

Original Article

Metabolic outcomes in young children with type 1 diabetes differ between treatment centers: the Hvidoere Study in Young Children 2009*

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Objective: To investigate whether center differences in glycemic control are present in prepubertal children <11 yr with type 1 diabetes mellitus.

Research Design and Methods: This cross-sectional study involved 18 pediatric centers worldwide. All children, <11 y with a diabetes duration ≥ 12 months were invited to participate. Case Record Forms included information on clinical characteristics, insulin regimens, diabetic ketoacidosis (DKA), severe hypoglycemia, language difficulties, and comorbidities. Hemoglobin A1c (HbA1c) was measured centrally by liquid chromatography (DCCT aligned, range: 4.4–6.3%; IFFC: 25–45 mmol/mol).

Results: A total of 1133 children participated (mean age: 8.0 ± 2.1 y; females: 47.5%, mean diabetes duration: 3.8 ± 2.1 y). HbA1c (overall mean: $8.0 \pm 1.0\%$; range: 7.3–8.9%) and severe hypoglycemia frequency (mean 21.7 events per 100 patient-years), but not DKA, differed significantly between centers ($p < 0.001$ resp. $p = 0.179$). Language difficulties showed a negative relationship with HbA1c ($8.3 \pm 1.2\%$ vs. $8.0 \pm 1.0\%$; $p = 0.036$). Frequency of blood glucose monitoring demonstrated a significant but weak association with HbA1c ($r = -0.17$; $p < 0.0001$). Although significant different HbA1c levels were obtained with diverse insulin regimens (range: 7.3–8.5%; $p < 0.001$), center differences remained after adjusting for insulin regimen ($p < 0.001$). Differences between insulin regimens were no longer significant after adjusting for center effect ($p = 0.199$).

Conclusions: Center differences in metabolic outcomes are present in children <11 yr, irrespective of diabetes duration, age, or gender. The incidence of severe hypoglycemia is lower than in adolescents despite achieving better glycemic control. Insulin regimens show a significant relationship with HbA1c but do not explain center differences. Each center's effectiveness in using specific treatment strategies remains the key factor for outcome.

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Optimizing metabolic control in association with optimal quality of life is the major goal in childhood type 1 diabetes mellitus (T1DM). Despite attempts to improve metabolic outcomes through intensified management, recent studies by the Hvidoere Study Group (HSG) have shown persistent differences between diabetes centers with respect to metabolic control in adolescents in Europe, North America, Japan, and Australia (1, 2). The study in 2005 provided

evidence that family dynamics and targets of control may be of more significance than insulin regimens in explaining center differences in adolescents despite the fact that since the previous study there had been a marked switch toward increased injection frequency (3–5). Insulin regimens *per se* had only a modest relationship with hemoglobin A1c (HbA1c), with the exception of premixed insulins (resulting in significantly higher HbA1c), and could not fully explain

the observed center differences. Adolescence, however, is a period characterized by major physical and psychological changes, which are often more important than changes in insulin or dietary regimens (6–8). Intensifying treatment through increased injection frequency or pumps may give more freedom to adjust the treatment around peer-oriented lifestyle, but whether this leads to improved metabolic outcome depends on the ability to adhere to treatment and education (8). In the younger children, the role of the parents as caregivers is central and most influential compared with the transitional phase toward self-management in the early teenage years and afterward.

We, therefore, hypothesized that center differences in glycemic control and acute complications might not be so marked or might not be present in a young cohort of children and that perhaps recent developments in insulin regimens would have a more profound effect on glycemic control compared with adolescents.

The purpose of this study was to identify the relationship between current diabetes management and center differences in metabolic outcomes in a large cohort of younger children with T1DM.

Research design and methods

All children with T1DM, treated at the Hvidoere Centers below 11 yr of age and with a diabetes duration of at least 1 yr, were invited to participate with informed parental consent. In centers with more than 200 children aged <11 yr, only those seen by the member of the Hvidoere Group were invited. For all children, Clinical Record Forms (CRFs) including questions on clinical characteristics, treatment, and acute complications were collected. Detailed descriptions of the insulin regimens, episodes of severe hypoglycemia (seizures or loss of consciousness in the past 3 months), diabetic ketoacidosis (DKA requiring hospital admission within the past 12 months), and information on comorbidities (celiac disease, hypothyroidism, and asthma) were obtained. Questions on language difficulties with the parents or the children were included to obtain some insight into possible minority groups within the centers. Reports of type 1 and 2 diabetes in first- and second-degree relatives were obtained. A centralized HbA1c measurement was performed by the TOSOH® liquid chromatography (DCCT aligned, normal range: 4.4–6.3%; IFFC: 25–45 mmol/mmol).

Statistical analysis

Data were all double entered at a central administration center. Ambiguous data on the CRF were resolved by direct contact with participating centers. For descriptive analysis, mean and SD were calculated for

continuous variables and percentages for categorical variables. Rates of ketoacidosis and hypoglycemia were estimated by the patient-years (PYs) method and given as incident number of events per 100 PYs ± SE. All analyses were completed using SPSS v19. Independent t-tests were used, when two groups were compared. When Levene's tests showed non-equal variance between groups, the appropriate corrected t and p values are quoted. Associations between the different variables and HbA1c were tested using analysis of variance (ANOVA). Where the dependent variables were not normally distributed, Kruskal–Wallis test was utilized. For non-parametric correlations between ordinal variables, Spearman's rho correlation coefficient was applied, whereas for mixed-level data Kendall's Tau was used and for parametric data Pearson's product moment coefficient (with all results being significant at $p < 0.001$, unless otherwise stated). The association between center and HbA1c was tested by adding demographic and medical characteristics as covariates, with categorical covariates dummy coded.

Results

Of 1209 eligible children in 18 centers during the recruitment period, 1133 (93.7%) children (47.4% females; mean age: 8.0 ± 2 yr; diabetes duration: 3.8 ± 2.1 yr) and their parents agreed to participate and 1107 (91.6%) provided a blood sample. Duration of diabetes differed among the centers (center range: 2.9–4.3 yr; $F = 1.907$; $p = 0.014$), but age ($F = 1.405$; $p = 0.125$) did not. Language difficulties were observed in 4.5% of the families, varying significantly between centers (center range: 0–11.5%; $\chi^2 = 40.92$; $p = 0.001$). Comorbidities were present in 13.8% of the children (center range: 1.9–27.5%) and differed significantly across centers ($\chi^2 = 48.79$; $p < 0.001$) with celiac disease (5.8%), followed by hypothyroidism (1.7%) and asthma (1.4%) as most frequent concomitant pathology. A total of 12.8% of the children had one or more first- or second-degree relatives with T1DM, with no significant difference between the centers ($\chi^2 = 14.24$; $p = 0.649$). A relative with type 2 diabetes (first or second degree) was reported by 27.2% of the children, with significant center difference ($\chi^2 = 85.17$; $p < 0.001$).

Metabolic control

The grand mean HbA1c was $8.0\% \pm 1.0$ ($n = 1107$) (64 mmol/mol; range: 4.7–13.6%) with 30.5% of the children in good (<7.5%), 24.8% in acceptable (7.5–8.0%), 31.6% in fair (8.1–9%), and 12% in poor control (>9.0%). Glycemic control differed significantly between the centers [ANOVA ($F = 22.24$; $df = 17$; $p < 0.001$)] (Fig. 1A), with mean HbA1c levels

varying between $7.3 \pm 0.8\%$ and $8.9 \pm 1.1\%$ (56 vs. 75 mmol/mol)]. There were no significant relationships between age, gender, or diabetes duration and HbA1c in this sample.

In 45 children (4% of the sample), 61 severe hypoglycemic events were reported within the last 3 months, which is a frequency of 21.7 events/100 PYs. In 26 children (2.3% of the sample), 42 DKA episodes were reported for the last 12 months, representing a frequency of 3.7 events/100 PYs. Mean HbA1c of children with severe hypoglycemia did not differ from those without severe hypoglycemia (7.9 ± 0.9 vs. 8.0 ± 1.0 ; $t = 0.71$; $p = 0.47$) nor did the mean HbA1c of children with or without DKA (8.1 ± 0.7 vs. 8.0 ± 1.0 ; $t = 0.46$; $p = 0.65$).

The incidence of severe hypoglycemic events differed significantly between centers ($\chi^2 = 44.66$; $p < 0.001$), whereas DKA frequency did not differ ($\chi^2 = 22.15$; $p = 0.179$). Although significantly higher HbA1c levels ($t = 2.09$; $p = 0.036$) were observed in individuals or families with language problems ($8.3 \pm 1.1\%$; 67 mmol/mol vs. $7.9 \pm 1.0\%$; 63 mmol/mol), it did not explain the variation in glycemic control among centers. Other cases of diabetes in the family were not associated with metabolic outcomes in the children.

Insulin regimens

Different insulin regimens were used: CSII 32.8%, basal bolus injections (BBIs) 16.9%, conventional twice daily (CT) 36.5%, premixed insulins (CT^{premix}) 6.3%, and twice daily variably free mixed with extra insulin when deemed necessary (CT^{freemix}) 7.5%. Premixed insulin consisting of a fixed percentage of short and intermediate/long-acting insulin, whereas the freemix insulin was defined as a variable combination of short and long/intermediate-acting insulins, being mixed at the time of injection, and given twice daily. ANOVA indicated significant differences in HbA1c between the insulin regimens ($F = 25.24$; $df = 4$; $p < 0.001$), with the highest HbA1c levels in the CT^{premix} group ($8.5 \pm 1.7\%$), CSII ($7.8 \pm 0.9\%$), BBI ($8.0 \pm 1.0\%$), and CT ($8.2 \pm 1.0\%$). The lowest HbA1c levels were found in the CT^{freemix} group ($7.3 \pm 0.5\%$).

No difference in DKA frequency was observed across insulin regimens ($\chi^2 = 4.36$; $p = 0.380$) contrary to the reported number of severe hypoglycemic events ($\chi^2 = 18.26$; $p = 0.001$), which was highest in the CT^{freemix} (42.4/100 PYs) and lowest in the CSII group (5.4/100 PYs). No severe hypoglycemia was seen in 96% of all children.

Different insulin regimens used within the centers are shown in Fig. 1B.

Mean insulin dose was $0.8 \text{ U} \pm 0.2/\text{kg}/\text{d}$, with considerable variation between centers (range: $0.68 \text{ U} \pm 0.2$ – $0.93 \text{ U} \pm 0.3/\text{kg}/\text{d}$) as well as between insulin

regimens. Children with CSII received the lowest ($0.73 \text{ U} \pm 0.2/\text{kg}/\text{d}$) and BBI the highest ($0.87 \text{ U} \pm 0.3/\text{kg}/\text{d}$) daily insulin doses. Analyzing the ratio between prandial and basal insulin (with exclusion of the CT^{premix}), the ratio in CSII and BBI is higher than in the CT regimens (0.55 vs. 0.32).

Frequency of blood glucose measurements (BGM values, average over the past week) varied significantly across centers (range: 2.5–8.3/d; $F = 34.68$; $df = 17$; $p < 0.001$) and between insulin regimens with the highest frequency in the CSII group (7.55 ± 2.25) and the lowest in the CT^{premix} group (3.51 ± 1.76). Frequency of BGM was higher in the younger children < 6 yr (6.7 ± 2.4 vs. 5.8 ± 2.1 ; $t = 5.10$; $p < 0.0001$) and showed a significant but weak inverse relationship to HbA1c ($r = -0.170$; $p < 0.0001$), but this could not explain the observed center differences in glycemic control nor hypoglycemic events.

Comparison of metabolic outcome in adolescents vs. younger children

When comparing the data obtained in adolescents in 2005, the centers achieving better metabolic control in adolescents also show better outcome in the younger population ($r = 0.76$; $p = 0.01$) (Fig. 2).

Discussion

This multicenter international study shows that both HbA1c and frequency of severe hypoglycemia are lower in a young cohort of children compared with adolescents (1). Center differences in metabolic control are already apparent in the young children and cannot be clearly explained by any of the variables so far tested. Current discussions concerning diabetes care and long-term outcome include metabolic memory as one of the predictors of outcome (9). This suggests that one should strive for near normoglycemia starting at the onset of diabetes. In this large cohort of young children with T1DM, more than 50% had either good or acceptable glycemic control (HbA1c $< 8.0\%$) compared with 41% of the under 11-yr olds in the 1998 study. Although nobody under 11-yr old in the 1998 study used either CSII or analog insulins, 32.8 and 100% used CSII and analog insulins, respectively, in this study (5). Frequency of CSII differed from around 15% in the adolescents (2005) to 32.8% in these younger children (2), but 42.8% still receive conventional twice daily insulin. Although the types of insulin therapy show a significant relationship with metabolic outcome, center differences persist and are not explained by the treatment regimens, comorbidities, language difficulties, or by frequency of BGM. As in the adolescent study, it appears that differences in the way that staff at a center apply

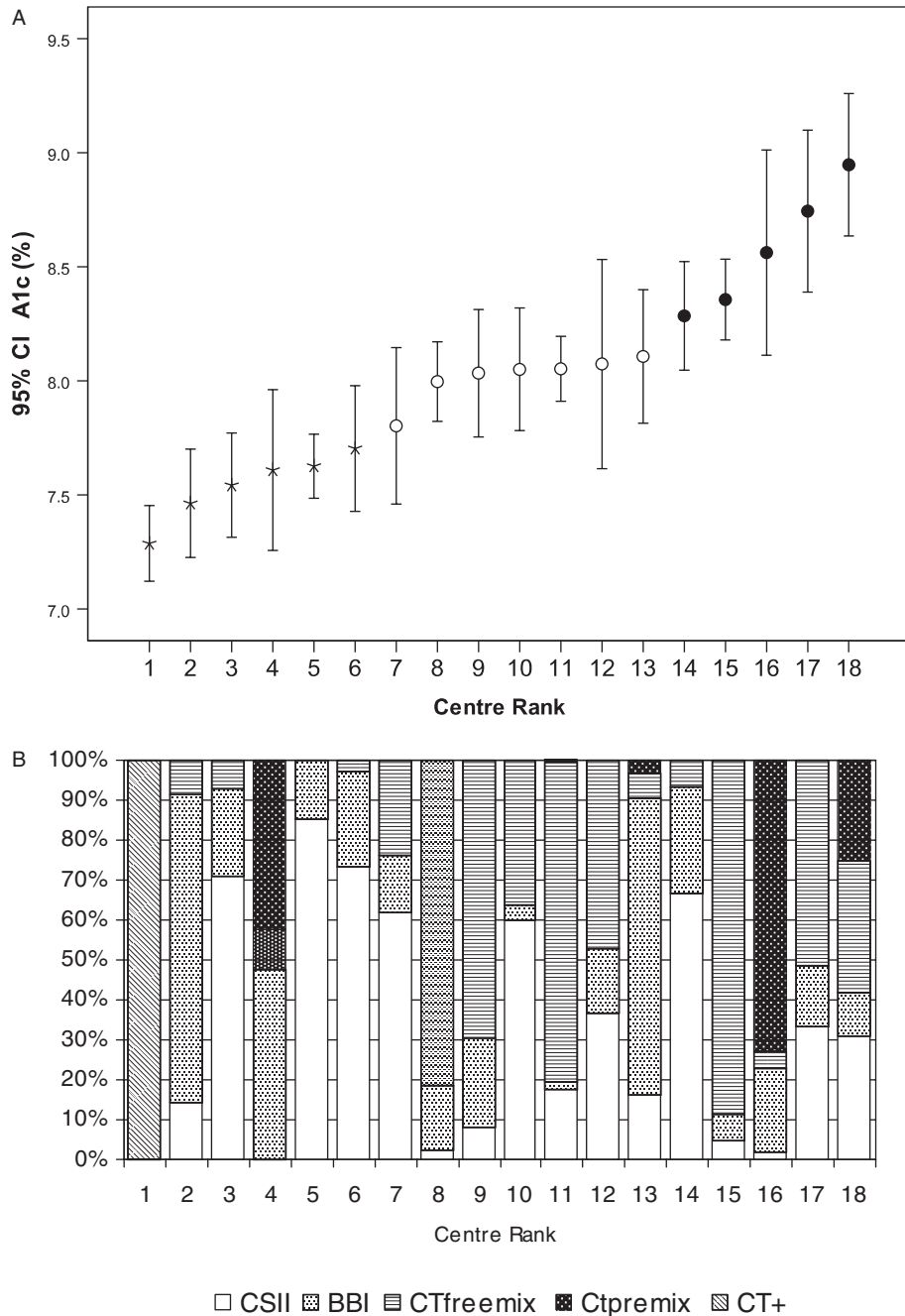


Fig. 1. (A) Glycemic control in the participating centers ranked according to hemoglobin A1c (HbA1c) levels (* < grand mean for the whole sample; ○ = grand mean for the whole sample; and > grand mean for the whole sample). (B) Distribution of insulin regimens in the participating centers ranked according to HbA1c levels.

a given insulin regimen seem to affect the mean HbA1c achieved by the patients at each center, more so than the insulin regimen used (4). In the 2005 study, team composition and services contributed less to the differences in metabolic outcome among centers than target setting and family dynamics; data on the staffing structure and professional-patient relationships have been collected and are being analyzed. Conventional injection therapy with twice daily premixed insulin in this young population

shows a significantly worse outcome than any of the other regimens. This builds on our evidence from previous studies showing poorer glycemic control using premixed insulins in adolescents in 1998 and 2005 (1, 5). Perhaps, this approach to insulin therapy in all children should be reappraised especially with the available evidence on metabolic memory (9). Not only long-term complications but also neurocognitive deficits appear to be influenced more by persistent hyperglycemia than by hypoglycemia, as previously suggested (10–13).

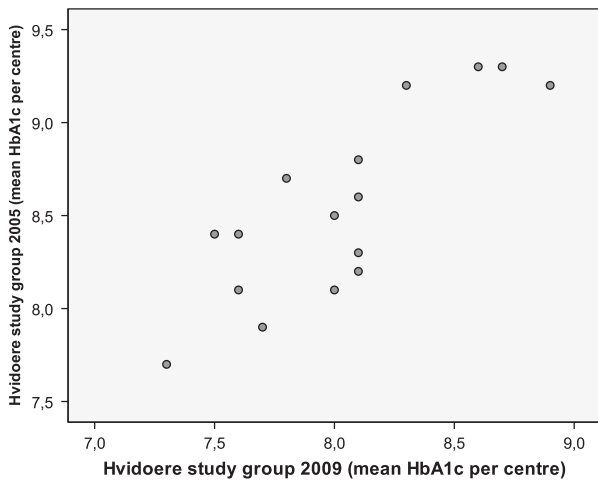


Fig. 2. Comparison of metabolic outcome of the centers participating in both studies, 2005 and 2009 ($r = 0.76$; $p = 0.01$) (1).

On the other hand, children with major compliance problems and significant family dysfunction may be more comfortable with twice daily insulin regimens, which in those situations give acceptable HbA1c values with avoidance of DKA and hospitalization. In the adolescent group, premix insulins may have been introduced because of already established poor metabolic control. In this study, optimal metabolic control was achieved in a substantial proportion of young children without excessive hypoglycemia. Interestingly in this group, CSII was not associated with the lowest HbA1c level, perhaps related to greater freedom in lifestyle and eating behaviors among these younger children. Some studies suggest that insulin pump treatment reduces the risk of hypoglycemia compared with conventional treatment (14). Traditionally twice daily insulin regimens are associated with higher rates of hypoglycemia, because of the difficulty in balancing the intermediate-acting insulins with food intake and their erratic absorption characteristics especially during physical activity. The beneficial effect of CSII in young children when started early has been reported by Sulmont et al. (15).

The relatively high rate of severe hypoglycemic events (21.7/100 PYs) in this study deserves some discussion. Although significantly lower than in the adolescents (27/100 PYs), only three children were responsible for 11 events, leading to relatively high incidence. In the remainder of the cohort, the frequency of severe hypoglycemia was gratifyingly low (17.7/100 PYs), which supports the view that trying to obtain good glycemic control in young children is not necessarily associated with a high risk of hypoglycemia. Whether the same results would have been obtained with 12 months reporting of hypoglycemia (instead of 3 months) is uncertain, but retrospective questions on hypoglycemia are fraught with difficulties (16, 17). It should be noted that the incidence of severe

hypoglycemic events is lower, in all insulin regimens, than in the intensive-therapy group of the DCCT, with 62 severe hypoglycemic episodes per 100 PYs (18).

In conclusion, in a large cohort of young children with T1DM, center differences in metabolic control are present. Individual HbA1c levels are related to insulin regimens, but these regimens are not significantly associated with center differences. The success in which the staff at a specific center apply a given insulin regimen seems to be associated with the HbA1c achieved more than the insulin regimen itself. The incidence of severe hypoglycemia in this young cohort was lower than in adolescence despite achieving a significantly lower HbA1c. Further analysis of quality of life, team composition, team relationships, and services is currently being conducted to evaluate whether these indicators are associated with metabolic control. Finally, examining the education and proficiency of parents in day-to-day fine-tuning of insulin adjustments might be a future step for the HSG to explore center differences.

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Author contributions

CdB, KL, PGFS, and HBM wrote the manuscript, KL analyzed the data, JA, FC, LC, HD, LF, HH, EK, MK, AN, PRN, MP, ES, JJR, TB, TU, TD, HJA, and MV contributed to data collection and/or commented on the article. Dr CdB is the Guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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