The Diabetes Control and Complications Trial: Implications for the Child and Adolescent

Position Paper Authors

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SUMMARY:
The Diabetes Control and Complications Trial (DCCT) confirmed that glycaemic control is a major contributor to the risk and progression of microvascular complications in insulin dependent diabetes. Approximately 18% of the DCCT patient group were adolescents and they showed a similar reduction in complication risk and a similar increased risk of adverse events (namely hypoglycaemia and weight gain with improvement of glycaemic control). However the adolescents had higher HbA1c levels and more severe and moderate hypoglycaemic episodes than adults, in both the conventional and intensive treatment groups. Children less than 13 years were not included in the DCCT. While there is accumulating evidence that prepubertal control also contributes to the development of diabetic

complications, a compromise for target glycaemia may be required to avoid recurrent hypoglycaemia. There are greater concerns about the consequences of hypoglycaemia in the younger child. The risk/benefit ratio of intensive insulin therapy needs to be judged on an individual basis for each patient. Not all adolescents will be suitable candidates for intensive insulin therapy; ideally, all should have access to a comprehensive management team of health professionals who are expert in their age group.

The highly publicised results of the Diabetes Control and Complications Trial (DCCT) released in 1993 confirmed conclusively that glycaemic control is a major contributor to the risk and progression of microvascular complications in insulin dependent diabetes. Specifically, near-normoglycaemia that was maintained for 3 to 9 years reduced both the risk and the progression of retinopathy, nephropathy and neuropathy by 34-76% (1). This was achieved with only a 1.8% difference in mean HbA1c between the DCCT conventional and intensive treatment groups. The conventional treatment group maintained a mean HbA1c of 9.0%; the intensive treatment group achieved and maintained a mean HbA1c of 7.2% (normal range 4.0 to 6.05%). Furthermore there was a direct and continuous relationship between diabetes control and the risk of complications. The Australian Diabetes Society has presented a position statement in relation to these findings (2). More recently separate analysis of the adolescent subgroup aged 13-18 yrs was released (3,4). This reported a similar reduction in complications risk in the adolescent age group as well as a similar risk of adverse events in those receiving intensive therapy. However there were differences between the adolescent and adult subjects in the DCCT in terms of their HbA1c levels and incidence of hypoglycaemia in both conventional and intensive treatment groups.

What relevance do these findings have to the child and adolescent with diabetes?
The DCCT study group had an age range of 13 - 39 years and was the first randomized trial of intensive therapy to include a substantial number of adolescents. The adolescent group, aged 13 - 18 years, comprised 19% and 16% of the conventional and intensive treatment primary prevention groups and 9% and 10% of the conventional and intensive treatment secondary prevention groups respectively. Contrary to initial concerns, they did not compromise the study design, and while those who were considered unlikely to comply were not included in randomisation, they were otherwise regarded as a representative group. The DCCT research group did note that the adolescents were the most challenging group to manage and required a disproportionate share of the support provided by the treatment team (4). Those adolescents who were randomised to the intensive therapy group were able to achieve and maintain a mean HbA1c of 8.1%. This improvement in metabolic control afforded a 53 - 70% reduction in the development and progression of retinopathy and microalbuminuria, compared with the conventional treatment group, which maintained a HbA1c of 9.8% (3,4). Those adolescents randomised to receive intensive therapy received insulin via multiple injection regimens of three or more injections per day or via an external pump, in conjunction with 24 hour support from a team including the diabetes nurse educator, dietitian, psychologist and diabetes specialist; this support was crucial to the therapeutic regimen.

For some adolescents a regimen of four injections per day works well; for others it may lead to insulin omission particularly at lunch when school activities take precedence. A three times daily regimen may be more feasible and effective in improving control in this age group (5). However if these regimens are not accompanied by regular blood testing and adequate management support, they are unlikely to succeed. For those adolescents who achieve HbA1c levels of less than 8 % on a twice daily regimen, intensive insulin management is unlikely to offer further advantages other than perhaps convenience of lifestyle.

Adverse Effects of Strict Glycaemic Control

Hypoglycaemia:
The DCCT indicated an inverse relationship between metabolic control and the risk of moderate and severe hypoglycaemia - overall the intensive therapy group had a three-fold increased risk compared to the conventional therapy group. Specifically, in the intensive therapy group there were 62 episodes per 100 patient years of hypoglycaemia that required assistance from another individual and 16 episodes per 100 patient years of hypoglycaemic coma or seizures. Sub-analysis of the adolescent group showed significantly higher rates of moderate and severe hypoglycaemia with both intensive and conventional therapy. However the increase in the incidence of hypoglycaemia with intensive therapy did not differ from the adult cohort in the DCCT. Adolescents receiving intensive therapy had 86 episodes per 100 patient years of hypoglycaemia that required assistance from another individual and 27 episodes per 100 years of hypoglycaemic coma or seizures; adolescents receiving conventional therapy had 28 and 10 episodes per 100 patient years respectively. The higher incidence of moderate and severe hypoglycaemia occurred despite higher HbA1c levels in the adolescents . This may relate to the larger insulin doses required during adolescence and more irregular diet and exercise. Despite the increased risk of hypoglycaemia, the risk/benefit ratio for the majority of patients was judged to be favourable.

It should be noted that the DCCT did not study children younger than 13 years of age and caution needs to be used in applying the recommendations of the DCCT to the pre-teenage group. While no differences in cognitive function were found between the patients receiving intensive therapy or conventional therapy at follow up over 3 to 9 years, these results cannot be extended to the young child. Rapid growth and development of the brain occurs from birth to 3 years, continuing to 7 years of age. There are thus greater concerns about the consequences of hypoglycaemia in the young as it is more likely that hypoglycaemia occurring early in life, has long-term adverse effects (6,7). Cognitive deficits, particularly in visuo-spatial tasks and lower I.Q. scores have been reported in children who develop diabetes before 5 years of age as compared to their siblings. In children who develop diabetes after 5 years, this impairment has not been found (8). Both inadequate metabolic control and the sensitivity of the young brain to hypoglycaemia may account for these findings (8).

As well as increased concerns about the sequelae of severe hypoglycaemia in the younger child, this age group is at greater risk of significant hypoglycaemia because of their unpredictable activity and eating patterns. In addition, as children's responses to hypoglycaemia are different, studies examining the counter regulatory and symptomatic responses to low glucose levels in adults cannot be extrapolated to the young patient. For example, normal children experience symptoms of hypoglycaemia and mount counter regulatory hormonal responses at higher glucose levels than adults. In addition, there is an independent effect of metabolic control in altering counter regulatory responses: children with poor glycaemic control can experience symptoms and hormonal responses at higher glucose levels than non-diabetic children (9). Whether thresholds for neuroglycopaenia also vary in a similar way in children is not known. Thus, although the effects of hypoglycaemia and strict metabolic control on counter regulatory and symptomatic responses to hypoglycaemia have been studied extensively in adults, such studies have not been performed in pre-pubertal children.

A further relevant issue is compliance. Fear of hypoglycaemia is real to the parent of the young child and often interferes with any attempts to improve control. Similarly, for the adolescent, an unexpected hypoglycaemic episode is an embarrassment that he or she may seek to avoid even at the expense of hyperglycaemia and poorer glycaemic control.

Weight gain:

The second major adverse effect of intensive treatment in both the adolescent and adult groups of the DCCT was weight gain. The intensive therapy group showed a significant weight increase of approximately 4 kilograms over 5 years. The risk of becoming overweight, defined as greater than 120% of ideal body weight, was close to twofold greater in the intensively treated adolescent group. This weight increase may have adverse effects on compliance for the adolescent given the anxieties about weight and body image at this age, particularly in females.

How much does pre-pubertal control contribute to the development of long-term complications?

This question has not been answered conclusively. The hypothesis that control is less important prior to puberty arose because prepubertal duration has appeared to contribute little to the later development of nephropathy or retinopathy in epidemiological studies (10). However more recent literature, including Australian data, suggests that : (i) metabolic control from diagnosis is an important risk factor for early signs of nephropathy (11,12) and (ii) prepubertal duration contributes to the onset of retinopathy (13,14) in the adolescent and young adult years. Prepubertal children may occasionally have early changes of background retinopathy detected on fundal photography or intermittent microalbuminuria; however in general, evidence of early complications is not seen before the onset of puberty.

Recommendations:

The findings of the DCCT reinforce the recommendation that all children and adolescents with diabetes should have access to a comprehensive management team expert in their age group. They and their families should be appropriately advised of the DCCT findings. Although not all patients will be able to achieve near normoglycaemia or be suitable candidates for intensive insulin therapy, all should have access to intensive management.

An important and encouraging message of the DCCT is that any improvement in metabolic control is beneficial in reducing risk of complications. Therefore the patient with a glycosylated hemoglobin of 11%, for example, will still benefit from improving control to a level of 9%.

Pre-schoolers:

One of the aims of diabetes management in this age group is the avoidance of hypoglycaemia. Preschoolers often have more erratic blood glucose patterns and therefore a compromise for target glycaemia may need to be reached. Management that aims for normoglycaemia is not indicated in this age group. However occasionally more than 2 injections a day are required to prevent hypoglycaemia or extreme lability of blood glucose control.

Pre-pubertal school age children:

Frequently good control (HbA1c of less than 8%) can be achieved with a twice daily insulin regimen in this age group. Diabetes management should aim for as optimal control as possible; however recurrent severe hypoglycaemia must be avoided. Successful medical, developmental and behavioural management at this age is likely to be important in providing a basis for better compliance and reduced risk of complications during adolescence.

Adolescents:

Adolescents in the intensive treatment arm of the DCCT were generally not able to achieve normoglycaemia but they achieved and maintained a significant improvement in metabolic control. The risk/benefit ratio was favourable for this treatment and the support of a highly motivated professional team was crucial for its success.

Therefore adolescents who are unable to achieve HbA1c levels of less than 8% with conventional management should be offered intensive therapy. They are likely to require considerable support and motivation in order to improve their control. It may be emphasised that any improvement in control will have long term benefits in reducing the risk of complications. This will encourage those patients who are not able to comply with intensive regimens and achieve near normoglycaemia. It is relevant that it appeared difficult to predict which adolescents were able to comply and benefit from intensive treatment in the DCCT (personal communication Denis Daneman, Toronto).

To translate the findings of the DCCT to the real world of paediatric diabetes, the risk-benefit ratio of intensive insulin therapy will need to be judged on an individual basis for each patient. The limitations of current technology and the normal physiological and psychological changes accompanying growth and development may combine to prevent ideal metabolic control being achieved. Therefore the child and his or her family should not be made to feel inadequate if intensive insulin therapy is not successful or not appropriate.

Even with intensive management and the achievement of near normoglycaemia some patients will still develop diabetes complications. More recent data provides justification to begin annual screening for complications from the onset of puberty, or in the case of the child presenting in the preschool years, from five years after diagnosis. This includes an ophthalmological examination and measurement of urinary albumin excretion, resting blood pressure and blood lipids. Efforts to improve glycaemic control should not detract from specific measures to prevent and treat complications such as hypertension and lipid abnormalities, nor from strategies for anti smoking education in adolescents with diabetes.

Practical Response to the DCCT:

Australian paediatric diabetes units have accepted the challenge presented by the findings of the DCCT and have begun programmes that aim to make optimal control achievable for more adolescents. The growing realisation that prepubertal control is also important is leading to strategies to improve control in these children. Practical initiatives include expansion of comprehensive outreach services, in conjunction with general practitioners and paediatricians, involvement of paediatric allied health professionals in ambulatory care, and intensive therapy programmes for adolescents. These programmes will only be successful with a team approach including the educator, dietitian, psychologist and diabetes specialist, all expert in the care of children and adolescents with diabetes It is inevitable that initiatives to improve glycaemic control will require increased resources to expand and support such teams. However there is now ample proof that improved metabolic control in our patients will ultimately reduce the long term human and financial costs of diabetes complications.

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