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The Diabetes Control and Complications Trial: Implications for Children and Adolescents

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THE DIABETES CONTROL AND COMPLICATIONS TRIAL: IMPLICATIONS FOR CHILDREN AND ADOLESCENTS

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 maintained for three to nine 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 levels of glycosylated haemoglobin (HbA_{1c}) between the conventional and intensive treatment groups. The conventional treatment group maintained a mean HbA_{1c} level of 7.2%. 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, a separate analysis of the adolescent sub-group aged 13-18 years was released.^{3,4} This reported a similar reduction in complications risk in adolescents as well as a similar risk of adverse events in those receiving intensive therapy. However, there were differences between adolescents and adults in the DCCT in terms of their HbA_{1c} levels, and incidence of hypoglycaemia in both conventional and intensive treatment groups.

WHAT RELEVANCE DO THESE FINDINGS HAVE TO CHILDREN AND ADOLESCENTS WITH DIABETES?

The DCCT study group ranged in ages from 13 to 39 years. It was the first randomised trial of intensive therapy to include a substantial number of adolescents. Adolescents 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, the adolescent age group did not compromise the study design and, while those who were considered unlikely to comply were not included in the 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 HbA_{1c} level 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 HbA_{1c} level of 9.8%.^{3,4}

The adolescents who were 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 HbA_{1C} levels under 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 a relationship between improved glycaemic control and the risk of moderate and severe hypoglycaemia overall, the intensive therapy group had a threefold increased risk compared with 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.

Subanalysis of the adolescent age 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 patient 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 HbA_{1C} levels in the adolescents. This may relate to the large insulin doses required during adolescence and their more irregular diet and exercise. Despite the increased risk of hypoglycaemia, the risk-benefit ratio for most patients was judged to be favourable.

It should be noted that the DCCT did not study children under 13 years of age and caution needs to be used in applying the recommendations of the DCCT to the pre-adolescent age group. While no differences in cognitive function were found between the patients receiving intensive therapy or conventional therapy at follow-up over three to nine years, these results cannot be extended to the young child. Rapid growth and development of the brain occur for three years after birth, continuing until the child is seven years of age. Thus, there are greater concerns about the consequences of hypoglycaemia in young children, 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 IQ scores, have been reported in children who develop diabetes before five years of age as compared with their siblings. In children who develop diabetes after five years of age, 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

Younger children are also 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, children generally experience symptoms of hypoglycaemia, and mount counter-regulatory hormonal responses, at higher glucose levels than adults. 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 neuroglycopenia also vary in a similar way 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 done in prepubertal 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

Adolescent and adult members of the intensive therapy group showed an average significant weight increase of about 4kg over five years. The risk of becoming overweight defined as over 120% of ideal body weight, was close to twofold greater in the intensively treated adolescents. This weight increase may have adverse effects on compliance in adolescents given the anxieties about weight and body image at this age, particularly in girls.

HOW MUCH DOES PREPUBERTAL CONTROL CONTRIBUTE TO THE DEVELOPMENT OF LONG TERM COMPLICATIONS?

This question has not been answered conclusively. The hypothesis that control is less important before puberty arose because prepubertal duration of diabetes has appeared to contribute little to the later development of nephropathy or retinopathy in epidemiological studies.¹⁰ However, more recent literature, including Australian data, suggest that glycaemic control from diagnosis is an important risk factor for early signs of nephropathy,^{11,12} and prepubertal duration contributes to the onset of retinopathy in the adolescent and young adult.^{13,14} Prepubertal children may occasionally have early changes of background retinopathy detected on fundal photography, or intermittent microalbuminuria, but generally evidence of 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 respective age group. Patients and their families should appropriately be 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, reducing the risk of complications. Therefore the patient with HbA_{1C} level of 11.0%, for example, will still benefit from improving control to a level of 9.0%.

PRESCHOOLERS

One of the aims of diabetes management in this age group is to avoid 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 two injections per day are required to prevent hypoglycaemia, or for extreme lability of blood glucose level.

PREPUBERTAL SCHOOL-AGE CHILDREN

Frequently, good control (HbA_{1C} levels under 8.0%) can be achieved in this age group with a twice-daily insulin regimen. 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. This 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 HbA_{1C} levels under 8% with conventional management should be offered intensive therapy. They are likely to require considerable support and motivation to improve their control. It should 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 was difficult to predict which adolescents in the DCCT were able to comply and benefit from intensive treatment (Denis Daneman, the Hospital for Sick Children, Toronto, personal communication).

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 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 from being

achieved. Therefore, the child and his or her family should not feel inadequate if intensive insulin therapy is unsuccessful or inappropriate.

Even with intensive management and the achievement of near normoglycaemia, some patients will still develop diabetes complications. More recent data provide justification to begin annual screening for complications from the onset of puberty or, in the case of children presenting in the preschool years, from five years after diagnosis. This includes an ophthalmological examination and measurement of levels 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 programs that aim to make optimal control achievable for more adolescents. The growing realisation that prepubertal control is also important is leading the 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 programs for adolescents. These programs will only be successful with a team approach that includes 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 patients will ultimately reduce the long term human and financial costs of diabetes complications.

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