

## Managing Diabetes in Children and Adolescents—Is There an Optimal Regimen?

a report by

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### Treatment of Type 1 Diabetes in Children and Adolescents

Diabetes is one of the most common chronic conditions affecting children worldwide. Statistics gathered by the National Institutes of Health (NIH) in 2005 revealed that one out of every 400–600 children in the US had been diagnosed with type 1 diabetes.<sup>1</sup> This figure increases annually, with reports of the global incidence of diabetes in children and adolescents increasing at a rate of 3% per year.<sup>2–4</sup> The greatest increase in incidence has been reported in children  $\leq 5$  years of age.<sup>5</sup> This equates to approximately 190,000 children, with their families attending to the usual demands of ensuring the physical, intellectual, and emotional health of a toddler, school-age child, or adolescent while trying to maintain their blood-glucose levels in a range as close to normal as possible.

An optimal therapeutic regimen needs to minimize episodes of hyperglycemia and hypoglycemia while maintaining the hemoglobin A1C (A1C) within the target range. The Diabetes Control and Complications Trial (DCCT) established A1C as the gold standard by which diabetes control should be assessed. This is because of the clear correlation between the

decrease in A1C attained through intensive diabetes management and the decrease in subsequent incidence of both micro- and macrovascular complications.<sup>6,7</sup> There is growing evidence that glycemic excursions may play an important independent role in the development of complications.<sup>8</sup> This implies that insulin delivery that approximates physiological patterns of insulin secretion may decrease the incidence of micro- and macrovascular complications further than lowering A1C alone.

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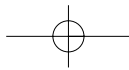
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research bench are made available to the patients as rapidly as possible. A major focus of Dr Goland's work is translational research and clinical trials in adult and pediatric patients with type 1 diabetes, type 2 diabetes, obesity, and impaired glucose tolerance. She is on the Boards of the Juvenile Diabetes Research Foundation and the New York Stem Cell Research Foundation. Dr Goland received her BA in History from Harvard College and her MD from Columbia University College of Physicians and Surgeons.

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There are only two regimens that come close to approximating physiological insulin delivery, both of which operate on the theory of 'basal-bolus' insulin dosing. Multiple daily injection (MDI) regimens that utilize non-peaking, long-acting insulin (glargine) with boluses of rapid-acting insulin analogs begin to mimic the pattern of endogenous insulin secretion. However, replication of an even more physiological pattern can be achieved by using continuous subcutaneous insulin infusion (CSII) via an insulin pump. CSII provides the user with the ability to deliver insulin doses in the most precise, flexible, and physiological pattern available. An optimal diabetes regimen should also allow for participation in all academic, social, and athletic pursuits that would be available to the child in the absence of the diagnosis. CSII provides children and adolescents with a flexible regimen that minimizes restrictions on activities that are important to their overall development.

A recent consensus statement presented a thorough discussion of the available evidence regarding the benefits and risks of the use of CSII in pediatric patients.<sup>9</sup> A randomized controlled trial in adults reported a reduction of 0.5–1.2% in A1C in subjects using CSII versus those using MDI.<sup>10</sup> A small, randomized trial that compared CSII with MDI in pediatric subjects found a significant reduction in A1C at short-term follow-up.<sup>11</sup> Longer follow-up has been reported in numerous observational studies that support that this benefit persists over time.<sup>12–15</sup> Recommended target values for A1C will differ between age groups and clinical centers. Generally, there is agreement that we should strive to keep the A1C as close to normal as possible while minimizing hypoglycemic events.



Hypoglycemic events are of particular concern in children  $\leq 5$  years of age because of the possible impact of severe hypoglycemia on cognitive function in this age group. However, studies have reported an absence of adverse findings in children exposed to severe hypoglycemia in the setting of type 1 diabetes and the supposition that severe hypoglycemia will lead to neurocognitive dysfunction has been called into question.<sup>16,17</sup> In children of all ages, there is concern that repeated episodes

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of hypoglycemia will lead to hypoglycemic unawareness. Severe hypoglycemic episodes may result in a degree of fearfulness in both the patient and his or her family that may become a barrier to attaining glycemic control.<sup>18,19</sup> Numerous observational studies in children have found that the use of CSII decreases the frequency of severe hypoglycemic events compared with MDI.<sup>12,20–21</sup> As technology advances, specifically with regard to the development of increasingly accurate continuous glucose monitors, the level of A1C that can be reached safely may continue to decrease and targets may be adjusted.

The management of diabetes in each stage of childhood and adolescence presents specific and unique challenges. In the toddler and pre-school-age group, children do not often experience or may not be able to recognize and/or verbalize hypoglycemic symptoms. In adolescence, psychosocial and body image concerns, increasing insulin resistance, and fluctuating insulin requirements during periods of growth present additional factors that must be managed by the patient and the team. While CSII seems to best fit the criteria for the ‘optimal regimen’ for the treatment of type 1 diabetes in children and adolescents, helping each individual reach his or her therapeutic goals will require insulin regimens that can be individually tailored. Increased frequency of blood glucose monitoring and of insulin boluses have both been associated with improved glycemic control. These are concrete behaviors that can be reviewed and encouraged at each quarterly visit with the diabetes team. As the age of diagnosis decreases, the potential cumulative exposure to hyperglycemia over the course of a lifetime and the subsequent lifetime risk of complications will increase. This suggests that ‘optimal control’ may need to be redefined in this population. Although A1C targets have generally been higher for younger patients, this group of children has the potential to live longer with diabetes than any group that has preceded them. This is a group that deserves special attention and careful study. The extent to which we are able to optimize glycemic control in this population may have profound effects not only on the individual, but also on the entire healthcare system.

### Treatment of Type 2 Diabetes in Adolescents

Until recently, nearly all diabetes in children and adolescents was type 1 diabetes. However, in the past few years type 2 diabetes has been noted to occur in youth, particularly those between eight and 19 years of age.<sup>22–24</sup> The

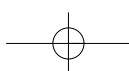
cause for the 33% increase in incidence in type 2 diabetes in children and adolescents is thought to be related to the coincident epidemics of obesity and inactivity.<sup>25–26</sup> Recently, type 2 diabetes has been reported to constitute up to 45% of all new cases of pediatric diabetes in some clinics in the US.<sup>22–24</sup> Optimal strategies for diagnosis, management, and prevention are under study. Childhood-onset type 2 diabetes occurs in the same populations as adult-onset type 2 diabetes. It is most often seen in obese, insulin-resistant patients, particularly those from ethnic minority populations and those with a family history of type 2 diabetes and gestational diabetes. It is likely that both genetic and environmental factors play a role in pathogenesis, although the exact genes involved have not yet been identified. The environmental factors that cause hyperglycemia in a genetically susceptible child or adolescent appear similar to those that play a role in adults, and include increased bodyweight and decreased physical activity.<sup>25–26</sup> There is growing evidence that an abnormal intra-uterine environment, such as that in a pregnancy complicated by maternal gestational diabetes or severe obesity, may play a role in predisposing the offspring to obesity and diabetes, perhaps by affecting the normal growth and development of the pancreatic insulin-secreting cells or the central nervous system appetite-control centers in the developing fetus.<sup>27,28</sup>

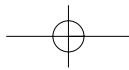
Recent studies have documented the dramatic increase of overweight and obesity in childhood, as well as an increasing incidence of insulin resistance and the metabolic syndrome.<sup>29–32</sup> However, studies have not demonstrated that population-based screening with glucose tolerance testing uncovers sufficient numbers of patients with type 2 diabetes to be recommended. Guidelines from the American Diabetes Association (ADA) advise performing a fasting glucose test in high-risk children starting at 10 years of age and then, if normal ( $<100\text{mg/dl}$ ), every two years.<sup>33</sup> High-risk children are those who are obese (body mass index (BMI)  $>85$ th percentile for age and sex) plus any of the two risk factors that follow: family history of type 2 diabetes or gestational diabetes, high-risk ethnicity—including Native Americans, Hispanic, Asian, or Pacific Islander—and signs of insulin

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resistance, including acanthosis nigricans, hypertension, polycystic ovarian syndrome, and dyslipidemia. A diagnosis of diabetes is made when the fasting blood sugar exceeds  $125\text{mg/dl}$  and pre-diabetes is diagnosed when the blood sugar is between  $100$  and  $125\text{mg/dl}$ . Distinguishing between type 1 and type 2 diabetes may be challenging in some cases as some patients with type 2 diabetes may present with diabetic ketoacidosis.<sup>34</sup> The presence of islet cell autoantibodies is strongly suggestive of type 1 diabetes, while those with absent autoantibodies, elevated C-peptide, signs of obesity, and insulin resistance are more likely to have type 2 diabetes.

The goals for glucose control in pediatric type 2 diabetes are similar to those in pediatric type 1 diabetes: individualized goals aiming for the blood sugar





## Diabetes Management

and hemoglobin A1C levels to be as close to normal as possible, while avoiding hypoglycemia and excessive weight gain and fostering normal growth and development.<sup>35-37</sup> As in adults, diet and exercise are first-line

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therapies. If these are inadequate in helping the patient achieve euglycemia, oral medications approved for use in children can be used, such as metformin. In many pediatric patients with type 2 diabetes, diet, exercise,

and oral medication will not be sufficient to achieve euglycemia and insulin will be required. In some patients, the combination of metformin and night-time glargine insulin has been successful. The NIH-sponsored 'Treatment Options for Type 2 Diabetes in Adolescents and Youth' multicenter study is seeking to identify the optimal treatment for pediatric type 2 diabetes (<http://www.niddk.nih.gov/patient/today/today.htm>).<sup>38</sup> Children and adolescents with type 2 diabetes often have other components of the metabolic syndrome, such as dyslipidemia (hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol), hypertension, and central obesity. These conditions, as well as inactivity, predispose them to cardiovascular as well as microvascular complications.<sup>39</sup> These comorbidities must be treated too. Surveillance for vascular complications of diabetes must be undertaken.<sup>40,41</sup> Preliminary reports suggest that vascular complications may be appearing more rapidly in pediatric patients than in adults with type 2 diabetes for reasons that are unclear and require additional study. Prevention of obesity and prevention of type 2 diabetes, especially in young people, is the goal. ■

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