Continuous Subcutaneous Insulin Infusion

A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes

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OBJECTIVE — Recommendations from the Diabetes Control and Complications Trial (DCCT) indicate that adolescents with type 1 diabetes should be treated with intensive therapy involving multiple daily injections (MDI) of insulin or insulin pump therapy (continuous subcutaneous insulin infusion [CSII]) to help obtain better metabolic control and prevent later complications. Interest has thus focused on insulin pump therapy to help adolescents meet this challenge. The purpose of this study was to examine responses to CSII and MDI in a large group of adolescents with established type 1 diabetes during a 12-month period and to determine whether either treatment regimen more favorably affected clinical and psychosocial outcomes.

RESEARCH DESIGN AND METHODS — One-third of 75 youths aged 12–20 years who were candidates for intensive therapy chose CSII as their mode of treatment. Patients received intensive treatment and education as described by the DCCT investigators. Psychosocial data (e.g., quality of life, depression, self-efficacy, and coping) were collected at baseline and at 6-month intervals, and clinical data (e.g., HbA_{1c} levels, adverse events) were collected every 4–6 weeks.

RESULTS — Although both MDI- and CSII-treated adolescents initially exhibited improved metabolic control, this level of control was more difficult to sustain for 12 months in the MDI group (at 6 months HbA_{1c} = 8.1, at 12 months HbA_{1c} = 8.3), whereas average HbA_{1c} levels in the CSII group continued to decrease during the 12 months of treatment (at 6 months HbA_{1c} = 7.7, at 12 months HbA_{1c} = 7.5). Despite lower HbA_{1c} levels in CSII- versus MDI-treated patients, the rate of severe hypoglycemic events was reduced by almost 50% in the CSII group (P = 0.01). Self-reported questionnaires demonstrated that there was improvement in self-efficacy, depression, and quality of life in both MDI- and CSII-treated patients. Finally, adolescents using CSII found coping with diabetes to be less difficult than adolescents using MDI did.

CONCLUSIONS — CSII is an alternative means to lower HbA_{1c} levels and reduce the risk of hypoglycemia without adversely affecting psychosocial outcomes in adolescents with type 1 diabetes.

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Abbreviations: ABC's of Diabetes Study, Adolescents Benefit From Control of Diabetes Study; ANOVA, analysis of variance; CDE, Certified Diabetes Educator; CDI, Children's Depression Inventory; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; DKA, diabetic ketoacidosis; DQOLY, Diabetes Quality of Life: Youth; MDI, multiple daily injections.

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

Continuous subcutaneous insulin infusion (CSII) via battery-powered pumps was introduced to treat type 1 diabetes 20 years ago (1,2). Although this approach to insulin replacement provided a closer approximation of normal plasma insulin profiles and increased flexibility regarding timing of meals and snacks, compared with conventional insulin injection regimens, CSII has been used infrequently in the treatment of adolescents and children with diabetes (3–11). For example, in the Diabetes Control and Complications Trial (DCCT), only eight adolescents selected treatment with CSII on randomization to an intensive treatment group (10). As recently as 1996, sales data from MiniMed indicated that <5% of patients starting pump therapy were <20 years of age.

Obstacles to the use of pump therapy in youths with diabetes has included the size and technical limitations of early pump models, psychosocial issues regarding continuously wearing an external device, and a lack of commitment by patients, families, and clinicians to achieve the goals of intensive therapy before the completion of the DCCT (12). However, with the results of the DCCT demonstrating that improved control dramatically decreases the risk of late complications of type 1 diabetes in adolescents (11) and in adults (13), professionals who care for adolescents with diabetes have been challenged to find more effective ways to achieve intensive treatment goals in this age-group. Moreover, advances in pump technology have made these devices much easier to use (14). Consequently, CSII appears to be a much more viable alternative than multiple daily injections (MDI), which involves ≥3 injections of insulin a day, in the intensive management of adolescents with type 1 diabetes. Although insulin pump use by youths with diabetes has indeed risen sharply during the past 2–3 years, the comparative effectiveness of CSII and MDI in adolescents has not been established.

The ABC's of Diabetes (Adolescents Benefit from Control of Diabetes) Study is a prospective study undertaken at our center to examine ways to translate the DCCT recommendations regarding intensive ther-

apy in a large representative group of adolescents with type 1 diabetes. All of the patients enrolled in the study received intensive management as in the DCCT, including advice to self-monitor blood glucose at least four times a day and dietary counseling that emphasized carbohydrate counting. Patients were seen every 4–6 weeks and were contacted frequently by telephone between visits to adjust treatment regimens. Psychosocial outcomes were assessed every 6 months by using well-established self-report questionnaires (15–17), and clinical outcomes were assessed by measuring HbA_{1c} levels and systematic collection of adverse events and other data by using standardized clinical report forms during outpatient visits.

As in the DCCT, adolescents in the ABC's of Diabetes Study were allowed to self-select MDI or CSII, and approximately one-third of the patients selected CSII. Consequently, this analysis of the ABC's of Diabetes Study database was undertaken to examine responses to CSII and MDI regimens in our study group. We were particularly interested in determining whether either treatment regimen more favorably affected clinical and psychosocial outcomes.

RESEARCH DESIGN AND METHODS

Setting and sample

Patients were drawn from the Yale Children's Diabetes Clinic, which cares for more than 500 children, adolescents, and young adults with type 1 diabetes. Adolescents attending the clinic were eligible for inclusion in the ABC's of Diabetes Study if they were between the ages of 12 and 20 years, had no other health problem except for treated thyroid disease, had been treated with insulin for at least 1 year, had a recent HbA_{1c} level between 7.0 and 14% (normal 4.3–6.3%), had no more than two severe hypoglycemic events within the past 6 months, and were in a school grade appropriate to their age within 1 year. Between 1 November 1995 and 1 September 1998, 105 patients who met the criteria were invited to participate in the study, and 77 (33 boys and 44 girls) agreed to participate. Only 28 subjects refused participation, and the patients who refused were not significantly different regarding sex ($\chi^2 = 1.42$, df = 1, $P = 0.25$), ethnicity ($\chi^2 = 1.98$, df = 1, $P = 0.18$), age ($t = -0.42$, $P = 0.68$), and metabolic control ($t = -0.46$, $P = 0.67$) from patients who enrolled. This report presents data on the first 75 patients enrolled in the study who have completed 12 months of follow-up. The patients and their parents gave written informed consent for inclusion in the study, which was approved by the Yale School of Nursing Human Subjects Research Review Committee. A total of 74 subjects received insulin injections before the study (one was already using CSII), but 24 patients switched to CSII at the start of the study, and 50 chose MDI. One patient in each treatment group was also being treated for thyroid disease. Clinical data on entry to the study are shown in Table 1. No significant differences existed between the two treatment groups.

Procedures

Psychosocial data were obtained by trained research assistants for all subjects after routine follow-up visits during the intervention phase of the ABC's of Diabetes Study. Routine visits with advanced practice registered nurses (Certified Diabetes Educators [CDEs]) were conducted every 4–6 weeks and included diabetes education, management adjustments, and assessment of other clinical data, including episodes of hypoglycemia and HbA_{1c} measurements. All patients received intensive management similar to the DCCT protocol (13). All patients received diabetes education that was structured according to that received by DCCT subjects. Patients were taught carbohydrate counting by a registered dietitian (and CDE) and were taught how to vary insulin doses (either by pump or injection) based on varied food intake and planned exercise. Additional consultations were obtained with medicine, nutrition, and social work as necessary. Most pump-treated patients ($n = 23$) received buffered human regular insulin (Velosulin BR; NovoNordisk, Princeton, NJ) (two other patients received Humalog; Lilly, Indianapolis, IN), all delivered by MiniMed infusion pumps 506 or 507.

HbA_{1c}

Study staff members performed HbA_{1c} measurements by using the Bayer DCA (Tarrytown, NY) 2000 instrument (nondiabetic range 4.3–6.3%). The interassay coefficient of variation for our DCA 2000 instrument is 3.6% at a normal HbA_{1c} level (5.3%) and 2.7% at a moderately elevated level (9.2%). Blood was obtained by fingerstick at clinical visits, and results were available in 6 min.

Psychosocial assessments

Psychosocial self-report questionnaires used in this study were reported in detail previously (18) and are summarized briefly herein. Questionnaires were administered by one of three trained research assistants (graduate nursing students) in a private room in which only the subject and the data collector were present. Confidentiality was ensured by coding the instruments. Subjects completed these questionnaires at baseline and at 6 and 12 months.

The Self-Efficacy for Diabetes Scale developed by Grossman et al. (15) measures the self-perceptions or expectations of adolescents regarding their personal competence, power, and resourcefulness in successfully managing their diabetes. The scale consists of 35 items in three subscales: Diabetes-Specific Self-Efficacy (24 items), Medical Situations Self-Efficacy (5 items), and General Situations (6 items). Subjects are asked to rate their degree of confidence for all items on a 5-point scale ("very sure I can't" to "very sure I can").

The Issues in Coping with IDDM scale was developed by Kovacs et al. (19) to assess which type 1 diabetes-related issues children and adolescents find difficult to handle or experience as upsetting. The How Hard subscale consists of 14 diabetes tasks in which the respondent indicates how difficult the task is with a 0- to 3-point Likert scale. The Upset scale contains 12 items in which the respondent indicates how upsetting the activities or thoughts concerning diabetes are. Higher scores indicate that the tasks are harder or more upsetting.

Quality of life

Initially developed by the DCCT Research Group (20) and later modified by Ingersoll and Marrero (16), the Diabetes Quality of Life: Youth (DQOLY) assessment consists of three subscales: the 17-item Diabetes Life Satisfaction scale, the 23-item Disease Impact scale, and the 11-item Disease-Related Worries scale. Items are scored on a 5-point Likert scale so that total scores can range from 17 to 85 on the Satisfaction scale, from 23 to 115 on the Impact scale, and from 11 to 55 on the Worries scale. On the Impact and Worries scales, higher scores indicate lower quality of life, whereas on the Satisfaction scale, higher scores indicate better quality of life. The authors reported that all three scales were associated with adolescents' self-rated health status but that DQOLY scores were not correlated with HbA_{1c} values (16).

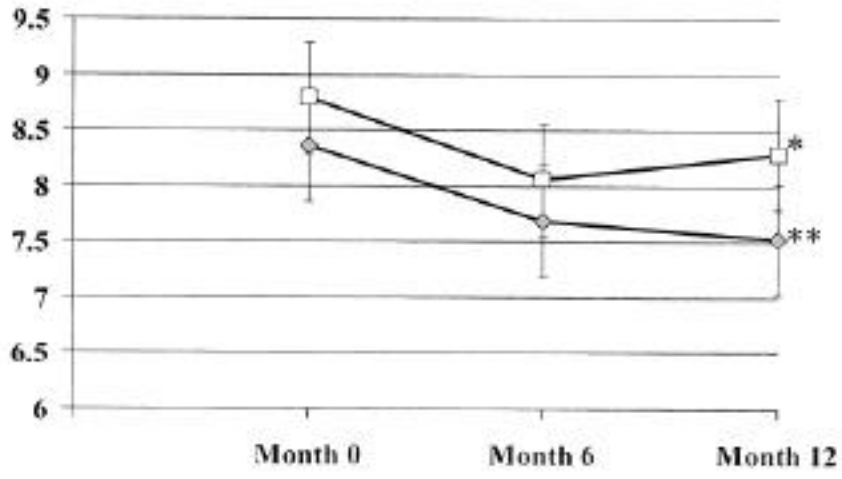

Figure 1—*Metabolic control with CSII versus MDI (n = 75). *P = 0.003 vs. baseline; **P = 0.02 vs. baseline. ◆, Pump; □, MDI.*

The Children's Depression Inventory (CDI) was developed by Kovacs (17) to measure self-reported depressive behavior in children and adolescents. The inventory assesses various depressive symptoms, including disturbance in mood and hedonic capacity, self-evaluation, vegetative functions, and interpersonal behaviors. The CDI contains 27 multiple-choice items that yield total scores from 0 to 54. Higher scores reflect greater symptomatology. A score of ≥13 is a criterion score in identifying clinical depression. Because depression is not normally distributed, CDI scores are treated with a logarithmic transformation before analysis.

Adverse events

Data regarding adverse events were collected by clinicians every 4–6 weeks by using standardized report forms. Severe hypoglycemia was defined as any hypoglycemic or suspected hypoglycemic event (when blood glucose measurement was not taken) requiring any assistance from another person to recover. This variable was further subcategorized to determine the frequency of severe hypoglycemic events that resulted in a seizure or coma. Patients were instructed to report severe hypoglycemic events immediately and were asked about the occurrence of any hypoglycemic event at each visit. Diabetic ketoacidosis (DKA) was defined as an acidotic event that required an emergency department or hospital admission in which the arterial blood pH was <7.30. Overweight was defined similarly to the definition used in the DCCT (11). Weight and height (using a wall-mounted stadiometer) measurements were used to calculate BMI (in kilograms per meters squared). Boys were considered to be overweight when their BMI was ≥27.8 kg/m^2, and girls were considered to be overweight when their BMI was ≥27.3 kg/m^2 (11).

Data analysis

All data were entered twice into a database and checked for accuracy. Analyses were performed with the SAS System Version 6.11 (Cary, NC) and SPSS Version 8 (Chicago). Descriptive statistics were used to describe the sample as appropriate. Baseline characteristics were compared with *t* test and χ^2 analyses, and when differences were found, they were controlled for in further analyses. Metabolic control and psychosocial measures were compared for 12 months with repeated measures analysis of variance (ANOVA) that used an unbalanced design. Rates of severe hypoglycemia were compared by using Mantel-Haenszel tests for density follow-up studies (21). For the first 12 months of follow-up, no subjects dropped out of the study, and all scheduled visits for data collection were completed. Three patients who originally selected CSII switched to MDI after 6 (*n* = 2) and 9 months (*n* = 1) because of personal preference (*n* = 1) or because they did not meet specific treatment objectives (frequent self-monitoring of blood glucose) (*n* = 2). All data from these subjects during the year of follow-up were included in the CSII group for analyses. Data are means ± SD where appropriate.

RESULTS — As shown in Fig. 1, baseline HbA_{1c} levels in the CSII group (8.4 ± 1.7%) were slightly but not significantly lower than in the MDI group (8.8 ± 1.6%). In both groups, HbA_{1c} levels decreased significantly ($P < 0.02$) during the study and were greatest during the first 6 months (HbA_{1c} after 6 months: CSII 7.7 ± 1 and MDI = 8.1 ± 1.0%). From 6 to 12 months, HbA_{1c} levels rebounded modestly in MDI-treated patients but not in CSII-treated patients (HbA_{1c} after 12 months: CSII = 7.5 ± 0.9 and MDI = 8.3 ± 1.3%).

Although the differences in total daily dose of insulin were not significant at baseline (CSII 1.18 ± 0.3 and MDI 1.33 ± 0.6 U/kg, $P = 0.243$), adolescents using CSII used significantly less insulin (1.05 ± 0.4 U/kg) than subjects using MDI (1.49 ± 0.6 U/kg, $P = 0.009$) after 12 months of treatment (Table 1).

Adverse events occurring during CSII and MDI treatment are summarized in Table 2. Despite lower HbA_{1c} levels in CSII- versus MDI-treated patients, the rates of all hypoglycemic events requiring assistance or resulting in coma were reduced by almost 50% in the CSII group ($P < 0.01$ vs. MDI). There were no significant differences in the number of DKA events between the two treatment groups. Although not statistically significant, the percentage of patients who were classified as overweight increased in both groups, especially among the boys.

Table 1—*Demographic comparisons of adolescents using CSII or MDI regimens*

Variable	CSII	MDI	*P*
Age (years)	13.8 ± 2.1	14.6 ± 2.0	0.10
Duration (years)	7.7 ± 3.8	9.5 ± 3.7	0.06
Sex (% male)	40	44	0.74
Race (% white)	96	94	0.53
Total daily dose (U/kg)			
Time 0 months	1.2 ± 0.3	1.3 ± 0.6	0.24
Time 12 months	1.0 ± 0.4	1.5 ± 0.6	0.009*

Data are means ± SD. *$P < 0.05$.

Table 2—*Adverse events in adolescents using CSII and MDI regimens*

Event	MDI	CSII
All hypoglycemic events requiring assistance (rate per 100 patient-years)	134	76*
Hypoglycemic events resulting in an unconscious state or seizure (rate per 100 patient-years)	46	24
DKA during the first 12 months of treatment (rate per 100 patient-years)	1	2
Weight gain (% patients overweight)†		
Girls (baseline)	4.8	14.3
Girls (12 months)	7.4	13.3
Boys (baseline)	5.6	12.5
Boys (12 months)	22.7	30

*$P < 0.05$; †overweight equals boys with BMI >27.8 kg/m^2 and girls with BMI >27.3 kg/m^2 (11).

At baseline, 5.6% of the boys using MDI, and 12.5% of the boys using CSII were overweight. After 12 months of treatment, the percentage of boys using MDI who were overweight increased by 4-fold (22.7%), and the number of boys using CSII who were overweight increased by 2.4-fold.

Psychosocial outcomes were analyzed with repeated measures ANOVA and are shown in Tables 3 and 4. The entire group reported improvements during the 12 months in self-efficacy subscales (General Situations $P = 0.01$, Diabetes-Specific and Medical Situations $P < 0.01$), depression ($P < 0.001$), and quality of life (Impact $P < 0.001$, Worry $P = 0.04$). Adolescents using CSII found coping with diabetes to be less difficult than adolescents using MDI ($F = 3.02$, df = 1, $P = 0.05$). However, no differences were noted in quality of life, depression, and self-efficacy between the two treatment groups.

CONCLUSIONS — Outcome data from the initial cohort of adolescents enrolled in our study confirmed our clinical impression that CSII is an effective treatment alternative for adolescents requiring intensive therapy. Adolescents choosing CSII in this study were able to achieve and maintain HbA_{1c} levels throughout the 12-month study period (7.5%) that were lower than mean values achieved in all adolescents in the DCCT who were randomized to intensive treatment (~8.1%) (11). These data are of great clinical significance. The DCCT clearly demonstrated that the reduction achieved by our patients using CSII (10%) may result in a reduction in retinopathy of as much as 42% (22). As expected, improved control was also achieved by patients who used MDI, but the improvement was more difficult to sustain in those patients.

Being an adolescent was an independent risk factor for severe hypoglycemia in the DCCT (11). Several factors, including the large insulin dosage required in this age-group because of the insulin resistance of puberty (23), have been implicated in the incidence of severe hypoglycemia. Our MDI-treated adolescents experienced a rate of severe hypoglycemia that was even greater than that reported for the intensively treated adolescents in the DCCT. However, the rates of severe hypoglycemia in our study and the DCCT are not directly comparable because the DCCT involved 9 years of follow-up versus 1 year of follow-up in our study. The highest rates of severe hypoglycemic events in the DCCT were observed in the first year of therapy (24), and, by the end of the DCCT study, most of the DCCT "adolescent" subjects were well into their 20s. Thus, that strict glycemic control was achieved with CSII in this study with much less severe hypoglycemia than with MDI is even more remarkable. Possible explanations for this include the more physiological insulin delivery that occurs with CSII, in which only quick-acting insulin is used and the basal infusion rate can be varied by the hour to accommodate changing insulin needs throughout the day and night. Changes in daily insulin dosages provide further support for the more physiological delivery system inherent with CSII. Before the start of the study, both groups of subjects received total daily insulin doses in the range of 1.0–1.5 U · kg body wt^{-1} · day^{-1}, in keeping with the physiological insulin resistance that normally occurs during puberty (23). During the study, improved control was achieved in the MDI group in association with a slight increase in insulin dosage but with a lower

Table 3—*Comparison of psychosocial outcomes at 0, 6, and 12 months*

Variable	Baseline		6 Months		12 Months		*F* (group × time)	*P*
	CSII	MDI	CSII	MDI	CSII	MDI		
Self-efficacy								
General	25.00 ± 2.3	25.52 ± 2.8	25.80 ± 2.4	26.54 ± 2.8	25.76 ± 3.2	26.36 ± 2.7	0.122	0.885
Diabetes	98.64 ± 7.1	96.54 ± 9.9	102.84 ± 10.9	101.94 ± 11.6	104.52 ± 9.9	102.00 ± 11.4	0.254	0.776
Medical	20.16 ± 2.6	20.44 ± 3.0	22.60 ± 2.4	22.26 ± 2.8	22.76 ± 2.0	22.76 ± 2.0	0.601	0.549
Coping								
Hard	18.92 ± 2.4	18.58 ± 3.5	17.21 ± 2.7	17.74 ± 3.2	16.83 ± 3.0	18.26 ± 3.3	3.02	0.052
Upset	16.79 ± 5.1	17.98 ± 3.6	15.08 ± 3.4	17.36 ± 4.0	14.87 ± 2.8	17.16 ± 3.5	1.35	0.261
Quality of life								
Impact	48.20 ± 11.1	50.06 ± 11.1	44.40 ± 11.5	46.62 ± 10.4	42.8 ± 10.0	47.02 ± 9.7	0.842	0.433
Satisfaction	64.52 ± 14.6	65.08 ± 12.2	69.83 ± 11.5	66.86 ± 14.6	68.48 ± 14.8	65.2 ± 15.4	0.797	0.453
Worry	20.48 ± 5.7	21.44 ± 7.6	19.44 ± 7.5	20.46 ± 6.8	18.64 ± 6.2	20.12 ± 6.7	0.104	0.902
Depression (CDI [2])	2.52 ± 1.3	2.39 ± 1.3	2.00 ± 1.1	2.01 ± 1.4	2.00 ± 1.1	2.01 ± 1.4	0.362	0.697

Data are means ± SD.

Table 4—*Psychosocial outcomes over time in all CSII and MDI patients*

Variable	Baseline	6 Months	12 Months	*F* (time)	*P*
Self-efficacy					
General	25.35 ± 2.7	26.36 ± 2.7	26.16 ± 2.9	4.65	0.01
Diabetes	97.24 ± 9.0	102.24 ± 11.3	102.84 ± 11.0	13.41	0.000
Medical	20.35 ± 2.9	22.37 ± 2.6	22.65 ± 2.4	40.45	0.000
Coping					
Hard	16.69 ± 3.2	17.57 ± 3.0	17.68 ± 3.4	7.94	0.001
Upset	17.59 ± 4.2	16.6 ± 3.9	16.41 ± 3.4	7.43	0.001
Quality of life					
Impact	49.44 ± 11.1	45.88 ± 10.8	45.6 ± 10.0	10.86	0.000
Satisfaction	64.83 ± 12.9	67.89 ± 13.6	66.23 ± 15.1	2.23	0.11
Worry	21.12 ± 7.0	20.12 ± 7.0	19.6 ± 6.5	3.28	0.04
Depression	2.44 ± 1.17	2.02 ± 1.2	2.00 ± 1.3	11.44	0.000

Data are means ± SD.

insulin dosage in the CSII group (Table 1). Buffered human regular insulin was used in most (>90%) of our CSII-treated patients because experience with lispro insulin in CSII was limited at the time of this study. More recent reports in CSII-treated adults (25) indicate that the rapid absorption of premeal bolus doses of lispro compared with regular insulin may provide better control of postprandial hyperglycemia without increasing the frequency of hypoglycemia before the next meal. This advantage of lispro over regular insulin with CSII should be even greater in adolescents because of the large premeal boluses that these youngsters characteristically require.

As was true in the DCCT (11), weight gain was a concern in this cohort of patients, especially for the boys. Although not statistically significant (most likely related to sample size), the number of boys who were overweight after 12 months of treatment increased by 2.4-fold to 4-fold, and this problem was worse in MDI- than in CSII-treated patients, which concerns providers who treat adolescents when implementing intensive regimens in this age-group. The risk of weight gain must be explored with patients, and dietary counseling is essential for every adolescent, particularly for boys.

A primary treatment aim of diabetes treatment in youths is to minimize the adverse psychosocial consequences of this chronic illness. Thus, providers are concerned that intensive therapy in general and CSII in particular may worsen psychosocial outcomes because of an increase in the burden of therapy, despite improved metabolic control. Results of the DCCT (11) and our preliminary findings in this cohort of patients (18,26) have not supported such concerns. Indeed, regardless of the method of insulin administration, the results of this study indicate that better control of diabetes can be achieved for up to a year without compromising psychosocial well-being or quality of life. In fact, improvements in quality of life, depression, and self-efficacy were noted in our entire group of adolescents for the 12-month period. Moreover, adolescents who chose CSII found coping with diabetes to be less difficult than those who chose MDI did. The flexibility and effectiveness of CSII appear to have compensated for potential problems in feeling "different" from peers by wearing an external device.

Some limitations are evident in interpreting these data. Although a large percentage of adolescents in this study were managed with CSII, the patients were not randomly selected for this regimen. Adolescents using CSII may have been more motivated to achieve better metabolic outcomes than patients using MDI. The observation that the results of psychosocial self-report questionnaires were similar at baseline argues against the idea that CSII-treated patients were more well adjusted or that they found diabetes care less burdensome. In addition, although the subjects were representative of the population of adolescents followed at our center, such positive results may not be obtainable at other tertiary diabetes care centers or office practices that do not have the resources provided by our research program. However, the marked increase in insulin pump use by patients aged <20 years across the country in multiple care centers argues against such an interpretation. MiniMed, Inc., has tracked the age of patients starting pump therapy for the past 3 years. Individuals aged <20 years comprised <5% of the pump patients in 1996. In contrast, this number increased nearly threefold to ~15% in 1998 (L. Fredrickson, personal communication). Thus, the new popularity of CSII does not appear to be unique to our center. As more teenagers engage in intensive therapy, our data demonstrate that CSII offers a treatment alternative that can lead to improved metabolic control and lower the risk of hypoglycemia without adversely affecting psychosocial outcomes.

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