Continuing Stability of Center Differences in Pediatric Diabetes Care: Do Advances in Diabetes Treatment Improve Outcome?

The Hvidoere Study Group on Childhood Diabetes

CARINE E. DE BEAUFORT, MD, PHD[1]
PETER G.F. SWIFT, MD[2]
CHAS T. SKINNER, PHD[3]
HENK J. AANSTOOT, MD, PHD[4]
JAN ÅMAN, MD[5]
FERGUS CAMERON, MD[6]
PEDRO MARTUL, MD[7]
FRANCESCO CHIARELLI, MD[8]
DENNIS DANEMAN, MD[9]
THOMAS DANNE, MD[10]
HARRY DORCHY, MD, PHD[11]
HILARY HOEY, MD[12]
EERO A. KAPRIO, MD[13]
FRANCINE KAUFMAN, MD[14]
MIRJANA KOCOVA, MD, PHD[15]
HENRIK B. MORTENSEN, MD[16]
PAL R. NJØLSTAD, MD, PHD[17]
MOSHE PHILLIP, MD[18]
KENNETH J. ROBERTSON, MD[19]
EUGEN J. SCHOENLE, MD[20]
TATSUHIKO URAKAMI, MD[21]
MAURIZIO VANELLI, MD[22]
ON BEHALF OF THE HVIDOERE STUDY GROUP ON CHILDHOOD DIABETES 2005

OBJECTIVE — To reevaluate the persistence and stability of previously observed differences between pediatric diabetes centers and to investigate the influence of demography, language communication problems, and changes in insulin regimens on metabolic outcome, hypoglycemia, and ketoacidosis.

RESEARCH DESIGN AND METHODS — This was an observational cross-sectional international study in 21 centers, with clinical data obtained from all participants and A1C levels assayed in one central laboratory. All individuals with diabetes aged 11–18 years (49.4% female), with duration of diabetes of at least 1 year, were invited to participate. Fourteen of the centers participated in previous Hvidoere Studies, allowing direct comparison of glycemic control across centers between 1998 and 2005.

RESULTS — Mean A1C was 8.2 ± 1.4%, with substantial variation between centers (mean A1C range 7.4–9.2%; $P < 0.001$). There were no significant differences between centers in rates of severe hypoglycemia or diabetic ketoacidosis. Language difficulties had a significant negative impact on metabolic outcome (A1C 8.5 ± 2.0% vs. 8.2 ± 1.4% for those with language difficulties vs. those without, respectively; $P < 0.05$). After adjustement for significant confounders of age, sex, duration of diabetes, insulin regimen, insulin dose, BMI, and language difficulties, the center differences persisted, and the effect size for center was not reduced. Relative center ranking since 1998 has remained stable, with no significant change in A1C.

CONCLUSIONS — Despite many changes in diabetes management, major differences in metabolic outcome between 21 international pediatric diabetes centers persist. Different application between centers in the implementation of insulin treatment appears to be of more importance and needs further exploration.

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The Hvidoere Study Group on Childhood Diabetes has investigated metabolic control in large cohorts of adolescents from >20 pediatric diabetes centers worldwide. Studies have shown that although the mean A1C was not much higher than in the intensively treated adolescent group in the Diabetes Control and Complications Trial (DCCT), few of the adolescents achieved A1C levels in an optimal range (29% < 8.0%) (1). Better metabolic control was associated with better quality of life with no increased rate of hypoglycemia (2,3), contrary to the results of the DCCT for adolescents (4,5). However, the Hvidoere Study Group also revealed substantial and persistent differences between the centers for which no clear explanations were found (2,6).

With the introduction of newer insulins, increased implementation of basal-bolus multiple-dose injection regimens, reentry of continuous subcutaneous insulin infusion (CSII) treatment, and the general trend toward intensification of in-

From the [1]DECCP, Clinique Pédiatrique/Centre Hospitalier, Luxembourg; the [2]Department of Paediatrics, Leicester Royal Infirmary Children's Hospital Leicester, U.K.; the [3]Department of Psychology, University of Wollongong, Wollongong, Australia; [4]Diabetes, Center for Pediatric and Adolescent Diabetes, Rotterdam, the Netherlands; the [5]Department of Pediatrics, Örebro University Hospital, Örebro, Sweden; the [6]Department of Endocrinology and Diabetes, Royal Children's Hospital, Parkville, Victoria, Australia; the [7]Endocrinology and Diabetes Research Group, Hospital de Cruces, Cruces, Spain; the [8]Department of Pediatrics, University of Chieti, Chieti, Italy; the [9]Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Canada; the [10]Kinderkrankenhaus auf der Bult, Hannover, Germany; the [11]Diabetology Clinic, Children's University Hospital Queen Fabiola, Brussels, Belgium; the [12]Department of Paediatrics, Trinity College, National Childrens Hospital, Dublin, Ireland; the [13]Department of Paediatrics, Peijas Hospital, Vantaa, Finland, the [14]Department of Pediatrics, Children's Hospital of Los Angeles, Los Angeles California; the [15]Pediatric Clinic, Medical Faculty Department of Endocrinology and Genetics, Skopje, Republic of Macedonia; the [16]Paediatric Department L, Glostrup University Hospital, Glostrup, Denmark; the [17]Department of Pediatrics, Haukeland University Hospital and Department of Clinical Medicine, University of Bergen, Bergen, Norway; the [18]National Center of Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel; the [19]Department of Paediatrics, Royal Hospital for Sick Children, Glasgow, Scotland; the [20]Department of Paediatrics, University Childrens Hospital, Zurich, Switzerland; the [21]Department of Paediatrics, Nihon University School of Medicine, Tokyo, Japan; and the [22]Centro di Diabetologia, University of Parma, Parma, Italy.

Address correspondence and reprint requests to Dr. Carine de Beaufort, Clinique Pédiatrique, Centre Hospitalier de Luxembourg, 4, rue Barblé, 1220 Luxembourg. E-mail: debeaufort.carine@chl.lu.

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Abbreviations: CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; DKA, diabetic ketoacidosis.

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

Table 1—*Demographic and clinical characteristics of participants by sex*

	Female subjects	Male subjects
n (%)	1,034 (49.4)	1,059 (50.6)
Age (years)	14.5 ± 2.1	14.5 ± 2.0
Diabetes duration (years)	6.3 ± 3.6	5.8 ± 3.4
BMI (kg/m^2)	22.8 ± 12.6	21.7 ± 3.7
Insulin dose (units · kg^{-1} · day^{-1})	1.0 ± 0.3	1.0 ± 0.3
Hypoglycemic episodes (last 3 months/100 patient-years)	27 ± 170	24 ± 114
DKA (last 12 months/100 patient-years)	4 ± 21	4 ± 30
A1C (%) (n = 2,036)	8.3 ± 1.5	8.1 ± 1.3
Different insulin regimens		
Miscellaneous	141 (13.6)	168 (15.9)
Twice-daily premix	77 (7.4)	83 (7.8)
Twice-daily free mix	128 (12.4)	168 (15.9)
Thrice daily	26 (2.5)	42 (4.0)
Basal bolus	487 (47.1)	439 (41.5)
CSII	175 (16.9)	159 (15.0)
Concomitant problems		
Celiac disease	45 (4.4)	36 (3.4)
Thyroid disease	94 (9.1)	29 (2.7)
Epilepsy	5 (0.5)	14 (1.3)
Asthma	26 (2.5)	35 (3.3)
Other	53 (5.1)	48 (4.5)

Data are means ± SD or *n* (%).

sulin treatment into pediatric diabetes, a new study was initiated (7–10). The aims of this study were to investigate whether demographic and ethnic factors, or the substantial regimen changes and information exchange between centers, had resulted in improved glycemic control in adolescents and reduced the differences between centers.

RESEARCH DESIGN AND METHODS

— An observational, multicenter, cross-sectional study involving 21 pediatric diabetes departments from 19 countries in Europe, Japan, Australia, and North America was performed between March and October 2005. Fourteen centers had participated in the 1998 Hvidoere Study. Adolescents (aged 11–18 years; diabetes duration >12 months), parents, and health care professionals were invited to participate. Each center was limited to a maximum of 200 adolescent participants. If a center had >200 eligible adolescents, only the patients seen by one Hvidoere member were invited.

The case report form included information on sex, age, height, weight, duration of diabetes, number of severe hypoglycemic events (defined as seizures or loss of consciousness in the 3 months preceding blood sampling), and number of episodes of diabetic ketoacidosis (DKA) necessitating hospital admission in the last year. The number of insulin injections, type of insulin, and injection device were recorded. Information on concomitant medical conditions (celiac disease, thyroid disease, epilepsy, asthma, or other) was obtained. As a marker for ethnicity/minority group status, the case report form recorded whether there were language difficulties leading to communication problems with the diabetes team. All members of the diabetes teams were asked what changes had been made "to improve diabetes care and outcomes in your clinic during the last 5 years. Include clinical, administrative, organizational, resource and any other changes."

A capillary blood sample was provided by participants and analyzed at Steno Diabetes Center, Gentofte, Denmark. A1C was DCCT aligned (normal range 4.4–6.3%, mean 5.4%, and interassay SD 0.15%, Tosoh method). For comparisons with 1998 data (A1C assayed by the Bio-Rad method), we used the correction equation for equivalence evaluated by the Steno laboratory ($A1C_{BioRad} = 0.590 + 0.971\ A1C_{Tosoh}$) (11). Details of transportation and stability of specimens have been published (1). 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

Data were all double entered at a central administration center, and ambiguous data on the case report form were resolved by direct contact with participating centers. Bivariate relationships with A1C, DKA, and hypoglycemic episodes were tested using ANOVA for categorical variables and Pearson's product moment correlation for continuous variables. The effect of center on A1C was tested by adding confounding demographic and medical characteristics as covariates, with categorical covariates dummy coded. Comparisons between the 1998 and 2005 studies were conducted, after ensuring comparable age range for participants, using repeated-measures ANOVA, with subsequent analysis controlling for all confounding variables with categorical covariates dummy coded.

RESULTS

Descriptives and demographics

A total of 2,269 eligible individuals attended clinics during the recruitment period. Demographic characteristics are summarized (Table 1). Of these, 2,093 (92%) adolescents completed a questionnaire and 2,036 (89%) provided a blood sample for assay. There were no significant differences in age, BMI, and frequency of DKA between those who provided A1C sample and those who did not. Those not providing A1C samples had a shorter duration of diabetes (with A1C, duration 6.1 ± 3.5 years; without A1C, duration 4.8 ± 2.8 years; $P < 0.001$).

The grand mean A1C for the whole sample was 8.2 ± 1.4%. Female subjects had significantly higher A1C values (female subjects 8.3 ± 1.5%; male subjects 8.1 ± 1.3%; $P < 0.0001$). Older participants ($r = 0.09$, $P < 0.001$) and those with a longer duration of diabetes ($r = 0.29$, $P < 0.001$) had significantly, but only modestly, higher A1C levels. Individuals with concomitant pathology did not have significantly different A1C. Adolescents whose families had language difficulties leading to communication problems with the diabetes team had higher A1C levels (language difficulties [$n = 79$] A1C 8.5 ± 2.0% vs. 8.2 ± 1.4% without language difficulties $P < 0.05$). There were no significant differences in frequency of hypoglycemia nor DKA for the people with language difficulties.

The majority of individuals (85.3%) were on one of five insulin regimens (Ta-

Table 2—*A1C and insulin dose by insulin regimen*

Regimen	A1C	Insulin doses (units · kg^{-1} · 24 h^{-1})
Miscellaneous	8.2 ± 0.1	0.66 ± 0.02
Twice-daily premix	8.6 ± 0.1*	1.01 ± 0.03
Twice-daily free mix	7.9 ± 0.1†	1.00 ± 0.02
Thrice daily	8.2 ± 0.2	1.24 ± 0.05
Basal bolus	8.2 ± 0.0	1.03 ± 0.01
Pumps	8.1 ± 0.1	0.92 ± 0.02

Data are means ± SE. *Significantly higher than the other insulin regimens ($P < 0.001$). †Significantly lower than the other insulin regimens ($P < 0.001$).

ble 1). The remaining 309 (14.7%) individuals were on regimens that could not be classified into any obvious category with meaningful numbers. This unclassified group had A1C 8.2% (not significantly different from other groups) but a significantly lower mean insulin dose ($F = 9.4$; df = 4; $P < 0.001$) than the classified groups. Those on thrice-daily injections had significantly higher doses than all other groups. There was a significant relationship between insulin regimen and A1C ($F = 6.629$; df = 5; $P < 0.001$), with post hoc analysis indicating individuals on twice-daily free-mix regimens (varying the quantity of short/analogue and intermediate insulin) having significantly lower A1C than those on basal-bolus, pumps, or twice-daily premixed/insulin regimens. Adolescents on twice-daily premixed insulin regimens had significantly higher A1C than all other regimens except thrice daily (Table 2). There was no significant relationship between insulin regimen and BMI, hypoglycemia, or the occurrence of DKA.

BMI was not significantly associated with A1C, hypoglycemia, or DKA

Insulin daily dosage was unrelated to frequency of hypoglycemia but was significantly correlated with DKA ($r = 0.09$, $P < 0.001$) and A1C ($r = 0.8$, $P < 0.001$), with higher insulin dose associated with poorer metabolic control and more frequent DKA.

Assessment of center differences

A1C in the 21 centers ranged between 7.4 and 9.2%. ANOVA indicated that there were significant differences between centers for A1C ($F = 12.88$; df = 20; $P < 0.001$) but not for frequency of hypoglycemia nor DKA. Six centers had a mean A1C significantly below the sample mean and six centers significantly above the sample mean (Fig. 1). However, there were also significant differences between centers for age of participants ($F = 3.4$; df = 20; $P < 0.001$), duration of diabetes ($F = 1.80$; df = 20; $P < 0.05$), insulin regimens ($\chi^2 = 2{,}300$; df = 80; $P < 0.001$), daily insulin dosage ($F = 6.40$; df = 20; $P < 0.001$), and BMI ($F = 2.91$; df = 20; $P < 0.005$). Two centers had more participants with language difficulties than the overall mean, and four centers had less than the mean ($\chi^2 = 114$; df = 2; $P < 0.001$). When the analysis of center differences was repeated adding these variables as covariates, the significant differences in A1C between centers remained, with the effect size remaining largely unaffected by the inclusion of any/all these covariates ($F = 13.61$; df = 20; $P < 0.001$).

Assessment of stability of center differences

Fourteen centers participated in both this and the 1998 study. This provided a sample size of 1,498 individuals from 1998 and 1,295 participating from the same centers in 2005. Although largely comparable, the 2005 cohort was significantly older (1998: mean age 14.27 ± 2.1 years, 2005: mean age 14.5 ± 2.0 years; $P < 0.05$) and had slightly longer duration of diabetes (1998: mean duration = 5.6 ± 3.7 years, 2005: mean duration = 6.0 ± 3.5 years; $P < 0.005$). Therefore, all further analyses comparing the two cohorts were undertaken controlling for age and duration of diabetes. Participants in 2005 had a higher BMI (1998: mean = 21.3 ± 3.5 kg/m^2, 2005: mean = 21.9 ± 3.9 kg/m^2; $F = 12.5$; df = 1; $P < 0.001$) and were on more intensive insulin regimens (1998 = 34% twice daily, 23% basal bolus, 0.3% CSII) without a significant increase in daily insulin dose (1998: mean = 0.98 ± 0.3 units · kg^{-1} · day^{-1}, 2005: mean = 1.0 ± 0.3 units · kg^{-1} · day^{-1}). No significant change was observed in A1C either by simple comparison ($F = 0.31$; df = 1; $P > 0.57$) or when controlling for different covariables

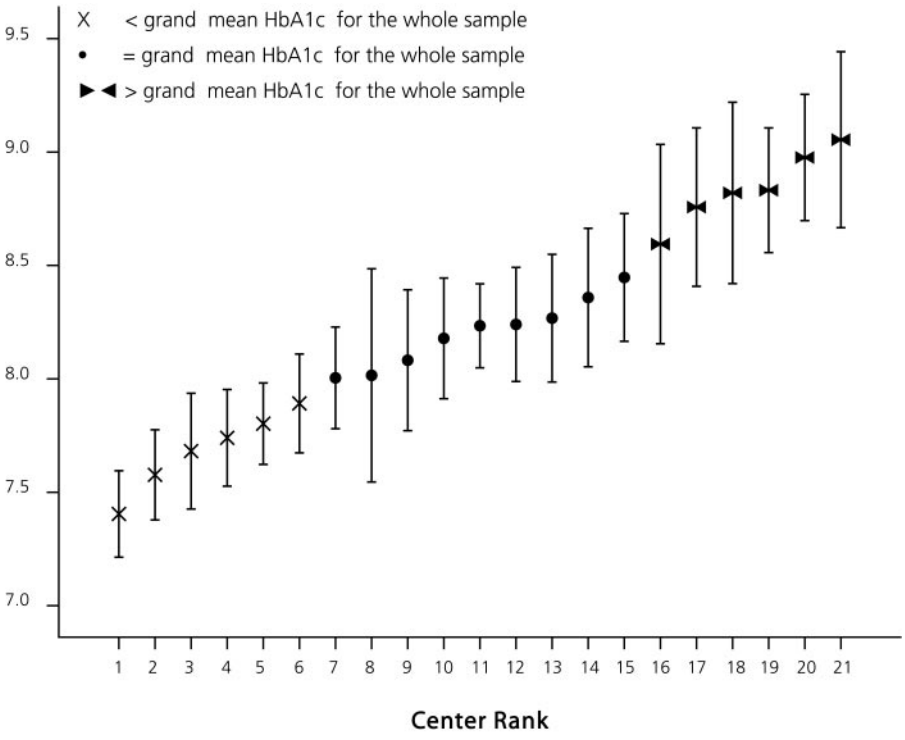

Figure 1—*Mean and SE of A1C (Tosoh method) for participating centers in rank order after controlling for confounding variables.*

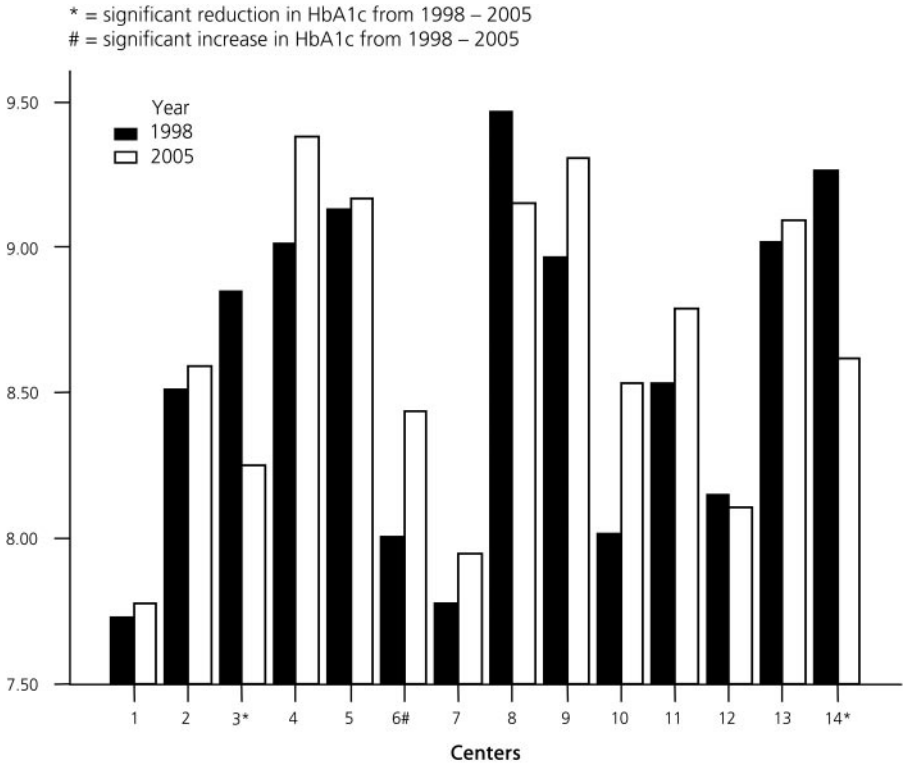

Figure 2—*Mean corrected A1C in 1998 and 2005 for centers in both studies after controlling for confounding variables.*

(1998: mean = 8.64 ± 1.6%, 2005: mean = 8.65 ± 1.5%; $F = 0.30$; df = 1; $P > 0.58$). There was also no significant difference between cohorts for frequency of hypoglycemia ($F = 0.92$; $P > 0.34$).

Controlling for demographic differences between cohorts, two centers showed a significant reduction (≥0.5%) in A1C from 1998 to 2005 and one center had a significant increase in A1C from 1998 to 2005 (Fig. 2). Although those centers that showed improved metabolic outcomes had increased the use of basal-bolus/CSII regimens (from 3 to 52% for center 3 and from 3 to 82% for center 14), this increase did not differ significantly from the other 12 centers (e.g., center 2 from 13 to 93%, center 5 from 4 to 60%). Some centers reported a decrease in basal bolus regimens with no detrimental effect on metabolic control (e.g., center 1 from 21 to 7%, with 93% of the patients being on twice-daily free mix).

None of the changes in the resources (increased staff), structure, and process of delivering care (more focus on outpatient care, written information, telephone hotline, annual reviews, more psychosocial support, and intensified insulin therapy) in the 14 centers, as reported by team members of each diabetes team, could explain the outcome. Centers demonstrating significantly reduced A1C report no strategy that was not used elsewhere, but they tended to implement more changes than reported by most other centers.

CONCLUSIONS — The management of children and adolescents with type 1 diabetes has undergone many changes over the past decade (7–10), aiming to improve glycemic control and reduce risks of vascular complications, without sacrificing quality of life (12). These have included increased usage of insulin analogues, basal-bolus regimens, and CSII (9,13–16).

Despite these substantial changes, it has been difficult to demonstrate significant improvements in metabolic outcome (2,6,7,10) This study in 21 international centers was initiated to investigate the impact of treatment changes on glycemic control and to establish whether the previously reported differences between centers were diminishing. The results confirm that that there has been no improvement in glycemic control over a decade, with mean A1C levels of 8.6% (1995), 8.7% (1998), and 8.6% (2005) (1), and the substantial differences between centers have remained stable.

Only two centers significantly improved glycemic control compared with 1998. This could not be explained by intensification of insulin regimens or attributed to major changes in their team approach, compared with other centers. However, the range of changes made suggests that the two centers may have undergone a more fundamental restructuring of care rather than just tinkering with service provision. Increased numbers of diabetes nurses, weekly staff meetings, written patient information, and increased visits may have lead to improved education and/or treatment adherence (17). In comparison, the DCCT/Epidemiology of Diabetes Interventions and Complications results in adolescents show that in both DCCT intensive and nonintensive groups the mean A1C levels of ~8.4% suggest that this age-group requires a fundamentally different approach to obtain a significant improvement in metabolic outcome (18).

The A1C achieved by individuals using twice-daily free mixing of insulin, most often using mixtures of soluble/regular plus NPH insulins, was lower than any other group. This suggests that the so-called conventional insulin regimens may be superior to more modern intensive regimens. However, this successful outcome seems to be the result of more optimal use of this regimen in specific centers. Those centers with lower mean A1C also have individuals with lower mean A1C using other regimens. In other words, as demonstrated previously (2,6), we cannot show that one insulin regimen is superior to another but only where and how that regimen is implemented. One should not assume that a multiple-injection basal-bolus regimen automatically represents an intensified insulin therapy and that a "conventional" twice-daily injection regimen is nonintensive. A multiple injection regimen not associated with intensified comprehensive education may be associated with deteriorating glycemic control. In contrast, a twice-daily injection regimen, with intensive consistent education, adjusted food intake, and appropriate adjustments of insulin doses, may lead to better metabolic outcome (14,19,20).

There were 309 (14.7%) individuals whose insulin regimen could not be easily classified into specific categories (e.g., unusual insulin combinations, multiple doses of different insulins, etc.). It is reassuring that this group's mean A1C was no different from the total cohort despite having perhaps more individualized insulin regimens. The explanation for individualized regimens is uncertain. For

example, individuals in this group may have been more difficult to control, but the result strengthens the conclusion that center differences are not strongly influenced by a particular insulin regimen. This applies also to the increased access to CSII in some centers. The A1C for individuals on CSII was not significantly different from the total group, and in centers where considerable numbers of patients were on pumps, metabolic control was not significantly different. Numerous audits have found that CSII reduces glycated hemoglobin when switching from one modality to another, especially in clinics where enthusiasm is high (16,21,22), but randomized controlled trials of CSII in adolescents have had too small sample sizes or too short a duration of study to be statistically relevant (23). These criticisms could also be leveled at reported studies of basal-bolus therapy (20,24). The effects of new therapies on glycemia alone may be exaggerated, and there is a need for new tools to assess the behavioral and psychosocial outcomes (23).

The study attempted to review the influence on glycemic control of ethnic differences both at an individual level and between centers. Previously, we reported a weak negative association between ethnic minority status and A1C (2). This area of investigation has proven to be one of the most controversial, especially in centers where ethnic groups are diverse and well established. Using language difficulties as a marker for recent ethnic diversification, we have shown that when there are problems in communication between the adolescent or parents and the team, A1C is significantly higher. However, this finding does not influence the differences between centers. Some ethnically diverse centers seem able to achieve excellent metabolic control perhaps because there are minimal language and communication difficulties.

In conclusion, we have shown that despite major and continuing changes in the use of newer insulin regimens (including CSII), modes of administration, and attempts to improve service provision, glycemic control has not improved over a decade in 21 international centers. Significant and stable differences between centers remain, which cannot be explained by demography, ethnic issues, or insulin regimens. Certain centers are able to implement different insulin regimens more successfully than others. Further analysis of this implementation as well as other factors influencing center differences require further exploration.

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