

Glycemic Control in Prepubertal Years

It has been suggested that prepubertal children with diabetes are protected against the adverse effects of poor diabetes control on the microcirculation. In this issue of *Diabetes Care*, Donaghue et al. (1) present evidence that the prepubertal years of diabetes add to the risk of diabetic complications, though not at the same rate as the postpubertal years. This is an important issue concerning the potential benefits and risks of intensive treatment in young patients.

A criticism of the Donaghue article might be the relatively small number of subjects, as only 90 of the original 193 adolescents were reassessed as young adults. The major factor examined in the article was duration of diabetes (prepubertal and postpubertal) in relation to eye and kidney damage. Duration obviously includes the many other influential factors (glycemic control, blood pressure levels, tobacco use, and other unknown factors). As in the Diabetes Control and Complications Trial (DCCT) (2), they found that a higher A1C during adolescence had an independent effect on the risk of retinopathy. There is no evaluation of prepubertal A1C levels mentioned, so the slower rate of development of retinopathy during the prepubertal versus the postpubertal years could have been due in part to lower A1C levels during that period of development. Parents have more control in the prepubertal years, and growth hormone and other hormone levels are not as high during that period.

The DCCT included adolescents aged 13–17 years at entry, but it did not study younger children. A1C levels were lowered from a mean of 9.8% in the conventionally treated teens to 8.1% in those receiving intensive therapy ($P < 0.001$) (2). After 3 or 4 years of additional follow-up post-DCCT, the A1C levels were similar for the intensive (8.4%) and conventional (8.5%) treatment groups (3). However, the intensive treatment group continued to have a reduced risk of worsening in retinopathy of three or more steps (by 74%, $P < 0.001$) or of progressing to proliferative or severe nonproliferative retinopathy (by 78%, $P < 0.007$). These results suggest that most patients

with type 1 diabetes should receive intensive therapy aimed at achieving glycemic control as close to normal as possible and as early in the course of their disease as possible to reduce the risk of microvascular complications.

The issue becomes more complicated in suggesting glycemic control “as close to normal” for younger children (as recommended for adolescents and adults by the DCCT). Lower A1C values were associated with a greater likelihood of severe hypoglycemia in the DCCT. There was a 60% increase in risk per 10% lower A1C in the conventional treatment group, and there was a 27% risk increase in risk per 10% lower A1C in the intensive treatment group (4). Several studies have demonstrated central nervous system damage as a result of hypoglycemia in children (5–9). This would be expected to be particularly true for children under 5 years of age, when myelin lipid development is still occurring (10); such a process is affected by hypoglycemia (11). Our family education manual has suggested different A1C levels for different aged children with higher levels for younger children (12). An alternative is to have a single target value (e.g., $<8\%$) that should apply for children of all ages. It might be easier for families and care providers to remember a single value. The value of $>8\%$ is a level for which the risk for microalbuminuria has been suggested to increase substantially (13–17).

The truth is that this is a moot issue because most pediatric diabetes programs are unable to get close to the A1C target of $<8.0\%$. The Joslin Clinic recently reported mean A1C levels of 8.7% for 300 of their children (18). The target is also lower than the mean of 8.6% reported for 2,873 children with type 1 diabetes in 18 countries in Europe plus Japan and the U.S. (19), and it is lower than the 8.97% mean reported in 2,579 French children (20). In these studies, approximately one-third of the children achieved A1C levels $<8\%$. Thus, an A1C target $<8.0\%$ may be a much more realistic target level for children than the suggested level of 7.0% for adults (21). It would help families who have children with diabetes to have a

consistent target level, such as $<8\%$, although it will likely require a recommendation from a national group such as the American Diabetes Association to make this common practice.

Opponents to setting target levels in children will cite the hypoglycemia risk discussed above, as well as the fact that a proper randomized trial, such as the trial conducted in adolescents and adults in the DCCT, has not been done for younger children. Such a study would be very costly and very lengthy, if not impossible. Conducting a prospective randomized trial is much different than evaluating longitudinal data, as in the Donaghue article. With the current DCCT data, the suggestive data from the Donaghue article, and the increased danger from hypoglycemia in young children, it might even be considered unethical. Yet, the best course for now seems to be to aim for an A1C level $<8\%$ in all children. With advances that have occurred since the DCCT, such as new insulin analogs, new methods of continuous glucose monitoring, easier to use meters (including alternate-site testing), and a rapid rise in the number of children using insulin pumps, it is expected that more children will have A1C values $<8\%$. Clearly, family practices in the prepubertal years provide a precedent for later years. Sadly, there will always be some individuals who will not achieve this goal. A “closed-loop” insulin pump or islet transplantation may eventually be the answer. In the meantime, more children with suboptimal glycemic control will likely be referred to diabetes care centers. Adequate numbers of care providers, adequate space in specialty clinics, and adequate reimbursement for intensive diabetes management (all of which are currently lacking) will be necessary. The future is now!

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