Outcome of Quality management in Pediatric Diabetes Care. Experiences from The Hvidoere Study Group on Childhood Diabetes.

Henrik B Mortensen, on behalf of the Hvidoere Study Group on Childhood Diabetes.

Address correspondence to Henrik Bindesbøl Mortensen, Dr Med Sci, Department of Pediatrics, Glostrup University Hospital, DK-2600 Glostrup, Denmark
Telephone : +45 43232967
Fax: +45 43233964
E-mail: hbmo@glostruphosp.kbhamt.dk

Introduction

The Hvidoere Study Group on Childhood Diabetes evolved in 1994 during a workshop to discuss strategies that could be important in improving the quality of paediatric diabetes cares. The name is taken from the house where the annual meetings are held. Hvidoere is a stately country mansion, which for 50 years was used as the Novo diabetes hospital. It is now a training and conference centre owned by Novo Nordisk A/S who work in partnership with the Study Group. It is an international study group covering paediatric centres from 18 countries across Europe, Japan and North America. The aim of the Hvidoere Study Group is to share and compare data with the overall objective of improving the treatment of childhood diabetes.

Activities.

The group has issued 4 publications reporting on observational international multicenter studies dealing with blood glucose control (1), insulin management (2), centre differences (3) and metabolic control and quality of life (4) reporting data from the two cross-sectional studies. The study group is now doing a long-term follow-up study starting at diagnosis of diabetes. The members of the Study Group who have contributed to the surveys and the new remission phase study are shown in Table 1.

In all the studies HbA_{1c} was centrally analysed at the Steno Diabetes Center using the same calibrator lots as the DCCT laboratory. By direct sample exchange the Steno Diabetes Center HbA_{1c} results were found to be 0.3 % higher than the DCCT level.

Blood glucose control

The first cross-sectional study was designed to evaluate the current level of metabolic control in children and adolescents with insulin-dependent diabetes mellitus (IDDM). This was presented in the paper: ***Comparison of metabolic control in a cross-sectional study of 2873 children and adolescents with insulin-dependent diabetes from 18 nations (1).***

In this cross-sectional survey with 21 paediatric departments, representing 18 countries in Europe, Japan and North America the grand mean HbA_{1c} value was 8.6 ± 1.7 % (mean ± SD) but varied significantly ($p<0.0001$) between centres, irrespectively of insulin regimen (figure1). The mean HbA_{1c} 8.6% corresponds to 8.3% in the DCCT (adjusted by direct sample exchange) and thus is comparable to the adolescents in DCCT, where the intensive treatment group had a mean HbA_{1c} of 8.1% (versus 9.8 % in the conventional treatment group).

Seven centers were significantly ($p<0.05$) above the grand mean for HbA_{1c} and six centers significantly ($p<0.05$) below while 8 centers did not differ significantly from the average HbA_{1c} value. Interestingly, blood glucose control was similar in patients treated with three or more daily insulin injections compared to patients on twice daily insulin. The centre differences were not readily explicable in terms of geography or the organisational structure of the clinics. In virtually all centres, diabetes management employed a multidisciplinary health care team approach with paediatric endocrinologists, diabetes nurses, dieticians, social workers and other health-care professionals involved in the care of these children.

Hypoglycaemia resulting in unconsciousness/seizures was related to younger age (0-8 years) (figure 2) and lower HbA_{1c} level. The overall incidence was 22 per 100 patient-years,

which compares with the numbers reported in the DCCT for adolescents on conventional treatment (5,6). A major obstacle to achieve and maintain near normalisation of blood glucose control is fear of inducing hypoglycaemia in children and adolescents with their greater irregularities in diet and exercise than adults. The increased incidence of severe hypoglycaemic episodes observed in the younger children reflects that it is more difficult for these children to be aware and to inform their surroundings that a hypoglycaemic episode is approaching and implies that tight control in this age group should be undertaken with extreme caution because hypoglycaemia may impair normal brain development (7).
The results of the study also confirmed that blood glucose control as assessed by HbA_{1c} was poorest during puberty (figure 3). The elevated level of HbA_{1c} (9.0-9.5%) was obtained despite the fact that 38 % of these young people were on 3 or more insulin injections daily. The unsatisfactory control during puberty may be due to decreasing levels of compliance with different aspects of the treatment regimen, as well as to decreased insulin sensitivity of peripheral tissues during adolescence. **In conclusion:** The overall glycemic control in this cross-sectional study was comparable with the adolescent group in the DCCT, though the rate of hypoglycaemic events was slightly lower. A significant difference in blood glucose control across centers was demonstrated.

Insulin management
In the second paper: ***Insulin Management and Metabolic Control of Type 1 Diabetes in Childhood and Adolescence in 18 Countries (2)*** we examined the insulin regimens that were used in the first Hvidoere study population and the various factors which may have an influence on these. There was no significant difference in insulin dosage between boys and girls until adolescence (11–18 years), when the insulin dosage in girls was considerably higher than in boys (figure 4). The average insulin dosages seen in these adolescents were comparable to those used in the adolescent group of the DCCT. The increase in insulin requirement during puberty has also been shown by Dorchy et al.(8) and Kerouz (9), again with girls needing higher doses than boys. The differential insulin requirement between girls and boys may be due, in part to earlier age of onset of puberty in girls, but also to the differential effect of sex hormones on glucose homeostasis (10,11). The insulin resistance during puberty leads to increased insulin requirements (12), which may be at least partly responsible for the increase in age-related BMI in boys and girls seen both during the prepubertal and the pubertal period when compared to healthy control children (13) (figure 5). The BMI, especially of the females with diabetes, continues to increase during adolescence. This finding is in agreement with the results of a recent Danish nation-wide investigation (14). It remains controversial whether multiple injection therapy *per se* is associated with weight gain. Some studies have shown a possible association (1,5,12,15), while others dispute this (16,17). Multiple daily injections allow more flexibility and the attitude of teenagers towards diet may become more relaxed on such intensive insulin therapy causing weight gain.
Most children aged under 9 years were on two (78%) or three (13%) insulin injections daily. Only a few children (7%) received one insulin injection daily, and most of these had a very short duration of diabetes. In the adolescent group, the use of three and four insulin injections increased at the expense of two insulin injections per day (figure 6). Of those on two or three injections daily, 37% received pre-mixed insulin, given either alone or in combination with short- and intermediate-acting insulin. Preadolescent children on pre-mixed insulin showed similar HbA_{1c} levels to those on a combination of short- and long-acting insulins, whereas in adolescents significantly better HbA_{1c} values were

achieved with individual combinations. Very young children were treated with a higher proportion of long-acting insulin. Among adolescent boys, lower HbA_{1c} was related to use of more short acting insulin. This association was not found in girls casting some doubt upon its clinical significance.
Conclusion: Numerous insulin injection regimens are currently used in paediatric diabetes centres around the world, with an increasing tendency towards multiple insulin-injections, particularly in older adolescents. Nevertheless, the goal of near normoglycaemia is achieved in only a few patients.

Center differences
Many potential explanations for the center differences have been discussed in the study group, but real evidence for any of these explanations has not been found. The feedback from the first study and the discussions of the center differences have caused each study group member to consider whether anything could be changed at their center in order to improve metabolic control. Three years after the first cross-sectional study a second study was made in order to restudy the center differences after this feedback. The third paper: ***Persistent differences among centers over 3 years in glycemic control and hypoglycaemia in a study of 3,805 children and adolescents with type 1 diabetes from the Hvidoere Study Group (3)*** investigated the reproducibility of the center differences and analysed factors potentially influencing the variation of glycemic control between centers including number injections, insulin dose and rate of severe hypoglycaemia. Twenty-one international paediatric diabetes centers from 17 countries participated.
Striking differences in average HbA_{1c} were found between centers; these differences remained after adjustment for the significant confounders of gender, age and diabetes duration. Three centers had improved significantly; 4 centers had deteriorated significantly in their overall adjusted HbA_{1c} while 14 centers did not change in glycemic control (figure7). 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 body mass index by 0.95 kg/m². To examine whether the center differences were particularly pronounced early or later in the duration of diabetes, the mean HbA_{1c} was calculated for each center separately for children with duration < 3 years, and ≥ 3 years. The differences were apparent even in patients with short diabetes duration and remained stable three years later (mean adjusted HbA_{1c} (1995): 8.62±0.03 vs. 8.67±0.04 (1998)) (figure 8). This may be due to the heterogeneity of type 1 diabetes itself as significant differences have been reported at onset of diabetes between children from different geographical locations (18). An alternative explanation for the good correlation between the average control in patients with short diabetes duration and those with a long-term course of the disease has to include differences in the diabetes education and management from the onset of the disease. Thus differing attitudes of the diabetes teams and/or differing degrees of patient empowerment may represent a major factor underlying these centre differences. Parameters of insulin therapy showed no clear-cut association with glycemic control or hypoglycaemia rates, neither in the original sample (1) nor in the present assessment of the centre differences. 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.

Furthermore, this strategy resulted in an unfavourable increase in the body mass index in many centers particularly in girls (19).
Similar to the experience with hypoglycaemia in the Diabetes Control and Complications Trial there was no clear-cut association between average control at an individual centre and the rate of severe hypoglycemia (20). At both sampling periods a higher rate of severe hypoglycaemia was associated with lower age and better glycemic control. However, some centers are more successful than others in preventing hypoglycaemia independent of the prevailing average HbA_{1c} level at the respective centre (figure 9). This important finding may relate to other features of management such as psychological support and more successful education in centers with low hypoglycaemia incidence.
Conclusion: This study revealed significant outcome differences across large international paediatric diabetes centres. Feedback and comparison of HbA_{1c} levels led to an intensification of insulin therapy in most centres, but improved glycaemic control in only a few. Centres with HbA_{1c} values below the average had fewer severe hypoglycaemic events may be as a result of better education programmes.

As the optimal insulin regimen for paediatric patients with type-1 diabetes remains controversial this issue was investigated in a separate paper: ***Relationship between insulin injection regimen and metabolic control in adolescents with type 1 diabetes over 3 years: Results from the Hvidøre Study Group*** (21). Out of the 2873 children and adolescents in the international survey in 1995 (1), 872 adolescents (433 boys, 439 girls, mean age in 1995: 11.3 ± 2.2 years) were restudied in 1998, relating insulin regimens to HbA_{1c} to investigate whether differences in insulin management were associated to outcome differences across centers.
Evaluation of the changes in HbA_{1c}, injection frequency, insulin dose, and BMI was done by a repeated measurements model for the 1995 and 1998 data in order to account for the effect of covariates and the fact that patients contribute with 2 measurements. Gender, centre, age and duration were included in order to adjust for these factors and the effect of the increase of age and diabetes duration during the 3-year period.
Over 3 years, the use of multiple injection regimens increased from 42 to 71 %: 251 children (Group1) remained on twice daily insulin, 365 (Group 2) remained on multiple injections and 256 (Group 3) shifted from twice daily insulin to multiple injections. In all 3 subgroups an increase in insulin dose, a deterioration of metabolic control, and an increase in body-mass-index (BMI) were observed in spite of insulin injection regimen. The increase in BMI was greatest in patients switching from twice daily to multiple injections, and higher in females compared to males.
Thus the HbA_{1c}-levels deteriorated irrespective of the insulin injection regimen prescribed, even in children who shifted from a conventional regimen with two daily injections to a more intensified regimen with multiple injections. This finding is in contrast to the adolescent subgroup in the DCCT, where a distinct and stable difference was observed between the conventionally treated group (one or two-injection regimen) and the group on intensified insulin therapy (multiple-injection regimen or pumps) (5,6). The DCCT was a prospective, highly intensive intervention study, comparing multiple-injection to standard ketosis-prevention-type insulin treatment. The present study was observational at two time-points 3 years apart. No information was available on the insulin therapy during the three years, nor on other interventions to improve metabolic control such as patient re-education, hospitalisation, camps etc. Each treatment centre was entirely free in their

choice of insulin therapy, and no information was collected on the reasons for individual patients to continue or change their respective insulin regimen.
Reports in the literature, based on retrospective or cross-sectional observations, on the relationship between insulin treatment regimen and metabolic control, are conflicting. While some studies report a significant improvement of metabolic control in adolescents with increasing injection frequency (22, 23, 24), others are in agreement with our data, and do not confirm such a relationship (25, 26,27). The number of insulin injections per day is only one aspect of treatment intensity in diabetes. Frequent self-monitoring of blood glucose, patient education, dietary counselling and effective self-management represent equally important areas.
Conclusion: In this international study, metabolic control was unsatisfactory in many adolescents with type-1-diabetes irrespective of the insulin regimen. No improvement in metabolic control was observed over three years in patients switching from twice to multiple injections, while the increase in body-mass-index was most pronounced in this group. This indicates that other factors such as attitudes of the treatment team, self-care behaviour, educational models and patient satisfaction may be more directly related to the outcome than insulin regimens.

Quality of life
Both the DCCT and the recent ISPAD guidelines have recommended a treatment target for HbA_{1c} at 7.5%. But how will the demands of good metabolic control influence the quality of life (QOL) for adolescents with diabetes? Stress created in connection with demanding therapeutic intervention may adversely influence QOL and restrict the patient. Therefore, the Hvidoere Study Group decided to investigate the relationship between QOL, diabetes treatment regimens and metabolic control in a large international cohort of adolescents with diabetes and their families in the study: ***Good Metabolic Control is Associated with Better Quality of Life in 2,101 Adolescents with Type 1 Diabetes (4).***
QOL in adolescents was assessed using a previously validated questionnaire (28). The questionnaire contained 52 items in four sections; "impact of diabetes, worries about diabetes, satisfaction with a life and health perception". For each adolescent, one parent and one health professional completed a questionnaire, including 5 items about their perceptions of the family burden related to the adolescent's diabetes.
This is the first large international multi-language study evaluating the relationship between metabolic control and QOL in adolescents with diabetes. This study suggests that better metabolic control is associated with a better QOL for adolescents and with a lesser-perceived burden by parents and health professionals. Figure 10 shows the change in QOL score with age according to gender and high and low HbA_{1c} selected as the 10^{th} (6.8%) and the 90^{th} percentiles (10.9%) in the population as perceived by adolescents, to illustrate what is a reasonable variation in QOL score due to metabolic control. All QOL scores were linearly transformed so that the best possible score was 0 and worst possible was 100. Few adolescents rated the disease impact as major (figure 10a). Moreover, a lower impact score was significantly associated with better HbA_{1c}. Impact of diabetes was similar in boys and girls with no effect of age or duration of diabetes on the scoring. More worries were evident with increasing age, and more so in girls (figure 10b). This may reflect the higher incidence of psychological disturbance widely reported in population studies of adolescent girls (29,30). The relationship between HbA_{1c} and worry was just significant. The scores for satisfaction followed the same pattern as worries, showing less satisfaction with increasing age, again more pronounced in girls (figure 10c). Teenage girls had poorer health perception than boys

(figure 10d). Thus, girls had worse metabolic control, higher BMI and significantly poorer overall QOL at an earlier age than boys. These findings may be associated with earlier hormonal and pubertal changes in teenage girls (31-34), and with their relative lack of physical activity and abnormal eating behaviours (35,36).
A lack of correlation between adolescent QOL and burden perceived by parents and health professionals was observed and this may reflect significant differences in perceptions of diabetes impact between adolescents and adults. Adolescents expressed less difficulty with diabetes than both adult groups. Also patient and health professional ratings were only modestly correlated. These findings suggest the importance of assessing the perceptions of all three groups in the adolescent diabetes management triad.
In contrast to the increasing worry and poorer satisfaction described by adolescents, parental assessment of family burden decreased with adolescent age, with parents of girls reporting lowest burden. Because girls enter puberty earlier than boys, with an earlier transfer of responsibility for self-care management from parent to child, perhaps the parent's burden is correspondingly decreased. By contrast, health professional scores for family burden showed no gender difference. For both parent and health professional ratings, higher HbA_{1c} levels were associated with greater family burden. Thus knowledge of the consequences of poor control may result in increased parental and health professional concern.
In conclusion, we have shown that lower HbA_{1c} is associated with better QOL. Although this study cannot determine a cause-and-effect relationship, efforts to achieve optimal metabolic control now appear justified on QOL as well as clinical grounds (5). The size and international nature of the study adds credence to this assertion. Since individuals with a higher QOL may be better equipped physically and psychologically to deal with the burdens of diabetes management, better QOL may facilitate better metabolic control through improved self-care as part of a positive circle.

New remission phase study
As it has been established that differences across centers are maintained over 3 years, and as it has been found that center differences in glycemic control are present early after onset of diabetes, the Hvidoere Study Group decided in future studies to focus on the early course of the disease. Therefore, the group has started a new study in order to investigate the remission phase in children and adolescents with newly diagnosed diabetes. In this prospective multicentre-survey it will be possible to investigate whether the differences between centers in glycemic control and hypoglycaemia are associated with the patients genetic or immunological background or are related to other factors such age, ketoacidosis and initial insulin treatment. In addition the study will show the effect of the initial insulin management on the preservation of the residual beta cell function.

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Further information on the Hvidoere Study Group on Childhood Diabetes can be accessed at: www.hvidoeregroup.org

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Legends to figures

Figure 1.
Centers sorted according to their mean HbA_{1c} levels adjusted for age, gender and diabetes duration. The grand mean for HbA_{1c} was 8.6% (indicated by horizontal line). Mean ± 1SE values is shown.
Reproduced from Danne et al. Diabetes Care 24: 1342-1347, 2001

Figure 2
Incidence of hypoglycemia (unconsciousness/seizures) during a 3-month observation period in 2807 children and adolescents with type 1 diabetes (n= number of patients in each age-group).
Reproduced from Mortensen et al. Diabetes Care 20: 714-720,1997

Figure 3.
Age-specific mean values for HbA_{1c} in 1443 males (dashed line curve) and 1430 females (full line curve) with type 1 diabetes. The error bars represent 1 SEM value.
* $p<0.05$, ** $p<0.01$ in comparison of males and females separately in each age-group.
Modified from Mortensen et al. Diabetes Care 20: 714-720,1997

Figure 4.
Age-specific mean values for insulin (U kg^{-1} $24h^{-1}$) in 1443 males and 1430 females with type 1 diabetes. The error bars represent 1 SEM value. *p<0.05, **p<0.01, ***p<0.001 in comparison of males and females separately in each age-group.
Modified from Mortensen et al. Diabetic Medicine 15:752-759, 1998

Figure 5.
Age-specific median values for body mass index (BMI) in 1443 males and 1430 females with type 1 diabetes with a group of healthy British children serving as controls.
Modified from Mortensen et al. Diabetic Medicine 15:752-759, 1998

Figure 6.
Age related frequency distribution of number of daily insulin injections in 2857 children and adolescents with insulin dependent diabetes mellitus.
Reproduced from Mortensen et al. Diabetic Medicine 15:752-759, 199

Figure 7.
Adjusted means ± 1SE (adjustment for gender, age, and diabetes duration) of the HbA1c at the participating centers at the baseline evaluation (1995, top panel) sorted according to their HbA_{1c} levels.
The bottom panel shows the change in the adjusted mean after three years. The three centers that significantly (p<0.05) improved their adjusted HbA1c are shown with light gray bars, the four centers that significantly worsened are shown with dark gray bars, those that had no significant change with empty bars.
Reproduced from Danne et al. Diabetes Care 24:1342-1347,2001

Figure 8
Relation between the average control of the short-term patients (during the first 3 years of diabetes) and those with diabetes duration >3 years at the 21 individual centers (open squares 1995, R_s: 0.83, p<0.001; solid squares 1998, R_s: 0.68, p=0.001; both time points combined: R_s: 0.77, p<0.001).
Reproduced from Danne et al. Diabetes Care 24:1342-1347,2001

Figure 9
Incidence of severe hypoglycemic episodes per 100 patients years in centers above, below and not signifcantly different from the mean level of HbA1c. To show the estimated rates of events, a standard person from the 1998 group is considered (male, of age 13 and with diabetes duration of 5 years). Then the predicted rate of events is shown in the figure as function of center class (dotted line center significantly below the mean) and individual HbA_{1c} using a Poisson loglinear regression model.
Reproduced from Danne et al. Diabetes Care 24:1342-1347,2001

Figure 10
The association of HbA_{1c} (6.8 or 10.9 %) and sex on (A) the impact of diabetes with the age of the patient (lower score= less impact), (B) worries score by age, (C) satisfaction score by age and health perception score by age.

Reproduced from Hoey et al. Diabetes Care 24:1923-1928,2001