

# A Randomized, Prospective Trial Comparing the Efficacy of Continuous Subcutaneous Insulin Infusion With Multiple Daily Injections Using Insulin Glargine

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**OBJECTIVE** — The efficacy of the insulin analogs now available for multiple daily injection (MDI) and continuous subcutaneous insulin infusion (CSII) therapy in type 1 diabetes has not yet been established in pediatric patients. Our principal aim in this short-term study was to compare the efficacy of CSII to MDI with glargine in lowering HbA<sub>1c</sub> levels in children and adolescents with type 1 diabetes.

**RESEARCH DESIGN AND METHODS** — Thirty-two youth with type 1 diabetes (age 8–21 years) were randomly assigned to receive either MDI treatment with once-daily glargine and premeal/snack insulin aspart or CSII with insulin aspart. Dose titration in both groups was based on home self-monitored blood glucose measurements and monthly HbA<sub>1c</sub>. HbA<sub>1c</sub>, total daily insulin dose (TDD), self-monitored blood glucose readings, and adverse events were compared after 16 weeks of therapy.

**RESULTS** — While there was no significant change in the glargine group (HbA<sub>1c</sub> 8.2% at baseline vs. 8.1% at 16 weeks), youth randomized to CSII had a sharp reduction in HbA<sub>1c</sub> levels, from 8.1 to 7.2% after 16 weeks of therapy ( $P < 0.02$  vs. baseline and  $< 0.05$  vs. glargine group). TDD was unchanged in the glargine group, but significantly dropped with CSII (1.4 units/kg at baseline vs. 0.9 units/kg at 16 weeks,  $P < 0.01$ ). Both groups had similar basal doses and insulin-to-carbohydrate ratios. Fasting self-monitored blood glucose was similar in both groups, but lunch, dinner, and bedtime readings were significantly lower in the CSII group ( $P < 0.01$ ).

**CONCLUSIONS** — Lower HbA<sub>1c</sub> and premeal glucose levels were more achievable in this short-term study with CSII than with glargine-based MDI treatment. CSII is an efficacious treatment to improve metabolic control in youth with type 1 diabetes.

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**Abbreviations:** CSII, continuous subcutaneous insulin infusion; DQOL-Y, Diabetes Quality of Life-Youth; MDI, multiple daily injection; TDD, total daily insulin dose.

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

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The Diabetes Control and Complications Trial (1,2) demonstrated the importance of lowering HbA<sub>1c</sub> levels as close to normal as possible. The urgency to achieve strict diabetes control has contributed to a sharp increase in the use of continuous subcutaneous insulin infusion (CSII) in children with type 1 diabetes. Reports from our program (3,4) and others (5–7) have demonstrated that CSII can lower HbA<sub>1c</sub> levels and rates of severe hypoglycemia in youth with type 1 diabetes. However, these findings can be questioned because prepump injection regimens varied in intensity and in the types of insulins that were used. Moreover, only the recent study of Weintrob et al. (7) was a randomized controlled trial of CSII versus multiple daily injections (MDIs) using NPH insulin.

With intermediate-acting insulins, there are considerable dose-to-dose variations in the amount of insulin that is administered and absorbed (8). Additionally, the peaking actions of these insulins make them less than ideal for basal insulin replacement (8). These limitations have been overcome by the introduction of glargine insulin, the first soluble insulin analog that has a flat and prolonged time-action profile. A disadvantage of MDIs with glargine is the large number of injections that are required daily. Glargine cannot be mixed with rapid-acting insulins and must be injected separately. Because glargine does not peak, injections of rapid-acting insulin are also required for each meal and large snack to control postprandial hyperglycemia. Compliance problems with the frequent daily injections may, in part, explain why pediatric trials have failed to show lower HbA<sub>1c</sub> levels with glargine compared with NPH insulin (9,10).

Insulin analogs in CSII and MDI therapies have provided pediatric practitioners with methods of optimizing met-

abolic control of type 1 diabetes that were not available during the Diabetes Control and Complications Trial. Nevertheless, the relative efficacy of these treatments in youth with type 1 diabetes has not been determined. The present randomized clinical trial was consequently undertaken with a principal aim of comparing the efficacy of CSII and MDIs with glargine in lowering HbA<sub>1c</sub> levels in youth with type 1 diabetes in this short-term study.

## RESEARCH DESIGN AND METHODS

— Patients were recruited from the Yale Children's Diabetes Clinic and were eligible for this study if they were aged 8–21 years, inclusively; otherwise healthy except for treated thyroid or celiac disease; treated with insulin for at least 6 months; naïve to CSII and glargine; were willing to perform at least four blood glucose tests per day; and had a screening HbA<sub>1c</sub> level between 6.5 and 11%. The parents and older patients (age ≥18 years) gave written, informed consent, and younger patients gave written assent for inclusion in the study, which was approved by the Yale University School of Medicine Human Investigations Committee.

### Procedures

Information regarding this study was posted in the waiting room of the diabetes clinic. Patients meeting eligibility criteria were invited to participate during a routine diabetes clinic visit. Once consent and assent were obtained, HbA<sub>1c</sub> was measured and baseline assessments were completed. Patients were given the Lifescan InDuo meter, asked to do four fingerstick blood glucose tests per day, and instructed to keep written records of blood glucose levels. The investigator evaluated each subject's ability to use carbohydrate counting. If further teaching was necessary, the subject met with a dietitian before the next visit. Patients were asked to treat all simple hypoglycemic events with glucose tablets. Patients were sent home with instructional aids (videos and written literature) on CSII and MDI therapy to review before randomization.

Patients returned in 1–2 weeks, and glucose measurements were reviewed to confirm that they had complied with study requirements. Patients were then randomized to treatment with CSII or MDIs with glargine insulin (henceforth

referred to as the glargine group). The randomization process was completed by the center's Investigational Pharmacy. Subjects were stratified according to sex and age (<18 and ≥18 years). Within each stratum, a randomization scheme was generated using a random number table with a block size of four.

CSII patients were treated with Medtronic MiniMed 508 or Paradigm 511 pumps with insulin aspart. They participated in a 90-min pump training session and a 45-min follow-up 2 days later. The initial basal CSII dose was ~50% of the total daily insulin dose (TDD), as previously described (4). Patients were instructed to treat two consecutive high blood glucose levels as potential catheter occlusions, change the site, and take a correction dose of aspart by injection. Pumps and pump supplies were provided. Glargine patients received a 45-min training session for the use of insulin using pens for premeal aspart insulin. The initial dose of glargine was calculated as 80% of their TDD of NPH or lente, according to usual practice guidelines with glargine. Glargine was given in the morning or at bedtime. In both groups, initial carbohydrate-to-insulin ratios and correction doses were based on their prandomization insulin doses or on age and pubertal stage (11). Patients were advised to use the prescribed carbohydrate-to-insulin ratio for all meals and snacks that were ≥15 g of carbohydrate and received education on the management of hypoglycemia and hyperglycemia. All education sessions were conducted as individual rather than group sessions. Parents were included for subjects aged ≤13 years. The coordinator contacted all patients daily by phone for dosage adjustments during the first 1–2 weeks of the study. After 2 weeks, subjects used the clinic's usual on-call service if any problems developed. Treatment goals were the same for both groups and included an HbA<sub>1c</sub> <7% according to the prevailing American Diabetes Association guidelines (12). Blood glucose targets were 70–120 mg/dl before meals and 90–150 mg/dl at bedtime.

Patients returned for monthly follow-up visits and were compensated US\$25 to cover travel expenses for each visit attended. Clinical data were recorded using a standardized case report form, HbA<sub>1c</sub> was measured, and blood glucose diary data were collected. Patients were instructed to report any severe hy-

perglycemia resulting in coma or seizure or any other unexpected adverse events to the study staff within 24 h.

### Measurements

HbA<sub>1c</sub> was measured using the DCA 2000 (Bayer, Tarrytown, NY) instrument (nondiabetic range 4.2–6.3%). The interassay coefficient of variation for our DCA 2000 instrument is 3.6% at a normal HbA<sub>1c</sub> level (5.3%) and 2.7% at a moderately elevated level (9.2%).

Quality of life was measured at baseline and 16 weeks with the Diabetes Quality of Life–Youth (DQOL-Y) scale of Ingersoll and Marrero (13).

### Data analysis

Demographic and clinical data were entered into the Yale Trial DB database and checked for accuracy. Descriptive statistics were used to describe the samples. Comparisons were carried out using intention-to-treat analysis with the last observation carried forward for missing data. Because HbA<sub>1c</sub> levels reflect the previous 3 months of metabolic control, only baseline and 16-week data were used for statistical comparisons. Paired *t* tests were used for within-group comparisons of HbA<sub>1c</sub> and insulin doses. ANOVA tests were used for between-group comparisons of HbA<sub>1c</sub> levels and insulin doses at 16 weeks. Analyses of postrandomization blood glucose values were restricted to the four required preprandial blood tests, sorted by meal, and compared using unpaired *t* tests. Repeated-measures ANOVA tests were used to determine whether the frequency of self-monitored blood glucose varied over time. Change in BMI was calculated as the actual change in BMI from baseline to the 16-week visit, measured in kilograms per square meter. Data are presented as means ± SD.

**RESULTS**— An on-site investigator was notified if an eligible patient expressed interest in the study during a routine diabetes visit. The study was then described at length by an investigator, who reinforced that this study was of short duration and could potentially serve as an excellent opportunity to improve diabetes control. The first 32 patients who met all eligibility criteria were invited to enroll in the study, and all agreed to participate. Seven patients (three in the glargine group and four in the CSII group) required additional education in

Table 1—Baseline clinical characteristics of the two treatment groups

	CSII	MDI	P
n	16	16	—
Age (years)	12.5 ± 3.2	13 ± 2.8	0.637
Sex (F/M)	10/6	8/8	0.722
Race (white/Hispanic/black)	11/3/2	13/2/1	0.705
Duration of diabetes (years)	6.8 ± 3.8	5.6 ± 4.0	0.391
Initial treatment (no. of injections)	12 b.i.d./4 MDI	14 b.i.d./2 MDI	0.654
TDD prestudy enrollment (units/kg)	1.4 ± 0.5	1.1 ± 0.3	0.087

Data are means ± SD.

carbohydrate counting. As shown in Table 1, both groups were similar with respect to baseline clinical characteristics. All of the patients completed the 16-week treatment phase of the study, with the exception of an adolescent in the glargine group who was withdrawn after 8 weeks due to two episodes of dehydration and ketosis. One pump patient had a nonprotocol visit after an admission for diabetic ketoacidosis to assess compliance and control. One 8-week visit was missed in the glargine group. All other protocol visits were completed.

### Metabolic control

Changes in HbA<sub>1c</sub> levels during the study are shown in Fig. 1. Baseline HbA<sub>1c</sub> levels were similar in the glargine and CSII groups (8.2 ± 1.1 vs. 8.1 ± 1.2%, respectively,  $P = 0.89$ ). After 16 weeks of glargine treatment, HbA<sub>1c</sub> levels (8.1 ± 1.2%) were not significantly different from baseline. In contrast, HbA<sub>1c</sub> levels fell sharply in the CSII group to 7.2 ± 1.0 at 16 weeks ( $P < 0.02$  vs. baseline and  $P < 0.05$  vs. glargine group). Fifty percent of the patients took their glargine before breakfast, and 50% took the dose later in the day; there was no significant difference in the HbA<sub>1c</sub> levels based on the time of day that glargine was administered (HbA<sub>1c</sub> 8.2 ± 0.9 vs. 8.0 ± 1.4%, respectively). At randomization, two subjects in the CSII group and one patient in the glargine group met the American Diabetes Association treatment goal of a HbA<sub>1c</sub> ≤ 7%. In contrast, 8 of the 16 subjects in the CSII group and only 2 of the 16 in the glargine group met this goal at 16 weeks ( $P < 0.05$ ).

Both groups completed a similar number of blood glucose tests per day (3.9 ± 0.6 for CSII and 3.6 ± 0.5 for glargine group,  $P = 0.09$ ), and the frequency of testing did not vary over the

4-month period between the two groups ( $P = 0.45$ ). As shown in Fig. 2, blood glucose levels before breakfast were similar in the glargine and CSII groups (149 ± 95 vs. 148 ± 94 mg/dl). However, all other mean blood glucose levels were lower in the CSII than in the glargine group ( $P < 0.01$ ).

### Insulin doses

Patients randomized to CSII treatment had a mean total daily dose of 1.4 units/kg pre-CSII, whereas those randomized to MDI had a mean TDD of 1.1 units/kg ( $P = 0.087$ ) (Table 1). After 16 weeks of therapy, there was no significant change in the TDD in the glargine group. However, the CSII group had a significant decrease in TDD to 0.9 units/kg ( $P < 0.01$  vs. CSII at baseline and  $P < 0.01$  vs. glargine group at 16 weeks). Basal and bolus doses in the CSII and glargine group at 16 weeks are shown in Table 2. There were no significant differences between the treatment groups with respect to daily basal insulin dose or carbohydrate-to-insulin ratios reported by the patients.

### Adverse events

There were five episodes of severe hypoglycemia among four patients in the glargine group. One of these events occurred during a night before the randomization visit (i.e., before glargine was started). The other four events all occurred during daytime hours (the glargine was administered in the morning in three of the four events and in the evening in the other). Two patients in the CSII group each had one nocturnal hypoglycemic event. In one patient, this occurred the night before she started on the pump. One glargine patient had two hospitalizations for dehydration and ketosis, and there was one hospitalization for diabetic ketoacidosis in the CSII group. There was no significant change in BMI in either group (change of <1 kg/m<sup>2</sup> in both groups).

One CSII patient had to return her study pump to the company twice because of pump software errors, and another patient also returned her pump for software errors. There were no site infections.

### Poststudy follow-up care

At the end of the study, patients were given the opportunity to choose their poststudy treatment modality. Fourteen of the 16 in the CSII group chose to remain on CSII and 12 of the 16 MDI patients switched to CSII.

### Quality of life

DQOL-Y data were collected from only eight patients in each group. There were no differences in DQOL-Y scores between the two groups at baseline or 16 weeks (data not shown).

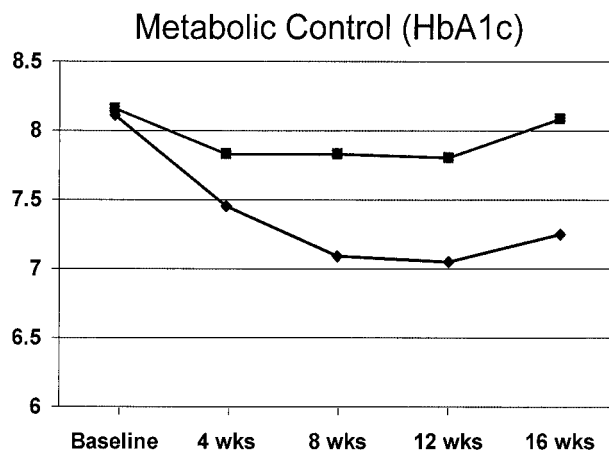
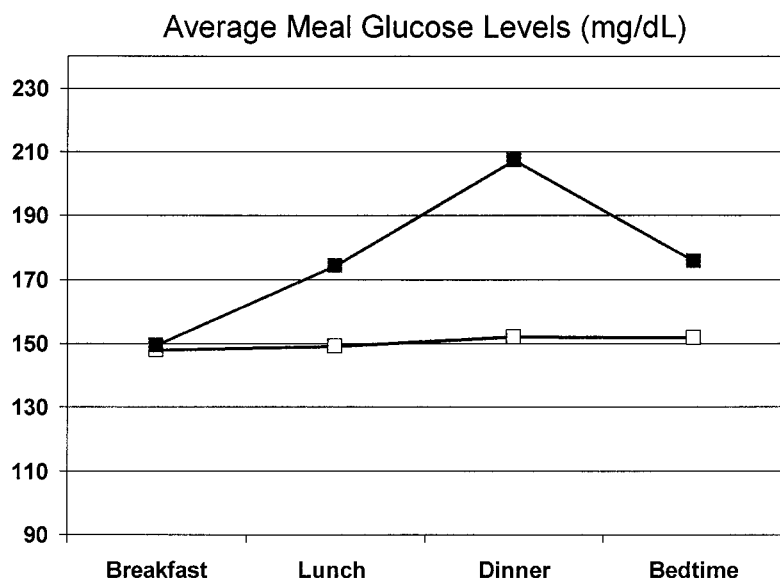


Figure 1—HbA<sub>1c</sub> levels in the two treatment groups. The difference between CSII (◆) and glargine (■) at baseline is not significant. At 16 weeks, HbA<sub>1c</sub> levels in the CSII group were significantly lower than baseline ( $P < 0.02$ ) and versus glargine ( $P < 0.05$ ).



**Figure 2**—Mean fingerstick blood glucose levels for each meal. The difference between CSII (□) and glargine (■) at breakfast is nonsignificant. The differences between CSII and glargine at all other time points are significant ( $P < 0.001$ )

**CONCLUSIONS**— This study represents the first direct comparison of CSII and glargine-based MDI therapy in youth with type 1 diabetes using a randomized, prospective study design of short duration. The randomization process was successful in establishing two groups similar with respect to clinical characteristics, prestudy treatment regimens, and HbA<sub>1c</sub> levels. Patients in the glargine group were able to maintain a level of control that they had previously achieved with more conventional injection therapy using intermediate-acting insulins. The finding of similar HbA<sub>1c</sub> levels before and after glargine in our patients is consistent with the results of two prior randomized studies (9,14) in children and adolescents. In those studies, there were no significant differences in HbA<sub>1c</sub> levels during MDI treatment with glargine versus MDI treatment with NPH insulin.

In contrast, patients who were randomized to CSII were able to significantly lower HbA<sub>1c</sub> levels, and one-half were able to lower HbA<sub>1c</sub> values to  $\leq 7.0\%$ . Improved control was achieved in this group even in the face of lower daily insulin doses compared with the prepump requirements and similar basal insulin doses of patients in the glargine group. The frequency of phone contacts was similar between the two groups within the first 2 weeks of the study. Data on the number of dose changes and frequency of telephone contacts beyond the first 2 weeks were not systematically collected. If CSII patients had more frequent telephone contacts and/or dose changes, this

could have contributed to the difference in metabolic control. CSII patients received a longer initial educational session. However, this session specifically dealt with the technology of CSII, so one would not expect this difference to explain their better metabolic control.

To the extent that fasting morning blood glucose levels represent the adequacy of overnight basal insulin replacement, there was no difference between the two groups. On the other hand, premeal and bedtime blood glucose levels were 25–55 mg/dl lower in the CSII group than in the glargine group. These differences can, in part, account for the lower HbA<sub>1c</sub> levels with CSII. Higher daytime blood glucose levels were observed in the glargine group, even though these patients reported using slightly greater insulin-to-carbohydrate ratios than CSII subjects. This discrepancy could be explained by poorer compliance in the glargine group in administering premeal and presnack doses of aspart insulin. For

example, failure to cover large afternoon snacks with an extra injection of aspart may have caused the elevated presupper glucose levels in the glargine group. The “bolus history” is one of the memory functions of insulin pumps used during clinical follow-up in this study. It allows clinicians to review and reinforce the need for the administration of a premeal bolus in CSII-treated patients. Such objective data are not available with MDI treatment. Various basal rates, possible only with CSII, may also have contributed to better metabolic control in this group.

Only one-half of each group successfully completed the DQOL-Y questionnaire. Although there was no difference between the groups at baseline and 16 weeks, the poor completion rate does not permit any conclusions to be drawn about diabetes-related quality of life in the current study. This issue needs to be addressed in future work.

It is also important to acknowledge the limitations of this study. Only a rela-

**Table 2**—Basal/bolus doses at 16 weeks in the two treatment groups

	CSII	MDI	P
n	16	16	—
TDD (units/kg)	0.9 ± 0.2	1.2 ± 0.2	0.003
Daily basal dose (units/kg)	0.6 ± 0.1	0.7 ± 0.1	0.137
Carbohydrate-to-insulin ratio (no. of grams per 1 unit insulin)	14 ± 7	10 ± 3	0.071
No. daily basal rates	5.4 ± 1.0	—	—
Mean day (7:00 A.M. to 9:00 P.M.) rate	1.6 ± 0.8	—	—
Mean night (10:00 P.M. to 6:00 A.M.) rate	1.4 ± 0.7	—	—

Data are means ± SD.

tively small number of patients were studied over a brief period of time. Consequently, insufficient data were available to compare the relative safety of CSII to MDIs with glargine. Further studies are needed in larger groups of patients to clarify safety issues. While some investigators (15) have reported a later deterioration in metabolic control after months of using CSII, we have previously demonstrated (4) in a large group of young patients that the early initial lowering of HbA<sub>1c</sub> levels achieved with CSII is sustainable for  $\geq 2$  years. Because glargine is a new insulin preparation, it could be argued that our clinicians were not as adept at titrating the insulin as we are with CSII. However, both groups had similar fasting blood glucose levels and similar daily basal insulin doses, suggesting that titration of basal insulin requirements were equivalent in both groups.

Weintrob et al. (7) recently compared CSII with MDIs using NPH in a randomized crossover trial. In that study, HbA<sub>1c</sub> levels did not differ between the two regimens. However, 67% of the subjects chose CSII over MDI treatment at the end of the study. Similarly, the majority of our youngsters chose CSII for their ongoing treatment at study completion.

The principal aim of this study was to compare the HbA<sub>1c</sub>-lowering effects of CSII and MDIs with glargine. In the context of a short-term randomized clinical trial, we observed a considerably greater improvement in HbA<sub>1c</sub> levels with CSII than with glargine. It should be noted, however, that no single approach to treatment is ideal for every patient. The availability of multiple therapeutic options will allow clinicians who care for children with type 1 diabetes to choose the best treatment for that individual patient at that particular time.

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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. DCCT Research Group: The effects of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial. *J Pediatr* 124:177–188, 1994
3. Boland EA, Grey M, Yu C, Oesterle A, Tamborlane WV: CSII: a “new” way to achieve strict metabolic control and lower the risk of severe hypoglycemia in adolescents. *Diabetes Care* 22:1779–1784, 1999
4. Ahern JH, Boland EA, Doane R, Vincent M, Tamborlane WV: Insulin pump therapy in pediatrics: a therapeutic alternative to safely lower HbA<sub>1c</sub> levels across all age groups. *Pediatric Diabetes* 3:10–15, 2002
5. Sulli N, Shashaj B: Continuous subcutaneous insulin infusion in children and adolescents with diabetes mellitus: decreased HbA<sub>1c</sub> with low risk of hypoglycemia. *J Pediatr Endocrinol Metab* 16:393–399, 2003
6. Maniatis AK, Klingensmith GJ, Slover RH, Mowry CJ, Chase HP: Continuous subcutaneous insulin infusion therapy for children and adolescents: an option for routine diabetes care. *Pediatrics* 107:351–356, 2001
7. Weintrob N, Benzxaquen H, Galatzer A, Shalitin S, Lazar L, Fayman G, Lilis P, Dickerman Z, Phillip M: Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. *Pediatrics* 112:559–564, 2003
8. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and Ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 49:2142–2148, 2000
9. Murphy NP, Keane SM, Ong KK, Ford-Adams M, Edge JA, Acerini CL, Dunger DB: Randomized cross-over trial of insulin glargine plus lispro or NPH plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. *Diabetes Care* 26:799–804, 2003
10. Schoenle E, on behalf of the HOE 901/3003 Study Group: Insulin glargine (HOE901) lowers fasting glucose in children with type 1 diabetes mellitus without increasing the risk of hypoglycemia (Abstract). *Diabetologia* 42:A234, 1999
11. Tamborlane WV, Fredrickson LP, Ahern JH: Insulin pump therapy in childhood diabetes mellitus: guidelines for use. *Treat Endocrinol* 2:11–21, 2003
12. American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position Statement). *Diabetes Care* 26 (Suppl. 1):S33–S50, 2003
13. Ingersoll GM, Marrero DL: A modified quality of life measure for youths: psychometric properties. *Diabetes Educ* 17:114–118, 1991
14. Schober E, Schoenle E, Van Dyk J, Wernicke-Panten K, Pediatric Study Group of Insulin Glargine: Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 15:369–376, 2002
15. Plotnick LP, Clark LM, Brancati FL, Erlinger T: Safety and effectiveness of insulin pump therapy in children and adolescents with type 1 diabetes. *Diabetes Care* 26:1142–1146, 2003