Continuing Stability of Center Differences in Pediatric Diabetes Care: do advances in diabetes treatment improve outcome? The Hvidoere Study Group on Childhood Diabetes

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Running title: insulin regimen and center differences

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Objective
To re-evaluate 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
Observational cross sectional international study in 21 centers, with clinical data obtained from all participants and HbA1c levels assayed in one central laboratory. All individuals with diabetes aged 11-18 yrs (49.4 % females), with duration of diabetes of at least one 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 HbA1c was 8.2 ± 1.4%, with substantial variation between centers (mean HbA1c range 7.4-9.2% ; p<0.001). There were no significant differences between centers in rates of severe hypoglycemia nor DKA. Language difficulties had a significant negative impact on metabolic outcome (HbA1c 8.5±2.0 % vs 8.2±1.4 % ;p<0.05). After adjustment for significant confounders of age, gender, 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 HbA1c.

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.
Introduction

The Hvidoere Study Group (HSG) on Childhood Diabetes has investigated metabolic control in large cohorts of adolescents from more than 20 paediatric diabetes centers worldwide. Studies have shown that although the mean HbA1c was not much higher than in the intensively treated adolescent group in the DCCT, few of the adolescents achieved glycated hemoglobin 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 HSG studies 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 (MDI), re-entry of continuous subcutaneous insulin infusion (CSII) treatment and the general trend towards intensification of insulin 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 multi-center, 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 HSG 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 more than 200 eligible adolescents, only the patients seen by the one Hvidoere member were invited.

The Case Report Form (CRF) included information on gender, 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 was 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 CRF 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 five years. Include clinical, administrative, organisational, resource and any other changes”.

A capillary blood sample was provided by participants and analyzed at Steno Diabetes Center, Gentofte, Denmark. HbA1c was DCCT aligned ( normal range 4.4 – 6.3 %, mean 5.4% and an interassay SD 0.15% Tosoh method ). For comparisons with 1998 data (HbA1c assayed by Biorad method), we used the correction equation for equivalence evaluated by the Steno laboratory (HbA1cBioRad = 0.590+0.971HbA1cTosoh)(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 CRF were resolved by direct contact with participating centers. Bi-variate relationships with HbA1c, DKA and hypos, were tested using Analysis of Variance for categorical variables and Pearson’s Product Moment correlation for continuous variables. The effect of center on HbA1c 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 a repeated measure Analysis of Variance, 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 summarised (Table 1). Of these, 2093 (92%) adolescents completed a questionnaire and 2036 (89%) provided a blood sample for assay. There were no significant differences in age, BMI and frequency of DKA between those who provided HbA1c sample and those who did not. Those not providing HbA1c samples had a shorter duration of diabetes (with HbA1c, duration 6.1±3.5 yrs; without HbA1c, duration 4.8±2.8 yrs; p<0.001).

The grand mean HbA1c for the whole sample was 8.2±1.4%. Females had significantly higher HbA1c (females 8.3±1.5%; males 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 HbA1c levels. Individuals with concomitant pathology did not have significantly different HbA1c.

Adolescents whose families had language difficulties leading to communication problems with the diabetes team had higher HbA1c levels (language difficulties n=79; HbA1c 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 (Table 1b). The remaining 309 (14.7%) individuals were on regimens which could not be classified into any obvious category with meaningful numbers. This unclassified group had HbA1c 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 HbA1c (F=6.629; df=5; p<.001), with post hoc analysis indicating individuals on twice daily (Bi-Diurnal, BD) free mix regimens (varying the quantity of short/analogue and intermediate insulin) having significantly lower HbA1c than those on basal bolus, pumps or BD pre mixed insulin regimens. Adolescents on BD pre mixed insulin regimens had significantly higher HbA1c 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 HbA1c, 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 HbA1c (r=0.8; p<0.001), with higher insulin dose associated with poorer metabolic control and more frequent DKA.

Assessment of center differences
HbA1c in the 21 centers ranged between 7.4% and 9.2%. Analysis of variance indicated that there were significant differences between centers for HbA1c (F=12.88; df=20; p<0.001) but not for frequency of hypoglycemia nor DKA. Six centers had a mean HbA1c significantly below the sample mean and six centres significantly above the sample mean (Figure 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 (x^2=2300; 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 4 centers had less than the mean (x^2=114; df=2; p<0.001). When the analysis of center differences was repeated adding these variables as co-variates, the significant differences in HbA1c 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 1498 individuals from 1998, and 1295 participating from the same centers in 2005. Although largely comparable, the 2005 cohort was significantly older (1998 mean=14.27±2.1 years; 2005 mean=14.5±2.0 years; p<0.05) and had slightly longer duration of diabetes (mean duration1998=5.6±3.7 years; 2005 mean=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; 2005 mean=21.9±3.9; F=12.5; df=1; p<0.001), 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 u/kg/d; 2005: mean=1.0±0.3 u/kg/d). No significant change was observed in HbA1c either by simple comparison (F=0.31; df=1; p>0.57) nor when controlling for different co-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 HbA1c from 1998 to 2005, and one center had a significant increase in HbA1c from 1998 to 2005 (Figure 2). Although those centers that showed improved metabolic outcomes had increased the use of basal bolus/ CSII regimens (from 3% to 52% for centre 3 and from 3% to 82% for centre 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%, 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 out patient care, written information, telephone hotline, annual reviews, more psycho social support, intensified insulin therapy) in the 14 centers, as reported by team members of each diabetes team could explain the outcome. Centers demonstrating significantly reduced HbA1c report no strategy that was not used elsewhere, but they tended to implement more changes than reported by most other centers.

Discussion
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 HbA1c 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 nor to major changes in their team approach, compared to 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, increased visits, may have lead to improved education and/or treatment adherence . (17) In comparison, the DCCT/EDIC results in adolescents show that in both DCCT intensive and non intensive groups the mean HbA1c levels of around 8.4%, suggests that this age group requires a fundamentally different approach to obtain a significant improvement in metabolic outcome. (18 )

The glycated hemoglobin 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 HbA1c also have individuals with lower mean HbA1c 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 a "conventional" twice daily injection regimen is non-intensive. 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 (eg. unusual insulin combinations, multiple doses of different insulins etc). It is reassuring that this group’s mean HbA1c was no different from the total cohort despite having perhaps more individualized insulin regimens. The explanation for individualised regimens is uncertain. For example individuals in this group may have been more difficult to control but the result strengthens the view that no particular insulin regimen influences 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 HbA1c 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 randomised 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 levelled 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 behavioural and psychosocial outcomes (23).

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 nor 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.

Appendix

Members of the Hvidoere study group on Childhood Diabetes, participating in the Evaluation of Centre Differences 2005.

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Dorchy(MD,PhD), Hilary Hoey(MD), Eero A Kaprio(MD), Francine Kaufman (MD), Mirjana Kocova (MD,PhD), Henrik B Mortensen(MD), Pal R Njølstad. (MD,PhD), Moshe Phillip(MD), Kenneth J. Robertson(MD), Eugen J Schoenle(MD), Tatsuhiko Urakami (MD), Maurizio Vanelli (MD).

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22. Centro di Diabetologia, University of Parma, Italy

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REFERENCES


23. Danne T, Tamborlane WV. Insulin pumps in pediatrics: we have the technology. We have the evidence. Why are so few kids using it? Pediatric Diabetes 2006;7 (Suppl 4):2-3

24. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ 2002;325:746-749
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<thead>
<tr>
<th>Table 1. Demographic and Clinical Characteristics of Participants by Gender</th>
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<tr>
<td>Age (years)</td>
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<td>Duration (years)</td>
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<td>BMI (wt/m2)</td>
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<td>Insulin Dose (units/kg/d)</td>
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<td>Hypoglycemic episodes last 3 months/100 ptn yrs</td>
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<td>DKA last 12 months/100 ptn yrs</td>
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<td>HbA1c * (* n=2036)</td>
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### Table 1b Different Insulin Regimens

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<th>Female (n)</th>
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<th>Male (n)</th>
<th>%</th>
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<td>15.9</td>
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<td>Twice daily Pre Mix</td>
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<td>83</td>
<td>7.8</td>
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<tr>
<td>Twice daily Free Mix</td>
<td>128</td>
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<td>Thrice daily</td>
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<td>2.5</td>
<td>42</td>
<td>4.0</td>
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<tr>
<td>Basal Bolus</td>
<td>487</td>
<td>47.1</td>
<td>439</td>
<td>41.5</td>
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<tr>
<td>CSII</td>
<td>175</td>
<td>16.9</td>
<td>159</td>
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### Table 1c Concomitant problems

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<td>36</td>
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<td>14</td>
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<tr>
<td>Asthma</td>
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<td>2.5</td>
<td>35</td>
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<tr>
<td>Other</td>
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<td>48</td>
<td>4.5</td>
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## Table 2. HbA1c and insulin dose by insulin regimen

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<th>SEM</th>
<th>Insulin Doses Mean</th>
<th>SEM</th>
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<td>BD pre-mix</td>
<td>8.6+</td>
<td>0.1</td>
<td>1.01</td>
<td>0.03</td>
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<tr>
<td>BD free mix</td>
<td>7.9*</td>
<td>0.1</td>
<td>1.00</td>
<td>0.02</td>
</tr>
<tr>
<td>Thrice daily</td>
<td>8.2</td>
<td>0.2</td>
<td>1.24</td>
<td>0.05</td>
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<tr>
<td>basal bolus</td>
<td>8.2</td>
<td>0.0</td>
<td>1.03</td>
<td>0.01</td>
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<tr>
<td>Pumps</td>
<td>8.1</td>
<td>0.1</td>
<td>0.92</td>
<td>0.02</td>
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</table>

+ significantly higher than the other insulin regimens (p< 0.001)
* significantly lower than the other insulin regimens (p<0.001)
Figure 1

X: < grand mean HbA1c for the whole sample
•: = grand mean HbA1c for the whole sample
△: > grand mean HbA1c for the whole sample

Centre Rank
Figure 2

* = significant reduction in HbA1c from 1998 – 2005
# = significant increase in HbA1c from 1998 – 2005