Hypoglycemia: The Achilles Heel of the Treatment of Children With Type 1 Diabetes

Danièle Pacaud MD FRCPC

Alberta Children's Hospital, Calgary, Alberta, Canada
University of Calgary, Calgary, Alberta, Canada

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ABSTRACT

Hypoglycemia is the Achilles heel of the treatment of all individuals with diabetes, and children and adolescents in particular. In the Diabetes Control and Complications Trial (DCCT), the relative risk of severe hypoglycemia due to intensive diabetes management was similar in adolescent and adult subjects; however, rates of severe hypoglycemia were almost doubled in adolescents compared to adults. The conclusions of the DCCT regarding pediatric subjects has led to intensification of diabetes management in all age groups, with particular emphasis on hypoglycemia. There are now significant data suggesting that severe hypoglycemia in younger children is associated with cognitive impairment. Furthermore, hypoglycemia and the fear of hypoglycemia can be disruptive to the developing child's activities of daily living. This paper focusses on the unique aspects of managing hypoglycemia in children and adolescents with diabetes, and reviews its incidence, risk factors, short- and long-term consequences, treatment and prevention.

RÉSUMÉ

L'hypoglycémie est le talon d'Achille du traitement de toutes les personnes atteintes de diabète, et peut-être surtout chez les enfants et les adolescents. Au cours de l'étude DCCT (Diabetes Control and Complications Trial), le risque relatif d'hypoglycémie grave attribuable au traitement intensif du diabète a été semblable chez les adolescents et les adultes, mais les hypoglycémies graves ont été près de deux fois plus fréquentes chez les adolescents que chez les adultes. En raison des conclusions de l'étude DCCT en ce qui a trait aux enfants, on a intensifié le traitement du diabète chez les personnes de tout âge en accordant une attention particulière à l'hypoglycémie. Une quantité considérable de données semblent maintenant indiquer que l'hypoglycémie grave chez les jeunes enfants est associée à une dysfonction cognitive. En outre, l'hypoglycémie et la peur de l'hypoglycémie peuvent perturber la vie quotidienne d'un enfant. Ce compte rendu met l'accent sur les aspects uniques de la prise en charge de l'hypoglycémie chez les enfants et les adolescents atteints de diabète. Il traite de l'incidence, des facteurs de risque, des conséquences à court terme et à long terme, du traitement et de la prévention de l'hypoglycémie.

Address for correspondence:
Danièle Pacaud
Alberta Children's Hospital
1820 Richmond Road Southwest
Calgary, Alberta
T2T 5C7 Canada
Telephone: (403) 943-2910
Fax: (403) 943-7649
E-mail: daniele.pacaud@calgaryhealthregion.ca

INTRODUCTION

Hypoglycemia is the most frequent complication of treatment of type 1 diabetes (1). Although the Diabetes Control and Complications Trial (DCCT) (2) demonstrated unequivocally the importance of tighter metabolic control in preventing long-term complications of type 1 diabetes, intensified diabetes management is also associated with increased frequency of hypoglycemia. Mild episodes of hypoglycemia are therefore expected in intensified diabetes management; however, the serious consequences of moderate or severe hypoglycemic events make this complication a barrier to tighter metabolic control. This article addresses the diverse aspects of this problem in the population of children and adolescents with type 1 diabetes.

DEFINITION OF HYPOGLYCEMIA

The classic definition of hypoglycemia is known as Whipple's Triad: 1) symptoms of hypoglycemia, 2) confirmed by a low plasma glucose (PG) level, 3) relieved by carbohydrate intake. However, this definition may not be applicable in the context of diabetes. Symptoms of hypoglycemia in diabetes are categorized as autonomic (tremor, hunger, sweating) and neuroglycopenic (difficulty concentrating, blurred vision, dizziness, convulsions, loss of consciousness). The DCCT (2) established a definition of hypoglycemia based on severity of clinical symptoms and the ability, or lack of ability, to self-treat. This definition has been adopted in both clinical research and practice.

A mild episode of hypoglycemia is defined as autonomic symptoms in an individual who is able to self-treat. A moderate episode includes autonomic and neuroglycopenic symptoms in an individual who is still able to self-treat. A severe episode includes autonomic and neuroglycopenic symptoms, and requires the assistance of another person to treat.

As most young children require assistance from an adult to treat even a mild hypoglycemic episode, the DCCT definition requires modification for children. Thus, in children, a moderate episode can be defined as the occurrence of altered central nervous system (CNS) function without loss of consciousness (i.e. confusion, disorientation, incoherence, relative lack of coordination). A severe episode would be one associated with loss of consciousness or convulsion. However, this approach has not been used consistently in the pediatric literature, which has resulted in variable reported incidence rates.

SYMPTOMS OF HYPOGLYCEMIA

The DCCT included a subgroup of 195 adolescents (13 to 18 years of age), allowing investigators to compare this age group to adult participants. Interestingly, in both the conventional and intensified diabetes management groups, adolescents had a significantly higher rate of hypoglycemia compared to adults (3). However, the relative risk of hypoglycemia associated with intensified diabetes management was about 3-fold in both adolescents and adults, with similar benefits in reduction of long-term complications (4).

This difference between adults and adolescents may be explained in part by the differing response to hypoglycemia seen in children compared to adults. Jones and colleagues (5) studied the counterregulatory hormone and symptomatic response to hypoglycemia in 13 children with poorly controlled type 1 diabetes, compared to 16 children and 19 adults without diabetes. In children with diabetes, hypoglycemic symptoms were identified as a PG level of 4.2 mmol/L, compared to 3.6 mmol/L in children without diabetes and <3.0 mmol/L in adults without diabetes. While experiencing low PG levels, the 2 children's groups had significantly higher symptom scores compared to the adult group. The epinephrine and growth hormone responses paralleled the symptom scores, with higher and earlier responses in children with diabetes. Both children's groups had significantly higher responses compared to the adult group at the end of the study.

The presentation of hypoglycemic symptoms in children also differs from adults, as reported in 2 studies. Tupola and colleagues (6), using a diary of symptoms of hypoglycemia over a 3-month period in 161 children with type 1 diabetes, found that during mild episodes, the majority of symptoms were either nonspecific (41%) or neuroglycopenic (20%), rather than autonomic (39%). This phenomenon was more marked in children <6 years of age. The most frequent symptoms reported were weakness, tremor, hunger and drowsiness. McCrimmon and colleagues (7) interviewed 100 parents and 43 children with diabetes. They found that autonomic and neuroglycopenic symptoms seemed to be present simultaneously in children. This contrasts with adults, in which autonomic and neuroglycopenic symptoms are well-identified as separate events, depending on the severity of hypoglycemia. Furthermore, both parents and children identified behavioural changes as a frequent and early sign of hypoglycemia. This has not been reported in adults.

INCIDENCE OF HYPOGLYCEMIA

Variation in definition and symptoms in children compared to adults may explain the disparity of hypoglycemia incidence reported in the literature. Reported incidence rates vary from 2 to 126 episodes per 100 patient years (1,4,8-12). Table 1 illustrates this variability. Two studies are notable for their large sample sizes in estimating the true incidence of hypoglycemia. The Hvidore Study Group on Childhood Diabetes (9) studied children from 22 pediatric diabetes clinics in 18 countries. Over a 6-month period, they gathered 1-time information and blood samples in 2873 children 1 to 18 years of age. They used a definition of coma or seizure to collect data on severe hypoglycemia. Based on a 3-month period of recall, the overall incidence was 22 episodes per 100 patient years.

Davis and colleagues (1) prospectively followed a total of 709 patients for 2027 patient years. The overall incidence was 15.4 and 7.8 episodes per 100 patient years of moderate and severe hypoglycemia, respectively. In this study, a moderate hypoglycemic event was defined as one requiring assistance

to treat for older children and one with obvious neuroglycopenic symptoms for younger children. Severe hypoglycemia was defined as an event associated with loss of consciousness or convulsions.

RISK FACTORS FOR HYPOGLYCEMIA

A number of studies have reported differing risk factors for hypoglycemia, showing a variation similar to the reported incidence rates of hypoglycemia. The only risk factor consistently reported is younger age (1,8,9,11). In preschool-age children, the rates reported are 3-fold higher than those in adolescents. In the Davis study, the rate in the <6 years-of-age group was 42 episodes per 100 patient years, compared to 14.9 for the overall study group (1,8,9,11).

The Hvidore Study Group on Childhood Diabetes (9) reported rates varying from nearly 60 episodes per 100 patient years in the 0-to-4 years-of-age group to about 15 episodes per 100 patient years in the 16-to-18 years-of-age group. The higher risk in younger children is probably multifactorial in etiology and includes longer overnight fasting, irregular eating and physical activity habits, more frequent intercurrent illnesses and relative hypoglycemia unawareness. Younger children may also be unable to recognize or communicate symptoms of hypoglycemia, which results in delayed recognition and increased severity of episodes.

Lower HbA_{1c} levels are cited frequently as the second risk factor for hypoglycemia (1,3,9,11). However, several studies have not found this association (8,10,12,13). In the multicentre study by the Hvidore Study Group on Childhood Diabetes (9), the 8 centres with HbA_{1c} significantly lower than the grand mean HbA_{1c} of the entire cohort had similar rates of severe hypoglycemia as the 8 centres with HbA_{1c} above the mean (22 vs. 19 episodes per 100 patient years). In the follow-up study by the same group (14), re-evaluation of these centres revealed that the rates of severe hypoglycemia were similar in the centres with HbA_{1c} either comparable to or above the grand mean; however, the overall rates tended to be lower in the centres with HbA_{1c} below the grand mean ($p=0.07$ between the 3 centre groups). This phenomenon suggests that the varying rates of hypoglycemia are probably due to different education and management of diabetes rather than actual metabolic control.

Other risk factors are also reported inconsistently in the literature. As in the adult literature, recurrent mild hypoglycemia (1,15) and a history of severe hypoglycemia (3,16) are reported as risk factors in children. Male gender also seems to predispose to a higher risk of recurrent severe hypoglycemia (1) and to an increased relative risk due to intensified management (3).

Longer duration of diabetes also appears to predispose a person to severe hypoglycemia (1,16,17). Duration of diabetes of <1 year and persistence of residual pancreatic function indicated by detectable C-peptide levels seem to offer protection against severe hypoglycemic events. Higher total

Table 1. Reported rates of hypoglycemia in children and adolescents

Authors	*Year*	*Study type (duration)*	*n*	*Age range (years)*	*Mean HbA_{1c} (%)*	*Rate of SH (per 100 patient years)*		
						U	*NU*	*U+NU*
DCCT (4)	1994	Prospective	195	13–17				
Conventional		(mean 7.4 years)			9.8 (N=6.1)	9.7		27.6
Intensive					8.1 (N=6.1)	26.7		85.7
Bognetti et al (8)	1997	Retrospective (3 years)	187	3.2–25.5	8.3 (N=6.1)			14.9
Mortensen et al (9)	1997	Cross sectional	2873	1–18	8.6 (N=6.3)	22		
Davis et al (1)	1998	Prospective (4 years)	709	≤18	8.8 (N=6.2)	7.8	15.4	
Ludvigsson et al (12)*	1998	Prospective (4 years)	130	<18		13–17		98–126
Dammacco et al (10)	1998	Cross sectional						
Children			300	6–11	7.6 (N=6.0)	2	10	
Adolescents			232	12–18	8.3 (N=6.0)	5	38	
Levine et al (11)	2001	Prospective (1 year)	300	7–16	8.9 (N=6.0)	8	54	62

*Yearly rates of hypoglycemia are provided over the study period

SH = severe hypoglycemia

N = upper limit of normal for nondiabetic subjects

U = hypoglycemia associated with loss of consciousness or convulsion

NU = hypoglycemia requiring assistance of another to treat, or associated with altered central nervous system functions without loss of consciousness

daily dose of insulin and a lower proportion of rapid-acting insulin in the total daily dose were identified as risk factors by Nordfeldt and Ludvigsson (13). Increased frequency of injections was found to be associated with an increased risk of severe hypoglycemia by Dammacco and colleagues (10).

NOCTURNAL HYPOGLYCEMIA

Nocturnal hypoglycemia is a significant problem in children, as it frequently goes unrecognized. Severe hypoglycemia often occurs at night or in the early morning (8,17). Cross sectional studies report 14 to 47% of children experience nocturnal hypoglycemia on any given night (10,18-20). The incidence increases with the frequency of sampling throughout the night. Newer technologies that allow continuous PG monitoring are likely to identify an even larger population of children with unrecognized nocturnal hypoglycemic events. Deiss and colleagues (21) studied 3-day profiles in 15 preschoolers; 9 of these patients experienced ≥1 episode of nocturnal hypoglycemia. These events had a mean duration of 58 minutes, with a range of 10 to 480 minutes. During a

Table 2. Reported impact of severe hypoglycemia on neuropsychological and intellectual functioning

Authors	*Year*	*Study type (duration)*	*# of subjects (age range [years])*	*Controls*	*Findings*
Northam et al (30)	2001	Prospective (6 years)	90 (6–17)	84 S: community Matched for age/sex	• History of SH associated with lower verbal and full-scale IQ • Age <5 years at onset associated with poorer performance on attention, processing speed and executive skills
Northam et al (29)	1998	Prospective (2 years)	123 (3–14)	129 S: community Matched for age/sex	• At baseline: no difference • At 2 years: lower vocabulary, block design and processing speed, particularly if age <5 years at onset
Rovet et al (31)	1999	Prospective (7 years)	16 (9–17)	16 S: siblings/cousins/ staff Matched for age/sex/ sociodemographic	• History of SH associated with deficits in perceptual, motor, memory and attention tasks
Rovet et al (32)	1997	Cross sectional	103 (9–18)	100 S: siblings/cousins/ staff Matched for age/sex/ sociodemographic	• History of SH associated with lower verbal IQ and greater difficulty with select, focus and inhibition attention components
Hershey et al (33)	1997	Cross sectional	38 (15–42)	21 S: unknown Matched for age	• History of SH associated with deficits in delayed recall of verbal information and inhibition of prepotent responses
Ryan et al (34)	1985	Cross sectional	125	83 S: siblings/staff Matched for age/sex/ sociodemographic/ handedness	• Age <5 years at onset associated with poorer performances on IQ, school achievement, visuospatial ability, memory, motor speed and hand-eye coordination
Holmes et al (35)	1985	Cross sectional	42 (6–16)	None	• Age <7 years at onset associated with higher reading and memory impairment

S = source of control
SH = severe hypoglycemia
IQ = intelligence quotient

study of sleep physiology in children with diabetes, Matyka and colleagues (22) also reported episodes lasting up to 380 minutes.

Identification of hypoglycemic episodes requires active testing throughout the night. This will interrupt sleep for both children and parents, which can have a negative impact on quality of life. It is important, however, to identify risk factors or situations where there is an increased risk of hypoglycemic events to target and limit the need for nocturnal testing.

In a cross sectional survey of 532 children 6 to 18 years of age, Dammacco and colleagues (10) found an increased rate of reported nocturnal hypoglycemia in the subgroup with the longest duration of diabetes (<2 years: 6.1%; 2 to 5 years: 32%; >5 years: 25.3%; chi-square analysis, $p<0.001$). In contrast, Beregszàzsi and colleagues (18) and Porter and colleagues (19) found that children <5 to 7 years of age had more episodes of nocturnal hypoglycemia. Beregszàzsi and colleagues (18) also reported that a daily insulin dosage >0.85 IU/kg/day, a previous history of ≥2 episodes of severe hypoglycemia and hypoglycemic values for >5% of PG measurements during the past month were risk factors for nocturnal hypoglycemia. Other factors, including long-acting insulin given at the evening meal rather than at night, a high evening dose of regular insulin and ≤2 injections per day have been noted as potential precipitants (23,24). It would seem that younger children, children with a longer duration of type 1 diabetes, children given long-acting insulin early in the evening and children with a recent history of frequent, mild episodes of hypoglycemia should be monitored more frequently at night.

CONSEQUENCES OF SEVERE HYPOGLYCEMIA

During hypoglycemic clamp studies maintaining a PG level of 3.3 mmol/L (25), children 9 to 19 years of age were found to have slower reaction times. The magnitude of change in mental efficiency observed during mild hypoglycemia varied from 13 to 68% and depended on the type and complexity of the tests used (25). It took up to 40 minutes after correction of PG levels before mental efficiency was restored to initial performance levels. These changes have been corroborated by changes in neurophysiologic markers such as electroencephalogram (EEG) (26) or cerebral blood flow (CBF) (27). In a manner similar to the release of counterregulatory hormones and symptom onset, increases in CBF seem to be more pronounced in children (27) than in adults (28). Although the acute changes seen in mental efficiency are transient and vary by individual, they may interfere with a child's ability to learn, especially if a hypoglycemic episode occurs during school hours.

There are now significant data suggesting that severe hypoglycemia in younger children is associated with cognitive impairment (Table 2). As discussed earlier, children diagnosed at <5 years of age are more likely to experience severe hypoglycemia. They are also more likely to show deficits in specific attention, psychomotor efficiency, memory and speed of processing (29-31). Researchers have found a link between hypoglycemia and lower results on verbal intelligence quotient (IQ) tests (30), poorer performance on the select, focus and inhibition components of attention but not the suppress, shift and sustain components of attention (32), and poorer results on delayed recall of verbal information (33). Northam and colleagues (29,30) and Hershey and colleagues (33) have also reported a decrease in speed of processing.

Finally, Ryan and colleagues (34) observed impairments that were evident in a broad range of neuropsychological measures, including attention, memory, visuospatial abilities, hand-eye coordination and mental and motor speed in adolescents in whom diabetes developed at <5 years of age. In addition, as a group, these adolescents earned significantly lower scores on measures of intelligence. Ryan and colleagues suggested that these deficits could be due to mild brain damage that developed as a consequence of multiple episodes of serious hypoglycemia early in life.

Diabetes has also been associated with underachievement in reading, spelling and arithmetic (29,35). The literature suggests that severe hypoglycemia has a negative impact on neurocognitive function, particularly memory, attention and speed of processing in children with early onset of diabetes. These deficits may become more evident as these children's neurocognitive abilities develop, and although they may not be significant in all children, they could result in certain children learning more slowly and requiring extra attention to maintain academic achievement.

FEAR OF HYPOGLYCEMIA

Few studies have examined the impact of hypoglycemia on the quality of life or the concerns of children and their parents. Green and colleagues (36) explored the use of a modified version of the Hypoglycemia Fear Survey (HFS) in 127 adolescents and children as young as 9 years of age, and found this tool to be reliable and valid. In a multiple regression analysis of a subgroup of 39 participants, higher worry score, history of severe hypoglycemia and younger age were predictive of a lower HbA_{1c}. When the HFS was adapted for use on parents (37), increased fear of hypoglycemia was associated significantly with a history of loss of consciousness in their child. Furthermore, in general, the group of 46 mothers studied had a higher fear of hypoglycemia than adult subjects with type 1 diabetes. In contrast to the previous study on children, the increased fear of hypoglycemia in mothers was associated with a higher HbA_{1c}. Marrero and colleagues (38) again found a relationship between past history of seizure or loss of consciousness and higher scores on the HFS in both parents and adolescents. This fear also resulted in greater worries about diabetes and greater negative impact of diabetes on the children's lives. Based on their study results pertaining to mothers of children with diabetes and in adults with diabetes, Gonder-Frederick and colleagues suggest that significant fear of hypoglycemia may lead to a worsening of metabolic control (39).

TREATMENT AND PREVENTIVE MEASURES

Three major organizations have issued recommendations for optimal metabolic control levels for diabetes in childhood: the Canadian Diabetes Association (CDA), the American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD). CDA (40) states that, "for children <12 years of age, targets for HbA_{1c} should be 120 to 140% of the upper limit of normal, with targets for glucose and HbA_{1c} graduated according to the child's age." The ADA (41) is less precise with the following statement: "PG and HbA_{1c} need to be modified to take into account the fact that most children <6 or 7 years of age have a form of hypoglycemia unawareness." Finally, the ISPAD (42) recommends that, "for each individual, the target should be the lowest achievable HbA_{1c} without the occurrence of frequent or severe hypoglycemia." The 3 sets of recommendations all recognize that children and adolescents are at higher risk for hypoglycemia than adults, a factor that must be considered when providing care for them.

The majority of episodes of hypoglycemia have an identifiable precipitating factor, making them potentially preventable. In these cases, one or a combination of the following factors may be involved: inadequate or delayed food intake, extra physical activity, excessive insulin dose due to either miscalculation or measurement error, intercurrent illness, or alcohol abuse. Education on the causes of hypoglycemia and strategies to avoid it are key elements to achieving effective prevention. Patients must be instructed about increased monitoring of PG levels in situations where they are susceptible to hypoglycemia. Identifying and treating a hypoglycemic episode during its mild phase will prevent progression to a more severe episode. Insulin regimens (appropriate doses, type and timing) should be chosen to best meet children's requirements, based on their individual lifestyles (43,44). For example, a child with frequent early night-time hypoglycemia would benefit from one or both of the following strategies: use of a rapid-acting insulin analogue at the evening meal rather than regular insulin, or use of a long-acting insulin at bedtime rather than at the evening meal.

Frequent adjustment of insulin doses based on PG trends should also reduce the frequency of hypoglycemia. A bedtime snack is mandatory to decrease the risk of nocturnal episodes. Some studies support the use of protein (45,46) or uncooked cornstarch (23) for a bedtime snack. Finally, younger children who are dependent on others to treat them must be taught to communicate using words that even people unfamiliar with their situation will understand, e.g. "I am low, I need a snack or sugar."

According to the CDA clinical guidelines on hypoglycemia, treatment of mild or moderate episodes of hypoglycemia is best achieved with 15 g of carbohydrate, preferably glucose tablets (47). PG should then be tested 15 minutes later. A second dose of carbohydrate should be given if PG levels have not normalized. Once PG levels have normalized, a snack should be given to prevent further episodes of hypoglycemia if the next meal or snack is >1 hour away. For severe episodes with a level of consciousness allowing for oral treatment, 20 g of carbohydrate should be administered as initial treatment. For severe episodes with loss of consciousness or inability to treat orally, subcutaneous (SC) or intramuscular (IM) glucagon (0.5 mg in children ≤5 years of age, 1 mg in older children) should be used. If intravenous (IV) access is available, 10 to 25 g of IV glucose should be given. The ISPAD guidelines (42) contain slightly different recommendations. However, due to the lack of scientific evidence available, both sets of recommendations are based on clinical judgement and both are likely to provide efficient approaches.

Two recent reports on novel approaches to the treatment of hypoglycemia are worth noting. First, Haymond and colleagues (48) reported on the use of mini-doses of glucagon, administered via SC injection, to treat impending hypoglycemia or mild hypoglycemia with the inability to treat orally due to intercurrent illness. They used a dose of 10 µg/year of age (minimum dose 20 µg, maximum dose 150 µg) to treat such episodes. If PG levels had not normalized at 30 minutes, a second dose of 20 µg/year of age (minimum dose 40 µg, maximum dose 300 µg) was given. Of 33 initial episodes of hypoglycemia treated in this manner, only 2 people required a second dose of glucagon. Children who, during the course of their illness, required a second or third dose of glucagon in the next 24 hours still had enough glycogen reserve to respond to repeated mini-doses of glucagon. These small doses did not lead to onset or worsening of nausea. This approach allowed families to manage mild hypoglycemia at home, rather than through emergency care services, in cases where oral treatment was not possible.

The second study, by Monsod and colleagues (49), evaluated the use of Epipen® (epinephrine) as an alternative to glucagon. This medication had the advantage of being premixed and was easier to administer. Unfortunately, the results of this study showed no correction of PG levels. Therefore, Epipen® should not be used to treat hypoglycemia.

CONCLUSIONS

Unrecognized hypoglycemia can be disruptive, can decrease children's performance in school and may predispose them to accidents. The fear of severe hypoglycemia can be devastating for both parents and children and may become a barrier to optimal PG management. This fear has been known to result in greater worries about diabetes and a greater negative impact of diabetes on a child's quality of life. In turn, this may lead to worsening metabolic control. Conversely, in an effort to obtain tighter metabolic control and avoid severe hypoglycemia, some parents may test a child's PG up to 12 or more times per day, which puts them at high risk of psychological and physical burnout. Families must be educated about the best approaches to hypoglycemia prevention, while

maintaining optimal metabolic control and balanced lives. Despite the current knowledge and interventions available, hypoglycemia still remains the Achilles heel of the treatment of children and adolescents with diabetes.

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