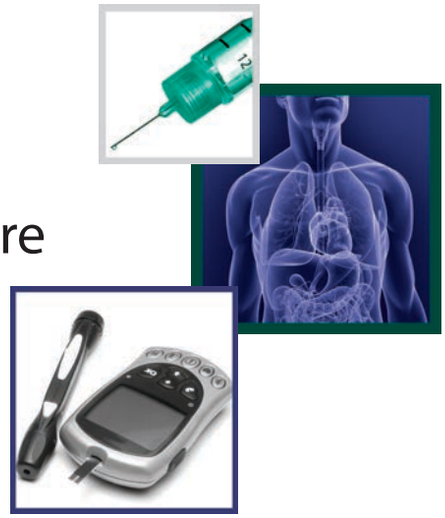
MANAGEMENT PERSPECTIVE

Managing hypoglycemia in children: what the clinician needs to know before advising parents



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Practice Points

- What are the differences in physiological responses in children & adolescents?
  - Adolescents release counter-regulatory hormones at a higher glucose level than adults.
- What happens when patients lose hypoglycemia awareness?
  - Impaired hypoglycemia awareness has been reported in up to 30% of children with Type 1 diabetes and has been associated with an increased risk of a severe hypoglycemic event.
  - Attempts to restore symptomatic responses by strict avoidance of hypoglycemia with the use of real-time continuous glucose monitoring, at least in preliminary studies, appear to be successful.
- How do you manage exercise & hypoglycemia?
  - Hypoglycemic risk may be increased both at the time of exercise and also in the 24 h following activity.
  - Management needs to take into account time of exercise in relation to food and insulin and type and intensity of activity.
- How should you treat hypoglycemia?
  - For mild and moderate hypoglycemia, treatment requires immediate provision of rapidly absorbed carbohydrate.
  - For severe hypoglycemia with coma or convulsions, glucagon administration is required.
- What are the current therapies that are available to help families manage hypoglycemia?
  - Blood glucose monitoring, insulin pump therapy and the use of insulin analog treatment.
  - Real-time continuous glucose monitoring with low glucose insulin suspension may reduce the incidence and duration of hypoglycemia.

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SUMMARY Hypoglycemia is one of the most common acute complications of Type 1 diabetes. 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. Managing hypoglycemia in children requires an understanding of the physiological differences in children and adolescents and the effects of clinical precipitants such as exercise and sleep. Current therapies, such as analog insulins and sensor-augmented pump therapy with insulin suspension, offer the potential to improve the incidence and duration of hypoglycemia in children.

Hypoglycemia is one of the most common acute complications of Type 1 diabetes (T1D) [1,2]. 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 [3]. For the child with T1D, 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 [4,5]. The landmark Diabetes Control and Complications Trial (DCCT) unequivocally demonstrated the importance of glycemic control in preventing and delaying the microvascular complications of T1D [6]. Intensive insulin therapy was, however, associated with an increased risk of hypoglycemia. The risk is even greater in those with reduced awareness of hypoglycemia, associated with recurrent hypoglycemic episodes.

In recent years, there have been improvements in insulin therapy, including availability of insulin analogs and insulin pump therapy. The introduction of continuous glucose monitoring systems (CGMS) via subcutaneously inserted sensors, particularly real-time monitoring, offers additional insight and opportunity to improve diabetes control. Although there are some data to suggest that severe hypoglycemia has reduced in incidence recently [7], hypoglycemia remains common [2]. In addition, despite advances in therapy, the majority of patients, particularly children, fail to achieve recommended glycemic targets [8]. Closed-loop insulin delivery, with automatic glucose sensing and insulin delivery without patient intervention, offers the potential to circumvent the significant glycemic excursions associated with conventional therapy. Early reports from small clinical studies evaluating closed-loop prototypes, suggest improved glucose control and a reduced risk of hypoglycemia [9–11].

What is the definition of hypoglycemia?

There is no consistent definition of hypoglycemia. Hypoglycemia is not defined by a single glucose value since glycemic thresholds for symptoms, CNS dysfunction and hormonal counter-regulation vary both between individuals and in the same individual over time [12,13]. In adults, cognitive changes and symptom responses are generally not observed until arterialized plasma glucose approaches 3.2 mmol/l. Based on this, the biochemical definition of hypoglycemia, as a blood glucose value of 3.9 mmol/l and below, has recently been challenged in a published debate in which it was suggested that a cut-off of 3.5 mol/l would be a more appropriate definition of hypoglycemia in clinical practice and in evaluating clinical studies where hypoglycemia is an outcome [14].

In children, symptom thresholds appear to be set at higher glucose values; however, cognitive dysfunction and hormonal responses in children are not usually evidential until blood glucose values fall below 3.5 mmol/l. Although arbitrary, blood glucose values between 3.3 and 3.9 mmol/l are generally agreed to place the individual at risk for severe hypoglycemia, as values in this range are associated with alterations in the counter-regulatory hormones essential to the spontaneous reversal of hypoglycemia [12,13,15].

What are the signs & symptoms of hypoglycemia?

Hypoglycemia is often accompanied by signs and symptoms of adrenergic activation and/or neurological dysfunction from glucose deprivation in the brain [16]. There are also nonspecific symptoms such as nausea, weakness and tiredness. As the blood glucose falls, the initial symptoms result from activation of the autonomic nervous system. These symptoms include shakiness, weakness, hunger and sweating, and pallor may be observed. These symptoms occur at a blood glucose level of approximately 3.2–3.6 mmol/l in children without diabetes, which is higher than

in adults [12]. 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 [17].

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, 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 [18]. 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 [19].

What are the differences in physiological responses in children & 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 versus 0.6 events requiring assistance per patient per year [20]. 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 would be expected to be associated with lower, not higher, rates of hypoglycemia.

There are a number of physiological and behavioral mechanisms that contribute to this difference. First, there are behavioral factors such as variable adherence that have been clearly associated with poor glycemic control in this agegroup [21]. Second, adolescents with or without T1D are more insulin resistant than adults during puberty [22]. Adolescents also have quantitative differences in counter-regulatory hormone responses. During hypoglycemia, adolescents with or without diabetes release catecholamines, cortisol and growth hormones at a higher glucose level than adults [12]. There is some evidence that neuroglycopenia may develop at a higher glucose level in children, suggesting a greater susceptibility to hypoglycemia in the young [12,17].

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 is likely to differ with age and neurodevelopmental stage.

What are the clinical precipitants of hypoglycemia?

Ultimately, excessive insulin or excessive insulin action causes hypoglycemia in the child with T1D. A range of clinical factors are associated with the occurrence of severe hypoglycemia in children and adolescents. These include:

- Changes in day-to-day management, such as an inappropriate insulin dose or missed meal;
- Exercise: both during the activity and in the hours afterwards;
- During sleep;
- Following alcohol ingestion.

In addition, there are risk factors that are associated with increased hypoglycemia incidence, which include:

- Young age (<6 years);
- Low A1c;
- Previous severe hypoglycemia;
- Longer duration of diabetes;
- Impaired awareness of hypoglycemia.

What are the risk factors for recurrent hypoglycemia?

The DCCT has demonstrated the value of systematically documenting hypoglycemic episodes, and many research groups and clinics now monitor and record rates of hypoglycemia. It is recognized that hypoglycemia is an important therapeutic outcome to measure for several reasons, including individual patient care, as an audit of overall clinic performance and to objectively evaluate the impact of changes in therapy. There have been numerous reports describing hypoglycemia incidence in defined samples of children with T1D. In the past, reports have been difficult to interpret due to methodological limitations, such as the use of retrospective

approaches. A further difficulty has been added by variations in the definitions of hypoglycemic events between studies. In adult studies, severe hypoglycemia is usually defined as an episode with symptoms consistent with hypoglycemia, in which the patient required the assistance of another person [23]. In childhood, this definition is problematic as most young children require assistance to correct even mild hypoglycemia. As a result, pediatric studies often use a stricter definition of severe hypoglycemia, limiting it to an event associated with severe neuroglycopenia, usually resulting in coma or a seizure [24]. This end point is unequivocal and reduces the likelihood of under- or over-reporting.

O'Connell *et al.* recently reported one of the largest studies monitoring the epidemiology of severe hypoglycemia in children with T1D [7]. This 10-year population-based cohort of childhood-onset T1D described 1683 children, yielding 7378 patient-years of data, and reported a decline in rates of severe hypoglycemia from 2000 to 2009. 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 and improved management guidelines, but this remains speculative. In contrast to previous studies from the same center [25], in this cohort, a glycated hemoglobin A1c <7% was not significantly associated with a higher risk of severe hypoglycemia, compared with the reference group of glycated hemoglobin A1c 8–9%, which was the average level in this cohort across the decade. Children with a duration of diabetes >1 year had a significantly higher risk than those with a duration of diabetes <1 year. In adolescents, pump therapy was associated with a reduced incidence of severe hypoglycemia.

The majority of children with T1D who experience severe hypoglycemia have isolated events; however, a small number suffer recurrent episodes. When hypoglycemia is recurrent it is important to exclude co-existing autoimmune disorders such as thyroid disease, Addison's disease and celiac disease. Impaired hypoglycemia awareness and hypoglycemia-associated autonomic failure [13] may develop in children and adolescents and should be considered in patients who experience recurrent hypoglycemia. Self-administration of insulin is a recognized cause of repeated and unexplained severe hypoglycemia and should be considered as a sign of psychological distress [26].

What are the neurological sequelae of hypoglycemia?

The impact of T1D on the developing brain remains controversial. Early onset of diabetes, before the age of 6 years, has long been identified as one of the strongest risk factors associated with cognitive dysfunction, ranging from poorer performance on general intellectual testing [27], 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 [28,29]. Moreover, a considerable limitation of many of these studies is the retrospective collection of hypoglycemia history.

We previously reported neurocognitive outcomes in 84 children with early-onset diagnosis of T1D, defined as T1D onset before 6 years of age [29]. In this initial study, we compared those subjects with a history of early severe hypoglycemia 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 years, there was no difference in general intellectual ability, memory and emotional difficulties in this cohort of young adults with early-onset T1D compared with control subjects, and no deterioration over time [30]. 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 T1D [31]. In a large sample of young patients with T1D, using voxel-based morphometry, regional brain volume differences were associated with both a history of hypoglycemia and hyperglycemia [32]. The role of early-onset diabetes and chronic hyperglycemia in the decrease of cognitive functioning in very young children has also received increased attention [33,34]. There is accumulating evidence that hyperglycemia in young children maybe an important factor, resulting in abnormalities in brain structure and function [35,36].

What happens when patients lose hypoglycemia awareness?

Impaired hypoglycemia awareness can be defined as the inability to perceive the onset of hypoglycemia, and in adults is associated with resetting the glycemic thresholds for the generation of symptoms, activation of counter-regulatory 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 [37]. Moderate exercise one day may also result in a decrease in symptoms of hypoglycemia and a decrease of hormonal response the following day [38]. 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 [12,39,40]. The blood glucose threshold for activation of autonomic symptoms is related to activation of counter-regulatory hormones and has been shown to be higher in children than in adults and to vary directly with the level of blood glucose control and with a higher A1c associated with a higher blood glucose threshold [12,41]. 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 [42].

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 T1D [43], we reported an impaired hypoglycemia awareness in 30% of the population, which is consistent with adult T1D studies. 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 weeks [44], 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 counter-regulatory hormone deficiency, is similar in young people as to that described in adults, since attempts to restore symptomatic responses by strict avoidance of hypoglycemia with the use of real-time CGMS, at least in preliminary studies, appear to be successful [45].

How do you manage exercise & hypoglycemia?

Physical activity is an essential component of childhood play and sport, and offers physiological and psychological benefits for all age groups with T1D. 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 counter-regulatory hormone deficits. Hypoglycemic risk may be increased both at the time of exercise and also in the 24 h following activity [46].

A report from the Diabetes Research in Children Network (DirecNet) has provided further clarification of the risks of exercise for a young patient with T1D [47]. In a study of 50 young individuals on two separate days, it was observed that 22% became hypoglycemic (plasma glucose <3.3 mmol/l) during afternoon exercise. Following the daytime exercise, 42% of subjects were noted to have an overnight plasma glucose value less than 3.3 mmol/l compared with 16% of subjects following a sedentary day [47].

In addition, studying nocturnal hypoglycemia risk following afternoon exercise, McMahon *et al.* used the euglycemic glucose clamp technique to compare the quantity of glucose required to

prevent hypoglycemia following afternoon exercise versus that following a sedentary day [46]. The glucose requirements to maintain euglycemia demonstrated a biphasic response on the exercise day. An increased glucose requirement was noted at the time of exercise and again between 7 and 11 h after the activity. This later increase in demand, which was probably due to repletion of hepatic glycogen stores, is likely to increase the risk of nocturnal hypoglycemia after exercise.

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 T1D have been published recently [48,49].

Why do children sleep through hypoglycemia at night?

Nocturnal hypoglycemia causes significant anxiety and morbidity for the families of children with T1D [50]. This is in part because our understanding of nocturnal glucose homeostasis and etiology of nocturnal hypoglycemia is very limited. The counter-regulatory responses to hypoglycemia are attenuated during sleep [51,52], and patients with T1D are much less likely to be awakened by hypoglycemia than individuals without diabetes [51]. Recent studies have reported an alarmingly high prevalence of prolonged, nocturnal hypoglycemia, up to 40% on any given night in children and adolescents with T1D [53–55]. Almost half of these episodes are undetected by carers or individuals with diabetes [53,56]. A recent report from the Juvenile Diabetes Research Foundation CGMS study group described frequent prolonged nocturnal hypoglycemia on 8.5% of nights in both children and adults, but more prolonged in children [2]. Such prolonged hypoglycemia may result in seizure and occasionally death. The same report stated that the median time spent in a hypoglycemia range approached 60 min per day. Such frequent hypoglycemic is likely to contribute to counter-regulatory 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 [24]. 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 CGMS to detect nocturnal hypoglycemia, there was a twofold increase, 45 versus 22% in the incidence of hypoglycemia with a bedtime glucose ≤5.5 mmol/l (100 mg/dl) [55]. Perhaps of greater value is the fasting glucose concentration, with values less than 7 mmol/l (126 mg/dl) suggesting that hypoglycemia has occurred overnight [53,54].

Studies of dietary intervention to prevent nocturnal hypoglycemia in adults with T1D have found that a bedtime snack containing carbohydrate and protein offers some protection from nocturnal hypoglycemia, compared with carbohydrates alone [57]. The beneficial effects of uncooked cornstarch have been variable in children [58,59].

The occurrence of severe nocturnal hypoglycemia has been reduced by the use of insulin pump therapy [60]. This effect is likely to result from the ability to finely adjust basal insulin delivery with the use of pump therapy. In a randomized crossover study of 23 children and adolescents, comparing multiple daily injections with pump therapy, pump therapy was associated with a smaller area under the curve for nocturnal hypoglycemia [61]. This same study also utilized continuous glucose monitoring, which has been helpful in identifying the frequency and duration of nocturnal hypoglycemia [61,62].

How should you treat hypoglycemia?

Prevention and treatment of hypoglycemia are dependent on the age of the child, the insulin regimen, the state of hypoglycemia awareness and the severity of the hypoglycemic event. The recently completed International Society for Pediatric and Adolescent Diabetes guidelines provide an excellent review of approaches to treatment of hypoglycemia in the young [24]. In brief, for mild and moderate hypoglycemia, treatment requires immediate provision of rapidly absorbed carbohydrate. The amount ranges from 5 to 15 g depending on the size of the child, the mode of insulin therapy and whether there has been recent exercise or insulin administration. For severe hypoglycemia with coma or convulsions, glucagon administration is required (intramuscular or subcutaneous; 0.5 mg if under 12 years and 1.0 mg

over 12 years). In hospital, intravenous glucose, in the form of 10–20% dextrose, is the first-line treatment (200–500 mg/kg; slow infusion over 10 min). It is important that glucose levels are monitored to ensure recovery is maintained.

What are the current therapies that are available to help families manage hypoglycemia?

Subcutaneous glucose sensors that continuously measure interstitial fluid glucose levels are now available and approved for use in children. The first generation of continuous glucose monitors provided blood glucose data in a retrospective manner. Interstitial fluid signals are calibrated with fingerstick blood glucose levels to generate continuous glucose tracings. These devices, such as Medtronic's iPro™2 System (MN, USA), can be easily inserted in the outpatient setting and require minimal set-up time. At the end of the monitoring period, the device is uploaded with fingerstick blood glucose readings. This allows generation of a continuous glucose tracing, an example of which is shown in **Figure 1**. This is particularly useful for patients to detect patterns of glucose variability, as well as episodes of prolonged hypoglycemia during sleep.

The advent of pump therapy with real-time CGMS with low glucose suspend (LGS) function (Medtronic Paradigm® Veo™ System, Medtronic Minimed, CA, USA), 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 and is a significant development towards full automation of insulin delivery in patients with T1D. Recently, Agrawal *et al.* presented the first real-world use of the Veo and found that in patients who used the system for ≥3 months, LGS usage was associated with fewer sensor glucose values both below 2.8 mmol/l (50 mg/dl) and greater than 16.7 mmol/l (300 mg/dl) [63]. In a user evaluation of the Veo, Choudhary *et al.* found that LGS use was associated with reduced nocturnal duration of sensor glucose ≤2.2 mmol/l (40 mg/dl) in patients in the highest quartile of nocturnal hypoglycemia at baseline [64].

In our report of 24 children and adults using the Veo system for up to 6 months, we found that the LGS function was frequently activated in patients with T1D with impaired awareness of hypoglycemia [65]. Most of these events were of short duration whereby the patient has overridden insulin suspension and resumed insulin delivery. Almost 40% of all LGS events occurred overnight and one in three events lasted the full 2-h duration. Approximately half of patients slept through the 2-h suspend period despite an alarm of 60 dB lasting 20 s occurring every 2 min during the 2-h period. The overnight suspend events with no patient intervention, provided a unique opportunity to evaluate the sensor glucose profile following full 2 h insulin suspension when the sensor glucose fell to <3.3 mmol/l. The initial fall in glucose levels was arrested promptly following insulin suspension and rose steadily during the 2-h suspended period. The mean glucose level at the end of the 2-h suspend event was 5.5 mmol/l, which is a near-normal value. The mean first morning meter glucose value entered into the pump was 10.3 mmol/l and there was no associated ketosis. We found that a 2-h insulin suspension overnight was not associated with severe hypoglycemia or diabetic ketoacidosis.

Sensor-augmented pump therapy at this stage may be difficult to sustain indefinitely, particularly in children and adolescents. This is, in part, 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.

Are there better insulin preparations available to prevent hypoglycemia?

Insulin therapy is designed to replace the deficient hormone and to attain normal blood glucose levels. This goal remains elusive owing to the difficulty in replicating the minute variations of physiologic insulin secretion and the difference in exogenous insulin delivery, compared with normal secretion of endogenous insulin directly into the portal vein. The failure of exogenous insulin to completely mimic physiologic insulin action results in the glycemic variability seen in the day-to-day care of diabetes.

Rapid-acting (e.g., lispro, aspart and glulisine) analog insulin and short-acting insulin (e.g., regular insulin) are typically administered as a premeal bolus based on carbohydrate content of food and the blood glucose level. Long-acting insulin preparations (e.g., insulin glargine and determir) are given once or twice daily. They provide a basal insulin level that suppresses hepatic glucose production and maintains near-normal glucose levels in the fasting state.

There are many different insulin preparations and delivery systems available. The selected

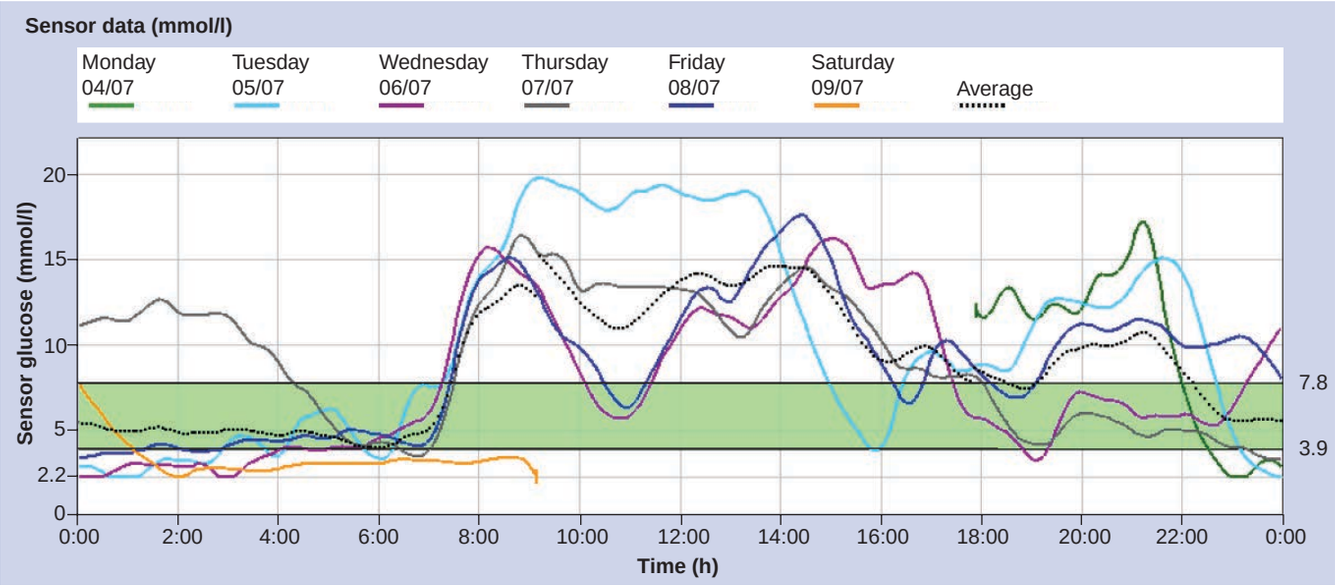

Figure 1. Retrospective continuous glucose sensor recording over 6 days. Patient is a 14-year-old boy with an A1c of 7.6%. He has impaired hypoglycemia awareness and rarely wakes overnight to nocturnal hypoglycemia.

regimen is individualized for the child and family to optimize convenience, as well as achieving optimal glycemic control. The type of insulin and regimen used vary among children and can change for the individual child over time.

Conclusion

Despite modern therapy, hypoglycemia remains a critical consideration and concern to patients, parents and clinicians. It is essential that hypoglycemic events be monitored for individual patient care, clinical audit and research. An understanding of the risk factors for hypoglycemia, regular glucose monitoring and individually tailored insulin regimens may help reduce the severity and/or the frequency of hypoglycemia; but effective closed-loop systems (mechanical or biological) will be required to eradicate the risk and allow glycemic treatment targets to be consistently reached and maintained. The long-term effects of hypoglycemia remain under debate and the situation has been made more complex by suggestions that hyperglycemia has adverse consequences for brain development.

Future perspective

Recent reports have suggested that the frequency of severe hypoglycemia has reduced. This is probably a result of the increased use of improved insulin delivery methods, both with pump therapy and analog insulin injection therapy. Although it is probable that this trend will continue, hypoglycemia and the fear of hypoglycemia will remain a major barrier to intensive therapy until such a time that hypoglycemia can be reliably prevented. Unless cell replacement therapy for T1D becomes feasible as a clinical therapy, the use of technological approaches is likely to provide the most effective method to reduce the impact of hypoglycemia. Hypoglycemia prevention using continuous glucose sensing, offers significant promise to reduce hypoglycemia incidence, particularly as the devices become more comfortable and less expensive. The linkage of continuous glucose monitoring with insulin pumps and automated systems that suspend insulin with hypoglycemia and impending hypoglycemia, will not only reduce hypoglycemia exposure, but also the fear of hypoglycemia. This, in turn, is likely to reduce the prevalence of impaired hypoglycemia awareness.

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