Diabetes—trials, tribulations and pay-off of tight control

In June 1993 the results of the Diabetes Control and Complications Trial (DCCT) were made public. It showed that intensive insulin therapy, designed to produce ‘near-normal’ blood glucose levels, resulted in a spectacular reduction in long-term risks of all microvascular complications of insulin dependent diabetes mellitus (IDDM) when compared with ‘conventional’ insulin therapy. On 6 April 1995 a well-attended conference, organised by Professor Stephanie A Amiel, was held at the Royal College of Physicians to discuss the issues arising from the DCCT, the practicalities of implementing change in diabetes care in the light of its results, the benefits and potential risk of such intensive therapy (tight control), the implications of the DCCT findings to patient groups not included in it and other ways of minimising the long-term complications of diabetes.

The physical, social and economic consequences of chronic diabetes mellitus were described by Professor Harry Keen (London). He reminded the audience first of the dramatic changes in health expectancy of those diagnosed with diabetes over the last 50 years, with the medical profession now having the power to influence the natural course of the disease. Despite this, he said, the WHO Multinational Study reported a standardised mortality rate (SMR) in the 1970s of 1.5–4 (national variations) for patients with non-insulin dependent diabetes mellitus (NIDDM) and 2–8 for patients with IDDM. The largest excess mortality risk in diabetes arises from coronary heart disease (CHD). Data from the Multiple Risk Factor Internation Trial (MRFIT) study indicate that diabetes adds to the ascending additive risks of CHD from hypertension, smoking and hypercholesterolaemia. These patients are also at greater risk of developing retinopathy, having a leg amputation (50% of all non-traumatic amputations in the UK are in diabetic patients) and suffering renal complications. However, present screening strategies of at-risk groups (e.g. diabetes patients with microalbuminuria), if efficiently implemented and acted upon, can significantly reduce the burdens of these problems. Professor Keen quoted the potential lifetime costs of diabetes in terms of medical care: £247,000 per patient or $91.8 billion per annum total USA cost (American Diabetes Association estimate 1992), and the potential for reducing this if complications (responsible for 70% of the total) were more efficiently prevented.

Glycaemic control and the DCCT was addressed by Professor William Tamborlane (Yale University School of Medicine, USA) who was involved in the regulation of the DCCT. He told the conference of the design and running of that study and summarised its results. The trial was designed to test the hypothesis that ‘treatments that result in a reduction of hyperglycaemia will prevent or delay the long-term complications of diabetes mellitus’, an attempt to prove ‘The Glucose Hypothesis’ first postulated in the 1930s. Despite its simple nature, a robust test of the hypothesis could not be conducted until reliable measures of control (such as HbA1c) and methods of insulin delivery (pumps or multiple injection regimens) and monitoring (home blood glucose monitoring) of ‘near normal’ glycaemia in IDDM patients were available. Recruitment of 13–39 year old IDDM patients began in 1981. Patients were placed into either a primary (no evidence of retinopathy) or secondary (mild to moderate background retinopathy already present) group. The aim of the trial for both groups was to determine the effects of intensive therapy (allocated randomly to 50% of each group) and ‘near-normal’ blood glucose on appearance and/or progression of retinopathy (chosen as the primary outcome measure because it is the first detectable complication and is easily quantified non-invasively). Of 7,000 patients screened, 1,441 were recruited and 1,422 completed the follow-up over nine years. Those on conventional therapy achieved a steady HbA1c of 9% (mean) compared with 7% for those on intensive therapy. Risk of new retinopathy was reduced by 76% on intensified therapy (IRx) and risk of progression by 50% in the secondary group. Similar reductions were seen in patients on IRx for rates of new microalbuminuria, proteinuria and neuropathy. He concluded that, despite the increased risks of hypoglycaemia with the intensified regimens and the increased costs of implementation (approximately twice those of conventional therapy), near-normoglycaemia should be the target for all patients with IDDM, as it reduces microvascular complication rates and therefore becomes money-saving after 20 years of diabetes.

The application of the DCCT in practice led Professor John Ward (Sheffield) to declare that ‘the road to good intentions is paved with hell’. He stressed that although important, the results from the DCCT should not overshadow other aspects of diabetes care, and its implementation should form an important part of the overall care package. He pointed out the particular features of the study sample of DCCT patients compared with the total IDDM population, their extreme motivation, the degree of professional (medical, nursing and psychological) support given during the study and, most importantly, the time spent by all involved in achieving the goals of the study. He felt this would be impossible to translate into everyday practice without a considerable increase of staff. In ‘straw polls’ of UK diabetic clinics about 25% of
patients fall into a group of ‘terrible’ diabetic control, and he felt it may be more useful to target strategies, time and personnel at this group to help them come to terms with their diabetes. Organisation of the service is most important, with appropriate registers, information storage, recall of patients and referral action taken when problems arise. The positive points arising from the DCCT, Professor Ward suggested, (apart from the clinical opportunities) were that in this time of ‘political games’ over medicine, it demonstrated the complexity of good diabetes care and the need for collaborative multidisciplinary care. These points should be made to local managers, using the DCCT results as a ‘stick’ for asking for adequate resources.

The patients’ view was given by Mrs Barbara Elster who has lived with diabetes (as the carer of a son with IDDM) for 25 years. She gave an impassioned and proudly personal view of the DCCT implications and spoke from the heart of the ‘emotional catch-22’ presented by the DCCT for diabetic patients and their families. She stressed that the medical profession need to empower their patients as equal members of the care team with simple, clear, non-jargonised and consistent information if individuals are to be confident of their ability to control the results of their home blood glucose monitoring. She felt that the way in which the DCCT goals are approached is of great importance to minimise the guilt felt by patients who do not fully achieve them: in particular, using positive statements such as ‘aiming for better control’ rather than terms such as ‘tighter control’ or ‘more intensive treatment’, and setting individualised targets would be helpful. She applauded the message that excessively low blood sugar levels are as undesirable as high levels, which she felt needs to be stressed. The DCCT should not be used as a ‘stick with which to bully patients’ and she begged the medical profession to avoid the trap of running diabetic clinics solely on biochemical results. In her words, ‘to begin the process of true education needs care and understanding: time must be given to all who need it’. Her recipe for the successful implementation of these goals is ‘the three Cs . . . non-Confrontation, Communication and Compromise’.

Hypoglycaemia is the most publicised hazard of insulin therapy within the DCCT. In a session titled ‘the problems of tight control’, this issue was discussed, both in terms of its longer-term risks (particularly relevant given that the aims of DCCT were to reduce long-term risks) and in how to achieve better metabolic control with minimum risk of hypoglycaemia.

Dr Brian Frier (Edinburgh) quoted survey results that reveal fear of hypoglycaemia to be as great as the fear of blindness and renal failure amongst IDDM patients, and quoted rates of severe hypoglycaemia nationally of about 1.1-1.6 episodes/patient/year. He reminded the audience that even the increased rates of hypoglycaemia seen in the DCCT may not represent the true extent of risk, as patients at high risk for hypoglycaemia were excluded from entering the trial. He gave examples of the neurological/psychological presentation of acute hypoglycaemia. Then, making a case for the existence of chronic adverse cerebral effects from recurrent severe hypoglycaemia, he drew an analogy between it and other repetitive forms of acute cerebral insult such as alcohol, boxing and hypoxia, all of which have been proven to cause long-term intellectual deterioration. He reviewed the data available regarding long-term effects of recurrent hypoglycaemia and drew the following conclusions:

1 The immature brain (in patients < 5 years old) is vulnerable to hypoglycaemia; retrospective studies having shown impaired intellectual performance in children with a past history of recurrent severe hypoglycaemia.
2 The evidence for a long-term effect in adults is equivocal. Retrospective studies have associated modest declines in performance IQ (measured using the Wechsler Adult Intelligence Scale and subtracting concurrent scores from tests of premorbid IQ) with recurrent hypoglycaemia, whilst prospective studies (eg the DCCT and Stockholm Diabetes Intervention Study) although not specifically designed to answer such questions, have not supported the retrospective data.
3 Caution should be taken when selecting patients for intensified therapy if problems related to hypoglycaemia are to be minimised; eg patients who have hypoglycaemia without warning symptoms are at six times the risk of severe hypoglycaemia as those with normal warning symptoms.

‘Tight control without tears’ was the title of Professor Stephanie Amiel’s (London) review of implementing tighter glycaemic control whilst minimising the risks of hypoglycaemia. Risk factors for problem-causing hypoglycaemia include age, duration of disease, previous severe hypoglycaemia, nocturnal hypoglycaemia and frequent episodes of ‘mild’ hypoglycaemia. She reviewed the physiological process of hormonal counterregulation and its characteristic symptoms, and described the known defects seen in patients who suffer from hypoglycaemia without warning symptoms (delayed and diminished counterregulatory hormone responses which result in a reversal of the normal hierarchy of symptoms preceding any cognitive deficit, such that by the time symptoms are generated, the individual is unable to make a rational response). The single most notable factor in causing these counterregulatory deficiencies is previous episodes of hypoglycaemia. Indeed, even a single episode of very mild hypoglycaemia (3 mmol/l) in non-diabetic subjects can induce counterregulatory deficiencies in a subsequent formal hypoglycaemic challenge and recurrent preceeding mild hypoglycaemia may be seen in all the patients at risk for severe hypoglycaemia and hypoglycaemia unaware-
ness. Professor Amiel quoted data from a study published in the *Lancet* last year showing that complete avoidance of all blood sugar levels below 3.5 mmol/l in the daily life of IDDM patients with problematic hypoglycaemia unawareness will restore symptoms and counterregulatory hormone responses. Over a period of three months careful individualised attention was given to patients with problematic hypoglycaemia and proven counterregulatory deficiencies. Particular attention was given to taking regular snacks for vigorous exercise (usually requiring an extra snack or intermediate insulin dose reduction the evening after as well as during the exercise!) as well as education regarding the actions of single insulin doses, alcohol and other daily activities on blood sugar levels. Successful avoidance of hypoglycaemia led in all cases to a return both of hypoglycaemia symptoms and counterregulatory hormone responses to controlled hypoglycaemic challenge such that the normal hierarchy of symptoms was restored. In none of these patients was there a significant deterioration of overall glycaemic control and in some there was even an improvement. The message from this study is that intensive insulin therapy and tight glycaemic control need not be associated with problem-causing hypoglycaemia if we can tailor therapy individually to patients, and remember that blood sugars below 4 mmol/l are no more desirable than those above 10 mmol/l.

‘Strict metabolic control in paediatrics’ by Dr Stephen Greene (Dundee) dealt with a special case for tight control. Patients who develop IDDM during childhood will, by definition, be those who have the longest duration of disease over their lifetimes and who are therefore most at risk from the long-term complications. At any one time there are likely to be about 12,000 patients under the age of 16 in the UK who have diabetes; 25% of these will have developed it before their fifth birthday. Poor control results in social and educational disruption, adverse effects on physical growth (± obesity) and the biophysical changes of microvascular disease. He challenged the old view that diabetes before puberty was ‘for free’ in terms of complications and quoted several examples where markers of early vascular disease have been found to be present in pre-pubertal children. Puberty accelerates the rate of progression of complications, and therefore ‘strict glycaemic control is a mandatory objective for children with diabetes’. Dr Greene was, however, careful to point out the risks associated with tightening glycaemic control in children. Severe hypoglycaemia occurs annually in 30% of children with diabetes on ‘conventional treatment’ and is recurrent in 20%. Whilst the long-term effects of hypoglycaemia remain the subject of debate, it is certain that behaviour and cognition are disrupted during hypoglycaemia, which can therefore be detrimental to schooling. He was cautious about applying the DCCT data regarding frequency of hypoglycaemia with IRx to children as data do not exist for this group, pointing out that, from an anecdotal clinical point of view, hypoglycaemia in children is as much associated with poor control and wide fluctuations of blood sugar levels as with tight control. With regard to the possibility of achieving the DCCT targets in children, he quoted the Scandinavian experience of tight glycaemic control in children, which, if achieved, mirrored the results of the DCCT but with potential problems with very high insulin doses in some and obesity in others. In summary, he suggested that the service for children in the UK needs to be dedicated, labour-intensive and multi-faceted in order to achieve better control and that IRx is only a part of the goal.

The implications to NIDDM and the UK prospective diabetes study (UKPDS) were addressed by Professor Robert Turner (Oxford). He started by questioning the relevance of the DCCT findings for NIDDM patients because of the shift in morbidity and mortality from microvascular to the macrovascular complications such as coronary heart disease and the possibility that the glycaemic threshold for microvascular risk may be higher than for macrovascular disease. He reminded the audience of the UGDP study of 1971 that led to the withdrawal of phenformin because of a 26:2 ratio of mortality in subjects taking it, and of a similar but less damning ratio for tolbutamide in the same trial. These instances he said made it imperative to question whether tight glycaemic control conferred long-term benefit specifically in NIDDM and were the reasons the UKPDS was designed. By the time of its projected completion in 1997, the UKPDS will have run for 20 years and recruited over 5,000 patients. Three basic treatment regimens (aiming for fasting plasma glucose levels less than 6 mmol/l) will have been compared against a ‘conventional’ dietary therapy where intervention is only made if fasting plasma glucose levels rise above 15 mmol/l. The aims of the study are therefore to determine if (a) tight control will benefit patients with NIDDM and (b) treatment with either sulphonylureas, metformin or insulin has specific benefit. Although the treatment codes have not yet been broken, several pieces of important information are already available from this study. Unlike the DCCT, it has been impossible in this group to maintain stable glycaemic control over the period of the study: both the ‘conventional’ and intervention groups (on all three options) have shown a slow but steady rise in HbA1c over the years (although a constant difference between the two groups of about 2 mmol/l has been maintained). Both diet and treatment with sulphonylureas or insulin has resulted in weight gain, whilst metformin treatment has resulted in stable weight with glucose control comparable with the other treatment groups and fewer hypoglycaemic episodes. Up to seven years of follow-up, almost all fatal events in both control and treatment groups have been macrovascular (5.5% of study group); 30% of the population have ECG evidence of CHD and 50% have...
hypertension. It remains to be seen in this study if the results of intervention to lower the fasting plasma glucose levels will affect morbidity and mortality from NIDD.

The final session of the meeting broadened the debate into prevention of complications by looking at ‘other opportunities for morbidity prevention’.

Dr David Dunger (Oxford) gave a stimulating talk on the physiological role of growth factors, in particular IGF-1, in glucose homeostasis and diabetic complications. He described the homology of both structure and function between insulin and IGF-1 and challenged the traditional ‘separate roles’ view of the two hormones, suggesting that their roles in glucose uptake, lipolysis, glycogen synthesis and protein catabolism are complementary. He further described the feedback mechanisms for the hepatic production of IGF-1 in response to insulin and the role of IGF-1 binding proteins (to which most of the circulating IGF-1 is bound and is therefore inactive). In normal puberty, both circulating insulin and IGF-1 increase. In IDDM, insulin replacement is inadequate to regulate the growth hormone (GH)–IGF-1 axis normally, partly because of risks of hypoglycaemia related to the non-physiological insulin administration. This results in measurably low levels of IGF-1 and IGF binding protein 3, whilst GH and IGF binding protein 1 are raised in IDDM. These abnormalities are most marked during puberty and adolescence although they persist throughout adult life. He suggested that lack of hepatic IGF-1 may result in oversecretion of GH and high local tissue IGF production, eg in the kidneys, which may be directly related to diabetic renal disease. Excess GH may itself also have a role in complications. IGF-1 replacement (as daily subcutaneous injections) in diabetic adolescents has had the result of reducing overnight insulin requirements, reducing ketone and GH levels and improving glycaemic control. Its longer-term role in complication prevention (both microvascular and weight-related) is yet to be proven in longer, blinded clinical studies, but the work indicates the important role of scientific research in clinical diabetic medicine.

Professor Giancarlo Viberti (London) took the role of ‘devil’s advocate’ to the DCCT by suggesting that over its course, even in the intensively treated group at nine years, there was an incidence of 25% of new microalbuminuria (a surrogate end-point for renal disease, which he chose as his example because of its high social and economic cost to the patient). This spoke clearly of factors other than glycaemic control being at least as important in the aetiology of microvascular complications. He referred to prospective studies (eg the Microalbuminuria Collaborative Study) describing predictors of developing microalbuminuria: blood pressure, starting level of albumin excretion, glycaemic control and smoking. He then tackled the prevention of renal disease in diabetes at primary, secondary and tertiary levels. Primary prevention he described as the prevention of development of microalbuminuria in people with diabetes. Although glycaemic control in the DCCT reduced the appearance of microalbuminuria, much more impressive primary prevention has been achieved in both animal and human studies by the use of ACE inhibitors, whose effects appear to be over and above those to be expected from blood pressure control alone, and are likely to be related to their effects on renal haemodynamics. He defined secondary prevention as stopping progression of microalbuminuria to overt nephropathy. In both the DCCT and other prospective studies, improved glycaemic control has had no influence in slowing progression after onset of microalbuminuria, whereas both blood pressure control and specifically ACEI inhibition with captopril has been shown to slow progression. Prevention of end-stage renal failure requiring renal replacement therapy he defined as tertiary prevention. Once again, glycaemic control seems to have no role in this area, whereas blood pressure control, low animal protein diets and again ACEI inhibition, along with general medical attention to prevention of urinary tract infection etc, have been shown to be beneficial. Whilst data from the DCCT regarding glycaemic control and long-term complications are clearly encouraging, it must not prevent studies on other measures of prevention that have been proven to be at least as effective and may be more easily achievable within the confines of our present system.

Summary

The meeting provided a comprehensive discussion forum for the pros and cons of the goals of tight glycaemic control, where practical issues were given highest priority. The costs of providing the levels of care required to implement intensive therapy safely are clearly high, both financially and in terms of patient and professional time. Equally, the implementation of this service would (theoretically) pay for itself after 20 years in the reduced rates of complications if the DCCT findings can be extrapolated to the diabetic population as a whole. At both national and local levels we should therefore campaign for the resources to achieve these goals in our IDDM patients and alter our practice to offer the individualised care and attention required to achieve them. This should not, however, deflect us from the attention to other risk factors for micro- and macrovascular disease which so often accompany diabetes and which are modifiable if detected in organised screening programmes. The goals of the St Vincents Declaration are realistic and achievable today for all our patients, whilst at present it is only IDDM patients who have been proven to benefit from very strict glycaemic control. The results of the UKPDS are awaited with great interest.