Disease Management in the Young Diabetic Patient: Glucose Monitoring, Coping Skills, and Treatment Strategies

Stuart A. Weinzimer, Elizabeth A. Doyle and William V. Tamborlane, Jr

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Disease Management in the Young Diabetic Patient: Glucose Monitoring, Coping Skills, and Treatment Strategies

Stuart A. Weinzimer, MD[1]
Elizabeth A. Doyle, MSN, APRN, CDE[1]
William V. Tamborlane, Jr, MD[1,2]

Summary: Type 1 diabetes mellitus was thought to be the prevalent type of diabetes in children and adolescents; however, increasing numbers of juvenile patients appear to have type 2 diabetes. Management of all diabetes in young patients should include regular assessment, careful monitoring for glycemic control and the presence of hypoglycemia, and educational training on disease management. Hypoglycemic episodes, especially nocturnal events, are frequent in the young diabetic patient. Improvements in glycemic control and nocturnal hypoglycemia have been observed with continuous subcutaneous insulin infusion and insulin glargine. A continuous glucose-monitoring system can provide important insight into 24-hour glycemic control. Overall, careful management, monitoring, and education can improve glycemic control and yield positive treatment outcomes in the child or adolescent with diabetes. *Clin Pediatr.* 2005;44:393-403

Introduction

Both type 1 and type 2 diabetes mellitus are increasingly important health problems in children and adolescents today.[1] Type 1 diabetes (juvenile or insulin-dependent diabetes) is due primarily to insulin deficiency caused by autoimmune destruction of the pancreatic beta cells. During adolescence, or in cases of poor control, superimposed insulin resistance directly influences the amount of insulin needed for glucose control and complicates diabetes management.[2] The major pathogenic factor in type 2 diabetes (adult-onset or non–insulin-dependent diabetes) is insulin resistance, resulting in a functional or relative insulin deficiency.[1] The complex molecular events that lead to the evolution of type 2 diabetes mellitus are not completely understood, especially in the pediatric population.[1] Historically, type 1 diabetes was considered the primary form of diabetes found in children.[3] Today, however, 8% to 46% of newly diagnosed cases of diabetes in children are type 2 (Table 1).[4,5] This surge in the incidence of type 2 diabetes has been described as an epidemic.[6]

This review will discuss strategies for treating young patients with diabetes, focusing on a treatment regimen that includes diet,

[1]Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [2]The General Clinical Research Center, Yale University, New Haven, CT.

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Reprint requests and correspondence to: Stuart A. Weinzimer, MD, Assistant Professor, Department of Pediatrics, Yale University School of Medicine, 333 Cedar Street, PO Box 208064, New Haven, CT 06520.

Table 1

ESTIMATES OF THE MAGNITUDE OF TYPE 2 DIABETES IN NORTH AMERICAN CHILDREN

Study Type	Date	Race/Ethnicity	Age (y)	Estimated Magnitude
Population-based				Prevalence/1,000
Arizona	1992–1996	Pima Indians	10–14	22.3
			15–19	50.9
Manitoba	1996–1997	First Nations	10–19	36.0 in girls
NHANES III (all US)	1988–1994	Whites, African Americans, Mexican Americans	12–19	4.1*
Clinic-based				Prevalence/1,000
Indian health services (all US)	1996	Native Americans	0–14	1.3*
			15–19	4.5*
Manitoba	1998	First Nations	5–14	1.0
			15–19	2.3
Clinic-based				Annual Incidence/100,000
Cincinnati, OH	1994	Whites, African Americans	10–19	7.2
Case series				Percentage of type 2 diabetes cases among all new diabetes cases
Cincinnati, OH	1994	Whites, African Americans	0–19	16
Charleston, SC	1997	African Americans	0–19	46†
San Diego, CA	1993–1994	Whites, African Americans, Hispanics, Asian Americans	0–16	8
San Antonio, TX	1990–1997	Hispanics, Whites	0–19	18
Ventura, CA	1990–1994	Hispanics	0–17	45

*Estimates include type 1 and 2 diabetes.

†Percentage of type 2 diabetes among nonincident cases of diabetes.

Adapted from Fagot-Campagna et al.[5]

NHANES III = Third National Health and Nutrition Examination Survey.

exercise, pharmacologic intervention, monitoring of glycemic control, and education/coping skills.

Diabetes in Adolescents

The major landmark clinical trials in diabetes, the Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) in patients ≥20 years of age with type 2 diabetes, provided strong evidence that intensive therapy with pharmacologic agents (insulin and oral antidiabetic agents) was needed to achieve lower daily blood glucose levels and limit diabetic complications. The increasing incidence of diabetes, especially in the adolescent and pediatric population, suggests that the paradigms for treating diabetes in the young (standard basal/bolus therapy in type 1 patients) must change so that young patients with type 2 diabetes are also considered. These changes can be made by adopting the principle of intensive therapy as used in the DCCT and the UKPDS. Currently, there are many agents (insulin, insulin analogs, oral antidiabetic agents) and delivery devices and systems (insulin pumps, insulin pens, and continuous glucose sensors) for the treatment of young patients with type 1 or type 2 diabetes to safely control daily blood glucose levels and limit quality of life issues.

Young Patients with Type 1 Diabetes

Continuous Subcutaneous Insulin Infusion

In the 1970s, the technology for the delivery of continuous exogenous insulin via battery-powered pumps for the management of type 1 diabetes was introduced.[7,8] However, in 1998, less than 5% of patients starting therapy with continuous subcutaneous insulin infusion (CSII) were under 20 years of age despite the benefits offered by this innovative approach.[9,10] The reasons for this low acceptance rate of CSII in young patients vary from psychosocial issues to cost.[9,11]

Perhaps the most critical barrier to the greater use of CSII in the young was the lack of clinical evidence correlating tight glycemic control and long-term benefits.[12] However, a subpopulation analysis of young diabetic patients (13–17 years of age) within the DCCT demonstrated the association between stringent glucose control and significant benefit with respect to both primary and secondary prevention of long-term complications of type 1 diabetes.[13] The dramatic increase in the number of children and adolescents starting on CSII therapy today is due at least partly to the findings of this study.[12]

CSII can be offered as a treatment alternative to multiple daily injections (MDI) of insulin in pediatric patients who are motivated to reach tight glucose control goals, who measure blood glucose at least 4 times per day, who experience repetitive episodes of hypoglycemia, particularly at night, and/or who desire increased flexibility for the amount and timing of meals and exercise.[12,14] Compared with injection therapy, CSII in this population has been successful in achieving both mean glycosylated hemoglobin (HbA_{1c}) concentrations of 7.5% and declines in severe hypoglycemia. Acceptance of CSII is high, and more than 98% of children who started on this therapy remained on it.[12] CSII has also been reported to decrease the rate of diabetic ketoacidosis in young patients with uncontrolled disease.[10]

A prospective study in adolescents evaluated the clinical and psychosocial outcomes of CSII and MDI of insulin over 12 months.[9] After 1 year, young patients with type 1 diabetes treated with CSII needed significantly less insulin than those who used MDI ($P=0.009$).[9] Both groups exhibited significantly decreased HbA_{1c} concentrations over the course of the study ($P<0.02$) vs. baseline. However, from 6 to 12 months, HbA_{1c} concentrations rebounded modestly in patients treated with MDI but not in those treated with CSII.[9] CSII was associated with a reduction of approximately 50% in hypoglycemic episodes resulting in coma or requiring assistance compared with MDI. The MDI-treated group experienced more weight gain and had more difficulty in coping with diabetes than did the CSII-treated group.[9]

Two recent reports[15,16] illustrate that even outside of a clinical research experience, CSII can be successfully implemented and maintained in a busy office practice. In the first report,[15] 161 children with type 1 diabetes, 18 months to 18 years of age, were switched from traditional mixed-dose insulin regimens to insulin pump therapy. HbA_{1c} concentrations fell from 7.1% to 6.5% in preschoolers, from 7.8% to 7.3% in school-age children, and from 8.1% to 7.4% in adolescents during the first year on pump therapy. Simultaneously, rates of severe hypoglycemia dropped significantly, from 56 to 38 episodes per 100 patient-years. These improvements were sustained for up to 2.5 years of follow-up. The analysis of very young children (<7 years of age) was extended and demonstrated that improvements in HbA_{1c} and rates of severe hypoglycemia persisted for up to 4 years after pump initiation. Furthermore, children who received daytime care from nannies or daycare centers benefited the most from CSII, showing that pump care could be easily taught to alternate care providers.[16]

Using CSII at night may be a viable treatment alternative for children who experience large fluctuations in nocturnal blood glucose levels but do not wish to use a pump during the day. An evaluation of 10 preadolescent children (7–10 years of age) with poorly controlled diabetes demonstrated a significant decrease in mean average, breakfast, and 3 AM glucose levels with CSII only at night compared with MDI therapy during the day ($P<0.003$).[17] Overall, in appropriately selected young diabetic patients, CSII improves quality of life, disease knowledge, adherence to treatment regimens, and responsibility for diabetes management.[17]

Injection of Insulin Analogs

Although the success of CSII has been documented, many patients require or request other options. Injectable insulin therapy can quickly restore glycemic control, but the biochemical changes associated with puberty that induce peripheral resistance to insulin[18] typically make larger doses necessary, increasing the risk of weight gain and/or unpredictable hypoglycemia.[9] Insulin analogs—such as insulin lispro, insulin aspart, and insulin

glargine modified for specific uses, either for prandial or basal insulin needs—have become particularly useful for adolescents with type 1 diabetes.[12] Human neutral protamine Hagedorn (NPH) insulin remains a poor choice for basal insulin in the young because of its substantial peak and relatively short duration (Figure 1).[19]

Insulin lispro, a rapid-acting insulin analog, is associated with reduced glucose fluctuation and less postprandial hyperglycemia and nocturnal hypoglycemia in young patients with type 1 diabetes than regular insulin.[20] The pharmacokinetics of insulin aspart have been evaluated in children and adolescents with type 1 disease.[21] Its more rapid onset of action compared with regular insulin was confirmed in this pediatric population. Insulin glargine, a new, long-acting insulin analog, forms microprecipitates after subcutaneous injection, allowing the slow release of small amounts of drug. The resultant relatively constant concentration-time profile makes it ideal for once-daily dosing as a basal insulin.[22] The efficacy and safety of insulin glargine have been established in 5 clinical studies in children and adolescents with type 1 diabetes (Table 2).[23-27] Insulin glargine therapy resulted in a dramatic reduction in hypoglycemia, including severe and nocturnal episodes, compared with short- and intermediate-acting insulins. Long-term (≤36 months) efficacy and safety have been established in this population.[25] A suggested management algorithm for youth with type 1 diabetes is illustrated (Figure 2).

Young Patients with Type 2 Diabetes

The UKPDS was conducted in patients 25 to 65 years of age with newly diagnosed type 2 diabetes.[28] Tight glucose control with either sulfonylureas or insulin produced a substantial decrease in the risk of microvascular complications.[28] Although children and adolescents did not participate in this landmark study, the results demonstrated the importance of intensive blood glucose control in patients with type 2 diabetes, regardless of age.

Compared with type 1 diabetes, type 2 disease has a more insidious onset, with more subtle increases in thirst or urination, hypertension, and acanthosis nigricans.[3] It is almost always associated with obesity and a family history of type 2 diabetes. In addition,

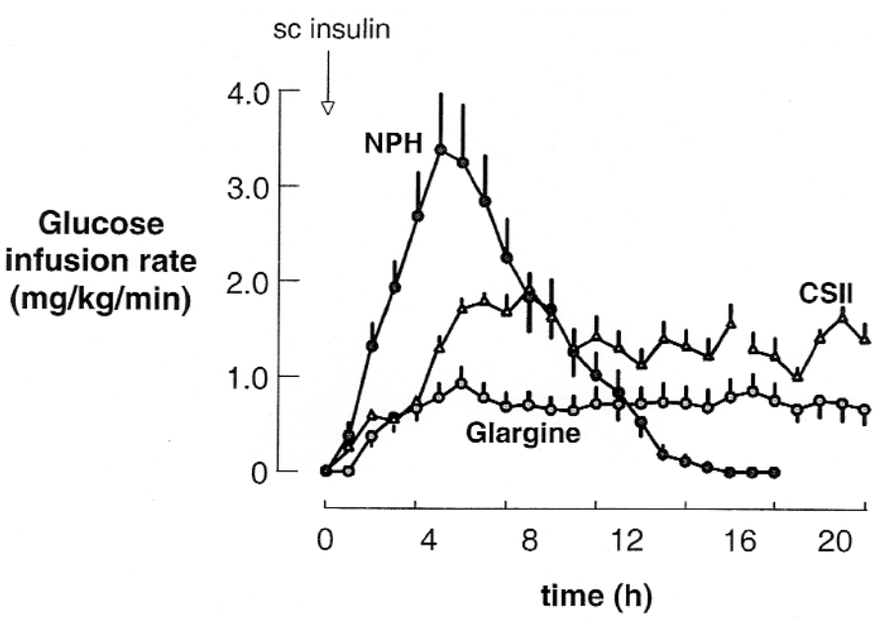

Figure 1. Insulin time-action profiles during glucose infusion. Glucose infusion rate required to maintain euglycemia indicates potency of insulin action. Adapted with permission from Lepore et al.[19] CSII = continuous subcutaneous insulin infusion; NPH = neutral protamine Hagedorn; sc = subcutaneous.

Table 2

SUMMARY OF CLINICAL TRIAL EXPERIENCE WITH INSULIN GLARGINE IN YOUNG PATIENTS WITH TYPE 1 DIABETES

Study	Description	Treatment	Population	Results with Insulin Glargine
Schober et al.[23]	Open-label, multicenter, randomized	1 bedtime injection of IG or NPH insulin once or twice daily	n = 349 Age, 5–16 y	• Lower fasting blood glucose levels (P=0.02) • Less risk of hypoglycemia, especially nocturnal hypoglycemia
Kordonouri et al.[24]	Open-label, crossover	2–4 injections of NPH and/or zinc lente insulin switched to 1 bedtime injection of IG for 4–8 wk	n = 30 Age, 14.2 y (median) 4.5–18.3 y (range)	• Significant reduction in nighttime hypoglycemia (P=0.002) • No change in HbA_{1c} • Similar hypoglycemic and hyperglycemic glucose levels as with NPH and/or zinc lente insulin
Dunger et al.[25]	Open-label, multinational, uncontrolled extension	1 bedtime injection of IG plus regular human insulin before meals for ≥36 mo	n = 143 Age, 11.9 ± 2.5 y (mean ± SD)	• Maintenance of HbA_{1c} <9.0% • No unexpected safety findings: severe hypoglycemia in 7 patients (4.9%); injection site reactions (subsided with no change in dose) in 10 patients (7.0%)
Murphy et al.[26]	Open-label, randomized, active-controlled, 2-way crossover	Two 16-wk treatment periods: 1 bedtime injection of IG or NPH insulin plus preprandial lispro or regular insulin	n = 26 Age, 14.8 ± 1.7 y (mean ± SD)	• Lower fasting blood glucose levels (P<0.0001) • Lower glucose levels in morning and before and after lunch (P<0.01 and P<0.002, respectively) • Lower incidence (43%) of asymptomatic nocturnal hypoglycemia (P<0.05) • Lower overall insulin use (P<0.01)
Pearson et al.[27]	Retrospective	MDI of short- and intermediate-acting insulin switched to IG for ≥3 mo	n = 140 Age, 2–21 y	• Reduction (73%) in severe hypoglycemic episodes

HbA_{1c} = glycosylated hemoglobin; IG = insulin glargine; NPH = neutral protamine Hagedorn; MDI = multiple daily injections.

30% of young diabetic patients will present with ketosis, and 5% will present with ketoacidosis.[3,4,29,30] Normal or elevated fasting insulin and C-peptide levels are more common in patients with type 2 diabetes,[3] while low or undetectable levels of serum insulin and C-peptide, and elevation of autoantibodies (i.e., anti-insulin, anti-islet cell, antiglutamic acid decarboxylase, antityrosine phosphatase), are more characteristic in type 1 disease.[3] There is often no family history of type 1 diabetes or other autoimmune disease.

Several risk factors for type 2 diabetes in adolescents have been identified (Table 3).[3,31,32] All have insulin resistance as a common denominator[32] and are consistent with the risk factors for type 2 disease in adults.[29] It is estimated that one third to one half of all cases of type 2 diabetes in adults are undiagnosed.[31,33-35] If this profile also holds true for adolescents, many young people may remain undiagnosed for some time,[31] resulting in an increased

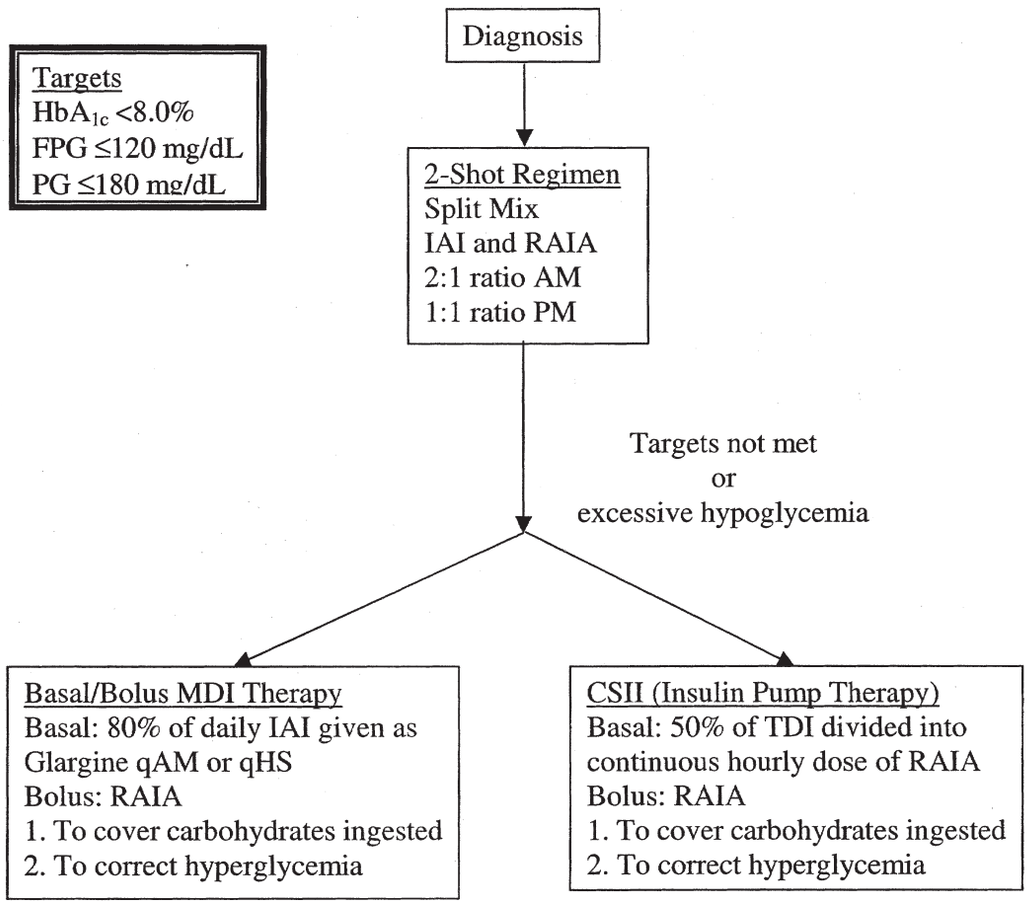

Figure 2. Suggested algorithm for insulin use (MDI or CSII) in youth with type 1 diabetes. CSII = continuous subcutaneous insulin infusion; FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin; IAI = intermediate-acting insulin; MDI = multiple daily injection; PG = preprandial glucose; RAIA = rapid-acting insulin analog; TDI = total daily insulin. RAIA to correct hyperglycemia: 1 unit RAIA lowers glucose by approximately 1,800/TDI.* RAIA to cover carbohydrates: 1 unit RAIA covers approximately 500/TDI g carbohydrate.* *These are guidelines and should obviously be adjusted by results of self-monitoring blood glucose.

potential for long-term complications of uncontrolled diabetes.

In the United States, 25% of children and adolescents are obese or are at risk for becoming obese. Obesity is the number one nutritional disease of children today.[36] Environmental and genetic factors play a part in the increasing prevalence of obesity in the young. However, in both adults and children, it is a modifiable risk factor that responds to increased physical activity and good eating habits.[3] Not only is obesity a risk factor for developing type 2 diabetes, it also increases the potential for impaired glucose tolerance. A recent clinical study of 167 obese children (body mass index >95th percentile for age and gender) demonstrated a high prevalence of impaired glucose tolerance and insulin resistance despite relatively well-preserved beta-cell function.[37]

Insulin is approved for treating children with type 2 diabetes; a strategy for insulin initiation is shown in Figure 3. However, these patients may benefit from treatment with oral agents to improve glycemic control, facilitate administration and compliance, maintain weight, and address comorbid conditions.[38] Used worldwide for more than 40 years, metformin, an oral antihyperglycemic agent, has been approved by the US Food and Drug Administration (FDA) for children and adolescents, 10 to 16 years of age, with type 2 diabetes.[38] It was studied in a randomized, multicenter, placebo-

Table 3

RISK FACTORS FOR INSULIN RESISTANCE AND TYPE 2 DIABETES IN ADOLESCENTS

Type of Factor	Risk Factor
Modifiable	• Obesity[3,31,32]
	• Inactivity[3]
	• High caloric intake with excessive carbohydrates and fats[3]
	• Syndrome X*[31]
Nonmodifiable	• Familial history of type 2 diabetes in first- or second-degree relative[3]
	• Member of high-risk ethnic group (African American, Hispanic, Native American, Asian/Pacific Islander)[3]
	• Puberty[31]
	• Acanthosis nigricans[31]
	• Polycystic ovarian syndrome[31]

*Characterized by hyperinsulinemia, glucose intolerance, increased very low-density lipoproteins and triglycerides, decreased high-density lipoproteins, and hypertension.

controlled trial in patients, 8 to 16 years of age, known to have type 2 diabetes.[39] Forty-two patients were randomized to receive metformin (≤2000 mg/day) for a mean of 80 days; 40 others received placebo for a mean of 44 days.[39] Metformin was associated with a significant decrease in fasting plasma glucose and HbA_{1c} concentrations compared with placebo ($P<0.001$).[39] Currently, the safety and efficacy of other antidiabetic agents used in adults with type 2 diabetes are being investigated in children.[38] Insulin therapy may also be introduced if oral agents fail in adolescents as their disease progresses.

In young patients with type 2 diabetes, glycemic control is as important as it is in young patients with type 1 disease. However, some of these patients, especially teenagers, are reluctant to use intensive MDI regimens. This population may benefit from long-acting insulin analogs, such as insulin glargine, or from the use of mixed-dose insulin pens that reduce the burdens of self-care.[40] For successful management of diabetes in this population, self-monitoring of blood glucose (SMBG), particularly in insulin-treated patients, comprehensive education and coping skills training, and regular assessment for comorbidity, such as hypertension, dyslipidemia, and microalbuminuria, are essential.[40]

Monitoring Glycemic Control in Young Diabetic Patients

Hypoglycemia is the most common acute complication of type 1 diabetes, particularly in younger patients, who have a limited capacity for timing meals and activities and maintaining self-care regimens.[41] SMBG has enabled young patients with type 1 disease to achieve better glycemic control. However, SMBG provides only "snapshots" of daily glycemic patterns. Marked excursions in 24-hour blood glucose levels are frequent, even in patients whose diabetes is considered well-controlled, and these wide glucose fluctuations are often not captured by SMBG[42] (Figure 4). Continuous glucose sensors that capture glycemic trends missed with SMBG are powerful adjuncts to SMBG.

The continuous glucose monitoring system (CGMS®) developed by Medtronic MiniMed (Northridge, CA) is the first such system approved by the FDA. Used as a Holter-type monitor, it measures glucose in subcutaneous tissue with a glucose oxidase–based sensor, inserted via a removable needle and a spring-loaded device.[12] Glucose measurements are not read by the patient but are downloaded electronically by the physician, allowing retrospective review of the 72-hour glucose profile, including postprandial and nocturnal levels.[12] The CGMS has been evaluated in clinical studies in young patients with type 1 diabetes.[42-45] This method of glucose monitoring detected abnormal patterns of glycemic control and allowed physicians to make changes in the diabetes regimens of patients that led to improvements in HbA_{1c} concentrations even after 1 reading.

The other approved continuous glucose sensor, the GlucoWatch® Biographer (Cygnus, Redwood City, CA) is a watch-like device that uses reverse iontophoresis to draw interstitial fluid across the skin surface onto

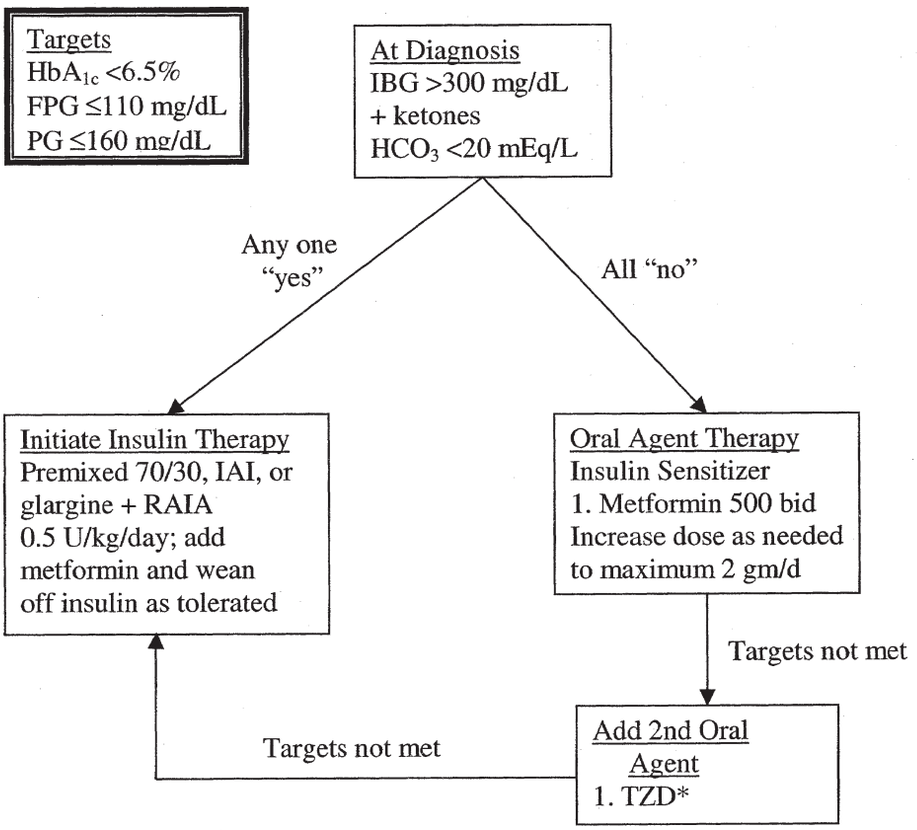

Figure 3. Suggested algorithm for management of youth with type 2 diabetes. FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin; IAI = intermediate-acting insulin; IBG = initial blood glucose; PG = preprandial glucose; RAIA = rapid-acting insulin analog; TZD = thiazolidinedione. TZDs: pioglitazone 15–45 mg daily or rosiglitazone 2–8 mg bid.* Secretagogues: glimepiride 1–4 mg/day, glipizide 2.5–10 mg daily bid, nateglinide 60–120 mg before meals, repaglinide 0.5–2 mg before meals.* *TZDs and newer secretagogues have not been approved for use in children.

a hydrogel disk for analysis of glucose concentrations. The GlucoWatch may be worn for up to 13 hours before the disks must be replaced and the device recalibrated. The GlucoWatch provides near real-time glucose levels at 10-minute intervals and is equipped with hypoglycemia alarms. In a small, short-term study, use of this device has been associated with improvements in HbA_{1c} concentrations and the detection of hypoglycemia.[45]

Current techniques of continuous glucose monitoring cannot replace SMBG because their accuracy has been shown to be inferior to that of traditional home glucose meters,[46-48] thus limiting their use as hypoglycemia alarms[49] (Figure 5). However, their use to analyze trends in glycemic excursions over time is becoming increasingly common.

Coping Skills Training

Adolescents with diabetes may find the physical, emotional, and social demands of managing a chronic disease difficult.[50] A recent study evaluated the potential benefits of a 12-month behavioral program that included coping skills training and intensive diabetes management.[51] All patients received intensive diabetes management consisting of 3 or more daily injections or CSII, SMBG at least 4 times a day, monthly outpatient visits, and interim telephone contacts. Patients were randomized to receive this disease management with (n = 41) or without (n = 34; control group) coping skills training. Regardless of treatment, all patients experienced significant declines in HbA_{1c} concentrations from baseline after 12

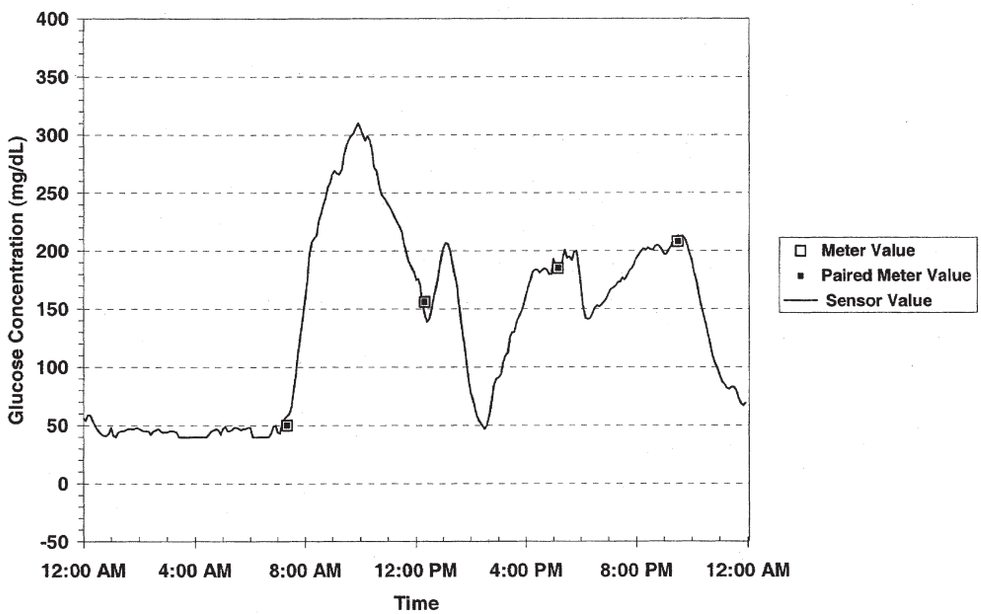

Figure 4. Illustrative example of wide glycemic swings (including postprandial hyperglycemia and nocturnal hypoglycemia) demonstrated with the continuous glucose monitoring system (CGMS) but missed by routine capillary glucose monitoring.

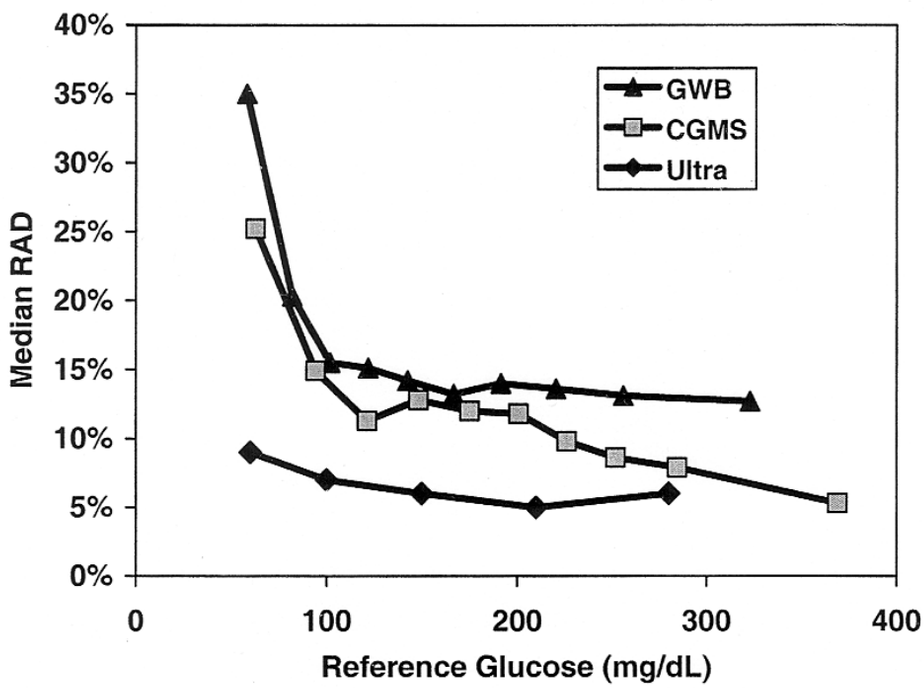

Figure 5. Point accuracy of currently available continuous glucose monitoring devices is inferior to traditional home glucose meters, particularly in the hypoglycemic range. GWB = GlucoWatch® Biographer, CGMS = Continuous Glucose Monitoring System®, RAD = relative absolute deviation, Ultra = One Touch® Ultra home glucose meter.

months (P<0.001). However, those who also received coping skills training experienced a faster and greater decline in HbA_{1c} concentrations after 6 and 12 months (7.9% and 7.5%, respectively) than did the control patients (8.4% and 8.5%, respectively).

The greatest improvement associated with training in coping skills was in quality of life and it occurred during the first 3 months, an effect that was maintained throughout the 12-month study.[51] Such training coupled with intensive diabetes management increased the adolescents' sense of competence by replacing inappropriate coping styles with more positive behavior patterns. Overall, these patients felt more capable of handling diabetes-specific situations than did the control group.[51]

Conclusions

Morbidity and premature mortality associated with diabetes have created a major socioeconomic burden. Historically, type 1 diabetes was considered the only prevalent type of diabetes in young and adolescent patients. However, the increasing incidence of type 2 disease (generally thought to be a disease of adults) in this population has been described as a new epidemic. Type 2 diabetes in juveniles or adolescents is due to a variety of factors, including obesity, sedentary lifestyle, and diets high in fat, carbohydrates, and sugars. The long-term complications of both type 1 and type 2 diabetes can be reduced by tight glycemic control, changes in nutrition and physical activity, and, when required, intervention with an oral antidiabetic agent or insulin regimen. Therapy with insulin or its analogs has been approved for use in young patients with either type 1 or type 2 disease. Most important, improved glycemic control—the goal of diabetes care—has been demonstrated with CSII or subcutaneous injection of insulin glargine.

Self-management of diabetes is often difficult for children and adolescents and requires support and education. Devices that continuously monitor glucose levels allow physicians to evaluate 24-hour glycemic control, also an important step in treatment. In the future, further improvements in technology promise to revolutionize the treatment of diabetes. Overall, careful management, monitoring, and education can improve glycemic control, bring about a better understanding of the disease process, and yield positive treatment outcomes in young patients with diabetes.

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