Persistent Differences Among Centers Over 3 Years in Glycemic Control and Hypoglycemia in a Study of 3,805 Children and Adolescents With Type 1 Diabetes From the Hvidøre Study Group

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OBJECTIVE — Twenty-one international pediatric diabetes centers from 17 countries investigated the effect of simple feedback about the grand mean HbA_{1c} level of all centers and the average value of each center on changes in metabolic control, rate of severe hypoglycemia, and insulin therapy over a 3-year period.

RESEARCH DESIGN AND METHODS — Clinical data collection and determination of HbA_{1c} levels were conducted at a central location in 1995 (n = 2,780, age 0–18 years) and 1998 (n = 2,101, age 11–18 years).

RESULTS — Striking differences in average HbA_{1c} concentrations were found among centers; these differences remained after adjustment for the significant confounders of sex, age, and diabetes duration. They were apparent even in patients with short diabetes duration and remained stable 3 years later (mean adjusted HbA_{1c} level: 8.62 ± 0.03 vs. 8.67 ± 0.04 [1995 vs. 1998, respectively]). Three centers had improved significantly, four centers had deteriorated significantly in their overall adjusted HbA_{1c} levels, and 14 centers had not changed in glycemic control. During the observation period, there were increases in the adjusted insulin dose by 0.076 U/kg, the adjusted number of injections by 0.23 injections per day, and the adjusted BMI by 0.95 kg/m^2. The 1995 versus 1998 difference in glycemic control for the seven centers could not be explained by prevailing insulin regimens or rates of hypoglycemia.

CONCLUSIONS — This study reveals significant outcome differences among large international pediatric diabetes centers. Feedback and comparison of HbA_{1c} levels led to an intensification of insulin therapy in most centers, but improved glycemic control in only a few.

Diabetes Care 24:1342–1347, 2001

In view of the complexity of the medical—but also the educational and psychological—aspects of pediatric diabetology, it has been suggested that the optimal therapeutic approach requires a competent multidisciplinary team (1). There is evidence that increasing numbers of children in some countries have access to such teams (2). The multidisciplinary approach is strongly supported by the results of the Diabetes Control and Complications Trial (3). In the adolescent subgroup of that study, however, a poorer average level of glycemic control was achieved, even though adolescents received more counseling than the adults in that study (4). So far, few studies have evaluated the variation of structure, process, and outcome data of the multidisciplinary approach for children with diabetes, which may provide key evidence for the improvement of quality of care (5).

The Hvidøre Study Group on Childhood Diabetes evolved during a workshop to discuss strategies that might be important in improving the quality of pediatric diabetes care. The prevailing insu-

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Received for publication 28 September 2000 and accepted in revised form 17 April 2001.

R.W.H. has received a grant and other funds from Novo Nordisk; K.J.R. has received funds for research from Novo Nordisk; and P.H. and H.L. hold stock in Novo Nordisk.

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

Table 1—*Clinical data*

	1995	1998
Total *n*	2,780	2,101
Males/females	1,404/1,376	1,085/1,016
Age (years)	11.97 ± 4.02	13.81 ± 2.12
Duration (years)	4.78 ± 3.70	5.23 ± 3.79
BMI (kg/m^2)	19.67 ± 3.39	21.28 ± 3.46
HbA_{1c} (%)	8.62 ± 1.64	8.74 ± 1.66
Insulin dose (U/kg)	0.85 ± 0.29	0.98 ± 0.32

lin regimens (6) and the level of glycemic control achieved by the study group patients in a cross-sectional survey were reported previously (7) and showed substantial differences in the average level of glycemic control among centers. The present study investigates the reproducibility of these differences and analyzes factors potentially influencing the variation of glycemic control among centers.

RESEARCH DESIGN AND METHODS

— A multicenter cross-sectional study involving 21 pediatric departments from 17 countries in Europe, Japan, and North America was performed in the two following sampling periods:

1) from March through the end of August 1995—data from 2,780 patients aged 0–18 years (subgroup 11–18 years of age: $n = 2,040$); and

2) from March through the end of September 1998—data from 2,101 patients aged 11–18 years.

The study sample included 4,835 HbA_{1c} measurements in 3,805 patients whose clinical data are given in Table 1. There were 891 patients (age in 1995: 11.3 ± 2.2 years; diabetes duration: 4.6 ± 3.0 years) who participated in both sampling periods. One center did not participate in the second sampling period and was therefore excluded from further analysis. Information on each patient's sex, age, height, weight, duration of diabetes, number of severe hypoglycemic events (defined as seizures or loss of consciousness in the 3 months preceding the blood sampling), insulin regimen, and daily insulin dose was recorded in each sampling period. A capillary blood sample was drawn from each patient for HbA_{1c} determination in each sampling period, and all samples were analyzed at Steno Diabetes Center, Gentofte, Denmark. Details of this assay (normal range: 4.4–6.3%) and the transport of specimens have been published previously (7). In 1995, each center supplied a mean HbA_{1c} determination for the participants and the mean of the HbA_{1c} determination for the nonparticipants for the same time period, giving no indication of a selection bias (7).

The study was performed according to the criteria of the Helsinki II Declaration and was approved by the local ethics committee at each center.

Statistical analysis

Summary statistics are expressed as means ± SD or means ± SEM. Comparisons of centers with the grand mean HbA_{1c} level were performed using a one-way analysis of variance, taking into account each center's contribution to the grand mean. To correct for differences in sex, age, and diabetes duration distributions, an adjusted center mean was evaluated by a multiple regression analysis including center as a class variable, and sex, age, and disease duration as continuous variables. By means of these values, the center effect was adjusted to correspond to the average values of the other explanatory variables. Evaluation of the change in HbA_{1c} level, insulin frequency, insulin dose, and BMI for each center was done by a repeated-measurements model (with random subject effects) to account for the fact that some patients contributed with two measurements and others with only one. Sex, age, and duration of disease were included to adjust for these factors. The rate of severe hypoglycemic events was analyzed by a loglinear Poisson model, including sex, age, and center class (i.e., above average, average, and below average) as covariates. This was calculated both with and without including each

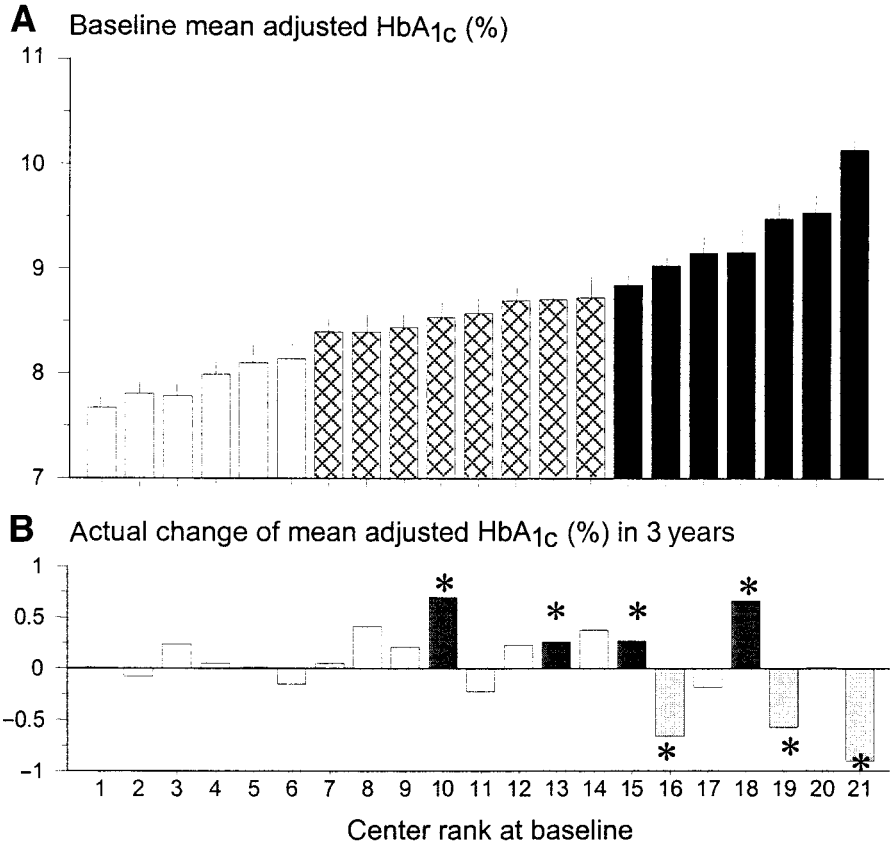

Figure 1—*Adjusted means ± SEM (adjustment for sex, age, and diabetes duration) of HbA_{1c} levels at participating centers at the baseline evaluation in 1995* (A). *Centers with an HbA_{1c} level significantly below average (□), with average HbA_{1c} concentrations (▨), and with levels significantly above average are shown (■). The change in the adjusted mean after 3 years* (B) *is also shown. The three centers that significantly (*$P < 0.05$) improved their adjusted HbA_{1c} levels are shown with light gray bars, the four centers that significantly worsened are shown with dark gray bars, and those that had no significant change are shown with empty bars.*

individual's HbA_{1c} level. To examine whether differences among centers were particularly pronounced early or later in the duration of diabetes, we calculated the mean HbA_{1c} level for each center separately for children with diabetes duration ≤3 years and >3 years. All data were analyzed in three different data sets: the total cohort, the subgroup of patients participating at both time points (i.e., repeat patients), and patients 11–18 years of age at both time points. However, as no major difference in the results among these analyses was apparent, except declining levels of significance due to the smaller sample size, only the results of the total cohort are described in the RESULTS section.

RESULTS

Differences among centers in glycemic control

Glycemic control as assessed by HbA_{1c} concentration varied significantly among centers in the first sampling period ($P < 0.0001$) (Fig. 1). The grand mean HbA_{1c} level in 1995 was 8.62 ± 0.03%. The HbA_{1c} concentration was higher in female subjects than in male subjects (0.22 ± 0.05, $P < 0.0001$, estimate ± SEM) and increased for each year of age (0.046 ± 0.008, $P < 0.0001$) or diabetes duration (0.079 ± 0.007, $P < 0.0001$). After adjustment for these factors, six centers were significantly above the grand mean for HbA_{1c}, eight centers were significantly below the grand mean ($P < 0.05$), and seven centers did not differ significantly from the average HbA_{1c} value.

Reproducibility of center differences in glycemic control

Three years later, three centers had improved significantly in their mean HbA_{1c} levels and four centers had deteriorated significantly in their overall HbA_{1c} levels (Fig. 1). The mean adjusted HbA_{1c} concentration remained unchanged: 8.67 ± 0.04%. Regarding the grouping in average, above-average, and below-average centers, only one center changed from being below average to being above average and one vice versa, respectively, whereas 14 centers did not change their position. Thus, the differences among centers are a reproducible finding.

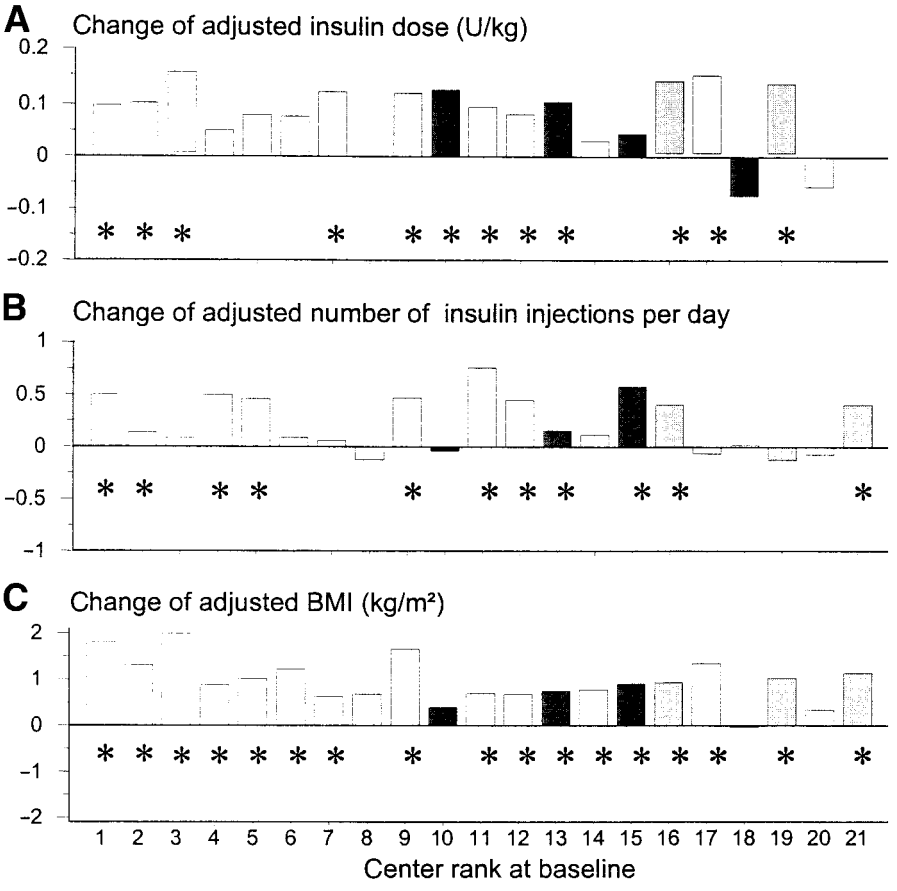

Figure 2—*Changes in the insulin dose* (A)*, number of insulin injections* (B)*, and BMI* (C) *between the baseline evaluation and 3 years later in the respective centers, sorted according to the center rank in the adjusted HbA_{1c} level at baseline (see Fig. 1). As in Fig. 1, the three centers that significantly improved their adjusted HbA_{1c} levels are shown with light gray bars, the four centers that significantly worsened are shown with dark gray bars, and those that had no significant change are shown with empty bars. *Significant ($P < 0.05$) changes from the first evaluation in the respective centers.*

Lack of association between changes in glycemic control and changes in the therapeutic regimen

The insulin dose in 12 centers increased significantly during the observation period (in two of three centers with significant improvement in HbA_{1c} levels and two of four with worsening of HbA_{1c} levels) (Fig. 2). The overall increase in insulin dose was 0.076 U/kg, after adjusting for the increase due to age and duration of diabetes. The change in insulin dose was unrelated to change in HbA_{1c} concentration. The number of daily injections increased overall by ~0.23 daily injections (adjusted for the increase due to age and duration), with a significant increase in 11 centers. This increase was not associated with changes in the average HbA_{1c} level of the respective centers (Fig. 2).

The BMI increased with age and duration of diabetes. Even after adjustment for this expected increase, however, a further overall increase of 0.95 kg/m^2 over 3 years occurred. A significant increase in BMI was found in all 11 centers where the number of daily injections had increased, but only in 6 of 10 centers with an unchanged frequency of injections (Fig. 2). Only 1 of 12 centers with an increase in the insulin dose had no significant rise in average BMI.

Better levels of glycemic control were not associated with higher insulin doses prescribed at different ages (Fig. 3). Centers with the best levels of glycemic control appeared to be successful in achieving good control from the onset of the disease, as a significant correlation was found in the mean HbA_{1c} concentration during the first 3 years of diabetes and the HbA_{1c} of patients with longer duration at the individual centers during both sampling periods (Fig. 4).

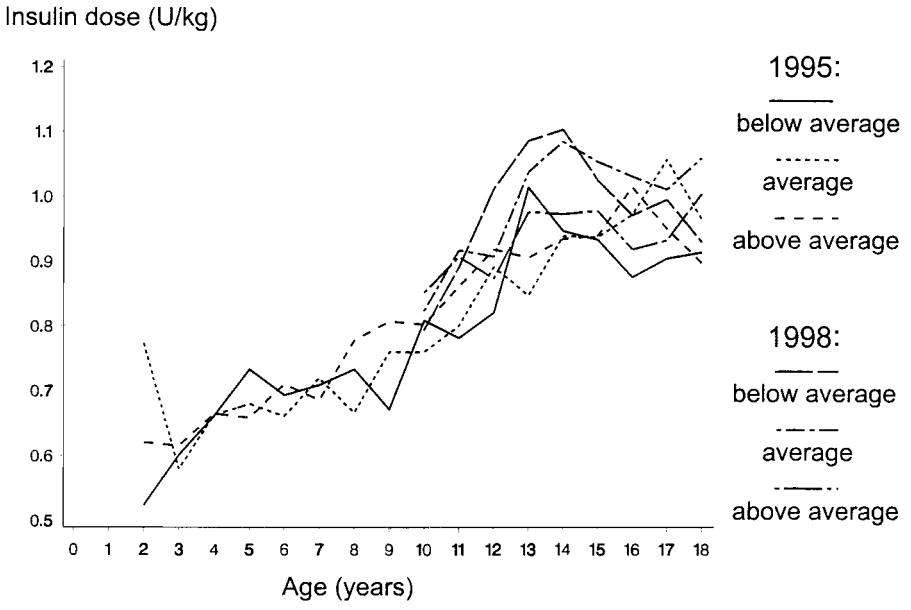

Figure 3—*Age-specific average curves (1995: age 2–18 years; 1998: age 10–18 years) for insulin doses in the centers significantly below the grand mean HbA_{1c} level, those centers not differing from the mean level, and those significantly above the mean level.*

Differences among centers in the rate of severe hypoglycemia

To quantify the differences among centers regarding the rates of hypoglycemia, a paired comparison of the three center groups with average, above average, and below average glycemic control was performed with a loglinear Poisson model. In this analysis, the relative risk of severe hypoglycemia was lowest in the group with the best glycemic control, regardless of whether the 1995 data or the 1998 data were used for analysis (Fig. 5, 1998 data). However, the center effect did not reach significance due to the low rates of hypoglycemia in this population ($\chi^2 = 5.46$, with 2 degrees of freedom; $P = 0.07$).

CONCLUSIONS — Substantial differences in the average HbA_{1c} level and the average rate of severe hypoglycemia were present among international multidisciplinary pediatric diabetes centers. Simple feedback about these differences led to an intensification of insulin therapy in most centers. However, only three centers were able to significantly improve their average glycemic control, and these changes were unrelated to parameters of insulin therapy investigated in the present study. However, cautious interpretation of the findings is warranted. Even though most of the participating centers claimed that the majority of their patients were from their geographic area, and no clear evidence of a selection bias could be found (7), this was not a population-based study. Moreover, the reasons why patients continue to attend a particular clinic may be directly related to the outcome of the management of their diabetes at that clinic.

Interestingly, the differences among centers were already apparent in patients with a very short duration of diabetes. This may have been due to the heterogeneity of type 1 diabetes itself, as significant differences have been reported at onset of diabetes among children from different geographic locations (8). Also, the HLA- DR3,DQ2 and -DR4,DQ8 haplotype distributions vary considerably among countries, and HLA-DR3,DQ2 has been reported to be associated with a milder course of the disease reflected by better metabolic control. However, when correlating the reported frequencies of these haplotypes (9) with the average control from patients representing these countries, we found no association. Ethnic or cultural differences have also been suggested to be related to differences in glycemic control (10,11). The present results are in agreement with those of other investigations that report that ethnic aspects appear to be of lesser importance than other factors (e.g., socioeconomic) for health-related behavior in adolescents (12,13), as geographic factors were unable to explain the observed differences (7). Low socioeconomic level and minority status are related to poor glycemic control (14). Potential heterogeneity of the patient populations due to varying proportions of immigrants or minorities at some centers may have a significant influence on results in some centers (11), but not in others (15).

In a nationwide study in France, glycemic control was better in university-affiliated hospitals and centers following >50 patients (16). Although specialized

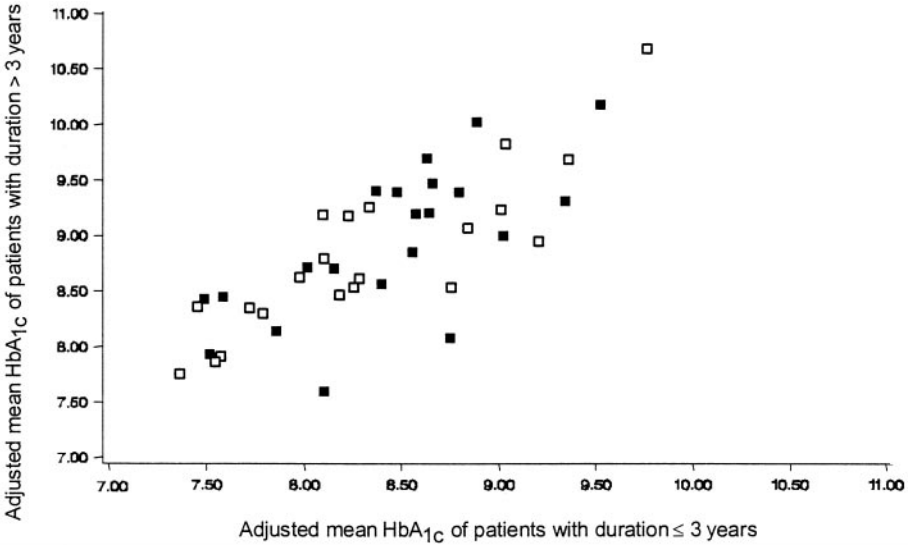

Figure 4—*Relation between the average control of the short-term patients (during the first 3 years of diabetes) and those with duration of diabetes >3 years at the 21 individual centers (□ 1995, R_s: 0.83, $P < 0.001$; ■ 1998, R_s: 0.68, $P = 0.001$; both time points combined, R_s: 0.77, $P < 0.001$).*

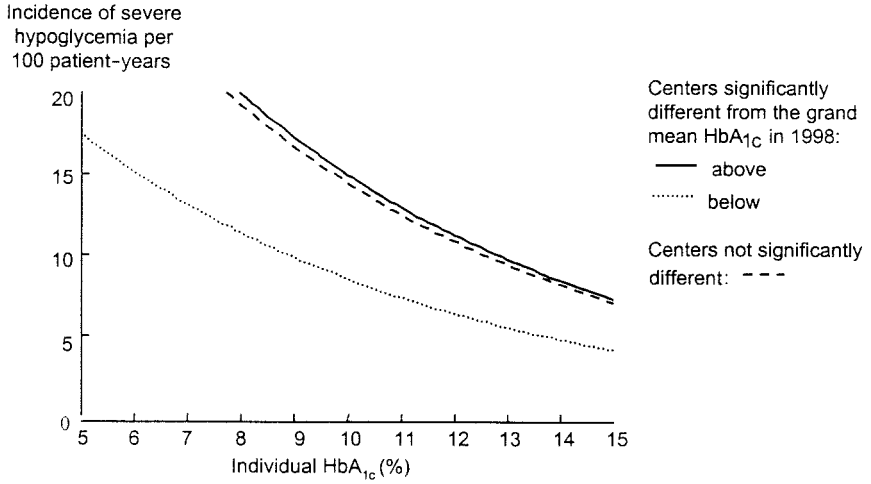

Figure 5—*Incidence of severe hypoglycemic episodes per 100 patient-years in centers above, below, and not significantly different from the mean level of HbA_{1c}. To show the estimated rates of events, a standard person from the 1998 group is considered (male, 13 years of age, and with diabetes duration of 5 years). Then, the predicted rate of events is shown as a function of center class (dotted line center significantly below the mean) and individual HbA_{1c} level using a Poisson loglinear regression model.*

diabetes care in general is associated with better glycemic control (17), significant differences were apparent in our study, even though only relatively large centers with special expertise in pediatric diabetology were included. In single-center analyses (15,18,19), an association was seen between the average HbA_{1c} level and the number of annual visits or the weekly time allocated for outpatient diabetes care by the members of the diabetes team. Indeed, in one center with significant improvement in the average HbA_{1c} level, structural improvements in the delivery of health care resulted in improved glycemic control (20).

Similar to the experience with hypoglycemia in the Diabetes Control and Complications Trial, there was no clear-cut association between average control at an individual center and the rate of severe hypoglycemia (21). For both sampling periods, a higher rate of severe hypoglycemia was associated with lower age and better glycemic control (7). However, some centers were more successful than others in preventing hypoglycemia independent of the prevailing average HbA_{1c} level at the respective center. This important finding may relate to other features of diabetes management, such as psychological support and more successful education in centers with low incidence of hypoglycemia (15,19,21,22).

Therefore, an alternative explanation for the good correlation between the average control in patients with a short duration of diabetes and those with a long-term course of the disease has to include differences in diabetes education and management from the onset of the disease. Thus, differing attitudes of the diabetes teams (e.g., regarding the use of sliding-scale insulin dosage adjustments) and/or differing degrees of patient empowerment may represent a major factor underlying these differences among centers. Parameters of insulin therapy showed no clear-cut association with glycemic control or hypoglycemia rates either in the original sample (7) or in the present assessment of the differences among centers. As a consequence of the unsatisfactory level of glycemic control in the first survey, it is possible that most centers had increased the number of injections and the insulin dose before reinvestigation at the second sampling. These changes were not associated with an improvement in glycemic control. As a possible side effect of this strategy, a substantial increase in the BMI was observed in many centers, particularly in girls (23).

In conclusion, it is naive to limit quality assessment in pediatric diabetology to comparing HbA_{1c} levels, hypoglycemia rates, or superficial structural aspects of diabetes care as suggested by contemporary guidelines. Factors such as the attitudes of treatment teams, self-care behaviors, educational models, or patient satisfaction may be more directly related to outcomes than insulin regimens. The demonstration of the differences among centers has been disquieting to the participants of the study, and the subsequent analyses have revealed more questions than answers. Now that it has been established that differences among centers are maintained over 3 years, future studies need to focus on the early course of the disease when differences are already present. Subsequent studies undertaken by the Hvidøre Group will therefore investigate the remission phase and health care delivery via a patient satisfaction survey.

Acknowledgments— We thank Novo Nordisk A/S for its enthusiasm and practical support throughout this study, with special appreciation to Lene Kaa Meier. We are also grateful to the Steno Diabetes Center for the assistance that it provided.

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