

Review Article

Lessons from the Hvidoere International Study Group on childhood diabetes: be dogmatic about outcome and flexible in approach

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Type 1 diabetes is one of the most common chronic diseases of childhood. Between 1989 and 2003, the incidence of type 1 diabetes in youth increased at approximately 3.9% per year with a projected doubling of cases in children aged <5 yr between 2005 and 2015 (1). This has substantial impact on those affected, their families, on pediatric diabetes care, and on national health care budgets. Much has changed over the last decade in terms of management strategies in type 1 diabetes, however, as Edwin Gale editorialized in 2005 that the challenges of diabetes remain much the same (2). In short, there are more cases resulting in increasing disease years characterized by greater medical and psychosocial complexity.

The Hvidoere International Study Group on Childhood Diabetes evolved in 1994 during a meeting that was held in the immediate post Diabetes Control and Complication Trial (DCCT, 3) era to discuss strategies that could improve the quality of pediatric diabetes care and thereby improve subsequent adult outcomes. The objectives and mission statement of the Hvidoere group can be found on its website <http://www.hvidoeregroupp.org/>. In short, this unique collaboration of 26 pediatric diabetes centers from 23 countries (Europe, North America, Japan, and Australia) has undertaken a series of research projects investigating critical determinants for long-term outcome of type 1 diabetes care discriminating in terms of outcomes and which aspects of care are universally effective. In all the Hvidoere studies, HbA1c was analyzed centrally at the Steno Diabetes Center, Denmark. In the period from 1997 to December 2002 HbA1c was analyzed using an automated high pressure liquid chromatographic method (Bio-Rad Variant, Bio-Rad Laboratories, Hercules, CA, USA) using the same calibrator lots as the DCCT laboratory. From 2003 till now, HbA1c was analyzed by the DCCT aligned TOSOH Automated Glycohemoglobin Analyzer HLC-723G7, Tosoh Corporation, Tokyo, Japan.

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Five major studies have been undertaken, both cross-sectional and longitudinal, serving this goal. The findings detailed below show that these studies have led to an internationally recognized remission parameter (4) and have validated well-being and quality-of-life (QOL) questionnaires (with relevant translation, (5). The key thematic and practical findings of this body of work (published in 28 peer reviewed medical and scientific journals) are summarized in this review.

Key findings

1995 – Comparison of metabolic control in a cross-sectional study of children and adolescents with type 1 diabetes from 18 countries

The Hvidoere Study Group started with a cross-sectional survey in 1995 in children and adolescents with type 1 diabetes in an international context. The purpose of the first study was to describe various insulin regimens and metabolic control in children and adolescents with type 1 diabetes in an international context. This cross-sectional study involved 21 pediatric diabetes centers (2873 children aged 0–18 yr) from 18 countries (6). The centrally measured overall mean HbA1c was 8.6%, with a mean HbA1c of $8.3 \pm 1.3\%$ in children under 11 yr compared with $8.9 \pm 1.8\%$ in those aged 12–18 yr. The average prepubertal dose of insulin was 0.65 units/kg/d; 60% of children were receiving two injections per day (37% using premixed insulins alone) and 37% of children were receiving more than three injections per day. Major and significant differences (center mean HbA1c values ranged between $7.6 \pm 1.4\%$ and $10.2 \pm 2.3\%$) were observed between the centers which were not readily explicable in terms of geography or staffing structure.

1998 – Metabolic control, QOL and insulin injection regimens in an international survey of adolescents with type 1 diabetes over 3 yr

The second study was intended to investigate cross-sectionally the association of metabolic control and QOL of adolescents. This was the first large international study evaluating the relationship between metabolic control and QOL among adolescents with diabetes (10–18 yr) and their parents in 2101. New international QOL assessment instruments were developed and evaluated in order to assess family burden, and parent and professional perspectives on QOL (5, 8). This study showed that good metabolic control is associated with better adolescent QOL and less parent perceived family burden. Adolescent girls, those of single parent families and ethnic minorities had poorer metabolic control and poorer QOL. Discordant views relating to adolescent QOL, and family burden were reported across adolescents, parents, and health

professionals groups and indicate the need to assess all three perspectives (7, 9). This study showed that better HbA1c was associated with better QOL for adolescents and with a lesser perceived burden by parents, however, as this was a cross-sectional study it was not possible to determine a cause-and-effect relation. It is likely that individuals with a higher QOL may be better equipped physically and psychologically to deal with the burden of diabetes management, hence better QOL may facilitate better metabolic control through improved self-care as part of positive circle. Efforts to achieve optimal metabolic control now appear justified on QOL as well as clinical grounds. The study indicated the need for further studies to evaluate the relationship between QOL and clinical outcomes including specific aspects relating to QOL, psychosocial issues, and vulnerable groups.

In addition, in order to investigate whether differences in insulin management were associated with metabolic differences across centers a longitudinal study was conducted on children who participated in both the first and second study. This study is related to insulin injection regimens and metabolic control including rates of hypoglycemia and changes in body mass index (BMI) over the intervening 3 yr period. The longitudinal component of the 1998 study was limited to children and adolescents who were aged 8–15 yr of age in 1995. Of the 1538 eligible patients, 872 adolescents provided blood samples and data in 1998. This study involved 21 pediatric diabetes centers from 17 countries. After the 3 yr period there was a marked overall increase in insulin injection frequency and the use of multiple injection (more than three injections = multiple daily injections [MDI]) regimens increased from 42 to 71% (10). The overall mean HbA1c remained high (8.9% in both the 1995 11–18 yr old and the 1998 12–18 yr old group). The change to MDI regimens was associated with significantly increased relative mean insulin dose, a significantly increased BMI, and approximate doubling of the rate of severe hypoglycemia without improved HbA1c values. Three centers significantly improved their mean HbA1c value, 4 centers significantly deteriorated, and the remaining 14 centers remain unchanged. The overall spread in center mean HbA1c values was largely unchanged from 10.1 to 7.7% and insulin regimen showed no association with center outcome (11). Interestingly, those centers with the lowest mean HbA1c values also had the lowest rates of severe hypoglycemia and reported better QOL (7).

2005 – Center differences: adolescent study

The purpose of the third study was to identify relevant factors influencing these persisting center differences with a special focus on diabetes team dynamic, family dynamic, demographic, linguistic, and clinical

factors. This cross-sectional study involved 21 pediatric diabetes centers, 14 of which had been previously involved in the 1998 study. This study was focused on adolescents aged 11–18 yr. Data was obtained for 2093 adolescents. The overall mean HbA1c was $8.2 \pm 1.4\%$ (12). Pooled data showed significant correlations between HbA1c and numerous variables, the most significant of which were metabolic target or goal setting, family communication, and parent well-being. Specifically, both parent and adolescent reported HbA1c targets and diabetes care team unanimity on HbA1c targets were very strong predictors of HbA1c achieved. Those parents and adolescents with the lowest HbA1c targets and the respective diabetes care teams most united in their goals achieved the best clinical results (13). Intensified insulin regimens (MDI and continuous subcutaneous insulin infusion [CSII]) showed no significantly lower HbA1c compared with twice daily free mixing (lowest HbA1c). Secondary outcome analysis failed to show an association between insulin regimen and BMI, rates of severe hypoglycemia, and diabetic ketoacidosis (DKA). Parent well-being was assessed using the World Health Organization (WHO)-5 Questionnaire. This study showed that most parents of children with diabetes (80%) report good well-being on the WHO-5 scale, however, 20% had poor scores (<50), and 8% had likely depression (<28) (14). Adolescents of parents with good well-being scores had significantly better HbA1c, fewer worries, and lower impact of diabetes than those of parents with poor well-being scores. In addition, maternal well-being was significantly poorer than that of fathers.

Of the 14 centers involved in both studies, significant changes were seen in only three centers with two improving and one deteriorating between 1998 and 2005. The overall spread of center's mean HbA1c was somewhat less than in 1995 and 1998 varying from 7.4 to 9.2%. Center differences were unable to be explained by demographic and clinical variables. When a sub-analysis of the 14 centers involved in the 1998 study was undertaken those centers that demonstrated consistently lower HbA1c results were not found to be adopting any strategy that the other centers were also using.

2009 – Center differences: child study

Optimizing metabolic control in adolescents may be a more challenging task because of many physiological and psychological processes involved and therefore the fourth study focused on children aged <11 yr. There were many reasons to expect that the findings in the 2005 adolescent cohort would not be recapitulated in a cohort of children whose management was largely undertaken by their parents. This study involved 1133 children from 18 centers with a comparable methodology as the 2005 study (15). The overall mean

HbA1c was $8.0 \pm 1.0\%$, slightly better than in the adolescents, with a lower rate of severe hypoglycemia. Best metabolic control was achieved for those <11 yr in the same centers as in the previous studies. The mean HbA1c values between centers varied between 7.3 and 8.9%. Again no association was observed between center outcome and demographic, resource, or clinical variables. Despite major changes in medical management ($>99\%$ on analog insulins and 32.8% with CSII) over the decade between the 1998 and 2009 studies, the proportion of children in this age group achieving HbA1c levels less than 8.0% had only increased from 41 to 53%. As with the 2005 adolescent study, the younger patients achieving the best metabolic control were receiving twice daily free-mixing insulin regimens (HbA1c = $7.3 \pm 0.5\%$). However, severe hypoglycemia was extremely uncommon (96% of patients did not experience it at all during the study window). When it occur it was most likely to happen in the twice daily free-mixing insulin group and least likely to happen in the insulin pump group. Whether this was simply an artifact of it occurring disproportionately in three children (with 11 events), the free mixing group having a mean HbA1c that was 0.5% lower than the insulin CSII group, or whether it related the mode of insulin delivery *per se* was not evident.

Lessons for team leaders: change is difficult

The first question that should be asked by team leaders is how generalizable are the data from the Hvidoere group and do they apply to my center? It should be acknowledged that the Hvidoere study centers are not necessarily representative of their respective countries. It was never the intention of the Hvidoere study group to present representative national data from 23 countries – rather the group has presented data from 26 centers in 23 countries and has studied variables within those centers to see if they explain differences in outcomes. The Hvidoere study group was not looking to define national characteristics that predict metabolic outcome, rather the group was investigating varying behaviors/philosophies from clinical teams that affect metabolic outcome – exploiting the varying national contexts to provide a potentially greater variance in those behaviors and philosophies. The patients themselves were recruited in such a way as to minimize the risk of selection bias. In the 1995 and 1998 studies (before the larger centers joined the Hvidoere study group), all patients attending centers were invited to participate. In the 1995 study, 67% of all patients treated at the centers during that year were included in the study and analysis of the HbA1c determinations, made locally at the individual centers, showed that there was no difference between the mean HbA1c level of patients participating in the study and

non-participants (10). In the 1998 study, samples and information from 79% of the patients registered at the centers were obtained. In the 2005 and 2009 studies, patients were recruited sequentially as they attended clinics over a specified 3 month time frame. In the large centers there were limits on the numbers of patients recruited (up to 200), whereas in the smaller centers all patients who presented in the specified time period were approached. This strategy was adopted to avoid large numbers of patients from only a few centers skewing the results of the study group overall.

What is perhaps most noteworthy of all the Hvidoere study tranches has been the inability of most centers to change their ranking in terms of metabolic control. While there has been an overall improvement in metabolic control between 1995 and 2009, individual centers have largely remained in the same relative position within the group as a whole. Importantly, teams that perform well do so consistently over time and over various age-groups. Moreover, centers that perform well are able to achieve better levels of metabolic control with less hypoglycemia than other centers. Thus, the DCCT finding that a lower HbA1c is associated with higher rates of severe hypoglycemia (3) appears to be no longer the case. This has also been described by other groups (16). In the same vein, the 2005 and 2009 Hvidoere studies did not find associations between either severe hypoglycemia or DKA and HbA1c at an individual level.

One Hvidoere center underwent a major restructure of their entire clinical team and approach after the 1995 study (17). This radical restructuring has resulted in a persistent change in the ranking. The consistency in center ranking has remained despite major changes in clinical practice and ongoing feedback from the various Hvidoere studies. Team leaders have both immutable and manageable variables that affect their clinical service and outcomes. Immutable variables include the demographic nature of their referral base (selective vs. population-based, percentage of ethnic minority groups, changing prevalence in age groups, etc.). There are a plethora of studies showing associations between demographic variables and outcomes at an individual level, however, in both the 2005 and 2009 Hvidoere studies patient characteristics did not explain differences in outcomes at a center level. Thus in our experience for a center as a whole ‘demography is not destiny’ and team leaders should not use this as an excuse to explain away poor outcomes. Manageable variables on the other hand, include the resources applied to service delivery, nature of medical therapy, and philosophy of care. Data from the 2005 study showed that increased frequency of patient contact with doctors was associated with lower HbA1c values, whereas increased contact with allied health staff was associated with higher HbA1c values. The vast majority of contact between

doctors and patients is planned or scheduled and thus the inference that more scheduled contact results in better control is self-evident. Contact with allied health staff though may be either planned or crisis-based and thus it is difficult to draw much by way of conclusion in terms of cause and effect from the above-mentioned data. However, it appears a conservative conclusion that more frequent scheduled clinic medical contact is more effective than frequent potentially crisis-based allied health contact in improving metabolic control. The 2005 study also highlighted the importance of 24-h telephone support. These supports are usually designed for crisis-based care to avoid DKA or major hypoglycemia. It was surprising then to note that while presence of such support resulted in significantly lower center’s HbA1c (8.1 vs. 8.4%), it did not impact on rates of either DKA or severe hypoglycemia between centers.

Lessons for individual doctors: it’s not what you do, it’s how you do it

As was concluded in both the 2005 and 2009 studies, it appears that the way in which staff at a center apply a given insulin regimen is more important in determining metabolic outcomes than the regimen itself (13, 15). While the DCCT showed the benefits of intensive diabetes therapy, many physicians subsequently focused upon just the intensive insulin therapy aspect of the DCCT care package. Hvidoere clinicians were not immune to this trend of enthusiastic and non-reflective uptake of MDI regimens in the early post-DCCT era. Unfortunately, this change in clinical practice did not improve medical control and resulted in increases in BMI and severe hypoglycemia rates (10). There are now numerous other national and group registry studies that have also reported a lack of association between specific insulin types and regimens and metabolic outcomes (18–24). The success of even the most sophisticated of insulin regimens combined with continuous glucose sensing still remains hostage to issues of patient adherence and usage (25). Thus, despite the theoretical advantages, simply ‘intensifying’ or increasing the complexity of an insulin regimen does not necessarily guarantee an improved outcome for patients. Rather it appears that the clinical and metabolic goals or targets that accompany any therapeutic regimen are more important in determining outcomes.

Potential lessons can be learnt from those Hvidoere centers that have consistently performed the best in terms of metabolic control. The one center that has consistently had the lowest HbA1c values from 1995 to 2009 is one of the smaller centers. The Hvidoere member in question is highly charismatic and has a very prescriptive, ‘recipe’-based approach to managing diabetes in his clinic (26). He prescribes mostly twice

daily free mixing injections of insulin and eschews, a flexible approach to dietary intake. This does not appear to be at the expense of either hypoglycemia or QOL in his patient group. Although many aspects of his practice are shared by other Hvidoere members, it has proved very difficult to translate this total approach into other contexts for a variety of reasons. However, this experience is emblematic that consistently excellent outcomes can be achieved by simple, ‘non-intensive’ insulin regimens that are underpinned by a strong philosophy of care.

Lessons for members of teams: unanimity of purpose is everything

Factor analysis of 2005 and 2009 studies showed that the ‘big picture’ issues such as team target HbA1c levels, team communication with families and family function were more strongly associated with metabolic outcomes when compared with ‘small picture’ issues such as insulin type, insulin delivery, types of insulin adjustment, variations in hypoglycemia management, etc. Family perceptions of within-team communication were also associated with HbA1c. The corollary of this was that those teams who had agreed upon metabolic targets or unanimity of purpose were more likely to achieve better center outcomes than those teams who had varied metabolic goals (13).

The 2005 study of adolescents showed that maladaptive dietary patterns were extremely common with all centers having at least 30% of patients who reported occasional binge-eating and 11% binge-eating at least once per week. Insulin omission to control weight was rare and consistent across centers with 2–3% and 1% of patients reporting insulin omission on a weekly and daily basis, respectively. Patients who omitted insulin more frequently than once per week had significantly poorer metabolic control. Physical activity on the other hand appeared to have no impact at all upon any of the clinical outcomes such as HbA1c, BMI, rates of severe hypoglycemia, and DKA, though it was associated with improved health perception (27).

Thus, teams that have unanimity of purpose and that focus together upon major issues such as goals, effective communication, family support, and dealing with non-adherence appear to achieve better outcomes than teams which are disunited and focused upon the minutiae of their own areas of diabetes care expertise.

Lessons for families: effective teamwork wins the day

Families where both parents are living together and there is paternal employment had better metabolic outcomes in the 2005 and 2009 studies (28). Just as for teams, parent and child report of target HbA1c was

strongly associated with metabolic outcomes (13). The other strongest determinant of outcome was whether or not there was agreement between parent and child as to who was responsible for blood glucose testing (i.e., it did not actually matter who did the work of glucose monitoring so long as both parties agreed whose job it was) (28). Parent reported trend-based insulin adjustment using several days of blood glucose data was also associated with improved metabolic control. Adolescent reported insulin adjustment had no relationship to HbA1c, rates of hypoglycemia or DKA. Adolescent perception of parental over-involvement in diabetes care, however, was associated with poorer outcomes. Synthesizing these various factors it would appear that a target-driven approach, agreed upon role responsibility, and ongoing parental involvement appears to be associated with the best metabolic outcomes. In addition, parental and particularly maternal well-being is pivotal. Families should focus holistically on the well-being of both the diabetic child and parents.

Conclusions: toward personalized pediatric diabetes care

In the two decades following the DCCT there has been an understandable push to ‘intensify’ therapy in children and adolescents with type 1 diabetes to improve metabolic outcomes. This change in practice has coincided with an increasing variety of new insulin types and delivery devices. Over this period most pediatric centers have experienced improvement in mean HbA1c values with an average quantum of 0.5–1.0%. Notwithstanding this overall improvement, the treatment cause and effect relationships is somewhat obscure and there remains a high proportion of children and adolescents who are unable to achieve agreed target HbA1c values. The Hvidoere studies undertaken over this same time period have shed some light upon what drives and conversely what impedes improved clinical outcomes. While some aspects of the Hvidoere group’s study findings are novel – particularly those that relate to the center by center comparisons, other findings at an individual level have been replicated in other contexts. In particular, the association between poorer metabolic outcomes with increased levels of diabetes-related family conflict the benefits of a treat-to-target approach and the lack of metabolic benefit associated with an unbalanced emphasis solely upon insulin delivery have been repeatedly described in the pediatric diabetes literature (29–33).

A simple yet valuable conclusion from the combined Hvidoere studies is that a ‘one size fits all’ approach to diabetes care in both children and adolescents with type 1 diabetes is not effective. When the Hvidoere datasets were either combined or analyzed center by center,

metabolic outcomes showed little relationship with traditional medical or clinical resource variables employed in each of the study tranches. This was evidenced by the general persistence of center differences despite large-scale changes in clinical practice. The aspect of clinical practice that has changed the most between 1995 and 2009 was insulin regimen with increasing use of analog insulins, MDI, and insulin pump therapy seen across almost every center. While there appears to have been an overall improvement in metabolic outcomes in Hvidøre group, patients between 1995 and 2009 (with HbA1c levels dropping from the mid to low 8's) at no stage has metabolic control been able to be correlated with insulin regimen. Thus dogmatic statements about one insulin regimen being inherently superior to any other are not supported by these findings and hence would appear to be inaccurate. On the other hand, the 2005 study in particular highlighted some very important 'non-medical' variables that were strongly associated with metabolic outcome. Both target setting and effective communication within families were stronger determinants of metabolic control than any other clinical, team resource, ethnic, or demographic variable.

The challenge for our group now is to intervene to try and improve outcomes in those centers that have consistently struggled to attain good levels of metabolic control. We plan to design an intervention based upon a distillation of the findings summarized above. We will then trial this intervention in an 'all of clinic approach' for those centers who currently have the highest mean HbA1c levels. We hypothesize that although the intervention will be undertaken in a variety of national and cultural contexts it will be universally effective due to its empirical basis.

Therapeutic strategies in and of themselves are not enough to obtain desired clinical outcomes. While all clinical regimens have some clinical utility, it is the underlying therapeutic philosophy based on a qualified common training for all team members delivering diabetes care and education to the families that drives improvement. The clinical aphorism of 'Ask for mediocrity and you will receive' holds true. Thus, it appears that the best results will be obtained by physicians who are target-driven and teams and families that have unanimity of purpose. Perhaps the conclusions relating the best clinical practice drawn from the entire body of work of the Hvidøre studies can be best summarized as – be dogmatic about outcome but flexible in approach.

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Appendix

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Cameron et al.

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