

## Diabetes in the young: from Leicester to Siena (via Oslo, Bethesda and Hvidore)

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*"The discovery of insulin was only the beginning, diabetes was a far more complicated disease than anyone had realised..."*

This quotation is taken from "The Discovery of Insulin" a wonderfully descriptive book by Michael Bliss published in 1982 (1). This book graphically describes the first patient, a child, chosen to receive an insulin preparation in January 1922. Leonard Thompson, aged 14 years, was given an extract of beef pancreas in a volume of 7.5 ml into each buttock. It was described as being "a thick brown muck". The blood sugar decreased marginally as did the 24 hour urinary excretion of glucose although there was no clinical benefit evident. A sterile abscess developed at the site of one of the injections!

This was only the beginning and since the 1970's pure uncontaminated manufactured insulin preparations have been available and the importance of providing children at diagnosis with "a good start with confident, clear, positive messages cannot be over-emphasized" (2). In Leicester, UK, our philosophy of treatment has certainly been consistent with the ideal of providing "a good start" by utilising the idea of managing children with diabetes on an ambulatory basis and trying not to admit them to hospital (3).

In the UK outpatient management of children with diabetes was initiated in the early 1950's in Leicester by Dr. Joan Walker and is described in her superb book (4). In 1950 she made the unique appointment of a community based health visitor (community nurse) attached to the hospital diabetic clinic and whose innovative work enabled most children to be

treated out of hospital helping them to give their first injections at home in the family environment so that "education begins immediately... when they are at their most receptive" (5).

Our diabetes team has built on this early experience and it has been fully described elsewhere (3, 6). Over the decades ambulatory care has become more acceptable particularly in America and indeed parts of Europe including Italy (7). Daneman carried out a worldwide systematic review of ambulatory vs inpatient care, reporting that the re-admission rate was lower in those not admitted to hospital at diagnosis, glycosylated haemoglobin was equal or lower, costs were lower and psychosocial outcomes slightly better (8). The question should always be asked "why admit children to hospital if there is an expert team available to manage diabetes outside the hospital in the patient's home environment?"

We believe that non-hospital based, ambulatory care during the traumatic early educational period of management avoids undue disruption of fundamentally important and supportive family relationships within the home environment. It also helps to firmly establish long term trusting relationships with the treatment team.

Ambulatory management at diagnosis has been criticised suggesting that it trivialises the seriousness of diabetes (9). Our experience in Leicester would completely contradict such a view and we would like to think that our approach helps not only to provide a confident and supportive initiation but also emphasises the importance of good metabolic control right

from the start, thus improving the prospects of preventing both short term crises and long term vascular complications.

### Preventing vascular complications

In 1977 it was reported that strict glucose control was able to prevent diabetic retinopathy. But this was in dogs (10)! Such a statement had been the subject of debate and controversy in human (and particularly childhood) diabetes for many years. It was only in 1982 that the Oslo study was initiated to try to answer this debate. Forty-five young people, diagnosed with type 1 diabetes between the ages of 10 and 29 years, were recruited. The average age of participants at the start of the Oslo study was 24 years, with duration of diabetes more than 7 years. They were divided into 3 groups: conventional therapy, insulin pumps, and multiple injection therapy. It was worrying that initially with more intensive therapy the tightening of blood glucose control in this and other studies, was associated with a worsening of retinopathy (11-13). This phenomenon had been termed "the paradox of normoglycaemic re-entry" (14). Fortunately, in Oslo this was found to be transient. (15). The improvement in retinal microvascular complications with continued intensified insulin treatment was also noted in the KROC study in London (16) and in the Steno Copenhagen studies (17) and its aetiopathogenesis has been the subject of speculation and debate (18).

In the Oslo study, after 4 years of improved control with near normoglycaemia and better glycated haemoglobin a delayed onset of microvascular complications was recorded. It was shown that both CSII and multiple injection therapy were superior to conventional therapy (19). Thereafter all patients were encouraged to use intensified insulin regimens and throughout the long term follow up of the study group, HbA<sub>1c</sub> values have been measured.

A similar long-term intervention study in adults with diabetes of 17 years duration was set up in Stockholm in 1982. The group was divided into an intensive group seeing the same physician every two weeks for a period of time and taking at least 3 injections of insulin per day. At the 7.5 year follow up the

differences between conventional therapy and intensive therapy showed HbA<sub>1c</sub> 8.5 vs 7.1 %, retinopathy 52 vs 27%, nephropathy 17 vs 2% but slightly more hypoglycaemia in the intensive group (20). This further study confirmed once again that the lower HbA<sub>1c</sub> resulted in lower *microvascular complications*.

The remarkable Oslo study has more recently focussed on *macrovascular disease* with further follow up after 18 years. Intracoronary ultrasound studies have shown silent coronary atheromatosis in 100% of the 29 patients studied at an average age of 43 years, duration of diabetes 30 years and average HbA<sub>1c</sub> 8.8%. Thirty-five% of the patients had 40% or more stenosis of one or more of the coronary arteries (21). It was noted that for every increment in :

- HbA<sub>1c</sub> of 1% there was a 6% increase in coronary artery stenosis
- serum cholesterol of 1 mmol/l there was a 10% increase in coronary artery stenosis
- duration in diabetes of 10 years there was a 16% increase in coronary artery stenosis.

At the time of the start of the Oslo study, 195 adolescents were being recruited into the diabetes control and complications trial (DCCT Bethesda) in the N. America. They were aged 13 to 17 years at entry and were studied for an average of 7.4 years. The intensive therapy group received extraordinarily intensive management with either multiple injections or continuous insulin infusions, self-monitoring of blood glucose at least 4 times per day, strict goals and targets, at least weekly telephone contact with a diabetes professional, monthly visits to the clinic and monthly HbA<sub>1c</sub> measurements. The impressive results of this arm of the study were reported in 1994 (22), showing a clear separation between the intensive group achieving an average HbA<sub>1c</sub> 8.1% (1% higher than in the adult DCCT group) and the conventional group having an average HbA<sub>1c</sub> 9.8%.

This group of adolescents showed that with the sustained decrease in HbA<sub>1c</sub> of around 2% there was a reduction in the risks of microvascular complications by 60 to 70%. This result was deemed to outweigh the adverse effects of a three-fold increase in severe hypoglycaemic events and a two-fold risk of becoming overweight. It was important to note that in the DCCT there was no threshold HbA<sub>1c</sub> below which complica-

tions did not occur. The risks of complications applied at all levels of HbA<sub>1c</sub> and what has become most important is that the *total glycaemic exposure* both in duration and level are important in the development of vascular complications (23). This report from the DCCT Research Group also emphasises that the risks of complications with HbA<sub>1c</sub> 9% in the intensive group are less than with HbA<sub>1c</sub> 8% in the conventional therapy group. Reasons for this finding are uncertain but

- (a) perhaps there is less variability of blood glucose control in the intensive group compared to the conventional therapy group
- (b) it may point to the importance of post prandial blood glucose levels and total glycaemic exposure.

Since the closure of DCCT the Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group has continued surveillance and has reported that four years after the end of the DCCT the HbA<sub>1c</sub> of the intensive therapy group has deteriorated somewhat, from 7.2% to 7.9%. The conventional therapy group, choosing more intensive therapy following the DCCT, has improved from 9.1% to 8.2%, thus showing virtual equality of glycated haemoglobin in the two groups. However, after four years the incidence of retinopathy and nephropathy remained lower in the original intensive therapy group showing the importance of preceding longer-term metabolic control of intensive therapy (24).

Furthermore the EDIC study has looked at intensive diabetes treatment and carotid intima-media thickness (IMT). It is assumed that IMT correlates with atherosclerosis (25). In the EDIC study IMT correlated with blood pressure, smoking, LDL/HDL levels, microalbuminuria and also with the mean HbA<sub>1c</sub> during the DCCT. Six years after DCCT the intensive therapy group continued to have significantly less IMT than the conventional group (26).

Follow up studies by the DCCT Research Group have also tried to define the relationship between blood glucose levels and HbA<sub>1c</sub>. In the study of Rohlfing et al. (27) 26,000 data points were analysed using the 7-point mean monthly plasma glucose levels of each individual and compared them with the HbA<sub>1c</sub> measurements throughout the DCCT. This confirms that the preceding 30 days of blood glucose levels con-

tribute at least 50% towards HbA<sub>1c</sub> levels; the fasting blood glucose tends to underestimate the HbA<sub>1c</sub>; but afternoon and evening blood glucose showed better correlation with HbA<sub>1c</sub>. Post-prandial blood glucose contributes appreciably to HbA<sub>1c</sub> and in order to achieve an HbA<sub>1c</sub> of 7% one would have to achieve a mean plasma glucose over some weeks of around 7 or 8 mmol/l (27).

## Conclusion

All these studies, particularly those comparing intensive diabetic treatment with conventional therapy, have shown conclusively that not only does better metabolic control reduce the risks of microvascular complications (retinopathy, nephropathy and neuropathy) but also lowers the risks of the life-threatening macrovascular complications of atherosclerosis. As atherosclerosis is now the most common cause of premature death in young people with diabetes (28), these results are of great importance and should be a major motivation for paediatricians in organising care which encourages and empowers young patients to achieve better metabolic control. The results have been associated with total glycaemic exposure and this has an effect at any age. It is wrong for paediatricians to assume that the prepubertal age in diabetes is any way safe from the risk of developing later vascular complications (29, 30).

In the USA as in other parts of the world the influence of the DCCT has been immense. In 1983 the average HbA<sub>1c</sub> in one large clinic in the USA was 8.7%. When the DCCT was reported in 1993 the mean HbA<sub>1c</sub> was 8.45%. Since 1999 the average HbA<sub>1c</sub> in the same clinic has been just in excess of 7.9% showing a gratifying reduction in glycated haemoglobin with reduced risks of complications.

## Outcome measures

In 1994 an international group of paediatricians initiated the Hvidore Study Group on Childhood Diabetes. The first study was to measure the HbA<sub>1c</sub> levels achieved in each of 22 centres. The results of

this were published in 1997 (31) and the figure shown published in 2001 (32). These results showed substantial differences in HbA<sub>1c</sub> levels achieved between the 22 international centres, some achieving excellent mean HbA<sub>1c</sub>'s below 8% whereas a number of centres had mean HbA<sub>1c</sub> levels above 9.2%.

The reasons for such centre differences have been difficult to tease out. On relatively superficial analysis it would seem that resources, facilities and clinic structures in the centres do not explain the differences. A further study in 1998 compared the insulin injection regimens in 872 adolescents between the years 1995-1998 which was really a comparison of adolescents aged 11 years compared with how they were 3 years later. There was no significant change in HbA<sub>1c</sub> whereas the pattern of injection regimens changed considerably between these two times. In 1995 over 50% of children were using only 2 injections a day compared with 27% in 1998. In contrast in 1995 17% were on 4 injections or more compared with 38% in 1998. Therefore, despite changes in insulin injection regimens no change of metabolic control was recorded (33).

One question that is often asked is whether those centres with significantly better metabolic control have higher levels of hypoglycaemia. The Hvidore Study has shown that those centres that have the best metabolic control also have the lowest incidence of severe hypoglycaemia throughout the range of HbA<sub>1c</sub> levels and moreover the better centres in 1995 also have better control in 1998 (32). These two results indicate that some centres are able to achieve better meta-

bolic control both in the short and long-term and have reduced levels of hypoglycaemia indicating that these centres of excellence have methods of management to which we should all aspire.

The Hvidore Study Group has also shown that the better metabolic control is associated with better levels of quality of life thus indicating that intensifying treatment regimens in order to improve metabolic control is not detrimental to the quality of life of young people (34).

In order to understand further the differences between centres, a unique anthropological qualitative study was performed by members of the Hvidore Study Group. Observational studies were performed to compare the clinics in Chieti (HbA<sub>1c</sub> 7.6%) and Dundee (HbA<sub>1c</sub> 9.1%). There seemed to be major cultural and social differences between the clinics. Chieti illustrated the egalitarian Italian society with strong persistent family values whereas Dundee was characterised by the libertarian and individualistic current culture of the UK. In Italy with the acceptance of more prolonged family support there was much better matching between the goals of diabetes treatment and expectations. In contrast, in Dundee, independence was given to young people too early when they were unable to accept responsibility and amongst families and professionals there was an expectation of non-adherence to treatment regimens. The observations suggested that adolescents' feelings of empowerment over diabetes are influenced by differences in the cultural matching and mis-matching of health strategies between young people and their health carers (35). In Chieti there appeared to be a provision of healthcare that takes advantage of the macro (diet, family structure) and micro cultural factors (family support, sense of individuality within the collective family, choice of the degree of support). In Dundee attempts to provide similar diabetes strategies to improve glycaemic control conflicted with the underlying macro and micro cultural factors inherent in UK society. It was also suggested that in Dundee in order to improve clinical outcomes professionals would need to overcome the negative cultural influences by developing innovative strategies. This would seem to be difficult in the context of many of the societal fashions in the UK.

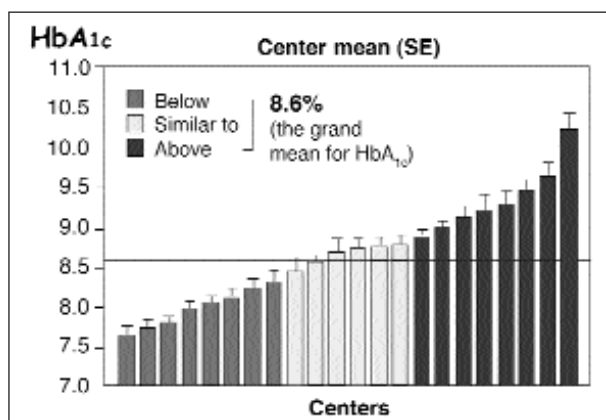


Figure 1. International survey of childhood diabetes (Hvidore Study Group. *Diab Care* 2001; 24: 1342-47)

One of the universally accepted but least well researched influences on diabetes care and metabolic control have been diet and nutrition although in Italy, Pinelli and colleagues have been active in the paediatric nutritional field (36). The first Hvidore study indicated that the global problem of increasing BMI was seen in children with diabetes. It was shown that the nadir of BMI which is said to occur between the ages of 5 and 7 in non-diabetic children was being reached at an earlier age between 4 and 5 years of age in children with diabetes and subsequently the average BMI of this large study group was higher than non-diabetic children (37).

In the DCCT, diet and nutritional behaviour were found to have a significant effect on HbA<sub>1c</sub>. The diet behaviours which improved the glycated haemoglobin by an average of nearly 1% were that patients adhered to a meal plan, they adjusted food and insulin if hyperglycaemic and treated episodes of hypoglycaemia more appropriately. They also had more consistent snacking behaviour and did not have frequent night time snacks (38). With respect to both short-term and long-term diabetes outcomes certain communities start with an advantage over others in that WHO data suggests that the Mediterranean countries such as Italy have higher intakes of fruit and vegetables and lower intake of saturated fat (39). Moreover if one looks at the percentage of 15 year olds who eat sweets and chocolates everyday, in the UK countries something like 70 or 80% of youngsters eat sweets everyday whereas in the Scandinavian countries the figures are more like 30 or 40%. Our colleagues from Leicester and Verona have compared the quality of food in Italy and UK and found that Italian youngsters are far more likely to eat healthier low fat and fruit and vegetable snacks than in the UK where high fat potato crisps and snack bars are more likely to be consumed.

It is these cultural variations added to differences in clinical approach which make diabetes management and outcomes so different in various countries.

### International collaboration

It is pleasing to report that much of the collaborative work that has occurred between individuals

and groups throughout the world has occurred as consequence of the meetings of the International Society for Pediatric and Adolescent Diabetes (ISPAD). ISPAD is the only global advocate for children with diabetes, it works closely with the IDF and members have important roles within the IDF. ISPAD makes major contributions in the science, education and advocacy for children and adolescents with diabetes. The well-reviewed and accepted consensus guidelines (2) were published in 2000 and have now been translated into 11 languages with more in progress (see [www.ispad.org](http://www.ispad.org)). These guidelines are based on many of the results of collaborative research which has been described in this paper particularly with respect to the need for improved metabolic control to prevent serious long term complications of type 1 diabetes.

### Conclusions

– Since 1923 insulin has been life saving but it has exposed the complex metabolic consequences of the long-term disease of diabetes.

– It has been shown conclusively that better metabolic control is associated with lower risks of both micro and macrovascular disease.

– Improved glycated haemoglobin with fewer severe hypoglycaemic episodes and better quality of life is being achieved in some paediatric centres. This level of excellence improves short-term and long-term prognosis and should be the aim of all centres looking after children with diabetes.

– In order to achieve satisfactory metabolic control the child and adolescent has to be considered in the total context of family, social and cultural environments which must be adapted in order to improve levels of empowerment and adherence to treatment.

– Global prospectives are required to encourage innovative methods worldwide of optimising the management of all young people with diabetes. Collaboration between individuals and teams of experts in childhood diabetes is facilitated by organisations such as the International Society for Pediatric and Adolescent Diabetes (ISPAD).

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