Limitations of Conventional Methods of Self-Monitoring of Blood Glucose

Lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes

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OBJECTIVE — Children with type 1 diabetes are usually asked to perform self-monitoring of blood glucose (SMBG) before meals and at bedtime, and it is assumed that if results are in target range, along with HbA_{1c} measurements, then overall glycemic control is adequate. However, the brief glimpses in the 24-h glucose profile provided by SMBG may miss marked glycemic excursions. The MiniMed Continuous Glucose Monitoring System (CGMS) has provided a new method to obtain continuous glucose profiles and opportunities to examine limitations of conventional monitoring.

RESEARCH DESIGN AND METHODS — A total of 56 children with type 1 diabetes (age 2–18 years) wore the CGMS for 3 days. Patients entered four fingerstick blood samples into the monitor for calibration and kept records of food intake, exercise, and hypoglycemic symptoms. Data were downloaded, and glycemic patterns were identified.

RESULTS — Despite satisfactory HbA_{1c} levels (7.7 ± 1.4%) and premeal glucose levels near the target range, the CGMS revealed profound postprandial hyperglycemia. Almost 90% of the peak postprandial glucose levels after every meal were >180 mg/dl (above target), and almost 50% were >300 mg/dl. Additionally, the CGMS revealed frequent and prolonged asymptomatic hypoglycemia (glucose <60 mg/dl) in almost 70% of the children.

CONCLUSIONS — Despite excellent HbA_{1c} levels and target preprandial glucose levels, children often experience nocturnal hypoglycemia and postprandial hyperglycemia that are not evident with routine monitoring. Repeated use of the CGMS may provide a means to optimize basal and bolus insulin replacement in patients with type 1 diabetes.

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The findings of the Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS) have demonstrated that the goals of treatment of diabetes should be to achieve glycemic control as close to normal and as possible (1,2). In youth with type 1 diabetes, strict diabetes control will optimize growth and normal pubertal development (3), as well as decrease the risks of microvascular complications. However, near-normal glucose control is more difficult to achieve in pediatric versus adult patients with type 1 diabetes. DCCT adolescents had a higher HbA_{1c} and a greater risk of severe hypoglycemia than adults in the intensive treatment group (4), and very young children with type 1 diabetes have been shown to be at high risk for asymptomatic nocturnal hypoglycemia (5).

Intensive treatment of type 1 diabetes was made possible by the introduction of new methods of monitoring glycemic control and new strategies of insulin delivery that were introduced in the late 1970s and 1980s. Self-monitoring of blood glucose (SMBG) with multiple daily injections or insulin pump therapy (continuous subcutaneous insulin infusion [CSII]) offered the possibility of controlling postprandial hyperglycemia and reducing the risks of severe hypoglycemia. However, most youths with type 1 diabetes only measure premeal blood glucose levels during the day and rarely measure glucose levels during the night, the time of greatest vulnerability to hypoglycemia (5). Thus, marked glycemic excursions are undoubtedly missed by the brief glimpses into the 24-h glucose profiles provided by SMBG. Consequently, the recent development of methods for home continuous monitoring of extracellular glucose has the potential to be the most important advance in the management of youth with type 1 diabetes in the past 20 years.

The Continuous Glucose Monitoring System (CGMS) developed by MiniMed is the first system for continuous glucose monitoring approved by the U.S. Food and Drug Administration. The MiniMed CGMS uses a glucose oxidase–based sensor to measure extracellular fluid glucose in subcutaneous tissue, which is calibrated against corresponding blood glucose levels. It is approved for use as a Holter-type monitor. The device does not give real-time glucose values to the wearer; data can only be downloaded by clinicians after the fact. It remains to be seen whether repeated use of the CGMS will have a favorable impact on overall diabetes control. However, because the wearer is masked to the sensor data, first-time use

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Abbreviations: CGMS, Continuous Glucose Monitoring System; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; SMBG, self-monitoring of blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical characteristics of sample*

Age (years)	11.6 ± 4.6
Male (%)	44.6
White (%)	96.4
Duration of diabetes (years)	5 ± 3
Treatment modality (*n*)	
One pump	42
Two injections daily	12
Three injections daily	1
Four injections daily	1
Insulin dose (units · kg^{-1} · day^{-1})	0.9 ± 0.3
HbA_{1c} (%)	7.7 ± 1.4

Data are means ± SD, unless otherwise indicated.

of the system provides a unique opportunity to examine how well standard SMBG reflects 24-h glucose excursions in youth with diabetes.

RESEARCH DESIGN AND METHODS

— Patients were drawn from the Yale Children's Diabetes Clinic, which cares for >600 youth with type 1 diabetes. This practice has a general goal of using therapy to attempt to achieve glucose control as close to normal as possible, with HbA_{1c} levels <8% in all patients. Patients were eligible for participation in this study if they were <18 years old, had no other health problem except for treated thyroid disease, and had been treated with insulin for at least 1 year. All patients meeting selection criteria were asked by an investigator to participate in this study during a routine diabetes clinic visit. The first 56 patients (age 2–18 years) invited to enroll in the study all agreed to participate, and they are included in this analysis. Most were using CSII rather than injection therapy, and all patients were using lispro as their quick-acting insulin. The parents and patients (where appropriate) gave written, informed consent for inclusion in the study, which was approved by the Yale University School of Medicine Human Investigations Committee. Clinical data on entry into the study are shown in Table 1. In general, the patients were well controlled, with an HbA_{1c} level (mean ± SD) of 7.7 ± 1.4%. Patients with shorter diabetes duration and those who were younger were more likely to have lower HbA_{1c} levels ($r = 0.51$, $P < 0.005$; $r = 0.31$, $P < 0.05$; respectively). However, sex and treatment modality were not related to HbA_{1c} levels.

Procedures

All subjects were seen in the outpatient Yale Children's Clinical Research Center, usually in the late afternoon after school. Demographic and clinical data were collected using a standardized data collection form. HbA_{1c} levels were measured, and the sensor was inserted by the same investigator (advanced practice nurse) for all subjects. Patients/families were instructed on the use of the CGMS, and they were asked to enter a minimum of four SMBG samples into the monitor for calibration and to keep detailed written records of insulin administration, food intake, exercise, and hypoglycemia symptoms. Patients also entered event markers into the monitor for these events. Participants were encouraged to call the investigator with any questions. After 3 days, the patient returned with the system, and data were downloaded using the MiniMed Solutions Software version 2.0b (Northridge, CA). Insertion sites were inspected for evidence of inflammation or infection, and families were questioned regarding problems with the use of the system.

The CGMS system

The CGMS system has been described in detail elsewhere (6). Briefly, the sensor is a glucose oxidase–based platinum electrode that is inserted through an insertion needle into the subcutaneous tissue of the anterior abdominal wall or other appropriate site using a spring-loaded device (the Senserter). Glucose oxidase catalyzes the oxidation of glucose in the interstitial fluid, which generates an electrical current. The current is carried by a cable to a pager-size monitor that analyzes the data every 10 s and reports average values every 5 min, giving a total of 288 readings per day. Sensor readings are calibrated by the monitor against capillary blood glucose measurements obtained with conventional SMBG meters. Patients were asked to perform at least four premeal/snack SMBG tests. Each sensor is used continuously for up to 72 h. Glucose values outside the range of 40–400 mg/dl are reported as ≤40 or ≥400 mg/dl. A representative 24-h sensor tracing is shown in Fig. 1.

HbA_{1c} measurements

HbA_{1c} was measured using the DCA 2000 (Bayer, Tarrytown, NY) instrument (nondiabetic range 4.3–6.3). The interassay coefficient of variation for our DCA 2000 instrument was 3.6% at a normal HbA_{1c} level (5.3%) and 2.7% at a moderately elevated level (9.2%).

Data analysis

Demographic data were entered into the Yale Trial DB database and checked for accuracy. Data from the sensors were imported into this database (Oracle 7.3 tables and Microsoft Access tables) for further data visualization and analysis. The analyses were performed with SPSS System (version 10). Descriptive statistics were used to describe the sample. Correlations (Pearson's) were used to compare sensor readings with SMBG results. The frequency of hypoglycemia was described

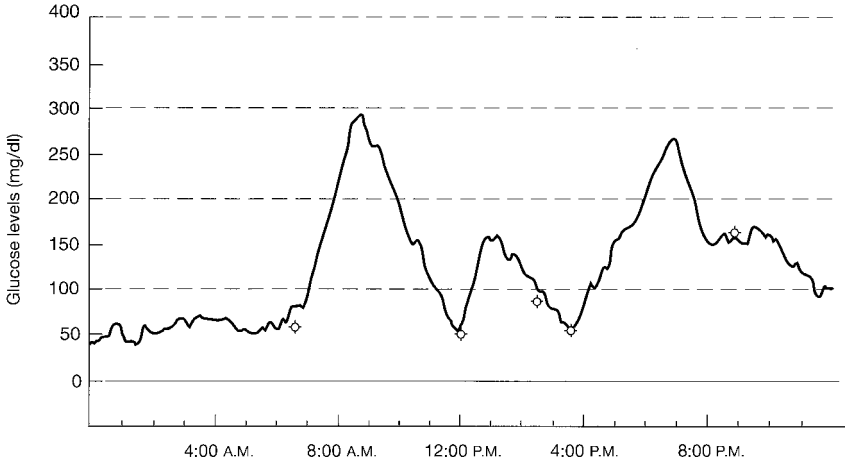

Figure 1—*An example of a representative 24-h glucose sensor profile obtained from one of our patients, a child aged 11 years and 9 months with type 1 diabetes of 3 years duration. ☼, Meter SMBG levels used to calibrate the sensor.*

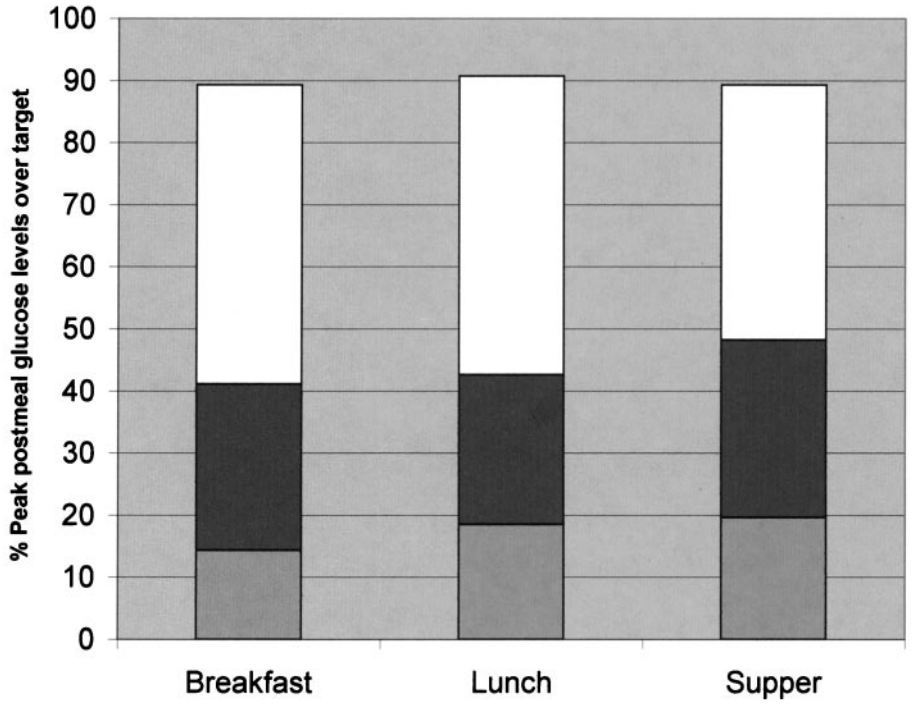

Figure 2—*Percentage of peak postmeal glucose levels over the target level of 180 mg/dl.* □*, >300 mg/dl;* ■*, 214–300 mg/dl;* ▨*, 181–240 mg/dl.*

using descriptive statistics. Two levels of biochemical hypoglycemia were used for these analyses, values from 41 to 59 mg/dl and those ≤40 mg/dl. Readings between 6:00 A.M. and 11:00 P.M. were considered daytime values, and those between 11:00 P.M. and 6:00 A.M. were nighttime values. The peak postprandial glucose level was the highest sensor value during the 3 h after each main meal.

RESULTS — In 2 of the 56 children, the first sensor had to be replaced during the initial visit because it failed to meet performance parameters. During home use, 50 of the 56 patients successfully used the CGMS for >60 h, which included three overnight profiles. In the other six children, the sensor was either dislodged or disconnected prematurely. The system was well tolerated by all subjects, and there was no evidence of infection or inflammation at the insertion site.

Overall glycemic control

The overall mean of the 10–15 SMBG levels obtained by the subjects before meals during the 3 days of sensor use was 155 ± 38 mg/dl. In comparison, the average of >800 sensor readings (which included the 10–15 points used for calibration) obtained during the day and night over the entire 3-day period was remarkably similar (150 ± 43 mg/dl). The overall mean glucose levels obtained by each method in each subject correlated closely with one another ($r = 0.78$).

Daytime (6:00 A.M. to 11:00 P.M.) glycemic control

In agreement with meter glucose readings, which were used to calibrate the sensor, premeal sensor values tended to be lower before breakfast than before other meals (126 ± 43, 134 ± 83, and 145 ± 92 mg/dl for breakfast, lunch, and dinner, respectively). Despite glucose levels in or near our target range before meals, the sensor demonstrated that peak postprandial values were markedly elevated (293 ± 84, 291 ± 81, and 280 ± 80 mg/dl for postbreakfast, postlunch, and postdinner). As shown in Fig. 2, after meals ~90% of the peak postprandial glucose levels exceeded our postprandial target of <180 mg/dl, with almost 50% of these readings being >300 mg/dl. There were also 0.9 events · patient^{-1} · day^{-1} in which sensor glucose levels fell below 60 mg/dl between breakfast and bedtime. Only 29% of these events were accompanied by hypoglycemia symptoms.

Nighttime (11:00 P.M. to 6:00 A.M.) glycemic control

The CGMS was particularly useful in detecting asymptomatic nocturnal hypoglycemia. As shown in Fig. 3, 67.8% of the subjects had a recorded nadir glucose level <60 mg/dl during at least 1 night of sensing, and 32.1% had levels ≤40 mg/dl. Glucose levels <60 mg/dl were observed on all 3 nights in 12 children. The duration of nocturnal hypoglycemia was also prolonged. When glucose levels from all nocturnal profiles were analyzed, sensor glucose levels were between 41 and 59 mg/dl for a mean of 52 min/night (median 32, range 0–280 min), and they were ≤40 mg/dl for 65 min/night (35, 0–178). Only one of the patients was awakened from sleep because of hypoglycemic symptoms. When the group as a whole was examined, no differences in the frequency of hypoglycemia were found to be related to factors such as age, sex, HbA_{1c}, and treatment modality (CSII versus injections). There were likewise no significant correlations between the duration of nocturnal hypoglycemia (time at <60, 41–59, and ≥0 mg/dl) and patient age, duration of diabetes, and HbA_{1c} levels. Similarly, treatment modality and sex did not significantly affect nocturnal hypoglycemia duration. However, the 12 youngsters with nocturnal hypoglycemia on all 3 nights had lower HbA_{1c} levels (6.9 ± 0.8%) than the other patients, who had at least 1 night without hypoglycemia (7.9 ± 1.4%, $P < 0.01$); other clinical factors did not differ between these two groups.

CONCLUSIONS — The present study demonstrates that standard premeal and bedtime SBGM provides a surprisingly accurate reflection of overall glycemic control in youth. During the 3-day period of study, the mean of the 12–15 m blood glucose levels were remarkably similar to the mean of >800 sensor glucose levels obtained during the day and night over the same time period. In addition, both mean meter and sensor levels were consistent with HbA_{1c} values. Normograms indicate that our patients' mean HbA_{1c} of 7.7% is equivalent to a 3-month average of 150–160 mg/dl (7). It is noteworthy that only 3 days of monitoring with either method related so well to HbA_{1c} levels.

Whereas SMBG may provide a surprisingly robust estimate of overall glu-

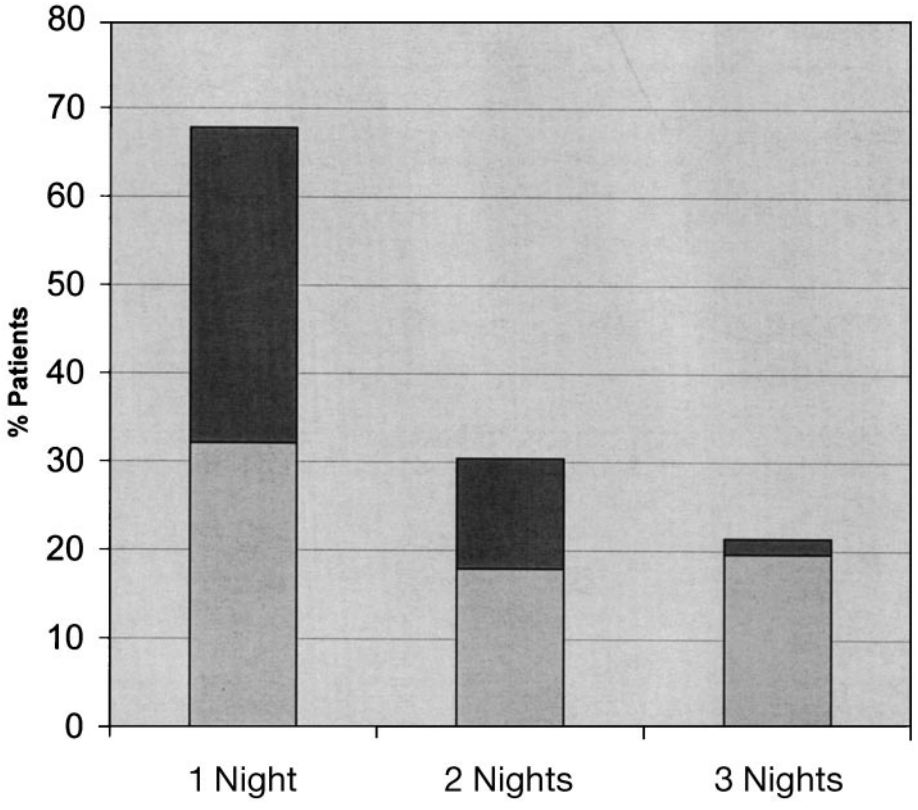

Figure 3—*Percentage of patients with nadir night sensor glucose level in hypoglycemic range (either 41–60 mg/dl or ≤40 mg/dl) for 1, 2, or all 3 nights of CGMS use.* ■*, 41–60 mg/dl;* ▨*, ≤40 mg/dl.*

cose control, results of the CGMS show that conventional glucose testing misses the marked day-to-day excursions in plasma glucose from high to low values that characterize type 1 diabetes in children. To limit the number of fingersticks, most children are asked to not test blood glucose levels immediately after meals, but rather to test before meals. It is often assumed that control of preprandial glucose levels is indicative of overall good daytime glucose control. Quite a different picture emerged from our patients' daytime CGMS profiles. Even though HbA_{1c} and premeal glucose levels suggested good diabetes control, peak postprandial values were almost always greater than our target value of <180 mg/dl, and almost 50% exceeded 300 mg/dl. This severe postprandial hyperglycemia was observed even though most patients received lispro before meals. These observations have important clinical implications, because recent evidence suggests that postprandial hyperglycemia plays a particularly important role in the development of vascular complications of diabetes (8). These data also illustrate the potential usefulness of monitoring postprandial as well as preprandial glucose levels in youth with type 1 diabetes. The sensor also detected many more hypoglycemic events during the day than were appreciated clinically.

In a recent study, Porter et al. (5) reported that asymptomatic, nocturnal hypoglycemia was common in young children with type 1 diabetes. On a single night of sampling blood glucose levels at only 11:00 P.M. and 2:00 A.M., the lowest glucose level was, respectively, <64 and <45 mg/dl in 37.8 and 13% of their patients, who were mostly treated with two injections per day. Continuous glucose monitoring for 3 successive nights provides a much more complete picture of the scope of this problem. Even though 75% of our patients were using CSII, asymptomatic nocturnal hypoglycemia was observed in two-thirds of our patients, regardless of age and sex. In addition to being frequent and significant (≤40 mg/dl), reductions in glucose levels during the night were also prolonged. This degree of nocturnal hypoglycemia was observed even though most patients were using insulin pumps that had the ability to vary insulin basal rates frequently. However, the minimal nocturnal glucose data that is available with SMBG to patients and clinicians limits their ability to fully exploit this capability of CSII.

Extensive studies have been performed in adults with type 1 diabetes, validating sensor accuracy in the 40–400 mg/dl range (9,10). Nevertheless, a note of caution needs to be sounded regarding interpretation of low glucose levels reported by the sensor at night in our patients. The relative error of all methods of glucose monitoring increases to some extent at the lower end of the detection range. In addition, it has not been established in type 1 diabetic children whether performance of the sensor is affected by pressure, temperature, or physiological changes that might occur while the patient is asleep. It should also be noted that the sensor measures the extracellular fluid glucose levels, but the monitor is calibrated against SMBG levels. Recent studies (11) have used microdialysis to measure glucose concentrations directly in extracellular fluid of muscle and adipose tissue during insulin-induced hypoglycemia. In comparison to values at euglycemia, the concentration gradient between plasma and extracellular fluid glucose increased when plasma glucose levels were lowered (9). If the same were true in subcutaneous tissue, the net result would be to artificially lower sensor estimates of blood glucose concentrations. Further studies are needed to validate the accuracy of sensor glucose measurements during hypoglycemia. Although there can be little doubt that our patients frequently experienced low glucose levels during the night, a question remains as to how low the sugar levels actually were.

The CGMS was well tolerated and used appropriately by our patients, and there was no evidence of infection or inflammation. The physical characteristics of the CGMS are very similar to an insulin pump. Interestingly, our youngsters found that wearing the CGMS was so easy that it encouraged 8 of the 14 injection patients to switch to CSII. These were children or parents who previously had been reluctant to try CSII because it involved wearing an external device.

Results of this study demonstrate that there is more to controlling diabetes than just lowering HbA_{1c} levels and premeal glucose levels toward normal. In our chil-

dren, these two parameters of glycemic control were closely related primarily because elevated postprandial levels were offset by low nighttime values. It is reasonable to assume, as small pilot studies in both adults (12) and children (13) have suggested, that the wealth of data provided by glucose sensors will provide clinicians and patients with a means to optimize basal and bolus insulin replacement with type 1 diabetes. Further studies in larger groups of youth with type 1 diabetes are needed to determine whether repeated use of the CGMS can lower HbA_{1c} levels and reduce the risk of hypoglycemia. It is even more exciting to consider that this technological advance may represent a first step toward the development of a true and practically applicable artificial pancreas.

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References

1. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 652:837–853, 1998
3. Peters AL, Davidson MB, Schriger DL, Hasselblad V: A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. Meta-analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels. *JAMA* 276:1246–1252, 1996
4. Diabetes Control and Complications Trial Research Group: Effect of intensive diabetes treatment on the development of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr* 125:177–188, 1994
5. Porter PA, Keating B, Byrne G, Jones TW: Incidence and predictive criteria of nocturnal hypoglycemia in young children with insulin-dependent diabetes mellitus. *J Pediatr* 130:339–341, 1997
6. Mastrototaro JJ: The MiniMed Continuous Glucose Monitoring System (CGMS). *J Pediatr Endocrin Metab* 12:751–758, 1999
7. Nathan D: Glycosylated hemoglobin: what it is and how to use it. *Clin Diab* 1:1–7, 1983
8. Ceriello A: The post-prandial state and cardiovascular disease: relevance to diabetes mellitus. *Diabete Metab Rev* 16:125–132, 2000
9. Gross TM, Bode BW, Einhorn D, Kayne DM, Reed JH, White NH, Mastrototaro JJ: Performance and evaluation of the MiniMed Continuous Glucose Monitoring System during patient home use. *Diabetes Technol Ther* 2:49–56, 2000
10. Gross TM, Mastrototaro JJ: Efficacy and reliability of the Continuous Glucose Monitoring System. *Diabetes Technol Ther* 2:S19–S26, 2000
11. Kamel A, Norgren S, Persson B, Marcus C: Insulin induced hypoglycaemia: comparison of glucose and glycerol concentrations in plasma and microdialysate from subcutaneous adipose tissue. *Arch Dis Child* 80:42–45, 1999
12. Bode BW, Gross TM, Thornton KR, Mastrototaro JJ: Continuous glucose monitoring used to adjust diabetes therapy improves glycosylated hemoglobin: a pilot study. *Diabetes Res Clin Pract* 46:183–190, 1999
13. Chase HP, Kim LM, Owen SL, MacKenzie TA, Klingensmith GJ, Murtfeldt R, Garg SK: Continuous subcutaneous glucose monitoring in children with type 1 diabetes. *Pediatr* 107:222–226, 2001