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ISPAD Clinical Practice Consensus Guidelines 2018: Assessment and management of hypoglycemia in children and adolescents with diabetes

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1 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Hypoglycemia is the commonest acute complication of type 1 diabetes. It may also occur in type 2 diabetes when treatment includes insulin or sulfonylurea therapy (B).

- Hypoglycemia presents a major physiological and psychological barrier to achieving optimal glycemic control and may result in significant emotional morbidity for patients and their caregivers (B).[1]

- Monitoring hypoglycemia is a key component of diabetes care as is education about its causes, prevention, and treatment (A). Parents and caregivers need to be reassured that good glycemic control can be achieved without severe hypoglycemic events (B).

- Hypoglycemia is best defined as a fall in 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 (E).

- The aim of diabetes treatment should be to maintain blood glucose level >3.9 mmol/L (70 mg/dL) while striving to achieve the best possible glycemic control without the occurrence of severe hypoglycemia (A).

- In clinical practice, a glucose value ≤3.9 mmol/L (70 mg/dL) is used as the clinical alert or threshold value for initiating treatment for hypoglycemia in diabetes because of the potential for glucose to fall further (E).

- Severe hypoglycemia is defined as an event with severe cognitive impairment (including coma and convulsions) requiring external assistance by another person to actively administer carbohydrates, glucagon, or take other corrective actions. Severe hypoglycemic coma is defined as a subgroup of severe hypoglycemia, as an event associated with a seizure or loss of consciousness (E).

- The incidence of severe hypoglycemic coma has fallen over the last 2 decades with a current rate of 3 to 7 per 100 patient years across international registries. Although lower hemoglobin A1c (HbA1c) was a risk factor for severe hypoglycemia, this association is no longer observed with contemporary therapy in recent surveys (B).[2]

- Young children remain at risk of severe hypoglycemia due to their reduced ability to communicate their need (B).[3]

- Symptoms of hypoglycemia in the young result from *adrenergic activation* (eg, shakiness, pounding heart, sweatiness) and *neuroglycopenia* (eg, headache, drowsiness, difficulty in concentrating). In young children, *behavioral* changes such as irritability, agitation, quietness, and tantrums may be prominent (B).

- 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 (ie, occur at a higher blood glucose level) or repeated hypoglycemia (ie, occur at a lower blood glucose level) (B).

- In type 1 diabetes, hypoglycemia results from imperfect insulin replacement. The risk of hypoglycemia is further increased by compromised counterregulatory hormone defects, including loss of glucagon response to hypoglycemia that 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 (B).

- Hypoglycemia with exercise may occur at the time of activity or may be delayed (7-11 hours later) (B). Caregivers 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 (B); because of this, glucose levels are recommended to be monitored overnight particularly if there is an additional risk factor that may predispose to nocturnal hypoglycemia (E). Increased availability of continuous glucose monitors (CGMs) may be especially useful for this (E).

- Impaired hypoglycemia awareness can occur 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).

1.1 | Treatment of hypoglycemia

- 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 (1 mg for children >25 kg and 0.5 mg for children <25 kg).

- 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). Intranasal glucagon is a promising alternative to IM glucagon and would provide an unmet need for an easily administered glucagon preparation.

- Milder hypoglycemic events should be treated with oral glucose (10-15 g glucose). Depending on the circumstances, rapid acting glucose should be followed by additional carbohydrates to prevent recurrence of hypoglycemia (B).

- Treatment of hypoglycemia should increase the blood glucose by nearly 3 to 4 mmol/L (54-70 mg/dL). This can be accomplished by giving glucose tablets or sweetened fluids. 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) (C).

- Following initial hypoglycemia treatment, blood glucose should be retested in 10 to 15 minutes. If there is no response or an inadequate response, repeat hypoglycemia treatment. Retest the blood glucose in another 10 to 15 minutes to confirm that target glucose (100 mg/dL) has been reached (E).

1.2 | Prevention of hypoglycemia

- Hypoglycemia should be prevented because its occurrence is frequently predictable, and it is often associated with significant psychosocial dysfunction; more importantly, it can rarely lead to permanent long-term sequelae and may be potentially life threatening.

- Diabetes education is critical to preventing hypoglycemia (A).[4]

- 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).

- Equipment for blood glucose measurement must be available to all children with diabetes for immediate confirmation and safe management of hypoglycemia (E).

- Blood glucose monitoring should be performed prior to exercise, and extra carbohydrates may be consumed based on the blood glucose level and the expected intensity and duration of exercise (B).

- Particular attention should be given to training children, parents, school teachers, and other caregivers to recognize the early warning signs of hypoglycemia and treat low blood glucose immediately and appropriately (E).

- 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 (ie, impaired hypoglycemia awareness) (E).

- In patients and families with significant fear of hypoglycemia, interventions through educational and/or behavioral strategies may be considered although evidence in children is limited (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).

- Blood glucose goals may need to be adjusted upwards in patients with recurrent hypoglycemia and/or impaired hypoglycemia awareness (B).

- If unexplained hypoglycemia is frequent, evaluation for unrecognized celiac and Addison's disease should be considered (E).

- Currently available technologies like CGM, automated insulin suspensions (suspend on low, suspend before low) have reduced the duration of hypoglycemia (A).[5–8] Newer technologies (artificial pancreas systems) improve glucose control and reduce hypoglycemia in outpatient settings compared to conventional pump therapy (A).[9]

2 | INTRODUCTION

Hypoglycemia is a common iatrogenic complication in the management of type 1 diabetes. It interferes with activities of day-to-day

living, poses a constant danger to patients and their families and in spite of the various advancements in treatment, still continues to be a limiting factor in achieving optimal glycemic control[1] and affects quality of life.[10] Therefore, it is vital to address this important clinical problem during diabetes education and management. The last 2 decades have experienced a paradigm shift in the management of type 1 diabetes through the availability of improved insulin analogues, insulin pump therapy, and advent of CGM with algorithms incorporated in sensor-augmented pump therapy to reduce and prevent hypoglycemia. Despite these advances, only a quarter of children and adolescents achieve the internationally established recommended HbA1c target of <7.5% (58 mmol/mol),[11,12] although there is increasing evidence to suggest that the rates of severe hypoglycemia have declined in recent years.[13–16]

Minimizing hypoglycemia in diabetes is an important objective of the International Hypoglycemia Study Group (IHSG) and this can be achieved by acknowledging the problem, evaluating the risk factors, and applying the principles of intensive glycemic management.[17] The Study Group also formed recommendations for which levels of hypoglycemia should be reported[18] and hence, it would be meaningful to have a common platform of definitions and objectives to harmonize with the IHSG and other groups to create proposed hypoglycemia levels. The recently published brief summary[19] and this ISPAD guideline aim to do so.

3 | DEFINITION AND INCIDENCE

3.1 | Definition

Hypoglycemic events include all episodes of a plasma glucose concentration low enough to cause symptoms and/or signs, including impaired brain functioning and expose the individual to potential harm. However, the glycemic thresholds for hypoglycemia symptoms shift to lower plasma glucose concentrations in individuals with well-controlled diabetes[20] and to higher plasma glucose concentrations in those with poorly controlled diabetes.[20,21] Hence, it is difficult to assign a numerical value to hypoglycemia. Nonetheless, it is important to identify and record a level of hypoglycemia that needs to be avoided because of its immediate and long-term danger to the individual. The definitions as below are intended to guide clinical care and reporting and are based on glucose values detected by self-monitoring of blood glucose, CGM (for at least 20 minutes), or a laboratory measurement of plasma glucose.[18]

1. *Clinical hypoglycemia alert*: A glucose value of ≤3.9 mmol/L (70 mg/dL) is an alert value that requires attention to prevent hypoglycemia. The alert 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.

2. *Clinically important or serious hypoglycemia:* A glucose value of <3.0 mmoL/L (54 mg/dL) indicates serious, clinically important hypoglycemia. These low levels may lead to defective hormonal counterregulation[22] and impaired awareness of hypoglycemia. Neurogenic symptoms and cognitive dysfunction occur below this

level[23,24] with subsequent increased risk of severe hypoglycemia. This level should be recorded in routine clinical care and reported in audit and in clinical trials of interventions directed toward reducing hypoglycemia as recommended by the IHSG.[18]

3. *Severe hypoglycemia* is defined as an event associated with severe cognitive impairment (including coma and convulsions) requiring external assistance by another person to actively administer carbohydrates, glucagon, or take other corrective actions. This aligns with the definition of severe hypoglycemia in adults in accordance with the American Diabetes Association Guidelines.[25] This will also enable complete recording of events vs underestimation of severe hypoglycemia frequency in children if defined by coma or convulsions only. This expanded definition has also been used in children in previous observational studies on severe hypoglycemia.[14,26,27] However, as young children require assistance to correct even mild hypoglycemia, the event requires an assessment by the caregiver and clinician as to the presence or not of hypoglycemia-induced cognitive dysfunction. A subgroup of severe hypoglycemia is severe *hypoglycemic coma*, which is described as a severe hypoglycemic event resulting in coma or convulsion requiring parenteral therapy. These events should be recorded independently as these events are unequivocal and significant in outcome.

3.2 | Incidence

The exact incidence of hypoglycemia is difficult to ascertain, but mild hypoglycemia is common. Asymptomatic events are more likely to be unrecognized and underreported, while symptomatic hypoglycemia occurs on an average of 2 episodes per week with multiple such episodes in the lifetime. In contrast, the recall of severe hypoglycemia is more likely to be robust although variations in definitions, sample sizes, and retrospective surveys have made comparisons between studies difficult.

Although there was a significant improvement in glycemic control and reduction of diabetes-related complications in patients on intensive glycemic therapy compared to conventional management in the Diabetes Control and Complications Trial (DCCT), there was a 3-fold increased risk of severe hypoglycemia events in patients who were randomized to the intensive management arm of the study.[28] The incidence of hypoglycemia requiring treatment assistance was 61 per 100 patient years in intensively treated vs 19 per 100 patient years in those conventionally treated with an incidence of coma and seizure of 16 per 100 patient years and 5 per 100 patient years, respectively. Similar high rates were reported in observational cohorts. The incidence of severe hypoglycemia was 16.6 per 100 patient years and 19 per 100 patient years in large pediatric cohorts in Western Australia[29] and Colorado.[30] Historically, these high rates of severe hypoglycemia were associated with lower glycated hemoglobin,[28,31,32] although this relationship has weakened in recent years as observed in large longitudinal cohort studies with a reduction in the rates of severe hypoglycemia.[14,33] A 12% annual rate of decline of severe hypoglycemia from 2000 to 2009 was observed in a population-based cohort of Western Australia,[15] while severe hypoglycemia rate halved nationwide in a Danish cohort between 2008 and 2013,[13] with no

association of severe hypoglycemia with glycemic control.[13,15] A similar decline was also noted in youth aged <20 years in Germany and Austria, between 1995 and 2012 despite simultaneous improvements in glycemic control. The mean rates of severe hypoglycemia requiring treatment assistance declined from 42 per 100 patient years in 1995 to 18 per 100 patient years in 2012, and mean rates of hypoglycemia coma (unconsciousness or convulsions) declined from 14 per 100 patient years in 1995 to 2 per 100 patient years in 2012.[14] Although younger age and lower HbA1c were risk factors for severe hypoglycemia, recent data from the type 1 diabetes exchange and the Diabetes-patient-documentation (DPV) registry did not find increased rates of severe hypoglycemia in those <6 years of age with HbA1c <7.5% (58.5 mmol/mol) compared to those with HbA1c 7.5% to 8.5% (58.5-69.4 mmol/mol) or >8.5% (69.4 mmol/mol).[34] Similarly, no difference in risk of severe hypoglycemia was observed in children <6 years and good glycemic control in a Western Australian population cohort.[16] The former strong association of low HbA1c with severe hypoglycemia is no longer as evident and low HbA1c is not a strong predictor of severe hypoglycemia in young patients with type 1 diabetes.[33] This observation was further confirmed across international registries with a severe hypoglycemia rate per 100 patient years of 7.1, 3.3, and 6.7 in the American (Type 1 diabetes Exchange), German/Austrian (DPV), and Western Australian children's diabetes database (WACDD), respectively, with no association with glycemic control.[2] This trend was also demonstrated in the Nordic countries[35] and can be attributed to a number of factors including increased use of insulin analogues and insulin pump therapy[13,16,36] and improved hypoglycemia education.[37] These studies highlight the important observation that optimal glycemic control can be achieved without an increase in severe hypoglycemia.

Rates of severe hypoglycemia are reported from high-income countries and are anecdotally based on patient's self-reporting and physician's appropriate capture record of these events in a clinical setting and hence there is likelihood of recall bias and under reporting. This is further reflected in the high rates of 4.9 events per patient year in a 4-week prospective record of hypoglycemic events in adults studied in the global HAT study.[38] Large variations between geographical regions were reported with the highest rate in Latin America (10.8 events per patient year).

4 | MORBIDITY AND MORTALITY WITH HYPOGLYCEMIA

4.1 | Mortality

It has been known for some time that hypoglycemia can kill experimental animals and there have been many reports of deaths associated with hypoglycemia in both type 1 and type 2 diabetes. There has been debate as to whether these associations reflect causality[39] and there is only one case report that directly links hypoglycemia to death in an adult.[40] Primary brain death may occur with profound and prolonged hypoglycemia, but a more likely mechanism of death is through the induction of arrhythmias as hypoglycemia is known to be pro-arrhythmogenic.[41–43] Hypoglycemic mortality rates have been reported in cohorts of patients with diabetes. In the pre and immediate post-DCCT period up to more than a decade ago, hypoglycemia was assigned as the cause of death in 4% (5 of the 134 deaths),[44] 7% (8 of the 108 deaths),[45] and 10% (10 of the 103 deaths)[46] in population-based cohorts and international registries of childhood-onset diabetes, with most deaths in adults. In a recent report from Wales, hypoglycemia was difficult to ascertain with certainty as the cause of death, although 6 out of the 30 deaths were thought to be the result of hypoglycemia based on clinical judgment and death certification.[47] Similarly, hypoglycemia was certain in 8 and considered probable in 12 of the total 20 hypoglycemia-related deaths in a Norwegian study with 241 deaths.[48]

Hypoglycemia is also proposed to play a role in the "dead-in-bed" syndrome, which is more prevalent in patients with type 1 diabetes than in the general population. In a coroner's case series, dead-in-bed syndrome accounted for ~15% of deaths in young adult males (≤40 years) with diabetes.[49] Although the etiology is not well established, it has been postulated that it may be secondary to prolongation of QT interval due to number of factors; acute hypoglycemia[50] on the background of autonomic neuropathy[51] and possible genetic influences.[52] These changes in cardiac repolarization can lead to fatal ventricular arrhythmias and may contribute to the sudden nocturnal death of young individuals with type 1 diabetes.[53] It is likely that the more widespread use of CGM and the increased use of population-based databases will shed clearer light on the true incidence of hypoglycemic death in the future.

4.2 | Morbidity

4.2.1 | Neurological sequelae of hypoglycemia

Previous studies have consistently shown that early onset of diabetes predicts poorer cognitive function and most researchers made the assumption that hypoglycemia played a critical role in the initiation of brain dysfunction.[54] Transient cognitive dysfunction occurs with both hypoglycemia[55,56] and hyperglycemia in school-aged children with diabetes,[55] although the long-term implication of severe hypoglycemia on cognitive function seems unlikely. This is best demonstrated during the Epidemiology of Diabetes Interventions and Complications follow-up study, approximately 18 years after the DCCT. Despite relatively high rates of severe hypoglycemia, cognitive function did not decline over an extended period of time in the youngest cohort of patients.[57] Likewise, similar neurocognitive outcomes were found in a cross-sectional[58] and longitudinal follow-up study of the same population-based cohort.[59] A history of early severe hypoglycemia was reassuringly not associated with a decline in full-scale IQ scores although there may be subtle deficits in executive function and fluid intelligence.[59] Another study showed that multiple severe hypoglycemic episodes specifically affect spatial memory function, particularly when these episodes began before the age of 5 years[60] and are associated with lower Wechsler Intelligence Scale for Children (WISC) processing speed, full-scale IQ score, working memory, and perceptual reasoning.[61]

Similarly, the association of brain abnormalities with severe hypoglycemia has received significant attention, although there is increasing evidence of neurological abnormalities demonstrated even without significant hypoglycemia in young patients with type 1 diabetes.

Neuropathological data in animals suggest that severe hypoglycemia may preferentially harm neurons in the medial temporal region, including the hippocampus.[62] Neuronal apoptosis and gliosis were shown following just one episode of hypoglycemia in non-diabetic rats. Mesial temporal sclerosis was reported in 16% of children with early onset type 1 diabetes,[63] although this was seen irrespective of the history of severe hypoglycemia. Larger hippocampal volumes[64] and reduced gray and white matter volumes have been reported in children who experienced hypoglycemic seizures.[61] However, studies have shown that neurological changes are not seen only with hypoglycemia but also in patients with hyperglycemia. 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.[65] Furthermore, widespread effects on both the gray and white matter are also evident in children with early onset diabetes, whose blood glucose levels are well within the current treatment guidelines for the management of diabetes[66] advocating the need for tighter glucose control and reducing glycemic excursions.

The net contribution of childhood dysglycemia on brain development has been described by the "diathesis hypothesis."[54] This model suggests that the most neurotoxic milieu seems to be young age and/or diabetic ketoacidosis at onset, severe hypoglycemia under the age of 6 years, followed by chronic hyperglycemia in later life along with the effect of diabetic ketoacidosis, glycemic, and hormonal variation.[67] The role of early onset diabetes and chronic hyperglycemia in the decrease of cognitive functioning in very young children has received increasing attention.[68,69] There is accumulating evidence that hyperglycemia in the young child is an important factor resulting in abnormalities in brain structure and function[70–72] with both gray and white matter changes[73] on neuroimaging.

Recent studies have also shown an association of recurrent hypoglycemia with an increased risk of epilepsy later in life[74,75] and although the causative mechanisms remain largely unknown, metabolic brain adaptations to recurrent hypoglycemia have been postulated to be a cause.[76] It has also been recently recognized that hypoglycemic episodes in patients with good glycemic control are associated with increased inflammatory markers[77] and these proinflammatory changes may promote a sustained inflammatory state.[78]

4.2.2 | Psychological impact of hypoglycemia

Severe hypoglycemic episodes tend to have negative psychosocial consequences and undesirable compensatory behaviors arising from hypoglycemia.[79] Moreover, the symptoms of hypoglycemia can be distressing and embarrassing to the individual potentially compromising academic, social, and physical activities. This fear can induce anxiety and although in some cases, this anxiety can be adaptive, leading to appropriate vigilance in glucose management, in many individuals and their families, significant levels of anxiety can lead to disruptions in daily activities and suboptimal diabetes management.[80] Given the negative consequences associated with hypoglycemic episodes, especially those that are severe in nature, it is not unforeseen that individuals with type 1 diabetes and their parents are at risk for increased anxiety, poor sleep and reduced quality of life.[10,81–83] Fear of hypoglycemia, especially overnight, continues to be a major problem in the

parents of young children with type 1 diabetes.[84] This fear could lead families and/or physicians to the acceptance of high glucose levels with behaviors directed toward avoiding hypoglycemia leading to suboptimal glycemic control.[10,85–87] Behavioral interventions (cognitive behavioral therapy) and psychoeducation have shown to reduce this fear in adults, but no studies have focused on children and adolescents although this intervention may be of benefit in older children. Similarly, the availability of real-time CGM and algorithms with automated insulin suspension and delivery has the potential to reduce this fear although the studies are limited in this field.[80,88]

5 | 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),[89] as shown in Table 1. As the blood glucose falls, the initial symptoms result from activation of the autonomic nervous system and include shakiness, sweating, pallor, and palpitation. In healthy individuals with no diabetes, these symptoms occur at a blood glucose level of approximately 3.9 mmoL/L in children and 3.2 mmoL/L in adults.[90] However, this threshold in individuals with diabetes will depend on their glycemic control[20,21,91,92] with an adaptive shift of the glycemic threshold for symptom onset to a higher glucose level with chronic hyperglycemia and lower glucose level with chronic hypoglycemia. 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.[93] 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.[94]

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 reported a higher rate of severe hypoglycemia in adolescents as compared to the adults; 86 vs 57 events requiring assistance per 100 patient years[28] despite adolescents having poorer glycemic control with HbA1c levels approximately 1% higher. There are a number of physiologic and behavioral mechanisms that contribute to this difference. First, there are behavioral factors, such as variable adherence, which have been clearly associated with poor glycemic control in the adolescents.[95] Second, during puberty, adolescents with or without type 1 diabetes are more insulin resistant than adults.[96] 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.[90] However, intensively treated young adults

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
Behavioral signs and symptoms
Irritability
Erratic behavior
Agitation
Nightmares
Inconsolable crying
Non-specific symptoms
Hunger
Headache
Nausea
Tiredness

with type 1 diabetes counterregulate and experience hypoglycemia symptoms at a lower glucose level than conventionally treated patients suggesting a greater susceptibility to hypoglycemia in the young.[90,92] To date, nearly all studies have been conducted in adolescents and young adults primarily due to difficulty in studying a younger age group. As a result, little is known about responses in preadolescents as to whether younger children demonstrate a similar or different effect although there is evidence that a developing brain is more susceptible to the influence of glycemic excursions.[66]

6 | HYPOGLYCEMIA AWARENESS

In non-diabetic individuals, endogenous insulin is shut down and counterregulatory hormones like glucagon, epinephrine, and norepinephrine are released in response to hypoglycemia.[97] However, glucagon responses to insulin-induced hypoglycemia are lost almost in all patients by 5 years,[98] although this loss of response has been demonstrated as early as 12 months after the onset of disease[99] and hence they are primarily dependent on epinephrine response to negate the hypoglycemic effect of insulin. Hypoglycemia begets hypoglycemia and recurrent episodes of mild hypoglycemia contribute to the development of defective counterregulatory hormone responses to subsequent reductions in blood glucose levels.

Impaired awareness of hypoglycemia (IAH) is a syndrome in which the ability to detect the onset of hypoglycemia is diminished or absent.[97] The syndrome has been reported to affect approximately 25% of adults with type 1 diabetes. Earlier studies of children and adolescents have similarly shown a significant proportion of youth to have IAH with a prevalence of 19% to 37%.[10,100,101] However, it is reassuring to note a change in prevalence over time (33% in 2002 vs 21% in 2015) in the same population-based cohort.[102] Although IAH has reduced, it still remains a concern in a substantial minority of adolescents.

IAH is associated with lowering of glycemic thresholds for the release of counterregulatory hormones and generation of symptoms. A 2- to 3-fold reduction in the epinephrine responses contributes to the impaired adrenergic warning symptoms during hypoglycemia.[103] Clinically, this is manifested as loss of some of the symptoms of hypoglycemia over a period of time. The loss of autonomic symptoms precedes the neuroglycopenic symptoms and the patients are less likely to seek treatment for low blood glucose levels. As the awareness of low blood glucose level is impaired, hypoglycemia is prolonged. These episodes, if unrecognized and prolonged over 2 to 4 hours can lead to seizures.[104] Patients with IAH have a 6-fold increase in severe hypoglycemic episodes.[105] Glycemic threshold for cognitive dysfunction may be triggered before autonomic activation and hence are the symptoms associated with IAH.

The blood glucose threshold for activation of autonomic signs and symptoms is related to glycemic control, antecedent hypoglycemia, antecedent exercise, and sleep. Tight glycemic control leads to adaptations that impair counterregulatory responses[106] with a lower glucose level required to elicit an epinephrine response.[20] 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.[107] Likewise, moderate-intensity exercise also blunts the hormonal response to subsequent hypoglycemia.[108] Most of the severe episodes of hypoglycemia occur at night as sleep further impairs the counterregulatory hormone responses to hypoglycemia in patients with diabetes and normal subjects.[109] On the other hand, the blood glucose threshold for neuroglycopenia does not appear to vary as much with the level of glucose control nor with antecedent hypoglycemia.[90,110,111]

IAH is not an "all or none phenomenon" but reflects a continuum in which differing degrees of impaired awareness can occur and can vary over time in any one individual. IAH is proposed to be a result of intracellular and extracellular physiological adaptations to recurrent hypoglycemia that are in essence survival responses designed to protect the cell from subsequent exposure to glucose deprivation.[112] This adaptive process is referred to as habituation.[113] A habituated response can also be, at least temporarily, reversed by the introduction of a novel (heterotypic) stimulus (dishabituation). Preliminary results of a recent study demonstrated that a single burst of high-intensity exercise restored counterregulatory responses to hypoglycemia induced the following day in a rodent model of IAH.[114]

There is evidence that IAH can be reversed by avoiding hypoglycemia for 2 to 3 weeks,[115] but this may be difficult to accomplish and has not been practical in a clinical setting with current therapies. Therapeutic options are limited although some individuals gain benefit

from structured education.[116] Technological advances could potentially have a role to play with the use of CGM[117] or sensor-augmented pump therapy with suspend functions[5,7] by reducing and/or eliminating hypoglycemia exposure.

7 | RISK FACTORS FOR HYPOGLYCEMIA

The main risk factor for hypoglycemia is a mismatch between administered insulin and consumed food. An absolute excess of insulin could result from increased doses due to poor understanding of insulin type and action or accidental delivery. Similarly, a relative insulin excess is seen with reduced food intake or missed meals and in situations where glucose utilization is increased (during exercise) or endogenous glucose production is decreased (after alcohol intake).

Recurrent hypoglycemia

The majority of children with type 1 diabetes who experience severe hypoglycemia have isolated events, however, a few experience recurrent episodes. When hypoglycemia is recurrent, it is important to exclude IAH and rule out coexisting autoimmune disorders such as subclinical hypothyroidism,[118] coeliac disease,[119] and Addison's disease.[120,121] The introduction of a gluten-free diet and appropriate treatment of Addison's disease and hypothyroidism may reduce the frequency of hypoglycemia. Rarely, undisclosed self-administration of insulin causes repeated and unexplained severe hypoglycemia and should be considered as a sign of psychological distress[122] with underlying risk factors such as eating disorders (anorexia and bulimia) and depression.

The clinical factors associated with an increased risk of hypoglycemia are shown in Table 2.

Exercise

The blood glucose response to exercise is affected by many factors including the duration, intensity, and type of exercise, the time of day when exercise is performed, plasma glucose and insulin levels, and the availability of supplemental and stored carbohydrates.[123] The risk of hypoglycemia is increased with moderate-intensity exercise, immediately after as well as 7 to 11 hours after exercise.[124] The pathophysiology of post exercise-induced hypoglycemia is multifactorial and includes increased insulin absorption, increased insulin sensitivity, increased peripheral glucose utilization with depletion of glucose stores, and exercise-induced counterregulatory hormone deficits. Furthermore, children on fixed insulin doses are at "triple jeopardy" for hypoglycemia on nights following exercise as apart from the effect of exercise per se, counterregulatory hormone responses are impaired in sleep, and insulin concentrations are unchanged because of the treatment regimen.[125]

Glycemic management is based on frequent glucose monitoring, adjustments to both basal and bolus insulin dosing, and consumption of carbohydrates during and after exercise. Blood glucose levels below 6.7 to 8.3 mmol/L (120-150 mg/dL), prior to sustained aerobic exercise (75 minutes) in the afternoon, are associated with a high probability of hypoglycemia within 60 to 75 minutes.[126] Hence, reasonable starting blood glucose between 7 and 10 mmol/L (126-180 mg/dL) is

TABLE 2 Clinical factors associated with hypoglycemia

Precipitants
Excess insulin
Less food consumption
Exercise
Sleep
Alcohol ingestion
Risk factors
Impaired awareness of hypoglycemia
Previous severe hypoglycemia
Longer duration of diabetes
Co-morbidities
Coeliac disease
Addison's disease
Hypothyroidism
Psychological distress

recommended prior to commencement of exercise lasting for an hour.[127] Treatment guidelines to help individuals exercise safely have been published recently[127] and are updated in this edition of the ISPAD guidelines.

Alcohol

Alcohol inhibits gluconeogenesis[128] and hypoglycemia is further exacerbated if there is an inadequate intake of carbohydrates. Furthermore, the symptoms of hypoglycemia may be obscured or masked by the cerebral effects of alcohol. Even moderate consumption of ethanol may reduce hypoglycemia awareness and impair the counterregulatory response to insulin-induced hypoglycemia.[129] Apart from the acute effects, moderate consumption of alcohol in the evening may predispose patients to hypoglycemia on the subsequent morning with reduced nocturnal growth hormone secretion.[130] Although an increase in insulin sensitivity with alcohol intake has been postulated, this remains inconclusive.[131]

Nocturnal hypoglycemia

Nocturnal hypoglycemia continues to cause significant anxiety and morbidity for the families of children with type 1 diabetes.[84,132] The counterregulatory responses to hypoglycemia are attenuated during sleep[109,133] and patients with type 1 diabetes are much less likely to be awakened by hypoglycemia than individuals without diabetes.[109] The concern of seizures, coma, and death induces significant fear of nocturnal hypoglycemia. This fear often leads to an increase in parental anxiety and stress with an impact on parental sleep and quality of life, which is one of the most commonly, reported areas of distress for families.[132]

An alarmingly high prevalence of prolonged, nocturnal hypoglycemia, up to 40% on any given night in children and adolescents with type 1 diabetes was reported in earlier studies,[134–136] although recent studies report 15% to 25% of episodes on any given night.[137,138] Almost half of these episodes are undetected by caregivers or individuals with diabetes.[134,139] Juvenile Diabetes Research Foundation CGM study group described frequent prolonged nocturnal hypoglycemia on 8.5% of nights in both children and adults, but more prolonged

TABLE 3 Evaluation and management of hypoglycemic events

Potential cause	Factors	Management
Insulin action profile	What was the timing of insulin administration? What is the peak insulin action?	• Consider rapid-acting and long-acting insulin analogues for multiple daily injections for more physiological insulin delivery • Consider insulin pump therapy[183] ±dual-wave insulin bolus with low glycemic meals[184]
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[185] • 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, if intermediate-acting insulin is used
Recent physical activity	What was the timing, duration and intensity of recent activity?	• Preexercise and postexercise snacks (15-30 g) may be required • Suspension of pump basal rate during exercise[153] • If exercise occurs at peak insulin action, additional carbohydrates may be required
Recent hypoglycemia/lack of hypoglycemic symptoms or hypoglycemia unawareness	Has there been recent recurrent, severe hypoglycemia? (this may be associated with reduced counterregulatory response) At what glucose level do you start to recognize hypoglycemia? What types of symptoms do you have?	• Glucose targets may need to be adjusted upwards in patients with recurrent hypoglycemia and/or hypoglycemia unawareness[115,186] • Consider increased monitoring of blood glucose levels • Consider sensor-augmented pump therapy with automated insulin suspension with sensor detected hypoglycemia[7] or sensor predicted hypoglycemia[5] • Screen for underlying co-morbidities that can predispose to recurrent hypoglycemia
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 • Review insulin profiles • Consider real-time CGM with or without sensor-augmented pump therapy

in children.[140] In this study, the mean time spent in nocturnal hypoglycemia (<60 mg/dL) was 81 minutes. This is significant as prolonged nocturnal hypoglycemia for 2 to 4 hours has been associated with seizures.[104]

Nocturnal hypoglycemia should be suspected if prebreakfast blood glucose is low, and/or the patient experiences confusional states, nightmares or seizures during the night, or if impaired thinking, lethargy, altered mood, or headaches are reported on waking.[141] 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. Younger age, lower HbA1c levels, antecedent exercise and hypoglycemia are associated with a greater frequency of nocturnal hypoglycemia.[137]

Studies of overnight hypoglycemia in children have been unable to identify a glucose value, which reliably predicts a low risk of hypoglycemia. In a study using CGM to detect nocturnal hypoglycemia, there was a 2-fold increase, 45% vs 22% in the incidence of hypoglycemia with a bedtime glucose ≤5.5 mmol/L (100 mg/dL).[136] Similarly, the fasting glucose levels were significantly lower (6.6 mmol/L; 118 mg/dL) in those with hypoglycemia than those without (9.9 mmol/L; 179 mg/dL).[142] In contrast, in patients on twice daily soluble and isophane (NPH) insulin therapy, hypoglycemia was partially predicted by a midnight glucose of <7.2 mmol/L; 130 mg/dL.[135]

To reduce nocturnal hypoglycemia, a carbohydrate meal before bed for children on insulin injections was recommended based on studies using intermediate-acting insulins with peak action 4 to 12 hours and duration 16 to 24 hours.[143] However, insulin analogues, such as glargine and detemir[144] due to their less pronounced

peak effect, have reduced overnight hypoglycemia. Hence, extra snacks may be unnecessary[145] and enforcing prebed meals may contribute to nocturnal hyperglycemia and/or additional calories contributing to weight gain. The recommendation for inclusion of prebed meals should be individually tailored and not mandatory.[145] Newer insulin analogues like the ultralong-acting basal insulin degludec further have the potential to provide similar glycemic control while reducing the risk of nocturnal hypoglycemia in children with type 1 diabetes.[146]

The occurrence of severe nocturnal hypoglycemia has been reduced by the use of insulin pump therapy.[147] This effect is likely to result from the ability to finely adjust basal insulin delivery with the use of pump therapy. Pump therapy is associated with less nocturnal hypoglycemia and this is further reduced with the availability of sensor-augmented pump therapy with control algorithms which suspend basal insulin with sensor-detected[8] or sensor-predicted hypoglycemia.[5]

8 | HYPOGLYCEMIA TREATMENT

Diabetes education should be focused toward recognition of risk times of hypoglycemia; ability to detect subtle symptoms; and confirm low glucose levels through regular self-monitoring, followed by appropriate hypoglycemia treatment. If the blood glucose is ≤3.9 mmol/L (70 mg/dL), remedial actions to prevent further drop in glucose are recommended. In adults, 20 g of carbohydrate in the form of glucose tablets raised glucose levels by approximately 2.5 to 3.6 mmol/L

(45-65 mg/dL).[148–150] This has been extrapolated to 0.3 g/kg in children which would be approximately 9 g of glucose for a 30 kg child and 15 g for a 50 kg child. A pediatric study has shown that 0.3 g/kg of rapidly acting carbohydrate containing preparations (excluding jellybeans), effectively resolve hypoglycemia in most children and raise median blood glucose by 1 to 1.3 mmol/L in 10 minutes and 2 to 2.1 mmol/L in 15 minutes without rebound hyperglycemia at the next meal.[151] A similar weight-based approach was also found to be effective in children on insulin pumps.[152] In clinical practice, insulin delivery is usually suspended if blood glucose is <2 mmol/L (56 mg/dL).

After treatment, retest blood glucose after 10 to 15 minutes. If there is no response or an inadequate response, repeat oral intake as above. In general, the initial therapy with rapidly acting carbohydrate is followed with a serve (eg, 15 g) of slower-acting carbohydrate, such as bread, milk, biscuits, or fruit. However, this is not always required, particularly for those on insulin pump therapy. Essentially, it is important 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, and other factors.[148,153] The type of carbohydrate is also important as 40 g of carbohydrate in the form of juice results in approximately the same rise as 20 g in the form of glucose tablets.[148] Sucrose likewise requires a greater amount to provide the same increase in blood glucose compared to oral glucose.[149] Milk containing 20 g of carbohydrate causes 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.[148]

Severe hypoglycemia

Urgent treatment is required in the event of severe hypoglycemia and can be safely reversed by injection of glucagon, a potent and effective agent that can be administered intravenously, IM or SC.[154] Recombinant crystalline glucagon is available as a lyophilized powder that is mixed with an aqueous diluent to a concentration of 1 mg/mL. Commercially available glucagon rescue kits include GlucaGen HypoKit 1 mg (Novo NordiskA/S, Bagsvaerd, Denmark) and Glucagon Emergency Rescue Kit (Eli Lilly and Company, Indianapolis, Indiana). The recommended glucagon dosing is weight based: 1 mg for adults and children >25 kg and 0.5 mg for children <25 kg (according to Novo Nordisk manufacturer guidelines) while Eli Lilly uses a weight cut-off of 20 kg. The evidence for these recommendations is unclear. Glucagon often induces nausea and vomiting on regaining consciousness and hence it is important to continue close observation and glucose monitoring after treatment.[155] Side effect profile increases with repeated doses. The efficacy of glucagon is also dependent on the glycogen stores in the liver and hence would be predicted to be less efficacious in cases of prolonged fasting and parenteral glucose would be the therapy of choice.[155] Currently 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. To overcome this barrier, an intranasal single-use glucagon preparation has undergone trial in pediatric patients[156] and adults[157] with type 1 diabetes and was found to

be a promising alternative to IM glucagon. Intranasal glucagon is now being developed as a needle-free device that delivers glucagon for the treatment of severe hypoglycemia. A single dose of 3 mg can be used in children and adults with type 1 diabetes, which would potentially simplify prescription across the entire age range (≥4 years) of patients with type 1 diabetes.[156,157] Administration of nasal glucagon is faster and has a much higher success rate for delivery of the full dose with fewer errors than injectable glucagon.[158]

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% to 20%, for a total of 200 to 500 mg/kg of glucose. Rapid administration or excessive concentration (ie, glucose 50%) may result in an excessive rate of osmotic change with risk of hyperosmolar cerebral injury.[159] In the event of recurrent hypoglycemia, the child will require additional oral carbohydrates and/or intravenous infusion of 10% glucose, 2 to 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.

Glucagon is not readily available in countries with limited resources. In countries where neither glucagon nor glucose gel may be available; a powder form (glucose D 25 or anhydrous glucose) is used. Sugar or any other powdery substance or thin liquids like a glucose solution or honey should not be given forcibly to the semi/unconscious child. The child should be put in a lateral position to prevent aspiration and a thick paste of glucose (glucose powder with a few drops of water or table sugar crushed into powdered sugar with consistency of thick cake icing) smeared onto the dependent cheek pad; the efficacy of this practice is anecdotal. Although an earlier study in healthy adult volunteers demonstrated poor buccal absorption of glucose,[160] sublingual glucose was found to be a child-friendly and effective method of raising blood glucose in severely ill children with malaria.[161] In situations where there is a danger of aspiration with no intravenous access available, parenteral glucose solutions may be administered via nasogastric tubes.[162]

Minidose glucagon

Children with gastrointestinal illness and/or poor oral carbohydrate intake with a blood glucose ≤4.4 mmol/L can benefit from minidose glucagon by their caregivers at home to avoid impending hypoglycemia and hospitalizations.[154,163] A 100 U insulin syringe is used to administer the dose of reconstituted glucagon (1 unit ~10 µg of glucagon.). The dose is administered SC and is age-based; 2 units (20 µg) for children ≤2 years and 1 unit/year for children ≥3-15 years (with a maximum dose of 150 µg or 15 units). If blood glucose failed to rise over the first 30 minutes, a repeat injection was given using twice the initial dose. The minidose glucagon regimen resulted in an increase of 3.3 to 5 mmoL/L of glucose (60-90 mg/dL) within 30 minutes of administration with an average increase of 4.7 mmoL/L.[154]

Technology in the reduction and prevention of hypoglycemia

The rapid technological advances in the management of type 1 diabetes with stand-alone CGM systems or systems with integrated CGM and insulin pump use have empowered individuals with type 1 diabetes to further address and reduce hypoglycemia.

1. Continuous glucose monitoring

The use of CGM reduces time spent in hypoglycemia with a concomitant decrease in HbA1c in both children and adults.[164–166] Although the use of CGM is associated with reduced severe hypoglycemia in adults,[117,167] this is not demonstrated in children. Adolescents have a high acoustic arousal threshold from sleep,[168] sleep through 71% of alarms[169] and therefore can have a severe hypoglycemic event.[104] Studies have not demonstrated a change in the rates of severe hypoglycemia with the use of CGM in children and young adults.[170]

2. Sensor-augmented pump therapy with low glucose suspension (suspend on low)

The incorporation of algorithms in sensor-augmented pump therapy further reduces the time spent in hypoglycemia due to pump suspension. Low glucose suspension (LGS) automatically suspends basal insulin delivery for up to 2 hours in response to sensor-detected hypoglycemia thereby reducing the duration of hypoglycemia, especially at night.[171] This function also reduces moderate and severe episodes of hypoglycemia in patients with IAH.[7] Furthermore, LGS was not associated with deterioration in glycemic control or ketosis.[166,172]

3. Sensor-augmented pump therapy with predictive low glucose management (suspend before low)

Predictive low glucose management (PLGM) system suspends basal insulin infusion with the prediction of hypoglycemia. Basal insulin infusion is suspended when sensor glucose is at or within 3.9 mmoL/L (70 mg/dL) above the patient-set low limit and is predicted to be 1.1 mmoL/L (20 mg/dL) above this low limit in 30 minutes. In the absence of patient interference, following pump suspension, the insulin infusion resumes after a maximum suspend period of 2 hours or earlier if the auto-resumption parameters are met. PLGM reduced hypoglycemia under in-clinic conditions[173–175] and in short-[6,176–179] and long-term[5] home studies. There was also no deterioration of glycemic control with the use of the system in a 6 month randomized controlled home trial.[5]

4. Closed-loop 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. The systems utilize a control algorithm that autonomously and continually increases and decreases the SC delivery of insulin on the basis of real-time sensor glucose levels. Closed-loop artificial pancreas systems have been under development for several years with numerous algorithms and tested in clinical research centers, hotels, camps, supervised outpatient settings, and free-living conditions. Although most systems are single-hormone insulin, dual-hormone systems (bionic pancreas) that infuse both insulin and glucagon have also been studied in clinical trials.[180,181] Despite variable clinical and technical characteristics, artificial pancreas systems uniformly improve glucose control with a 50% relative risk reduction in hypoglycemia in outpatient settings compared to conventional pump therapy.[9] One such system is a FDA-approved semi-automated hybrid closed-loop (HCL) insulin delivery, which involves automated insulin infusion based on sensor glucose levels and requires patient-initiated meal bolus for meals, which was studied in a trial of 124 adolescents and adults for 3 months and was safe during in-home use.[182] The advancements in this field are ongoing in the pursuit of a fully automated closed-loop system, which can improve time spent in target glucose and reduce the burden of disease in individuals with type 1 diabetes.

Table 3 provides a summary of evaluation and management of hypoglycemic events.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.