Management of the Young Child
With Diabetes Mellitus:
How Do We Measure Success?

The optimal concentration of plasma glucose in patients with diabetes mellitus has been an intensely discussed and highly controversial issue ever since the realization that insulin is not a cure but rather simply a treatment for diabetes—and indeed an imperfect treatment at best. With the report of the results of the Diabetes Control and Complications Trial (DCCT) in 1993, the controversy has quieted somewhat. Experts now generally agree that lower mean plasma glucose, as reflected in a lower glycated hemoglobin (HbA\textsubscript{1c}), maintained for many years (a mean of 6.5 years in the DCCT) results in a considerable delay in the onset and progression of diabetes-related microvascular and neuropathic complications and an improved risk factor profile for development of macrovascular complications. The conclusions of the DCCT Research Group are that the lower the HbA\textsubscript{1c}, the lower the complication rate and that no threshold exists below which a further decline will not be beneficial.\textsuperscript{2} Although some investigators question this latter point,\textsuperscript{3} most now accept that attempts should be made to maintain the HbA\textsubscript{1c} below 7%.

The DCCT, however, also demonstrated that severe hypoglycemia frequently occurs during implementation of intensive diabetes therapy aimed at lowering or near-normalization of the HbA\textsubscript{1c}.\textsuperscript{1,4,5} With use of the currently available, imperfect modes of insulin replacement therapy, severe hypoglycemia may be unavoidable in some, if not many, patients with diabetes. Defective glucose counterregulation and hypoglycemia unawareness occur with even mild episodes of hypoglycemia;\textsuperscript{6} these disorders can be prevented and even reversed by strict avoidance of hypoglycemia.\textsuperscript{7,8} Hypoglycemia continues to be "the limiting factor in the treatment of diabetes mellitus with insulin."\textsuperscript{9} Although the DCCT findings indicate that the increased rate of severe hypoglycemia is not associated with deterioration of neuropsychologic function,\textsuperscript{10} sufficient data and case reports suggest that hypoglycemia cannot be ignored as a benign consequence of treating diabetes mellitus.\textsuperscript{11}

The controversy surrounding the risks and benefits of tight glycemic control of diabetes mellitus is even more fierce when the patients involved are children. Three additional elements add to this controversy, as it relates to children: (1) children (especially those who are very young) seem to be at greater risk than adults for the development of neuropsychologic impairment as a result of hypoglycemia, (2) available data suggest that the effect of hyperglycemia on the development of complications of diabetes is less important before puberty than later, and (3) the DCCT did not study any subjects younger than 13 years who were not at least in the early stages of puberty (Tanner stage II). In this issue of Mayo Clinic Proceedings (pages 211 to 216), Lteif and Schwenk report on their experience in the management of 59 children with onset of diabetes by age 9 years who underwent follow-up at Mayo Clinic Rochester for at least the first 2 years after diagnosis. Although the study cohort may be too small to yield results that can serve as the basis for firm recommendations, their results do indicate the importance of modifying and individualizing goals of diabetes treatment depending on the age of the patient and other factors.

The results of Lteif and Schwenk lead to two general conclusions. First, the younger patients had a more rapid onset of disease and more severe initial manifestations than did the older children. This fact is evidenced by the higher frequency of diabetic ketoacidosis at onset, the shorter duration of symptoms, and the lower HbA\textsubscript{1c} (an indication of shorter duration of hyperglycemia before manifestation of the severe symptoms or ketoacidosis). In addition, the youngest children seem to have a more rapid progression of pancreatic \(\beta\)-cell loss. This situation is indicated by the shorter "honeymoon" period (that is, phase of recovery of some \(\beta\)-cell function shortly after diagnosis of diabetes) and the higher insulin doses (in units per kilogram daily) for the younger patients during the first 6 months of therapy.

Second—and what I consider the most important aspect of the findings reported by Lteif and Schwenk—the younger children had more hypoglycemic episodes than did the older children, even though they also had higher HbA\textsubscript{1c}. Indeed, 55% of patients from 0 to 2 years old, 45% of those between 2 and 5 years old, but only 13% of those from 5 to 9 years old at diagnosis of diabetes experienced at least one episode of severe hypoglycemia during the first 2 years of follow-up. Hypoglycemia-induced seizures also occurred most frequently in the youngest children (22% of the infant group versus 10% of the preschool group and 3% of the oldest group). The children in the youngest group
had more than twice the rate of severe hypoglycemic episodes as those in the preschool group (66 versus 30 episodes/100 patient-years) and 10-fold more such episodes than those in the oldest group studied (66 versus 5 episodes/100 patient-years). These increased rates of severe hypoglycemia occurred even though the HbA1c during the period of follow-up was higher in the younger patients. Most severe hypoglycemic reactions had no identifiable cause in the youngest group, whereas a cause was identified in most of the preschool group.

Finally, although not addressed by Lteif and Schwenk, previous reports have suggested that tight glycemic control may contribute to some preservation of β-cell function or at least slowing of the destruction of β-cells during the early years of diabetes. My experience with a randomized, controlled trial of 34 children (age range, 7 to 17 years; mean age, 11.7) with newly diagnosed type 1 diabetes mellitus, however, suggests that intensive therapy with the aim of maintaining near-normal plasma glucose levels for the first 2 years after diagnosis does not preserve residual β-cell function, as measured by C-peptide release in response to Sustacal (unpublished data). This result occurred despite the fact that the study subjects who received intensive therapy had a threefold increased risk of severe hypoglycemia. The reasons for differences between my observations and the results reported by the DCCT and Shah and associates are unclear, but they could be related to the younger age of the patients in my study and the more rapid progression of β-cell loss in younger patients. In any event, when goals for plasma glucose levels in children with diabetes are being established, consideration of the well-known risks of hypoglycemia as well as the potential benefits of intensive therapy is important.

These results have salient implications. Severe hypoglycemia is common among infants and very young children with diabetes mellitus. Because numerous studies have suggested that hypoglycemia during the early years of life—when maturation of the central nervous system may be incomplete— is not benign and may result in some degree of permanent cognitive impairment, the avoidance of hypoglycemia in this age-group is even more important than at other times of life. Infants and very young children are often unable to recognize and react to a low plasma glucose level; therefore, constant vigilance by the parents or caretaker is essential, or hypoglycemia may go unnoticed until it reaches a potentially dangerous level. My own experience agrees with the findings reported by Lteif and Schwenk that the avoidance of hypoglycemia must be an even more important goal in the management of diabetes in infants and very young children than the avoidance of mild or moderate degrees of hyperglycemia. Guidelines for the management of diabetes in children must be modified and individualized. Optimal diabetes control cannot be based solely on the measurement of HbA1c. The avoidance of severe hypoglycemia and the prevention of hypoglycemia-associated autonomic failure (including defective glucose counterregulation and hypoglycemia unawareness) must also be considered important components of control. In children, physical and emotional growth and development must also be elements of assessing the results of treatment of diabetes.

On the basis of the prevailing literature, Bolli suggested that the target for HbA1c in adults with type 1 diabetes mellitus should be in the 6 to 7% range. This recommendation is based on data suggesting that higher HbA1c values (more than 7.0 to 7.5%) are associated with more frequent development or progression of long-term complications, whereas lower HbA1c values (less than 6.0 to 6.5%) are associated with higher rates of hypoglycemia. The targets for HbA1c below 7% and preprandial plasma glucose values of 70 to 120 mg/dL, however, are inappropriate for infants and children younger than 5 years old. As children reach the school-age years, a point at which they can begin to recognize and treat mild hypoglycemic episodes appropriately, glycemic goals can be lowered and gradually approach those appropriate for adolescents and young adults.

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REFERENCES


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