

Outcome of Quality Management in Paediatric Diabetes Care

Experiences from the Hvidøre Study Group on Childhood Diabetes

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



The Hvidøre 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 care. The name is taken from the house in which the annual meetings are held. Hvidøre 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, which works in partnership with the study group. The Hvidøre Study Group is an international group covering paediatric centres from 18 countries across Europe, Japan, and North America. Its aim is to share and compare data with the overall objective of improving the treatment of childhood diabetes.

I would like to thank all the members of the study group for their commitment, which has led to an enthusiastic, stimulating collaboration throughout the years, with benchmark evaluation of the centres' current situation and prospective follow-up studies of their patients.

A BRIEF HISTORY OF HVIDØRE

The name "Hvidøre" originally meant "a white gravelly beach", and refers to the sandy spit of land at the foot of the cliff on which the house now stands, overlooking the blue waters of the Øresund dividing Denmark from southern Sweden.

At the beginning of the 16th century, King Hans built a royal seat at Hvidøre, chosen as a site commanding the only landing place to the north of Copenhagen. Christian II kept his mistress and her mother there after his marriage to Princess Elisabeth of Hapsburg in 1515.

The royal castle changed hands many times over the centuries, and was eventually bought and demolished in 1871 by Counsellor Frederik Bruun, who built a magnificent mansion in its place for use as a summer residence for his family. From then on, the name Hvidøre denoted the house rather than the place. The architect of the house was Johan Schrøder. In the house, he blended features from the English and Italian Renaissance, with details taken from classical Greek architecture.

Counsellor Bruun died in 1887, but his widow kept Hvidøre until 1906, when she put it up for sale. The house was bought by Alexandra, Queen of England, and Maria Feodorovna Dagmar, Empress of Russia, two of the daughters of Christian IX who had recently died. They made many improvements, both inside and outside the house, and furnished it luxuriously. They lived in it from September to November every year until the outbreak of World War I, and Dagmar was exiled there in 1919.



Finally, in 1937, it was bought by Harald and Thorvald Pedersen, joint owners and founders of Novo Therapeutic Laboratory, for conversion to a sanatorium for the treatment of diabetes. The idea was that people with diabetes would stay there while learning how to live with their disease and about its treatment with insulin – in other words, self-care. The sanatorium had room for 25 patients, including children, and was run with a substantial grant from Novo.

In 1949, Hvidøre Diabetes Sanatorium was renamed Hvidøre Hospital, but it continued to do the same work, which included testing new forms of therapy. By its golden jubilee in 1988, the hospital employed 14 doctors, three dieticians, and 25 nurses. The basis of its diabetes management remained education, control, and individualised treatment.

In 1989, Novo's Hvidøre Hospital was amalgamated with Nordisk Gentofte's Steno Memorial Hospital, with the latter being deemed more suitable for future use as a hospital. The last patients left Hvidøre in 1991, and the researchers finally left in 1992. Hvidøre remains in Novo Nordisk's ownership and has been converted into a training and conference centre, home in recent years to the annual meetings of the Hvidøre Study Group.



The group has issued five publications reporting on observational, international, multicentre studies dealing with blood glucose control,¹ insulin management,² centre differences,³ the relationship between insulin injection regimen and metabolic control over 3 years,⁴ and metabolic control and quality of life,⁵ reporting data from the two cross-sectional studies. The study group is now doing a long-term, follow-up study starting with the 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.

CENTRAL ANALYSIS OF HbA_{1c}

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

Table 1. Members of the Hvidøre Study Group on Childhood Diabetes

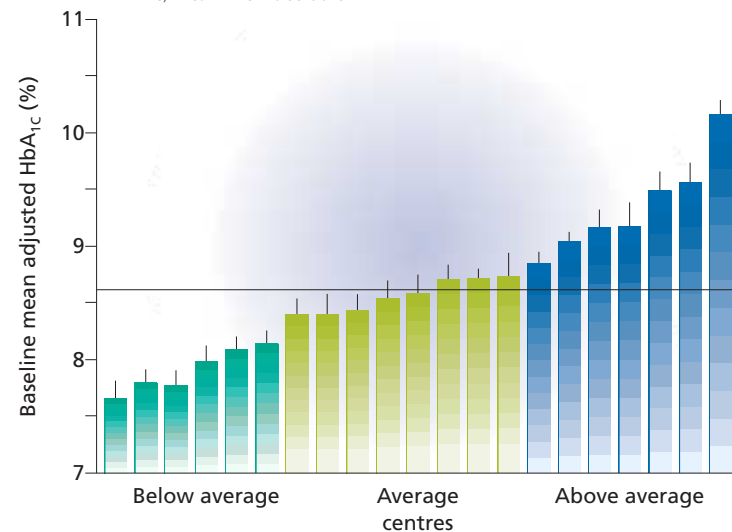
H Dorchy	Brussels, Belgium
D Daneman	Toronto, Canada
HB Mortensen	Glostrup, Denmark
L Hansen	Clinical Genetics, Novo Nordisk A/S, Denmark
L Kaa Meier	Organiser, Novo Nordisk A/S, Denmark
P Hougaard, H Lynggaard	Statisticians, Novo Nordisk A/S, Denmark
EA Kaprio	Vantaa, Finland
P Garandeanu	Montpellier, France
T Danne	Hanover, Germany
RW Holl	Ulm, Germany
HMCV Hoey	Dublin, Ireland
F Chiarelli	Chieti, Italy
M Vanelli	Parma, Italy
N Matsuura	Kanagawa, Japan
C de Beaufort	Barblé, Luxembourg
M Kocova	Skopje, Republic of Macedonia
H-J Aanstoot	Rotterdam, The Netherlands
O Søvik	Bergen, Norway
H Bjørndalen Göthner	Oslo, Norway
K Dhal-Jørgensen	Oslo, Norway
RM Tsou, M Fontoura	Porto, Portugal
P Martul	Baracaldo, Spain
J Åman	Örebro, Sweden
EJ Schönle	Zurich, Switzerland
S Greene	Dundee, UK
KJ Robertson	Glasgow, UK
PGF Swift	Leicester, UK
JA Atchison	Birmingham, USA

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 2,873 children and adolescents with IDDM from 18 countries*.¹

In this cross-sectional survey of 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, irrespective of the insulin regimen used (Figure 1). The mean HbA_{1c} of 8.6% corresponds to 8.3% in the DCCT

Figure 1 Centres sorted according to their mean HbA_{1c} levels adjusted for age, sex, and diabetes duration. The grand mean for HbA_{1c} was 8.6% (indicated by horizontal line). Mean ± 1 SE value is shown.

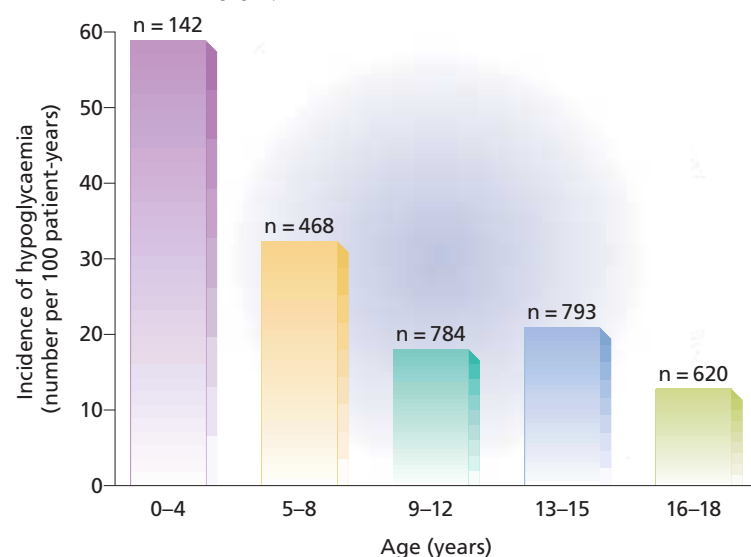


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and is thus comparable with that of the adolescents in the DCCT, in which the intensive treatment group had a mean HbA_{1c} of 8.1% (versus 9.8% in the conventional treatment group). Seven centres had a mean HbA_{1c} significantly above the grand mean for HbA_{1c} ($p < 0.05$) and six centres significantly below ($p < 0.05$), while eight centres 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 with patients on twice-daily insulin. The differences between centres were not readily explicable in terms of geography or the organisational structure of the clinics. In virtually all centres, diabetes management used a multidisciplinary healthcare team approach, with paediatric endocrinologists, diabetes nurses, dieticians, social workers, and other healthcare professionals involved in the care of children with diabetes.

Hypoglycaemia resulting in seizures/unconsciousness 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 is comparable to the numbers reported in the DCCT for adolescents on conventional treatment.^{6,7} A major obstacle to achieving and maintaining near-normalisation of blood glucose control is the fear of inducing hypoglycaemia in children and adolescents, with their greater irregularities in diet and exercise than adults. The higher incidence of severe hypoglycaemic episodes observed in younger children reflects the fact that young children are less likely to be

Figure 2 Incidence of hypoglycaemia (seizures/unconsciousness) during a three-month observation period in 2,807 children and adolescents with type 1 diabetes (n = number of patients in each age group).

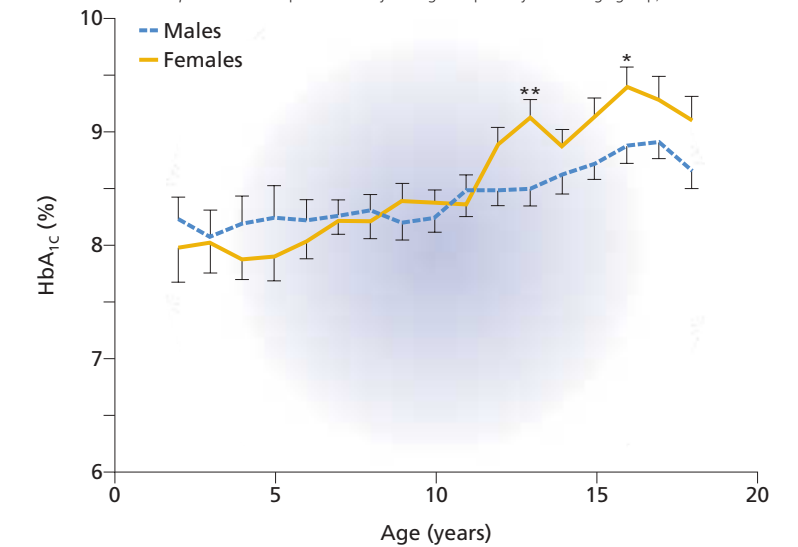


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aware that a hypoglycaemic episode is approaching and to warn people around them, and implies that tight control in this age group should be undertaken with extreme caution as hypoglycaemia may impair normal brain development.⁸

The results of this 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 found despite the fact that 38% of these young people were on three or more insulin injections daily. The unsatisfactory control observed during puberty may be due to decreasing levels of adherence to different aspects of the treatment regimen, as well as to the decreasing insulin sensitivity of peripheral tissues during adolescence.

Figure 3 Age-specific mean values for HbA_{1c} in 1,443 boys (dashed line curve) and 1,430 girls (full line curve) with type 1 diabetes. The error bars represent 1 SEM value (* $p < 0.05$, ** $p < 0.01$ in comparison of boys and girls separately in each age group).



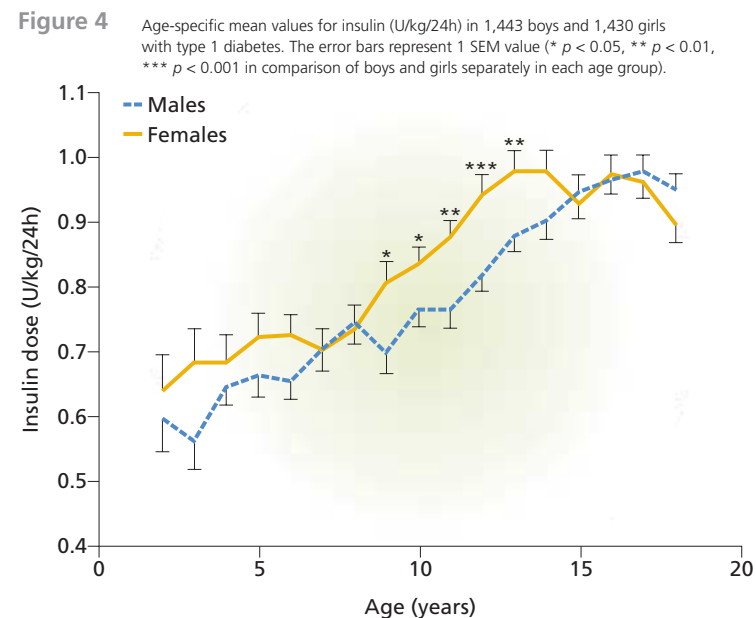
Adapted from Mortensen *et al.* Diabetes Care 1997; 20(5): 714-20.

Conclusion: The overall glycaemic control in this cross-sectional study was comparable to that of the adolescent group in the DCCT, though the rate of hypoglycaemic events was slightly lower. A significant difference in blood glucose control across centres was shown.

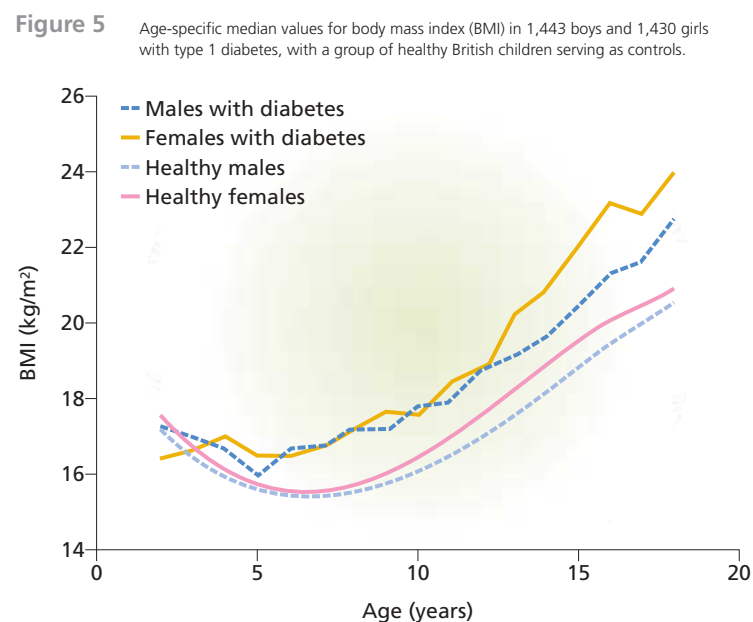


INSULIN MANAGEMENT

In the second paper, *Insulin management and metabolic control of type 1 diabetes mellitus in childhood and adolescence in 18 countries*,² we examined the insulin regimens that were used in the first Hvidøre study population and the various factors that may have influenced 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*⁹ and Kerouz,¹⁰ with girls again needing higher doses than boys. The difference in insulin requirement between girls and boys may be due, in part, to the earlier age of onset of puberty in girls, but also to the differential effects of sex hormones on glucose homeostasis.^{11,12}

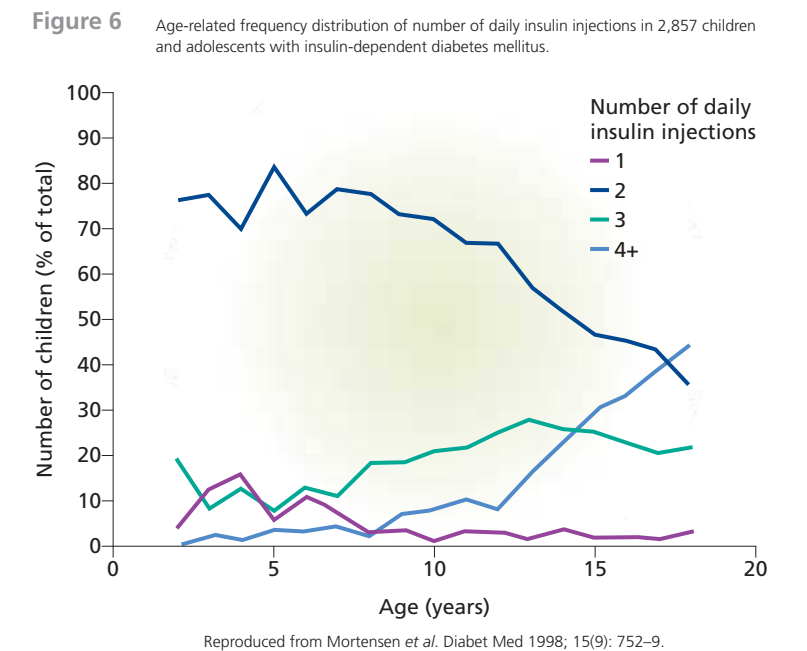


Increasing insulin resistance during puberty leads to increased insulin requirements,¹³ which may be at least partly responsible for the increase in age-related body mass index (BMI) seen in boys and girls with type 1 diabetes during both the prepubertal and the pubertal periods when compared with healthy control children (Figure 5).¹⁴ BMI, especially in girls with diabetes, continues to increase during adolescence. This finding is in agreement with the results of a recent nationwide Danish investigation.¹⁵



Controversy remains as to whether multiple injection therapy *per se* is associated with weight gain. Some studies have shown a possible association,^{15,13,15} while others dispute this.^{16–18} Multiple daily injections allow more flexibility, and the attitude of teenagers towards their diet may become more relaxed on such intensive insulin therapy, leading to 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 premixed insulin, given either alone or in combination with short- and intermediate-acting insulin. Pre-adolescent children on premixed insulin had 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 on its clinical significance.

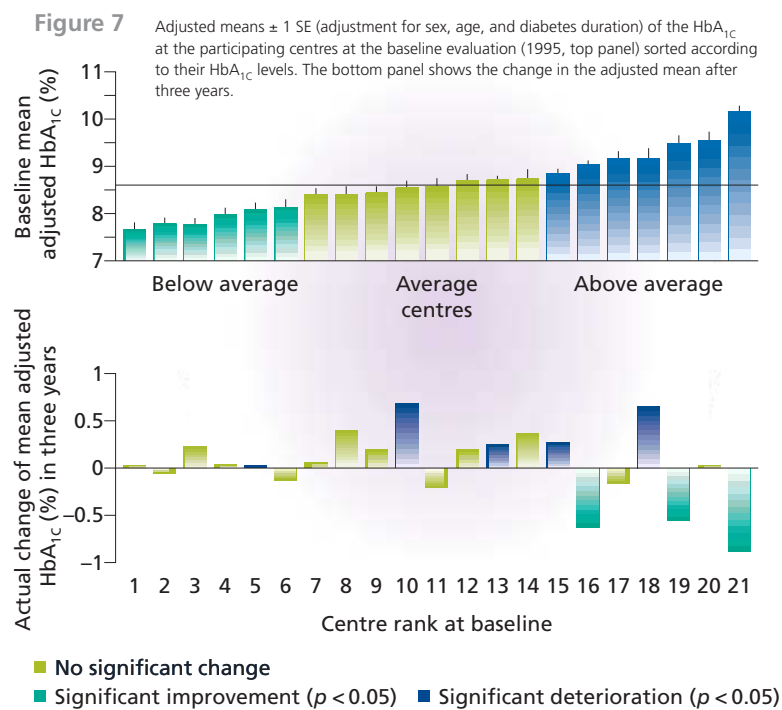


Conclusion: Numerous insulin injection regimens are currently used in paediatric diabetes centres around the world, with an increasing tendency towards multiple insulin injections, particularly in older adolescents. Nevertheless, the goal of near-normoglycaemia is achieved in only a few patients.



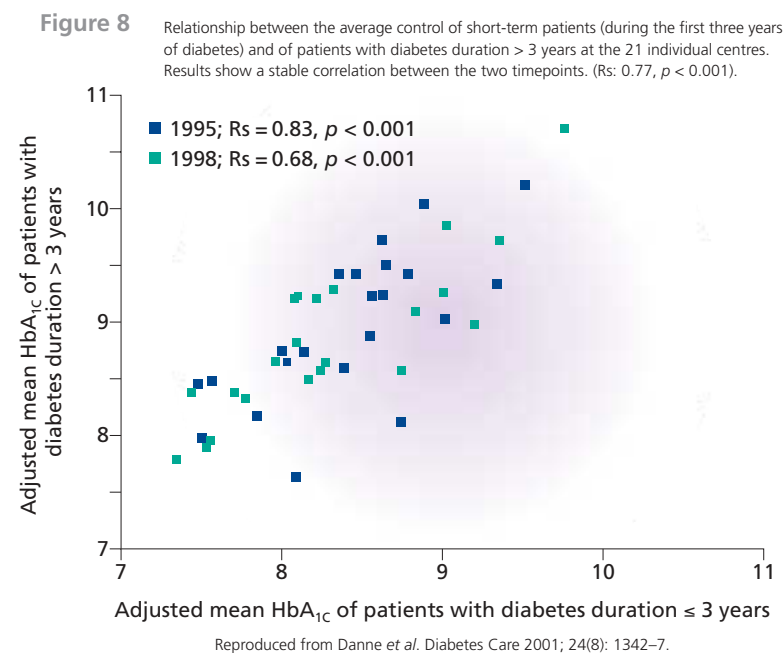
DIFFERENCES BETWEEN CENTRES

Many potential explanations for the between-centre 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 centre differences have caused each study group member to consider whether anything could be changed at their centre in order to improve metabolic control. Three years after the first cross-sectional study, a second study was carried out to restudy the between-centre differences after this feedback. The third paper, *Persistent differences among centers over 3 years in glycaemic control and hypoglycaemia in a study of 3,805 children and adolescents with type 1 diabetes from the Hvidøre Study Group*,³ investigated the reproducibility of the between-centre differences and analysed factors potentially influencing the variations in glycaemic control between centres, including number of injections, insulin dose, and rate of severe hypoglycaemia. Twenty-one international paediatric diabetes centres from 17 countries participated.



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To examine whether the between-centre differences were particularly pronounced early or later in the course of diabetes, the mean HbA_{1c} was calculated for each centre separately for children with duration \leq 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} 8.62 ± 0.03 [1995] versus 8.67 ± 0.04 [1998]) (Figure 8). 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 could



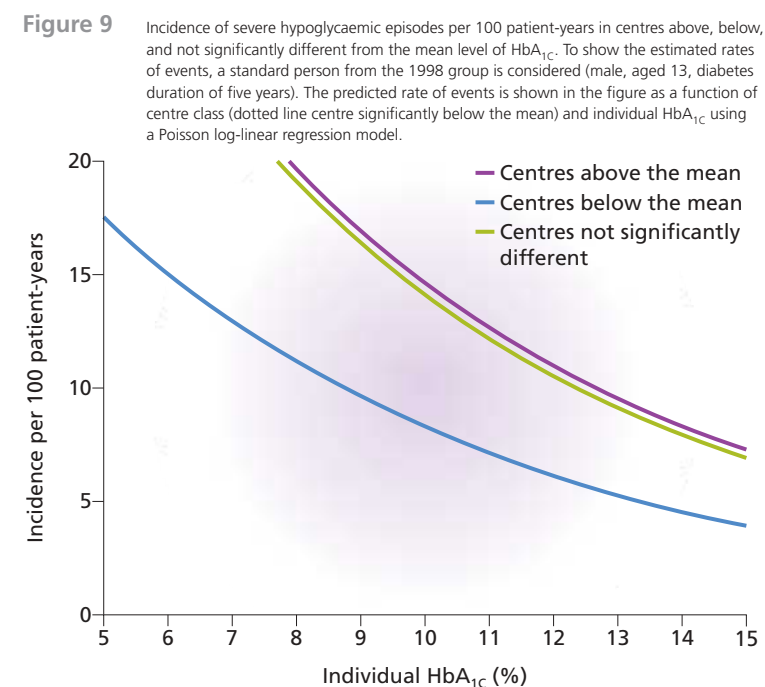
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Striking differences in average HbA_{1c} were found between centres; these differences remained after adjustment for the significant confounders of sex, age, and diabetes duration. Three centres had improved significantly, and four centres had deteriorated significantly in their overall adjusted HbA_{1c}, while glycaemic control did not change in 14 centres (Figure 7). During the observation period, there were increases in the adjusted insulin dose by 0.076 U/kg, in the adjusted number of injections by 0.23 injections per day, and in the adjusted BMI by 0.95 kg/m².

be 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 differences between centres.

Parameters of insulin therapy showed no clear-cut association with glycaemic control or hypoglycaemia rates, either in the original sample¹ or in the reassessment of the between-centre differences. As a consequence of the unsatisfactory level of glycaemic control in the first survey, it is possible that most centres 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 glycaemic control. Furthermore, this strategy resulted in an unfavourable increase in BMI in many centres, particularly in girls.¹⁹

Similar to the experience with hypoglycaemia in the DCCT, there was no clear-cut association between average control at an individual centre and the rate of severe hypoglycaemia. At both sampling periods, a higher



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rate of severe hypoglycaemia was associated with lower age and better glycaemic control. However, some centres are more successful than others in preventing hypoglycaemia, independent of the prevailing average HbA_{1c} levels (Figure 9). This important finding may relate to other features of management, such as psychological support and more successful education in centres with a low incidence of hypoglycaemia.

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, possibly as a result of better education programmes.



RELATIONSHIP BETWEEN INSULIN INJECTION REGIMEN AND METABOLIC CONTROL OVER THREE YEARS

As the optimal insulin regimen for paediatric patients with type 1 diabetes remains controversial, this issue was investigated in a separate paper, *Insulin injection regimens and metabolic control in an international survey of adolescents with type 1 diabetes over 3 years: results from the Hvidøre Study Group*.⁴ Of the 2,873 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} in order to investigate whether differences in insulin management were associated with outcome differences across centres.

The changes in HbA_{1c}, injection frequency, insulin dose, and BMI were evaluated by using a repeated measurements model for the 1995 and 1998 data in order to account for the effect of covariates and the fact that patients each contributed two measurements. Sex, centre, age, and diabetes duration were included in order to adjust for these factors and the effect of the increase in age and diabetes duration during the three-year period.

Over three years, the use of multiple-injection regimens increased from 42% to 71%: 251 children (group 1) 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 three subgroups, an increase in insulin dose, a deterioration of metabolic control, and an increase in BMI were observed regardless of insulin injection regimen. The increase in BMI was greatest in patients switching from twice-daily to multiple injections, and greater in girls than in boys.

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).^{6,7} 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 three years apart. No information was available on the insulin therapy during the three years or on other interventions to improve metabolic control, such as patient re-education, hospitalisation, camps etc. Each treatment centre was entirely free in its choice of insulin therapy, and no information was collected on the reasons for individual patients continuing or changing their 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 in metabolic control in adolescents with increasing injection frequency,^{17,20,21} others are in agreement with our data and do not confirm such a relationship.^{9,13,22} 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.

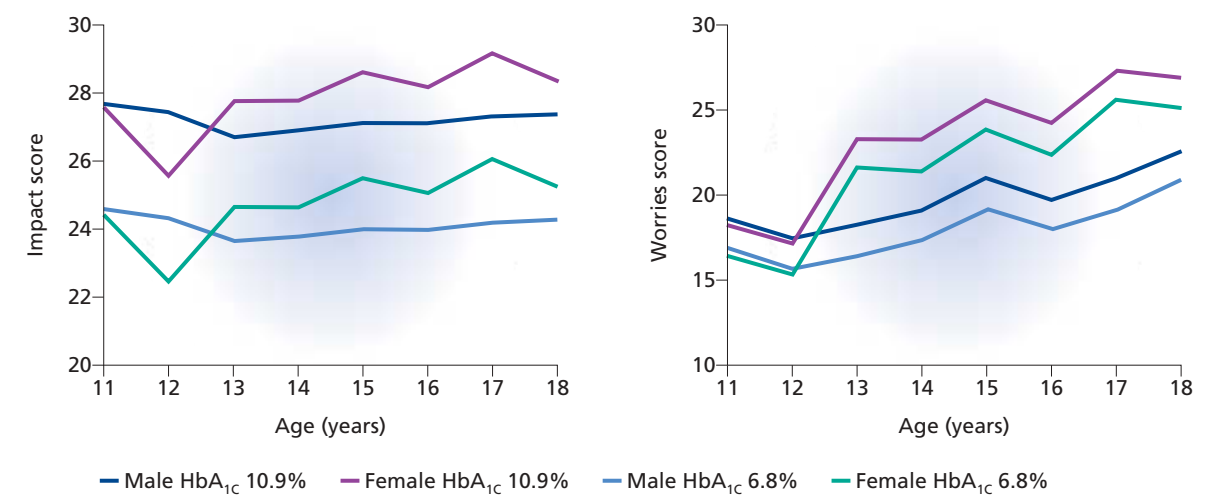
Conclusion: In this international study, metabolic control was unsatisfactory in many adolescents with type 1 diabetes, irrespective of the insulin regimen. No improvement in metabolic control was observed over three years, not even in patients switching from twice-daily to multiple injections, while the increase in BMI 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.

Both the DCCT and the recent ISPAD guidelines have recommended a treatment target for HbA_{1c} of 7.5%. But how will the demands of good metabolic control influence the quality of life (QoL) of adolescents with diabetes? Stress caused by a demanding therapeutic intervention may adversely influence QoL and restrict the patient. The Hvidøre Study Group therefore 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. The results are presented in *Good metabolic control is associated with better quality of life in 2,101 adolescents with type 1 diabetes*.⁵

QoL in adolescents was assessed with a previously validated questionnaire.²³ The questionnaire contained 52 items in four sections: impact of diabetes, worries about diabetes, satisfaction with life, and health perception. For each adolescent, one parent and one health professional completed a questionnaire, including five items about their perceptions of the burden on the family 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 lower perceived burden by parents and health professionals. Figure 10 shows the change in QoL score with age, according to sex and high and low HbA_{1c}, selected as the 10th (6.8%) and the 90th percentiles (10.9%) in the population as perceived by adolescents, to illustrate 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 score 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, and neither age nor duration of diabetes had an impact on the scoring. More worries were evident with increasing age, especially in girls (Figure 10b). This may reflect the higher incidence of psychological disturbance widely reported in population studies of adolescent girls.²⁴⁻²⁷ The relationship between HbA_{1c} and worry was just significant.

Figures 10a and b The association of HbA_{1c} (6.8% or 10.9%), sex, and age on (a) the impact of diabetes (lower score = less impact), and (b) worries about diabetes.

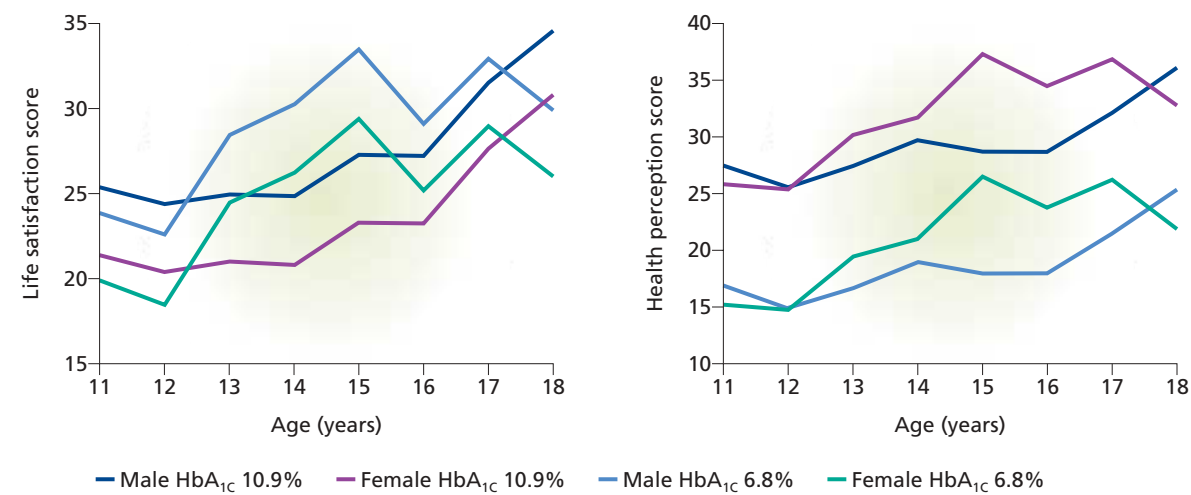


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The scores for satisfaction followed the same pattern as worries, showing less satisfaction with increasing age, again more pronounced in girls (Figure 10c, overleaf). Teenage girls had poorer health perception than boys (Figure 10d, overleaf). Thus 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,^{28,29} and with their relative lack of physical activity and abnormal eating behaviours.^{30,31}

NEW REMISSION PHASE STUDY

Figures 10c and d The association of HbA_{1c} (6.8% or 10.9%), sex, and age on (c) satisfaction with life, and (d) health perception score.



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No correlation between adolescent QoL and burden perceived by parents and health professionals was observed, and this may reflect significant differences in perceptions of the impact of diabetes 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 trial.

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 the lowest burden. Because girls enter puberty earlier than boys, with an earlier transfer of responsibility for self-care management from parent to child, the parents' burden may be correspondingly decreased. By contrast, health professionals' scores for family burden showed no sex 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.

Conclusion: Lower HbA_{1c} is associated with better QoL. Although this study could not determine a causal relationship, efforts to achieve optimal metabolic control now seem justified on QoL as well as clinical grounds.⁵ The size and international nature of the study add credence to this assertion. As people 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 cycle.

As it has been established that differences across centres are maintained over three years, and as it has been found that between-centre differences in glycaemic control are present soon after onset of diabetes, the Hvidøre Study Group decided to focus on the early course of the disease in future studies. The group has therefore started a new study to investigate the remission phase in children and adolescents with newly diagnosed diabetes.^{32,33} In this prospective multicentre survey, it will be possible to investigate whether the differences between centres in glycaemic control and hypoglycaemia are associated with the patients' genetic or immunological background or are related to other factors such as 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.

FUTURE PERSPECTIVES

The Hvidøre Study Group has a record of conducting multicentre studies, and in the years to come we are planning further joint studies to shed light on the between-centre differences and to use the network that has already been established in order to improve quality of healthcare programmes.

ACKNOWLEDGEMENTS

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Further information on the Hvidøre Study Group on Childhood Diabetes can be found at: www.hvidoergroup.org

References

1. Mortensen HB, Hougaard P. Comparison of metabolic control in a cross-sectional study of 2,873 children and adolescents with IDDM from 18 countries. The Hvidøre Study Group on Childhood Diabetes. *Diabetes Care* 1997; 20(5): 714–20.
2. Mortenson HB, Robertson KJ, Aanstoot HJ *et al.* Insulin management and metabolic control of type 1 diabetes mellitus in childhood and adolescence in 18 countries. Hvidøre Study Group on Childhood Diabetes. *Diabet Med* 1998; 15(9): 752–9.
3. Danne T, Mortensen HB, Hougaard P *et al.* 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. *Diabetes Care* 2001; 24(8): 1342–7.
4. Holl RW, Swift PG, Mortensen HB *et al.* Insulin injection regimens and metabolic control in an international survey of adolescents with type 1 diabetes over 3 years: results from the Hvidøre Study Group. *Eur J Pediatr* 2003; 162(1): 22–9.
5. Hoey H, Aanstoot HJ, Chiarelli F *et al.* Good metabolic control is associated with better quality of life in 2,101 adolescents with type 1 diabetes. *Diabetes Care* 2001; 24(11): 1923–8.
6. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr* 1994; 125(2): 177–88.
7. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329(14): 977–86.
8. Rovet JF, Ehrlich RM, Czuchta D *et al.* Psychoeducational characteristics of children and adolescents with insulin-dependent diabetes mellitus. *J Learn Disabil* 1993; 26(1): 7–22.
9. Dorchy H, Roggemans MP, Willems D. Glycated hemoglobin and related factors in diabetic children and adolescents under 18 years of age: a Belgian experience. *Diabetes Care* 1997; 20(1): 2–6.
10. Kerouz N, el-Hayek R, Langhough R *et al.* Insulin doses in children using conventional therapy for insulin dependent diabetes. *Diabetes Res Clin Pract* 1995; 29(2): 113–20.
11. Arslanian SA, Heil BV, Becker DJ *et al.* Sexual dimorphism in insulin sensitivity in adolescents with insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1991; 72(4): 920–6.
12. Widom B, Diamond MP, Simonson DC. Alterations in glucose metabolism during menstrual cycle in women with IDDM. *Diabetes Care* 1992; 15(2): 213–20.
13. Mortensen HB, Villumsen J, Vølund A *et al.* Relationship between insulin injection regimen and metabolic control in young Danish Type 1 diabetic patients. The Danish Study Group of Diabetes in Childhood. *Diabet Med* 1992; 9(9): 834–9.
14. Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. *Arch Dis Child* 1995; 73(1): 25–9.
15. Mortensen HB, Hougaard P. Microvascular complications in childhood. In: Shield JPH, Baum JD (Eds). *Bailliere's Clinical Paediatrics*. Volume 4. London: Baillière Tindall, 1996: 641–61.
16. Danne T, Kordonouri O, Enders I *et al.* Factors influencing height and weight development in children with diabetes. Results of the Berlin Retinopathy study. *Diabetes Care* 1997; 20(3): 281–5.
17. Bougnères PF, Jos J, Garandeanu P *et al.* Improvement of diabetic control and acceptability of a three-injection insulin regimen in diabetic adolescents. A multicenter controlled study. *Diabetes Care* 1993; 16(1): 94–102.
18. Holl RW, Grabert M, Heinze E *et al.* Why do children with type 1 diabetes develop overweight? *J Pediatr Endocrinol Metab* 1997; 10(Suppl 2): A39 (366) (Abstract).
19. Diabetes Control and Complications Trial Research Group. Weight gain associated with intensive therapy in the Diabetes Control and Complications Trial. *Diabetes Care* 1988; 11(7): 567–73.
20. Nordfeldt S, Ludvigsson J. Adverse events in intensively treated children and adolescents with type 1 diabetes. *Acta Paediatrica* 1999; 88: 1184–93.
21. Scottish Study Group for the Care of the Young Diabetic. Factors influencing glycemic control in young people with type 1 diabetes in Scotland: a population-based study (DIABAUD2). *Diabetes Care* 2001; 24: 239–44.
22. Wysocki T, Hough BS, Ward KM *et al.* Diabetes mellitus in the transition to adulthood: adjustment, self-care, and health status. *J Dev Behav Pediatr* 1992; 13(3): 194–201.
23. Ingersoll GM, Marrero DG. A modified quality-of-life measure for youths: psychometric properties. *Diabetes Educ* 1991; 17(2): 114–18.
24. Petersen AC, Compas BE, Brooks-Gunn J *et al.* Depression in adolescence. *Am Psychol* 1993; 48(2): 155–68.
25. Angold A, Costello EJ, Worthman CM. Puberty and depression: the roles of age, pubertal status and pubertal timing. *Psychol Med* 1998; 28(1): 51–61.
26. Satin W, La Greca AM, Zigo MA *et al.* Diabetes in adolescence: effects of multifamily group intervention and parent simulation of diabetes. *J Pediatr Psychol* 1989; 14(2): 259–75.
27. Kovacs M, Goldston D, Obrosky DS *et al.* Psychiatric disorders in youths with IDDM: rates and risk factors. *Diabetes Care* 1997; 20(1): 36–44.
28. Moran A, Jacobs DR Jr, Steinberger J *et al.* Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes* 1999; 48(10): 2039–44.
29. Holl RW, Siegler B, Scherbaum WA *et al.* The serum growth hormone-binding protein is reduced in young patients with insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1993; 76(1): 165–7.
30. Bryden KS, Neil A, Mayou RA *et al.* Eating habits, body weight, and insulin misuse. A longitudinal study of teenagers and young adults with type 1 diabetes. *Diabetes Care* 1999; 22(12): 1956–60.
31. Daneman D, Olmsted M, Rydall A *et al.* Eating disorders in young women with type 1 diabetes. Prevalence, problems and prevention. *Horm Res* 1998; 50(Suppl 1): 79–86.
32. Holl RW, Swift P, Hougaard P *et al.* Clinical characteristics of newly diagnosed type 1 diabetes mellitus in children and adolescents from 19 centres. Hvidøre Study Group on Childhood Diabetes. *J Pediatr Endocrinol Metab* 2001;14(Suppl 3):1033, Abstract No. OP-17.
33. Swift PGF, Holl RW, Mortensen HB *et al.* Influence of initial presentation and insulin treatment on metabolic control at one month after diagnosis in an international cohort of young people with type 1 diabetes. Hvidøre Study Group on Childhood Diabetes. *J Pediatr Endocrinol Metab* 2001;14(Suppl 3):1072, Abstract No. PP-150.

