Metabolic Control in Children with Type 1 Diabetes

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Abstract

Since 1993, diabetes therapy has been intensified in several ways: insulin analogues have been introduced and insulin pump therapy has been established as a standard therapy in paediatric diabetology, improved devices for self-control have been developed and continuous glucose measurement has been introduced in diabetes monitoring. These technical improvements have been accompanied by new training programmes for children and adolescents with diabetes and their relatives. These programmes aim to empower the patient and his or her family to self-manage diabetes and not to depend on professional advice, as was previously the case. Interdisciplinary teams have been established to train and support families in the management of diabetes. There was a big hope that these improvements would result in a significantly better metabolic situation. This article reviews the changes in diabetes treatment and the outcomes over the last few years: the average glycated haemoglobin (HbA_{1c}) levels fell only marginally, although insulin therapy was intensified considerably; the insulin dose increased and resulted in weight gain. However, the proportion of patients with good metabolic control increased and the proportion of patients with bad metabolic control dropped. Intensifying therapy also resulted in fewer hypoglycaemic episodes, particularly if insulin pumps were used. As well as technical improvements, it is important to address the patient's situation, problems and needs, and it is necessary to individually tailor diabetes therapy. The new devices and training programmes will help us to reach this goal and eventually reduce the rate of diabetic complications.

Keywords

Type 1 diabetes in children, metabolic control, intensified conventional insulin therapy (ICT), insulin pump (CSII), multiple-dose injections (MDIs), insulin analogues

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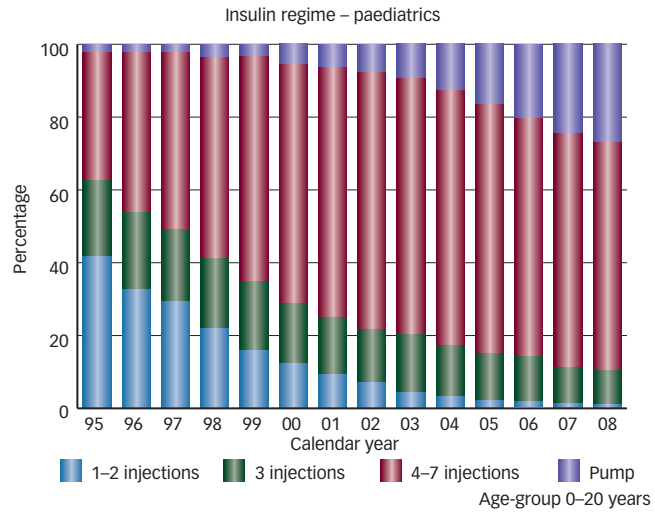
In 1993, the Diabetes Control and Complication Trial (DCCT) clearly showed that intensified diabetes treatment improves clinical outcome and reduces long-term complications in patients with type 1 diabetes. We also learned from the DCCT that metabolic control needs to be optimised from the diagnosis of diabetes to delay or at least slow the progression of diabetic retinopathy, nephropathy and neuropathy.[1] Children with diabetes onset in early life and therefore a lengthy diabetes duration are at particularly high risk of diabetic micro- and macrovascular complications. Therefore, paediatric diabetologists in particular have to strive for normoglycaemia in their patients.

Since the DCCT, more than a decade of improvements in diabetes management has passed. New treatment options are available, such as analogue insulins and insulin pumps, continuous subcutaneous insulin infusion (CSII), better and easier-to-handle devices for self blood glucose measurements, continuous glucose monitoring (CGM) and intensified diabetes education based on standardised evaluated training programmes. Treatment of children and adolescents with diabetes affects not only patients and their needs, but also parents, siblings, grandparents and, in adolescents, peer group. Therefore, modern paediatric diabetes treatment can only be achieved by a multidisciplinary team including diabetes nurses, dieticians, psychologists and paediatric diabetologists as recommended by the International Society for Pediatric and Adolescent Diabetes (ISPAD).[2] Most paediatric diabetes centres have adopted these guidelines and work accordingly. ISPAD recommends a glycated haemoglobin (HbA_{1c}) level <7.5% (DCCT standard) as the metabolic goal. This level is slightly higher than the 7% recommended by the DCCT, but takes into account that there is a higher risk of hypoglycaemia in smaller children and that metabolic control deteriorates during puberty.[3] A significant improvement in metabolic control is expected after 16 years of intensified diabetes management. This article reviews the changes in diabetes treatment and various clinical outcomes.

Changes in Therapy

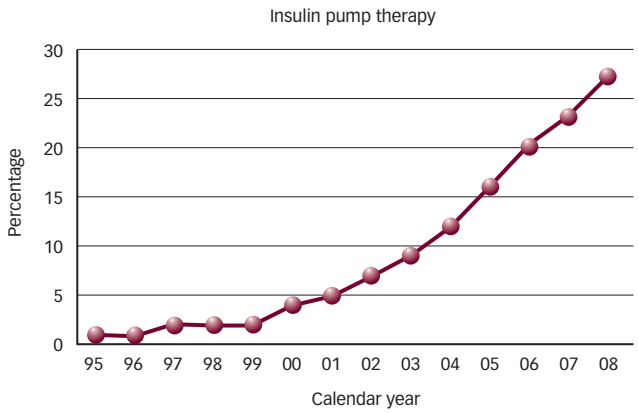
At the beginning of the 1990s, conventional insulin therapy with two daily injections of an individualised mixture of rapid- and intermediate-acting insulins was the standard therapy in paediatric diabetology. Meanwhile, insulin regimens have been intensified: multiple-dose injections (MDI), intensified conventional therapy (ICT) or CSII.

Figure 1: Insulin Therapy in German and Austrian Children with Type 1 Diabetes – Changes in Therapy Regimens from 1995 to 2008



The rates of intensified conventional therapy and continuous subcutaneous insulin infusion increased significantly, whereas conventional therapy decreased.

Figure 2: Increase of Insulin Pump Therapy in German and Austrian Children with Type 1 Diabetes from 1995 to 2008



In a Western Australian cohort of children with diabetes, the rate of CT decreased from 96% in 1992 to 60.2% in 2002. In 1992, 2.3% of the patients were treated with MDI; this number went up to 17.1% in 2002. The number of patients on CSII increased from 0.9% in 2000 to 8.2% in 2002, and the use of analogue insulins increased from 1.4% in 1997 to 36% in 2002.[4] In 2000, 57.8% of Danish children with type 1 diabetes <18 years of age were on two injections or fewer per day, 25.9% were on three injections per day and 16.3% were on four or more injections per day. In 2000–2005, >70% were on two injections or fewer per day. The use of both long- and short-acting analogues increased in this time period.[5] Similarly, in the paediatric diabetes centre in Hannover, the rate of CT decreased from about 90% in 1986 to approximately 1% in 2006, whereas ICT increased from approximately 10% in 1986 to more than 80% in 1999 and fell in the following years due to a significant increase in the use of CSII.[6]

The majority of paediatric diabetes centres in Germany and Austria collaborated in the Diabetes Prospective Documentation (DPV) quality initiative. The data are locally generated, documented and transmitted in anonymous form to the University of Ulm for central evaluation and analysis.[7] By September 2008, records of 44,693 patients <18 years of age with type 1 diabetes were documented in this database. DPV started in 1994; by that time almost 50% of children were being treated with conventional insulin therapy. At the time of the latest survey, only a negligible number of the patients were still on CT, but use of MDI and CSII had increased significantly. From 1996 to 2007, the use of analogue insulins increased significantly in all age groups, not only in long-term therapy but also at the onset of diabetes[8] (see *Figures 1* and *2*).

Insulin Dosage

In the Western Australian investigation from 1992 until 2002, the average daily insulin dose rose significantly from 0.83Uxkg^{-1}xd^{-1} to 1.00Uxkg^{-1}xd^{-1}.[4] During the decade from 1995 to 2005, the insulin dosage increased from 0.85Uxkg^{-1}xd^{-1} in 1995 to 0.98Uxkg^{-1}xd^{-1} in 1998 and to 1.0 Uxkg^{-1}xd^{-1} in the patients of the Hvidoere group.[9] Insulin dosage was not related to metabolic control in paediatric diabetes centres in Northern Ireland,[10] whereas a significant relation between HbA_{1c} and insulin dosage was reported for young people in Scotland.[11] In the German/Austrian patients using rapid- or long-acting insulin analogues, the daily dosage was 5–11% higher than in patients of comparable age who used regular human insulin and neutral protamine Hagedorn (NPH) or zinc insulin. The daily insulin dose increases from early childhood (0.67IU/kg) to adolescence (0.93IU/kg) and decreases towards adulthood (0.7IU/kg). Girls needed the highest insulin dose at 12 years of age; boys at 14 years of age. Patients receiving CSII had a lower total insulin requirement[12] and lower pre-prandial insulin boli than children of the same age with MDI. Girls needed more insulin boli and higher insulin doses per 10–12g carbohydrates than boys.[13] Insulin requirements were significantly lower in the CSII groups compared with MDI in a meta-analysis of investigations on adolescent patients with type 1 diabetes.[14]

Metabolic Control

Dorchy et al. showed that good metabolic control can be achieved using a regime of two daily injections of an individualised mixture of rapid- and intermediate-acting insulins.[15] In Western Australian children, HbA_{1c} fell from 10.9 to 8.1% from 1992 to 2002; the improvement in metabolic control was associated with higher insulin dosage (0.83Uxkg^{-1}xd^{-1} in 1992 and 1.0Uxkg^{-1}xd^{-1} in 2002) and an increased rate of severe hypoglycaemia (7.8 per 100 patient-years in 1992 and 16.6 per 100 patient-years in 2002).[4] In Hannover, the rate of patients with a good HbA_{1c} level <7.5% increased from 22 to 55%, whereas the rate of bad metabolic control (HbA_{1c} >9%) has dropped from 35 to <10% within the last 20 years.[6] From 1996 to 2006, a significant decrease in HbA_{1c} was shown in the Danish Childhood Diabetes Registry. HbA_{1c} was affected by the number of blood glucose measurements, but tended to be higher in the children using analogue insulins compared with non-users.[5]

However, the Hvidoere group of 21 paediatric diabetes centres from 17 countries failed to show a significant fall in HbA_{1c} from 1995 to 2005, despite intensified insulin therapy and an increase in insulin dosage.[9] The HbA_{1c} levels remained basically unchanged (1995 8.6%, 1998 8.7%, 2005 8.6%). In 2005, the lowest HbA_{1c} was achieved in the group with free mixed insulin twice daily (7.9 versus 8.6% twice daily pre-mix, 8.2% thrice daily, 8.2% MDI and 8.1% CSII). The quality of metabolic control differed significantly between the centres; these differences persisted throughout the decade of observation.[9,16]

In Germany and Austria, intensifying diabetes management resulted in a slight but significant reduction by -0.2% in overall HbA_{1c} levels: treatment period 1994–1998 HbA_{1c} (DCCT standard) 8.1%, 1999–2002 8%, 2003–2006 7.9%, 2007–2008 7.9%. However, in the decade from 1994 to 2004, the patients with good metabolic control (HbA_{1c} <7.5%) increased from 25 to 45%, whereas the percentage of patients with bad metabolic control (HbA_{1c} >9%) fell from 40 to 15%.[17] HbA_{1c} increased with age (see *Figure 3*), diabetes duration and female gender (female 8.2% versus male 7.9%). HbA_{1c} levels were slightly lower during the summer and significantly higher in children with a migration background (8.3% versus 8% German/Austrian). In 2005, 87% of the patients were treated with ICT or CSII, 13% with CT. HbA_{1c} was lower in the CT cohort (8.2% versus 8.3% ICT/CSII), and the children receiving CT were on average 1.5 years younger and slimmer. HbA_{1c} also depends on the type of insulin used: patients using analogue insulins had higher HbA_{1c} levels (8.2% versus 8.1% for short-acting analogues versus regular insulin and 8.4% versus 8% for long-acting analogues versus NPH or zinc suspensions).[13]

HbA_{1c} was significantly lower in patients on CSII during the first year of the new regimen, but rose to the same level as patients on MDI after three years. Diabetic ketoacidosis was significant lower in CSII treatment compared with MDI.[18] HbA_{1c} was significantly reduced in adolescents receiving CSII in a meta-analysis of three randomised controlled trials.[14]

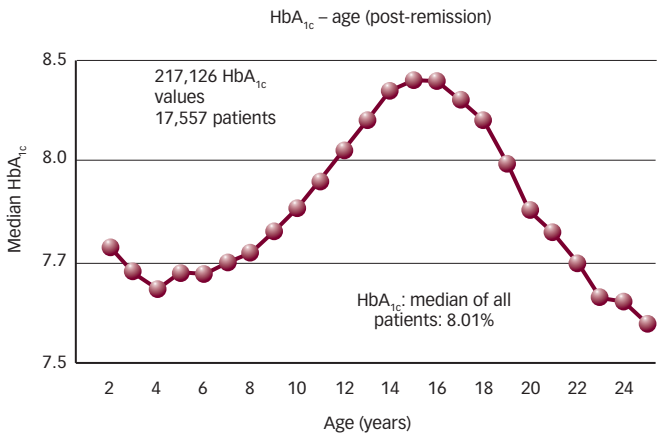
Hypoglycaemia

The rate of hypoglycaemia increased with the intensity of insulin therapy and improvement of metabolic control: in Western Australia from 7.8 to 16.6 per 100 patient-years (1992–2002).

According to a meta-analysis of three studies, the rate of severe hypoglycaemia in children with type 1 diabetes was low. Only three events were recorded for patients in the CSII groups, and six events in the MDI groups, taking all trials together.[14] However, using CGM hypoglycaemia prevalence was 10.1% and highest between 4:00 and 7:30am. Nocturnal hypoglycaemia was prolonged and mostly asymptomatic. The risk of nocturnal hypoglycaemia was associated with decreasing age, increased insulin dose, insulin regimen (with a two-injection regimen having a higher risk) and increased body mass index standard deviation score (BMI SDS).[19] In the centres of the Hvidoere group, the lowest rate of hypoglycaemia occurred in the centres with the best metabolic control and decreased with impairment of metabolic control; this trend was stable from 1995 to 1998.[16] The rate of hypoglycaemia seems to depend on the therapeutic regime: long-acting analogue insulins (glargine or detemir) do not seem to reduce the risk of severe hypoglycaemia compared with NPH insulin.[20]

A meta-analysis of 15 randomised trials showed that adolescent and adult patients with type 1 diabetes using CSII had non-significantly fewer minor hypoglycaemic episodes compared with MDI, whereas children on pump therapy had significantly more episodes.[21] By contrast, the severe hypoglycaemia rate was markedly reduced during CSII compared with MDI, particularly in older subjects. The greatest reduction in severe hypoglycaemia occurred in those subjects with the highest initial hypoglycaemia frequency.[22] In children from Germany and Austria, changing therapy from MDI to CSII was followed by a drop of hypoglycaemia from 25.1 to 17.9 per 100 patient-years.[18] After changing to short-acting analogue insulins, the reduction of severe hypoglycaemia with (6.1/100 patient-years) and without coma (6.2/100 patient-years) was significant. After changing to long-acting analogues the rate of severe hypoglycaemia without coma dropped significantly.[8] These data are supported by Pickup and Renard; in their investigation pump therapy reduced the average risk of severe hypoglycaemia in children with diabetes and adolescents by 66–79%.[20] In the Danish Childhood Diabetes Registry, there was a negative association between severe hypoglycaemic events and the HbA_{1c} level: in patients with HbA_{1c} of 8–10% the rate of severe hypoglycaemia increased from 7.4 to 10.7%, whereas there was a decrease from 12.2 to 7.9% in the patients with HbA_{1c} levels of 6–8%.[5]

Figure 3: Age Distribution of Average Glycated Haemoglobin Levels in Children with Type 1 Diabetes from Germany and Austria



Glycated haemoglobin (HbA_{1C}) levels are highest during puberty.

Bodyweight

Bodyweight is significantly increased in children and adolescents with type 1 diabetes in Germany and Austria. During puberty, girls with diabetes are particularly at risk of increased bodyweight (16.6%) and obesity (11.2%).[23] These findings do not seem to be specific for Germany and Austria, but are confirmed in several studies: in the Hvidoere group, the increase in the BMI of children with diabetes was much faster during adolescence compared with healthy children, especially in females.[24] In UK children with type 1 diabetes, BMI SDS was also significantly elevated: in Scotland BMI SDS was 0.61 for boys and 0.57 for girls[12] and in Northern Ireland BMI SDS was 0.85 for all paediatric patients.[11] Australian children with type 1 diabetes had elevated BMI scores compared with non-diabetic controls; the patients in the upper quartile for BMI SDS were younger and had higher HbA_{1c} levels and a shorter diabetes duration.[25]

There is a clear link between intensified insulin treatment and increased weight gain.[23] In patients using ICT or CSII, BMI SDS was higher (0.52 and 0.56, respectively) compared with the patients on CT (BMI SDS 0.42).[11] In Belgian children, BMI was significantly higher in girls and in adolescents on four daily injections compared with those on two injections.[15] An increase in insulin dosage and injections was associated with an increase in BMI in the children of the Hvidoere study.[16] BMI SDS was slightly, but significantly, higher in patients treated with either short- or long-acting insulin analogues compared with regular and NPH insulin.[8]

Although insulin dosage is lower using CSII, there was no significant effect on BMI in German/Austrian children after three years of

treatment: BMI SDS CSII 0.57 versus MDI 0.56.[18] However, children with type 1 diabetes with insulin resistance based on daily insulin dose per weight are not overweight to a greater extent than insulin-sensitive children with type 1 diabetes.[26]

Conclusion

During the last 15–20 years, diabetes therapy has been highly intensified in several ways. The use of new insulins or CSII did not lead to a significant fall in average HbA_{1c} levels, but the number of paediatric patients with good metabolic control seemed to increase.[6,17] CSII treatment only temporarily improved metabolic control for the first two years.[15] Intensified diabetes treatment (MDI and CSII) require higher insulin doses and lead to increased BMI.[23] However, modern treatment regimens, particularly CSII, have a positive effect on the rate of hypoglycaemia[18] and may be a useful tool in the treatment of nocturnal hypoglycaemia and the dawn and dusk phenomena.

Therefore, intensified therapy and a higher flexibility did not fulfil all expectations when the new treatment schemes were started. Other factors apart from the type of insulin, the therapy regimen or the way the insulin is applied seem to contribute to the success or failure of diabetes management. Such factors may be psychological or social: psychiatric disorders are associated with a higher rate of diabetic ketoacidosis,[27] poorer dietary self-care and being female were predictive of poorer glycaemic control,[28] and lower HbA_{1c} was associated with lower impact, fewer worries, greater satisfaction and better health perception.[29] Girls and patients from ethnic minorities had a significantly lower quality of life.[29] The maternal environment also plays a major role in diabetes management, particularly in the treatment of younger children. Financially stable mothers with coping resources felt more confident in managing their child's diabetes, and the mothers who were consistent in their diabetes management behaviours had children with better metabolic control.[30]

Although HbA_{1c} levels remain too high and do not reach the levels recommended by the DCCT or ISPAD, the intensification of diabetes management over the last 30 years has resulted in significantly reduced rates of retinopathy and nephropathy in children and adolescents with type 1 diabetes, as demonstrated in the Linköpping studies.[31] Therefore, we need to continue intensive diabetes treatment delivered by a multidisciplinary team that consists of intensive training of the patients and their family, individually tailored insulin treatment and the recognition of and response to possible psychological or social implications. ■

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