 yr. In adolescents, pump therapy was associated with a reduced incidence of severe hypoglycemia.

Signs and symptoms

Hypoglycemia is often accompanied by signs and symptoms of autonomic (adrenergic) activation and/or neurological dysfunction from glucose deprivation in the brain (neuroglycopenia) (19), as shown in Table 1. As the blood glucose falls, the initial symptoms result from activation of the autonomic nervous system and include shakiness, weakness, hunger, and sweating. These symptoms occur at a blood glucose level of approximately 3.2–3.6 mmol/L (58–65 mg/dL) in children without diabetes, which is higher than in adults (11). A third group of symptoms including behavioral changes such as tantrums, may be described in younger children. Chronic hyperglycemia and poor glycemic control can result in an adaptive shift of the threshold of onset for these hypoglycemic symptoms to a higher glucose level, which at times falls in the euglycemic range (20). Neuroglycopenic symptoms result from brain glucose deprivation and include headache, difficulty concentrating, blurred vision, difficulty hearing, slurred speech, and confusion. Behavioral changes such as irritability, agitation, quietness, stubbornness, and tantrums may be the prominent symptom particularly for the preschool child, and may result from a combination of neuroglycopenic and autonomic responses (21).

In this younger age group, observed signs are more important, and at all ages there is a difference between reported and observed symptoms or signs. The dominant symptoms of hypoglycemia tend to differ depending on age, with neuroglycopenia more common than autonomic symptoms in the young (22).

Physiological responses in children and adolescents

It is now well recognized that although many physiological responses are similar across the age groups, there can be significant developmental and age-related differences in children and adolescents. The DCCT demonstrated a higher rate of severe hypoglycemic events in the adolescent subgroup compared with the adult cohort, 0.9 vs. 0.6 events requiring assistance per patient per year (15). This occurred in both adolescent and adult intensive and conventional therapy groups despite adolescents having poorer glycemic control with A1C levels approximately 1% higher. This difference in glycemic control at the time was associated with lower, not higher, rates of hypoglycemia.

Table 1. Hypoglycemia signs and symptoms

Autonomic signs and symptoms
Shakiness
Sweatiness
Trembling
Palpitations
Pallor
Neuroglycopenic signs and symptoms
Poor concentration
Blurred or double vision
Disturbed color vision
Difficulty hearing
Slurred speech
Poor judgment and confusion
Problems with short-term memory
Dizziness and unsteady gait
Loss of consciousness
Seizure
Death
Behavioral signs and symptoms
Irritability
Erratic behavior
Agitation
Nightmares
Inconsolable crying
Non-specific symptoms
Hunger
Headache
Nausea
Tiredness

There are a number of physiologic and behavioral mechanisms that contribute to this difference. Firstly, there are behavioral factors such as variable adherence that have been clearly associated with poor glycemic control in the adolescents (23). Secondly, during puberty, adolescents with or without type 1 diabetes are more insulin resistant than adults (24). Adolescents also have quantitative differences in counterregulatory hormone responses. During hypoglycemia, adolescents with or without diabetes release catecholamines, cortisol, and growth hormone at a higher glucose level than adults (11). There is some evidence that neuroglycopenia may develop at a higher glucose level in youth, suggesting a greater susceptibility to hypoglycemia in the young (11, 20).

To date, nearly all studies have been conducted in adolescents and as a result less is known about responses in preadolescents, whether younger children demonstrate a similar or different effect is unknown primarily as a result of the difficulty of studying this age group. The susceptibility of the brain to the adverse effects of severe hypoglycemia may differ with age and neurodevelopmental stage.

Treatment

Goal

The goal of hypoglycemia treatment is to restore the blood glucose level to euglycemia or to 5.6 mmol/L (100 mg/dL).

Severe hypoglycemia

In the event of severe hypoglycemia, urgent treatment is required. Severe hypoglycemia with loss of consciousness and/or convulsions when it occurs out of the hospital environment is most safely and rapidly reversed by injection of glucagon, 0.5 mg for age <12 yr, 1.0 mg for ages >12 yr, or 10–30 mcg/kg body weight (25). Glucagon is given intramuscularly or subcutaneously. Current available preparations require glucagon reconstitution with sterile water and therefore parents and caregivers require instruction on how to prepare and administer glucagon with frequent reminder education.

In a hospital setting, intravenous glucose or glucagon may be given. Intravenous glucose should be administered by trained personnel over several minutes to reverse hypoglycemia. The recommended dose is glucose 10–30%, for a total of 200–500 mg/kg of glucose (glucose 10% is 100 mg/mL). Rapid administration, or excessive concentration (i.e., glucose 50%) may result in an excessive rate of osmotic change and risk of cerebral edema.

When glucagon is not available, a common practice is to administer a rapid-acting source of glucose such as glucose gel or honey into the buccal pouch; however, the efficacy of this practice is anecdotal and there is no scientific evidence for absorption of the glucose from the buccal mucosa. In one study in adults, there was no buccal absorption of glucose (26). In many developing countries neither glucagon nor glucose gel may be available; often a powder form (glucose D 25 g) of glucose is used.

In the recovery phase after treatment of severe hypoglycemia, close observation and glucose monitoring is essential. Vomiting is common and recurrent hypoglycemia may occur. In the event of recurrent hypoglycemia, the child will require additional oral carbohydrates and/or intravenous infusion of glucose at a suggested dose of glucose 10%, 2–5 mg/kg/min (1.2–3.0 mL/kg/h). In the outpatient setting, the predisposing events that led to the severe event should be evaluated to allow for prevention of future events. Caregivers need to be aware that following a severe hypoglycemic event the child will be at significantly higher risk of a future event and alterations to therapy may be appropriate.

Mild/moderate hypoglycemia

If the blood glucose is 3.3–3.9 mmol/L (60–70 mg/dL) and the child does not experience uncomfortable symptoms, immediate intake of carbohydrates will raise the blood glucose sufficiently. In adults, 20 g of carbohydrate in the form of glucose tablets raised glucose levels by approximately 2.5–3.6 mmol/L

(45–65 mg/dL) (27–29). This has been extrapolated to 0.3 g/kg in children or approximately 9 g of glucose for a 30 kg child and 15 g for a 50 kg child. It is important, however, to remember that the amount of carbohydrate required will depend on the size of the child, type of insulin therapy, active insulin on board, the timing and intensity of antecedent exercise as well as other factors (27, 30).

The type of carbohydrate is also important as 40 g of carbohydrate in the form of juice was needed to give approximately the same rise as 20 g in the form of glucose tablets (27). Sucrose likewise requires a greater amount to provide the same increase in blood glucose compared to glucose (28). Milk containing 20 g of carbohydrate gave only a rise of approximately 1 mmol/L (18 mg/dL). Chocolate, milk, and other foods containing fat will cause the glucose to be absorbed more slowly and should be avoided as the initial treatment of hypoglycemia (27).

After treatment, retest blood glucose after 10–15 min. If there is no response or an inadequate response, repeat oral intake as above. For initially lower glucose values, as symptoms improve or euglycemia is restored, complex carbohydrates in the form of fruit, bread, cereal, or milk, may be ingested to prevent recurrence of hypoglycemia.

Risk factors

Ultimately, it is excessive insulin or excessive insulin action that causes hypoglycemia in the child with type 1 diabetes. A range of clinical factors associated with the occurrence of severe hypoglycemia in children and adolescents are shown in Table 2. Hypoglycemia occurs more frequently in younger children due to unpredictable food consumption, physical activity, and increased sensitivity to insulin, although recent data from the Type 1 Diabetes Exchange and the Diabetes Patienten Verlaufsdokumentation (DPV) registry did not find increased rates of severe hypoglycemia in those <6 yr of age with A1C <7.5% compared to those with A1C 7.5–8.5% or >8.5% (31). The relation between severe hypoglycemia and lower A1C has been extensively explored, especially in children. Alcohol suppresses gluconeogenesis and glycogenolysis and may induce hypoglycemia unawareness. In addition, alcohol ingestion acutely improves insulin sensitivity. In combination with exercise, alcohol consumption can lead to severe hypoglycemia, which may occur up to 10–12 h after exercise or alcohol ingestion.

Education about the risk factors for hypoglycemia should be given to patients and families to alert them to times and situations when increased glucose monitoring is required and when treatment regimens needs to be changed.

Table 2. Clinical factors associated with hypoglycemia

Precipitants
Excess insulin
Less food consumption
Exercise
Sleep
Alcohol ingestion
Risk factors
Younger age, <6 yr
Lower A1C levels
Hypoglycemia unawareness
Previous severe hypoglycemia
Longer duration of diabetes

The majority of children with type 1 diabetes who experience severe hypoglycemia have isolated events, however a small number suffer recurrent episodes. When hypoglycemia is recurrent, it is important to exclude coexisting autoimmune disorders such as thyroid disease, Addison's disease, and celiac disease. Impaired hypoglycemia awareness and hypoglycemia-associated autonomic failure (HAAF) (12) may develop in children and adolescents and should be considered in patients who experience recurrent hypoglycemia. Undisclosed self-administration of insulin is a recognized cause of repeated and unexplained severe hypoglycemia and should be considered as a sign of psychological distress (32).

The comorbidities of celiac disease, present in 4–10% of children with type 1 diabetes, and Addison's disease, present much less commonly (33), may also increase the risk for hypoglycemia (34, 35). The introduction of a gluten-free diet and appropriate treatment of Addison's disease may reduce the frequency of hypoglycemia (36, 37).

Exercise

Physical activity is an essential component of childhood play and sport, and offers physiological and psychological benefits for all age groups with type 1 diabetes. Unfortunately, exercise can increase the risk of hypoglycemia through various mechanisms. These are not well understood and include increased insulin absorption, increased insulin sensitivity, depletion of glucose stores, and exercise-induced counterregulatory hormone deficits. Hypoglycemic risk may be increased both at the time of exercise and also in the 24 h following activity (38).

Evidence suggests that blood glucose levels <6.7–8.3 mmol/L (120–150 mg/dL), prior to sustained aerobic exercise (75 min) in the afternoon, is associated with a high probability of hypoglycemia within 60–75 min (39). Discontinuing continuous insulin infusion therapy for up to 2 h during exercise may help to prevent exercise-related hypoglycemia (39).

During prolonged exercise, 15 g of carbohydrate will raise the blood glucose by approximately 1 mmol/L (18 mg/dL) for a 50 kg child (27), therefore, 30–45 g of oral carbohydrate may be required to prevent hypoglycemia for a 30 kg child and 50–75 g for 50 kg child. Additional carbohydrate will usually be required if exercise occurs at the peak of insulin action (39–41). Likewise carbohydrate requirement will be lower if the premeal bolus prior to the exercise is lowered or if the exercise occurs several hours after the last meal bolus has been given. In many individuals, a lowering of the insulin dose after intense exercise should be considered to prevent nocturnal hypoglycemia.

The management of hypoglycemia during and after exercise adds to the complexity of the diabetes treatment regimen. Recent research has enhanced our comprehension of the underlying mechanisms responsible for hypoglycemia after activity. A number of excellent reviews and treatment guidelines for physical activity in children with type 1 diabetes have been published recently (41, 42) and are updated in this edition of the ISPAD guidelines.

Nocturnal hypoglycemia

Nocturnal hypoglycemia causes significant anxiety and morbidity for the families of children with type 1 diabetes (43). This is in part because our understanding of nocturnal glucose homeostasis and etiology of nocturnal hypoglycemia is very limited. The counterregulatory responses to hypoglycemia are attenuated during sleep (44, 45) and patients with type 1 diabetes are much less likely to be awakened by hypoglycemia than individuals without diabetes (44). Recent studies have reported an alarmingly high prevalence of prolonged, nocturnal hypoglycemia, up to 40% on any given night in children and adolescents with type 1 diabetes (46–48). Almost half of these episodes are undetected by carers or individuals with diabetes (46, 49). A recent report from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring (JDRF-CGM) study group described frequent prolonged nocturnal hypoglycemia on 8.5% of nights in both children and adults but more prolonged in children (3). Such prolonged hypoglycemia may result in seizure and occasionally death. The same report reported that the median time spent in a hypoglycemia range approached 60 min/ d. Such frequent hypoglycemia is likely to contribute to counterregulatory deficit and increased risk of further hypoglycemia.

Nocturnal hypoglycemia should be suspected if prebreakfast blood glucose is low, and/or confusional states, nightmares, or seizures occur during the night, or if impaired thinking, lethargy, altered mood, or headaches are experienced on waking (14). It is recommended that parents and patients monitor overnight glucose levels on a regular basis, particularly if there is an additional risk factor that may predispose to nocturnal hypoglycemia.

Studies of overnight hypoglycemia in children have been unable to identify a glucose value that reliably predicts a low risk of hypoglycemia. In a study using CGM to detect nocturnal hypoglycemia, there was a twofold increase, 45 vs. 22% in the incidence of hypoglycemia with a bedtime glucose $\leq$5.5 mmol/L (100 mg/dL) (48). Perhaps of greater value is the fasting glucose concentration, with values $<$7 mmol/L (126 mg/dL) suggesting that hypoglycemia has occurred overnight (46, 47).

Studies of dietary intervention to prevent nocturnal hypoglycemia in adults with type 1 diabetes have found that a bedtime snack containing carbohydrate and protein offers some protection from nocturnal hypoglycemia, compared with carbohydrates alone (50). The beneficial effects of uncooked cornstarch have been variable in children (51, 52).

The occurrence of severe nocturnal hypoglycemia has been reduced by the use of insulin pump therapy (53). This effect is likely to result from the ability to finely adjust basal insulin delivery with the use of pump therapy. In a study of 23 children and adolescents in a randomized, crossover study comparing multiple daily injections to pump therapy, pump therapy was associated with a smaller area under the curve for nocturnal hypoglycemia (54). This same study also utilized CGM, which has been helpful in identifying the frequency and duration of nocturnal hypoglycemia (54, 55).

Brain dysfunction and neurological sequelae of hypoglycemia

The impact of type 1 diabetes on the developing brain remains controversial. Early onset of diabetes, before the age of 6 yr, has long been identified as one of the strongest risk factors associated with cognitive dysfunction, ranging from poorer performance on general intellectual testing (56) to specific deficits with visuospatial tasks, attention, and psychomotor efficiency. The effect of early-onset diabetes however, is confounded by the impact of recurrent severe hypoglycemia. Repeated severe hypoglycemia has been reported to adversely affect various cognitive domains, in particular long-term memory, attention, and verbal IQ, although results have been inconsistent across studies (57, 58). Moreover, a considerable limitation of many of these studies is the retrospective collection of hypoglycemia history.

A recent study reported the neurocognitive outcomes in 84 children with early-onset diagnosis of type 1 diabetes, defined as type 1 diabetes onset before 6 yr

of age (59). In an earlier study (58) by the same group, subjects with a history of early severe hypoglycemia were compared to those with a history of late severe hypoglycemia and also compared those that had experienced severe hypoglycemia to subjects with no history of seizures. Surprisingly, there were no group differences revealed on intellectual, memory, or behavioral measures. Furthermore, there was no evidence that episodes of seizure or coma, even those occurring in early childhood, resulted in broad cognitive dysfunction nor was there evidence of specific memory difficulties at the time of testing. In a follow-up study evaluating a subset of these children at the mean age of 19.3 yr, there was no difference in general intellectual ability, memory, and emotional difficulties in this cohort of young adults with early-onset type 1 diabetes compared to control subjects and no deterioration over time (59). There were however, findings to suggest subtle changes leading to poorer performance on complex tasks of executive function. Larger prospective studies are required to explore this issue further.

Despite these reassuring findings on cognitive function, brain abnormalities have been associated with severe hypoglycemia in other studies. Repeated episodes of hypoglycemic seizures in young children may cause structural changes, as evidenced by the prevalence of mesial temporal sclerosis in 16% of a cohort of children with early-onset type 1 diabetes (60). In a large sample of young patients with type 1 diabetes using voxel-based morphometry, regional brain volume differences were associated with both a history of hypoglycemia and hyperglycemia (61). A recent report from the DirecNet group reported significantly reduced axial diffusivity, a measure of white matter structure, in a large cohort of children with type 1 diabetes compared to aged-matched control subjects (62) .

The role of early-onset diabetes and chronic hyperglycemia in the decrease of cognitive functioning in very young children has also received increased attention (63, 64). There is accumulating evidence that hyperglycemia in the young child may be an important factor resulting in abnormalities in brain structure and function (65–67).

Impaired hypoglycemia awareness

Impaired hypoglycemia awareness can be defined as the inability to perceive the onset of hypoglycemia, and in adults is associated with a resetting of the glycemic thresholds for the generation of symptoms, activation of counterregulatory hormonal secretion, and of cognitive impairment to lower levels of blood glucose. Typically, autonomic symptoms are lost before neuroglycopenic symptoms, which then predominate.

The threshold for autonomic symptoms may be affected by antecedent hypoglycemia. This may be accompanied by reduced intensity of symptoms following the hypoglycemic event, leading to impaired hypoglycemia awareness during this time (68). Moderate exercise one day may also result in a decrease in symptoms of hypoglycemia and decrease hormonal response the following day (69). The blood glucose threshold for cognitive dysfunction may then be triggered before autonomic activation. The blood glucose threshold for neuroglycopenia does not appear to vary as much with the level of glucose control nor with antecedent hypoglycemia (11, 70, 71). The blood glucose threshold for activation of autonomic symptoms is related to activation of counterregulatory hormones and has been shown to be higher in children than in adults and to vary directly with the level of blood glucose control, with a higher A1C associated with a higher blood glucose threshold (11, 72). This is important given that impaired hypoglycemia awareness is a major risk factor for severe hypoglycemia, accounting for 36% of the episodes of severe hypoglycemia that occurred in the DCCT while adult subjects were awake (73).

It is unclear whether an identical syndrome of impaired awareness of hypoglycemia develops in children and adolescents before puberty. In a series of 656 children with type 1 diabetes (74), impaired hypoglycemia awareness was reported in 30% of the population, which is consistent with adult studies with type 1 diabetes. In this study, impaired hypoglycemia awareness in children was associated with a threefold likelihood of having had a severe hypoglycemic event (coma or convulsion) in the preceding 12 months. An episode of antecedent hypoglycemia may reduce the symptomatic and autonomic response to subsequent hypoglycemia which in turn further increases the risk of subsequent severe hypoglycemia.

There is evidence that loss of hypoglycemia awareness can be reversed by avoiding hypoglycemia for 2–3 wk (75), but this may be very difficult to accomplish in young children. It is possible that the pathogenesis of impaired hypoglycemia awareness and the associated syndrome of counterregulatory hormone deficiency, is in young people similar to that described in adults, as attempts to restore symptomatic responses by strict avoidance of hypoglycemia with the use of real-time CGM, at least in preliminary studies, appear to be successful (76).

Current therapies

Continuous glucose monitoring systems

Data from large trials including the JDRF-CGM (3) and sensor-augmented pump therapy for A1C

Table 3. Evaluation and management of hypoglycemic events

Potential cause	Factors	Management
Insulin action profile	What was the timing and duration of insulin administration? What is the peak insulin action?	Consider rapid-acting and long-acting insulin analogs for multiple daily injections for more physiological insulin delivery Consider insulin pump therapy (89) Consider dual-wave insulin bolus with low glycemic meals (90) Consider sensor-augmented pump therapy with automated insulin suspension, which has been shown to duration and severity of severe hypoglycemia (80)
Recent food intake	What was the timing and amount of carbohydrates? What was the peak glucose effect of recent food intake?	Review determination of carbohydrates Review fat and protein content of meals (91) Adjust food intake so that glycemic peaks are more closely matched to insulin action peaks Daytime and bedtime snacks may need to be added, especially in younger children, or if intermediate-acting insulin is used
Recent physical activity	What was the timing, duration, and intensity of recent activity?	Pre-exercise and postexercise snacks (15–30 g) may be required Suspension of pump basal rate during exercise (30) If exercise occurs at peak insulin action, additional carbohydrates may be required
Recent hypoglycemia	Has there been recent recurrent, severe hypoglycemia? This may be associated with reduced counterregulatory response	Glucose targets may need to be adjusted upward in patients with recurrent hypoglycemia and/or hypoglycemia unawareness (75, 76)
Lack of hypoglycemic symptoms or hypoglycemia unawareness	At what glucose level do you start to recognize hypoglycemia? What types of symptoms do you have?	Consider increased monitoring of blood glucose levels Consider the use of real-time continuous glucose monitoring together with adjustment of glucose targets to avoid hypoglycemia and potentially reverse hypoglycemia unawareness (75, 76)
Prolonged, nocturnal hypoglycemia	What are the glucose values overnight? Blood glucose monitoring, in particular overnight, is important in detecting hypoglycemia and preventing serious and severe episodes	Consider increased overnight monitoring of blood glucose levels Consider retrospective continuous glucose monitoring to evaluate for patterns of asymptomatic nocturnal hypoglycemia Consider real-time continuous glucose monitoring

reduction 3 (STAR3) (77), have failed to show a reduction in hypoglycemia. Despite the use of CGM, there was still a high incidence of prolonged nocturnal hypoglycemia. There is evidence that patients sleep through 71% of alarms (78) and that adolescents with type 1 diabetes have a high acoustic arousal threshold from sleep (79). During the overnight period, the presence of CGM alone is unlikely to prevent severe nocturnal hypoglycemia.

Sensor-augmented pump therapy with low glucose insulin suspension

The advent of sensor-augmented pump therapy with low glucose insulin suspension allowing insulin to be automatically suspended for up to 2 h when sensor glucose falls below a preset threshold, has the potential to reduce the duration of hypoglycemia, in particular at night, and is a significant development toward full automation of insulin delivery in patients with type 1 diabetes.

A recent randomized controlled trial (80) has been the first to show a reduction in severe hypoglycemia, defined as hypoglycemic coma or convulsion, with the use of sensor-augmented pump therapy with low glucose insulin suspension. This study recruited 95 patients, aged between 4 to 50 yr, all with impaired awareness of hypoglycemia. Subjects were randomized to either insulin pump therapy only or sensor-augmented pump with automated insulin suspension

at a preset threshold of 3.3 mmol/L (60 mg/dL). At the end of the 6-month study, there were six severe hypoglycemia events in the pump-only group and no events in the automated insulin suspension group. There was also less sensor-detected time spend <3.9 mmol/L (70 mg/dL) during the day and night periods. This was achieved with no deterioration in A1C. This trial selectively recruited high risk patients with impaired awareness of hypoglycemia and demonstrated a significant reduction in severe hypoglycemia.

Sensor-augmented pump therapy at this stage may be difficult to sustain indefinitely, particularly in children and adolescents. This in part is related to calibration alarms, sensor signal alarms, accuracy, and skin irritation secondary to sensors and adhesives. Despite this qualification these systems offer potential for improved glycemic control without increased hypoglycemia.

Predictive low glucose insulin suspend algorithms based on continuous glucose measurements have been developed and tested in a number of clinical trials (81, 82). These algorithms are designed to suspend insulin delivery prior to hypoglycemia occurring and in contrast to fixed suspend algorithms, also have the ability to resume insulin delivery based upon the rate of change of sensor values. In a home study of 45 participants using a predictive low glucose suspend system over 6 wk, there were fewer nights with at least one sensor value ≤60 mg/dL on intervention nights (21%) compared to control nights (33%), $p < 0.001$) (82).

Closed-loop insulin delivery systems

Automated insulin delivery, with continuous glucose sensing and insulin delivery without patient intervention, offers the potential to circumvent the significant glycemic excursions associated with conventional therapy. Early reports from clinical studies evaluating closed-loop prototypes suggest improved glucose control and a reduced risk of hypoglycemia (83–86). In general, these systems utilize input from a CGM system, an insulin pump for insulin delivery and a control algorithm, which can be located on a bedside computer, a smartphone or potentially, be integrated into the insulin pump and sensor system. A recent study of overnight closed-loop control in children with type 1 diabetes over multiple nights at diabetes camp, demonstrated an increased percent time spent in range (70–150 mg/dL) during the overnight period for closed-loop nights (73%) compared to sensor-augmented pump nights (52%), as well as reduction in time spent in the hypoglycemic range (87). The move to outpatient, ambulatory studies testing both day and night glucose control requires a robust system demonstrating not only efficacy but also with appropriate safety modules such as limitations on maximum insulin delivered, fault detection algorithms for individual system components and flawless communication between devices (88). Perhaps most important is development of the user–device interface, given that with current available sensors and insulin, there will be some degree of patient input required for closed-loop operation (Table 3).

Conflicts of interest

The authors have declared no conflicts of interest.

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