

Hypoglycemia in Childhood Type 1 Diabetes Mellitus: Understanding and Managing the Dark Side of Intensive Insulin Therapy

William V. Tamborlane, MD

Professor and Chief of Pediatric Endocrinology, Department of Pediatrics and the Yale Center for Clinical Investigation, Yale University School of Medicine, New Haven, Connecticut

Karena Swan, MD

Associate Research Scientist, Department of Pediatrics and the Yale Center for Clinical Investigation, Yale University School of Medicine, New Haven, Connecticut

Stuart A. Weinzimer, MD

Associate Professor, Department of Pediatrics and the Yale Center for Clinical Investigation, Yale University School of Medicine, New Haven, Connecticut

ABSTRACT

Background: Despite the availability of advanced insulin delivery systems, blood glucose-monitoring equipment, and insulin analogue formulations, hypoglycemia remains a significant concern in the treatment of children and adolescents with type 1 diabetes mellitus (DM). Furthermore, patients who manage their blood glucose levels most effectively may also be the ones at greatest risk for hypoglycemia.

Objective: The aim of this article was to review current issues surrounding the pathophysiology and frequency of hypoglycemia in children and adolescents with type 1 DM.

Methods: Relevant articles for this review were identified through a search of MEDLINE (1992–2007; English-language articles only). The search terms used were *children, adolescents, hypoglycemia, diabetes, insulin, and continuous subcutaneous insulin infusion*.

Results: The threat of severe hypoglycemia remains a major obstacle to the effective treatment of type 1 DM. Basal-bolus therapy, using continuous subcutaneous insulin infusion or multiple daily injections, is the most effective and flexible method available for maintaining good glycemic control in children as well as in adults. Insulin analogues can be used effectively in these regimens and may be helpful toward addressing risks for hypoglycemia. Patient education should also be given a high priority in addressing the risk of hypoglycemia in children and adolescents with type 1 DM. The development of continuous glucose-monitoring systems offers the potential for an even brighter future for this group of patients.

Conclusions: Recent advances in DM technology reduce but do not eliminate the risk of hypoglycemia in youth with type 1 DM. These observations underscore the need for a closed-loop insulin delivery system in which the rate of insulin infusion is regulated by real-time changes in glucose concentrations. (*Insulin*. 2007;2:157–165) Copyright © 2007 Excerpta Medica, Inc.

Key words: type 1 diabetes mellitus, hypoglycemia, children, adolescents, insulin analogue, continuous subcutaneous insulin infusion, multiple daily injections, basal-bolus therapy.

INTRODUCTION

Results of the landmark Diabetes Control and Complications Trial (DCCT) clearly demonstrated the value of glycemic control in delaying the onset and progression of chronic complications of diabetes mellitus (DM).¹ As a result, it was recommended that youth with type 1 DM should strive to lower glycosylated hemoglobin (A1C) levels as close to normal as possible and as early in the course of the disease as possible. However, intensive therapy was associated with an ~3-fold increased risk for hypoglycemia versus conventional

treatment, and, irrespective of treatment group, the rate of severe hypoglycemia was >50% higher for adolescents than for adults.^{1,2} Hypoglycemia has become the most significant barrier to the pursuit and maintenance of tight glycemic control among people with DM, and effectively managing the risk for hypoglycemia is especially important in the treatment of children and adolescents with this disease.

Since the conclusion of the DCCT >13 years ago,¹ advances in insulin formulations, insulin delivery systems, and glucose-monitoring technology have emerged. The develop-

ment of rapid-acting and soluble, long-acting insulin analogues, with improved pharmacodynamic properties as compared with conventional human insulin formulations, has provided powerful tools for achieving improvements in glycemic control while managing the risk of hypoglycemia. Insulin pumps have become smaller and easier to use, while at the same time offering extended functionality through advanced features such as bolus calculators. Blood glucose meters are highly accurate³ and require very small blood samples and only a few seconds to obtain glucose measurements. These advances have allowed basal-bolus therapy, either through continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDIs), to be used more successfully and conveniently than ever before in children and adolescents with type 1 DM.

The development of rapid-acting and soluble, long-acting insulin analogues, with improved pharmacodynamic properties as compared with conventional human insulin formulations, has provided powerful tools for achieving improvements in glycemic control while managing the risk of hypoglycemia.

In spite of these advances, hypoglycemia remains a significant concern among patients, family members, and health care providers. There is a clear risk of hypoglycemia associated with the use of intensive insulin therapy, and a level of concern is justified because severe episodes of hypoglycemia can be life-threatening. Consequently, the current review focused on the pathophysiology and frequency of hypoglycemia as it relates to optimization of glycemic control in children and adolescents with type 1 DM.

MATERIALS AND METHODS

Relevant articles for this review were identified through a search of MEDLINE (1992–2007; English-language articles only). The search terms used were *children, adolescents, hypoglycemia, diabetes, insulin, and continuous subcutaneous insulin infusion*.

DEFINITIONS

The first step in effectively addressing the problem of hypoglycemia is to define our terms and to understand the physiologic factors that make young patients with type 1 DM especially vulnerable to marked reductions in plasma glucose. Biochemical hypoglycemia (with or without symptoms) is defined by the American Diabetes Association as any plasma glucose level ≤ 70 mg/dL.⁴ In nondiabetic adults, this is the plasma glucose level at which counterregulatory hormone responses engage and awareness of symptoms normally occurs. It should be noted, however, that such responses may be triggered at higher glucose levels in healthy

8- to 16-year-olds and in children and adolescents with type 1 DM who have poor glycemic control.⁵

Functional differentiation of hypoglycemic events, based on symptoms and treatment characteristics, is important clinically. Symptomatic episodes in which patients are able to treat themselves without the assistance of others (eg, by ingesting a carbohydrate-containing snack) are considered minor or mild hypoglycemia. Episodes of hypoglycemia during which there is sufficient cognitive impairment that the patient could not treat him- or herself, and which require the assistance of another person to treat, are considered major or severe hypoglycemic events. Applying this definition to very young patients who, by definition, require assistance for treatment of hypoglycemia, can be difficult. In severe hypoglycemia, ingestion of carbohydrates may be precluded due to loss of consciousness, seizures, or coma, and assistance may require administration of either a glucagon injection or IV glucose infusion.

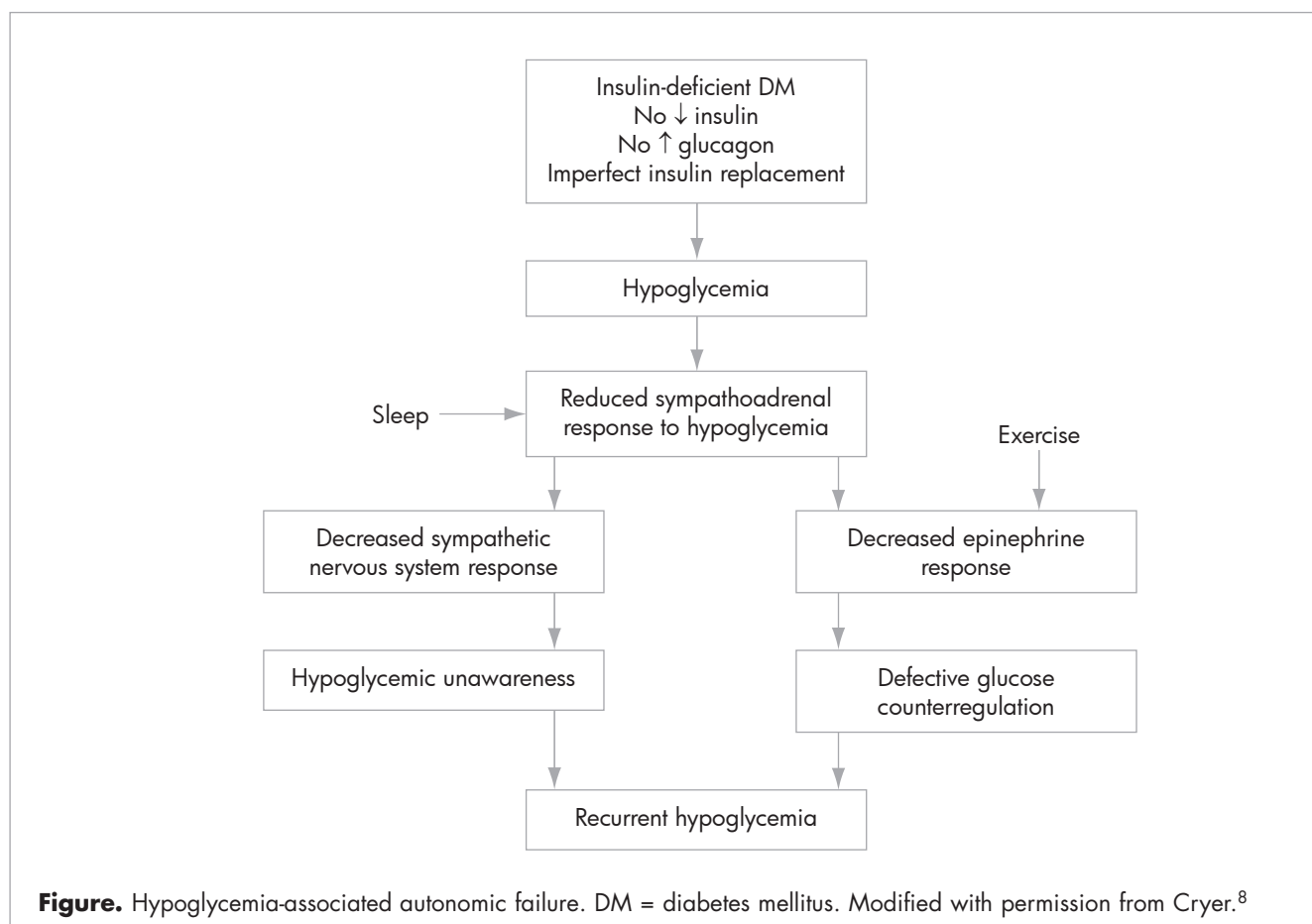
PATHOPHYSIOLOGY

In nondiabetic children, the initial response that normally occurs with falling plasma glucose levels is a prompt suppression of insulin secretion. If plasma glucose levels continue to fall and threshold values for release of anti-insulin, counterregulatory hormones are reached, there are abrupt increases in circulating concentrations of glucagon and epinephrine. Plasma growth hormone and cortisol levels also increase, but these hormones are less important in acutely counteracting the effects of insulin.^{6,7} Defective counterregulation occurs with type 1 DM because exogenously supplied insulin levels do not decrease in response to low blood glucose levels. Even though glucagon is the most potent anti-insulin hormone and pancreatic α -cells retain the ability to secrete glucagon to a variety of stimuli in patients with type 1 DM, the ability to secrete glucagon in response to hypoglycemia is generally lost early in the course of type 1 DM.⁸ Consequently, patients with type 1 DM depend on sympathetic nervous system responses, including increases in plasma epinephrine levels, to prevent hypoglycemia.

In our early experience with CSII, we noticed that as control improved, there was a substantial lowering of the plasma glucose threshold that was required to stimulate release of epinephrine and symptoms of hypoglycemia. It was later demonstrated that repeated episodes of mild hypoglycemia blunted catecholamine responses and symptom awareness to subsequent hypoglycemic challenges. This phenomenon has been called hypoglycemia-associated autonomic failure (HAAF),⁸ and it is a major contributing factor to the risk of hypoglycemia in patients whose DM is well controlled. The relationship between hypoglycemia unawareness, defective glucose counterregulation, and HAAF is illustrated in the **figure**.

OTHER CONTRIBUTING FACTORS TO HYPOGLYCEMIA

Surprisingly, the most common cause of defective catecholamine responses to hypoglycemia is sleep. Jones et al⁹ used



the hypoglycemic clamp to demonstrate that plasma catecholamine responses were blunted in adolescents with and without type 1 DM when hypoglycemia was induced during the night at the onset of deep sleep. In contrast, brisk catecholamine responses to the same hypoglycemic stimulus were observed when the subjects were awake during the day or night.

It has recently been shown that the risk of nocturnal hypoglycemia is increased nearly 2-fold on nights that follow days with exercise in the afternoon versus days without such exercise when subjects are maintained on the same basal insulin replacement regimen.¹⁰ Catecholamine responses to nocturnal hypoglycemia were blunted regardless of whether there had been antecedent exercise in the afternoon.¹¹ Using the glucose clamp technique, McMahon et al¹² showed that nonoxidative glucose disposal increased during sleep on nights following afternoon exercise, which may serve to support repletion of muscle glycogen stores. Thus, children with type 1 DM are at “triple jeopardy” for hypoglycemia on nights after exercise: peripheral glucose utilization is increased by exercise, counterregulatory hormone responses are impaired by sleep, and insulin concentrations are unchanged because of the treatment regimen.¹³

The insulin resistance of puberty and the pharmacodynamics of regular insulin are additional reasons why being

an adolescent was an independent risk factor for severe hypoglycemia in the DCCT.² The peripheral insulin resistance of puberty results in the need for relatively high bolus doses of insulin to maintain postprandial glycemic control. When given in large doses, the duration of action of regular insulin is markedly prolonged. This overshoot hyperinsulinemia, in turn, contributes to late postprandial hypoglycemia 5 to 8 hours after a meal.

Many of the factors that complicate treatment of children and adolescents with type 1 DM directly impact their risk of experiencing hypoglycemia. Poor adherence to therapy is commonplace, especially among young adolescents. Young people may be more prone to erratic eating behaviors, in terms of both meal composition and timing; erratic patterns of bolus dosing; and irregular bouts of activity and exercise that can affect appetite as well as blood glucose levels directly.

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SCOPE OF THE RISK FOR HYPOGLYCEMIA

Severe hypoglycemia occurs frequently in children and adolescents with type 1 DM, although an overall risk is difficult to assign because it varies from one study to the next and is influenced by the intensity of treatment, A1C levels that are achieved, age and developmental stages of the patients, definitions that are used, methods of ascertainment, and temporal changes in the methods of treatment. The highest reported incidence in the DCCT was among intensively treated adolescents, with rates of hypoglycemia requiring assistance reaching 85.7 events/100 patient-years and episodes resulting in seizures and coma totaling 26.7 events/100 patient-years.² As shown in **Table I**, the rate of severe hypoglycemia appears to have fallen somewhat in recent years.^{14–18} The widespread use of CSII and the availability of insulin analogue formulations that can more closely approximate “physiologic” insulin profiles have undoubtedly played a role in reducing the risk of severe hypoglycemia. Nevertheless, the rates of severe hypoglycemia remain unacceptably high.

A recent study involving 6309 children with type 1 DM identified several predictors of severe hypoglycemia—including younger age, longer duration of disease, higher daily insulin dose per kilogram of body weight, less experience of the treatment facility, and type of injection regimen.¹⁷ The frequency of nocturnal hypoglycemia is generally very high among youth with type 1 DM,^{19,20} and because these events occur with no warning or symptoms,²⁰ they are particularly frightening for parents.

GLYCEMIC TARGETS FOR CHILDREN AND ADOLESCENTS

Despite recognition of the value of glycemic control, consensus on glycemic targets for children and adolescents remains elusive, due in part to potential age-related differences in the benefits and risks of intensive treatment. For example, some data suggest that hypoglycemic seizures in young children may have a negative effect on selected cognitive functions.²¹ Conversely, more recent data indicate that chronic hyperglycemia may be equally damaging to the developing brain.²²

A recent statement of the American Diabetes Association has suggested target levels for A1C and plasma glucose that differ in youth with type 1 DM according to age group²³ (**Table II**). We believe that it is confusing to have higher glucose and A1C targets in 6- to 12-year-olds than in teenagers, even though A1C levels are characteristically higher in adolescents than in school-aged patients.²⁴ Moreover, the recommendation that A1C levels should not be lowered to $\leq 7.5\%$ in children < 6 years of age, even in the absence of problems with hypoglycemia, fails to take into account the potential damaging effects of hyperglycemia on the developing brain.²² Although this may be controversial, in the Yale Children’s Diabetes Clinic, the overall goal for all age groups is to lower A1C levels to $< 7.5\%$, and even lower if possible in the absence of frequent severe hypoglycemia or other major obstacles to successful treatment.

ADVANCES IN MULTIPLE DAILY INJECTION TREATMENT WITH INSULIN ANALOGUES

Rapid-acting insulin analogues (insulin aspart, insulin glulisine, and insulin lispro) have a faster onset of action than regular human insulin (RHI), sharper peak activity, and more rapid return to baseline level.²⁵ More rapid absorption of these analogues also means that much higher peak concentrations of insulin can be achieved in comparison to the same dose of RHI. In addition, fast onset of action of analogues allows dosing closer to mealtime than for RHI. Ideally, RHI should be injected 30 minutes before mealtime, but patients must then be able to judge, in advance, how much they are likely to eat. Hypoglycemia can result when a smaller amount of carbohydrates is consumed than was anticipated or if a meal is skipped after dosing.

Studies evaluating postprandial dosing of insulin aspart and insulin lispro in children and adolescents have yielded mixed results. In a study comparing preprandial (immediately before the start of a meal) and postprandial (immediately after a meal, or up to 30 minutes after the start of a meal) dosing of insulin aspart among a group of 42 children (6–12 years old) and 34 adolescents (13–17 years old) with type 1 DM,²⁶ postprandial administration proved to be safe and effective; however, it was noted that preprandial dosing was preferable. Among younger children (aged < 5 years), a study of pre- and postprandial insulin lispro (given either at the beginning or immediately after the meal) and RHI (given before the meal, with timing according to families’ normal schedules) demonstrated significantly lower 2-hour postprandial glucose excursions with postprandial insulin lispro than with preprandial RHI.²⁷ Glucose excursions were similar between the insulin lispro treatments (administration before vs after the meal) in this study. In a crossover study of 26 preschool children (2.4–6.9 years old) with type 1 DM,²⁸ postprandial insulin aspart administered up to 30 minutes after starting meals was compared with preprandial administration of RHI given 30 minutes before meals. The results showed no significant change or difference between treatments in A1C levels or postprandial glucose increments after 12 weeks, and the incidence of hypoglycemia was similar between groups. As part of this study, a quality-of-life questionnaire was given to parents, and the results demonstrated a greater satisfaction among parents for continuing therapy with insulin aspart rather than with RHI.²⁸

The pharmacokinetic and pharmacodynamic advantages of rapid-acting insulin analogues are especially useful in dealing with problems presented by the insulin resistance of puberty. The delayed peak and long duration of action associated with large bolus doses of RHI may jeopardize postprandial glucose control in the first 2 to 3 hours after eating and suppress hepatic glucose production 5 to 8 hours later. Given before the evening meal, such large doses of RHI may result in nocturnal hypoglycemia. A study comparing insulin lispro with RHI in 14 adolescents found that when equal doses of each product were given before dinnertime, there were lower mean free insulin levels between 10 PM and

Table I. Frequency of severe hypoglycemic events in children and adolescents in recent studies.

Author	Definition of Severe Hypoglycemia, No. and Age of Subjects	Rate of Severe Hypoglycemia
Ahern et al ¹⁴	Seizure or coma N = 161 Age range, 1–18 y (all CSII)	24 events/100 patient-years
Bulsara et al ¹⁵	Seizure or loss of consciousness N = 1335 Age, 9.5 (4.3) y*	16.6 events/100 patient-years
Craig et al ¹⁶	Unconsciousness or seizure N = 1190 Age range, 1.2–15.8 y	36 events/100 patient-years
Wagner et al ¹⁷	Seizures, loss of consciousness, disorientation, inability to arouse from sleep that required intervention with glucagon or IV dextrose n = 782 Age range, 0–<5 y (3.7 [0.9] y*) n = 1053 Age range, 5–<7 (6.1 [0.6] y*) n = 4474 Age range, 7–<9 y (8.6 [0.5] y*)	4.1 events/100 patient-years
Rewers et al ¹⁸	Loss of consciousness, seizure, or hospital admission or emergency department visit N = 1243 Age range, infant to 19 y	19.1 events/100 patient-years

CSII = continuous subcutaneous insulin infusion.

*Mean (SD).

3 AM, along with higher blood glucose levels and lower incidence of nocturnal hypoglycemia associated with insulin lispro.²⁹

The pharmacokinetic and pharmacodynamic advantages of rapid-acting insulin analogues are especially useful in dealing with problems presented by the insulin resistance of puberty.

Although rapid-acting insulin analogues can be used to provide postprandial coverage, long-acting insulin analogues (insulin detemir and insulin glargine) represent a significant advance over neutral protamine Hagedorn (NPH) insulin in providing basal insulin replacement, especially during the overnight period. Because the rate of hepatic glucose production at night is very sensitive to small

changes in circulating insulin levels, the flat time–action profiles of long-acting insulin analogues are useful in avoiding some of the problems associated with the peak effects of NPH during the overnight period.³⁰ Even more important, the variability in the time–action profile of the same dose of insulin given on 4 separate occasions to the same patient has been shown to be much greater with NPH (68%) than with either insulin glargine (48%) or with insulin detemir (27%), as measured by coefficient of variation for AUC of the glucose infusion rate from 0 to 24 hours.³¹ Less variation in dose-to-dose responsiveness could potentially explain why rates of nocturnal hypoglycemia are lower and fasting glucose levels are more predictable with these long-acting basal insulin analogues.

Data also exist concerning the use of rapid- and long-acting analogues together in basal-bolus therapy. Insulin aspart and insulin detemir in basal-bolus therapy were compared with insulin aspart and NPH in a 26-week study of 347 children and adolescents with type 1 DM.³⁰ Although A1C levels, along with risk of diurnal and 24-hour hypoglycemia, were similar between the groups, a significantly

Table II. Plasma blood glucose and glycosylated hemoglobin (A1C) goals for type 1 diabetes mellitus grouped according to patient age.

Values by Age	Plasma Glucose Goal Range, mg/dL (mmol/L)		A1C	Rationale
	Before Meals	Bedtime/Overnight		
Toddlers and preschoolers (<6 years)	100–180 (5.5–10.0)	110–200 (6.1–11.1)	<8.5% (but >7.5%)	High risk and vulnerability to hypoglycemia.
School-aged (6–12 years)	90–180 (5.0–10.0)	100–180 (5.5–10.0)	<8.0%	Risks of hypoglycemia and relatively low risk of complications before puberty.
Adolescents and young adults (13–19 years)	90–130 (5.0–7.2)	90–150 (5.0–8.3)	<7.5%*	Risk of hypoglycemia. Developmental and psychological issues.

Key concepts in setting glycemic goals:

- Goals should be individualized, and lower goals may be reasonable based on benefit–risk assessment.
- Blood glucose goals should be higher than those listed above in children with frequent hypoglycemia or hypoglycemia unawareness.
- Postprandial blood glucose values should be measured when there is a disparity between preprandial blood glucose values and A1C levels.

*A lower goal (<7.0%) is reasonable if it can be achieved without excessive hypoglycemia.
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reduced risk of nocturnal hypoglycemia, 26% lower than with NPH, was found to be associated with insulin aspart/detemir treatment. In addition to the reduction in risk for nocturnal hypoglycemia, insulin aspart/detemir was associated with a lower mean body mass index (BMI) z score and reduced intrasubject variability in self-monitored fasting plasma glucose values. Like many other current studies in youth with type 1 DM,¹⁴ BMI z scores showed an overall tendency toward overweight at the beginning of the study; however, there was a decrease toward normal in the group that received basal-bolus therapy with insulin aspart/detemir.³² These results demonstrate that basal-bolus therapy, using rapid- and long-acting insulin analogues, is a promising tool for use in the treatment of type 1 DM among children and adolescents.

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION IN CHILDREN AND ADOLESCENTS

In addition to MDIs, basal-bolus therapy using CSII holds tremendous practical value in addressing the problem of hypoglycemia among children and adolescents. One advantage associated with CSII is the fact that, unlike with MDIs, there is no large reserve of subcutaneous insulin, and minor hypoglycemia can generally be more rapidly reversed by consumption of less carbohydrates.³³ Rapid-acting insulin

analogues are most commonly used in CSII, so that the benefits associated with their pharmacokinetic characteristics are preserved with this mode of treatment.

In addition to MDI, basal-bolus therapy using CSII holds tremendous practical value in addressing the problem of hypoglycemia among children and adolescents.

The safety and effectiveness of CSII in older children and adolescents have been extensively reported.^{34–36} We have found that even in children <7 years of age, CSII provides an effective method for maintaining good glycemic control, while minimizing risks for hypoglycemia. In a recent study of 65 children with type 1 DM who started using CSII before the age of 7 years,³⁷ we found significant long-term A1C reductions, with a continual improvement extending for up to 4 years. A1C reductions were most substantial for children aged <3 years, decreasing from 7.9% (1.1%) to 6.9% (0.9%) (P = 0.01) while using CSII. There was a 53% reduction in the rate of severe hypoglycemia overall, with the largest improvements in children aged 3 to <5 years. Evidence also suggested

that the involvement of paid caregivers (as assistance to working parents) did not negatively affect glycemic control and was actually associated with greater reductions in A1C in this study. Overall, this study has provided confirmation of the effectiveness of CSII in the long-term maintenance of glycemic control among very young children, while reducing the risk of severe hypoglycemia.³⁷

There are many options associated with CSII that can be used to address the risk of hypoglycemia. Exercise affects the risk of hypoglycemia, and in children with type 1 DM, afternoon exercise may often lead to nocturnal hypoglycemia.¹⁰ With CSII, there is the option to set temporary basal rates or even temporarily discontinue basal insulin delivery to avoid hypoglycemia during and after exercise.³⁸ The memory of insulin pumps can also be extremely valuable for evaluating glycemic control,³⁹ and bolus history may be used to determine whether patients are overcorrecting for hypoglycemia. Features to assist in carbohydrate counting and avoid bolus stacking are also common among today's "smart" pumps. These features, along with the proven safety and effectiveness of CSII among children and adolescents, make CSII therapy a serious consideration in most cases of type 1 DM.

Self-monitoring of blood glucose (SMBG) is an important component of therapy for type 1 DM, for optimizing glycemic control as well as for reducing risk for hypoglycemia. Standard methods for SMBG are often limited by several factors, however, including the inconvenience of checking blood glucose during overnight hours and the potential for missing substantial glucose excursions between readings.⁴⁰ Continuous glucose-monitoring (CGM) systems have recently been developed, which allow more complete blood glucose profiles to be obtained. The potential of these systems is particularly attractive as a method to optimize CSII dose adjustments, to more accurately match insulin needs throughout the day and night. Although CGM technology will require further refinement to improve precision and accuracy before its promise can be fully realized, the availability of continuous data on blood glucose levels represents a tremendous advance toward optimal therapy for DM.^{41,42} The first integrated CSII/CGM system has recently been approved by the US Food and Drug Administration.

DISCUSSION

Insulin analogues represent a substantial advance over human insulin formulations and can play an important role in the pursuit of effective overall glycemic control and reduced risk for hypoglycemia. Basal-bolus therapy, using CSII or MDI, is the most effective and flexible method available for maintaining good glycemic control. Although MDIs can be safely used to achieve and maintain tight glycemic control, many will argue that rapid-acting insulin analogues used in smart pumps are currently the best method available to lower the risk of hypoglycemia.

Those who manage their DM intensively may often be at greatest risk for hypoglycemia, and the temptation to sacri-

fice tight glycemic control to avoid hypoglycemia can be a difficult issue to overcome. Patient education should emphasize the value of glycemic control in avoiding complications, in addition to the importance of preventing hypoglycemia. Evaluating hypoglycemia and hypoglycemia unawareness is highly recommended.⁴³ To the extent that early recognition of symptoms and self-treatment can be taught, it should be done so that progression from minor to major episodes of hypoglycemia may be averted. Patients and their families should be prepared, as much as possible, to deal with hypoglycemic emergencies. Kits for delivering an emergency injection of glucagon are available by prescription, for use in the event of a severe hypoglycemic episode. In addition, the role of frequent blood glucose monitoring in achieving and maintaining glycemic control, as well as in avoiding hypoglycemia, should be stressed. Assessment of current individual treatment regimens and glycemic targets should continually take into account the occurrence, frequency, and severity of hypoglycemia.

There are no simple methods for avoiding hypoglycemia that will work for all patients, but there are many tools available to help in attempting to manage the risks. Although modern therapeutic options may allow insulin therapy to be accomplished more safely and effectively than in the past, the risk of hypoglycemia—in particular, nocturnal hypoglycemia—remains a significant concern for young patients, even when insulin analogues and planning of bedtime snacks are used to ameliorate the problem.⁴⁴ It is unlikely that any insulin regimen will be ideal until there is real-time feedback control of insulin infusion rates. The desire for a consistently strict level of glycemic control coupled with minimal risk for hypoglycemia is likely to only be met through an artificial pancreas, which would accurately recognize and immediately correct blood glucose fluctuations. Although not currently available, a functional artificial pancreas may be in the near future.⁴⁵

CONCLUSIONS

Recent advances in DM technology reduce but do not eliminate the risk of hypoglycemia in youth with type 1 DM. These observations underscore the need for a closed-loop insulin delivery system in which the rate of insulin infusion is regulated by real-time changes in glucose concentrations.

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Address correspondence to: William V. Tamborlane, MD, Department of Pediatrics, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06520. E-mail: william.tamborlane@yale.edu