Leading Article

How to achieve optimal diabetic control in patients with insulin-dependent diabetes

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Introduction

Whether good diabetic control prevents or delays the onset of diabetic complications has been debated since the first clinical use of insulin in 1922. The recently published Diabetes Control and Complications Trial (DCCT)¹ shows that it does. Patients with insulin-dependent diabetes (IDDM) who had no complications (primary prevention group, $n = 726$) or minor retinopathy (secondary prevention group, $n = 715$) were randomized to receive 'intensified' or 'conventional' insulin therapy. The trial was halted after a mean of 6.5 years when it was clearly shown that intensive therapy (resulting in a mean blood glucose of 8.6 mmol/l versus 12.8 mmol/l in the conventional group) reduced the risk of development and progression of diabetic retinopathy by 54–76%, microalbuminuria by 39–54% and neuropathy by 60%. The results are similar to those of smaller but equally persuasive studies such as the Stockholm Diabetes Intervention Study² and provide conclusive evidence of a link between high blood glucose concentrations and microvascular complications (retinopathy, nephropathy and neuropathy).

As a result of the DCCT, the American and British Diabetic Associations recommend that a primary treatment objective in IDDM should be blood glucose control at least equal to that achieved in the intensively treated group of the DCCT.^{3,4} How this is to be achieved in ordinary practice is the question confronting diabetologists.

How was near-normal blood glucose control achieved in the DCCT?

The DCCT was designed to answer the scientific question 'Does near-normoglycaemia prevent or delay diabetic complications?' Previous work with captive diabetic dogs⁵ had shown that it did and a

major problem for the DCCT investigators was how to recruit human diabetics who would be as compliant as the dogs. It was solved by recruiting self-selected and highly motivated volunteers through newspaper advertisements. The success of this approach can be judged from the fact that 99% of patients completed the study and more than 95% of all scheduled examinations were done. While the patients are to be applauded for their adherence to the protocol, no one would suggest that they are typical of 13–39 year old insulin-dependent diabetics.

The goals of intensive therapy were preprandial blood glucose concentrations between 3.9 and 6.7 mmol/l, postprandial concentrations below 10 mmol/l, a weekly 3.00 a.m. blood glucose greater than 3.6 mmol/l and a normal glycated haemoglobin (GHb) concentration. The tools were four daily injections or continuous subcutaneous insulin infusion (CSII) with at least four self-monitored blood glucose measurements every day and GHb measurement every month. Intensive therapy patients met a team of doctor, diabetes specialist nurse, dietitian and psychologist monthly and were telephoned every week to discuss insulin dose adjustment. In contrast, the conventionally treated group took one or two injections of insulin per day and were seen every 3 months. They were not given specific glycaemic targets and both they and the team looking after them were masked to GHb values unless these became excessively high (over 13.11% where the upper limit of the normal range was 6.05%).

These differences in management resulted in a consistent difference in mean blood glucose concentrations of approximately 4.2 mmol/l and of GHb of about 2% for up to 10 years. It is important to emphasize that glycaemic control was not normal; nearly half the patients on intensive therapy had a normal GHb at least once during the study but less than 5% had a normal value throughout. The 'down' side of intensive therapy was a three-fold increase in the frequency of severe hypo-

glycaemia and an average weight gain of 4.6 kg compared to conventional therapy.

How are these results to be translated into practice in the average diabetic clinic? The Belgian diabetologist, Jean Pirart, suggested that in the best of all possible worlds the diabetic patient would be 'intelligent, educated, disciplined, persevering and perfectly acquainted with all details of his treatment . . . he (would) lead a normal life without sudden changes of routine . . . (and) . . . during thirty or forty years, our model patient attended by model doctors will never have been hospitalised because of diabetes'. This is, of course, pie in the sky, as is the idea that every insulin-dependent diabetic will be (or needs to be) telephoned every week and will (or needs to) attend the hospital every month for separate consultations with a physician, diabetes nurse specialist, dietitian and psychologist. It is also self-evident that perfect diabetic control cannot be achieved by simply switching all one's patients to four injections of insulin a day; good diabetic control depends on a complex and inter-dependent series of procedures and supportive measures.⁶ What are these?

Organization of diabetes services

Patients who took part in the DCCT were volunteers, who, apart from wishing to do their bit for science, had an important financial incentive in that they received all their diabetes supplies (syringes, blood glucose tests and insulin) free and also got free medical care – a saving of \$2,000 or more per year. For the ordinary patient with IDDM in the UK, attendance at a diabetic clinic is voluntary and is not rewarded financially. If the patient, to take the worse-case scenario, waits for an hour in uncongenial surroundings for a 5-minute interview with an inexperienced doctor and then receives no feedback (for example, their GHb value), one has to ask why they should bother to come. Purpose-built, dedicated diabetes centres have been built in many towns and, although they are not necessarily all they are cracked up to be, we all agree that 'overcrowded and badly housed diabetic clinics are a nightmare to doctors and useless to patients'.⁷ Patients in the DCCT were looked after by experts and we need to ask how many such experts are available in our health care system. As Dornan⁸ points out, most medical schools do not give the holistic training which is needed to look after a complex chronic disease such as diabetes. Examinations have a lot to answer for because, as Dornan says, 'You will fail if you cannot distinguish mitral stenosis from aortic incompetence, but would the examiner himself pass if performance at telling a surrogate patient that they were heading towards diabetic renal failure

were the subject of the exam?'. The diabetes knowledge of general practitioners and senior medical students leaves a lot to be desired⁹ and we think that general practitioners do not see enough patients with IDDM to become expert and that these patients should therefore be looked after by specialists.

Whether the specialists need to be doctors is a moot point. We do not have any evidence, but believe that expert diabetes specialist nurses might optimize glycaemic control as well as, or better than, doctors, and certainly might be more alert to and able to manage the psychological barriers which so often interfere.

Education

Dr R.D. Lawrence, himself an insulin-dependent diabetic, claimed that the diabetic patient must be his own 'doctor, biochemist and dietitian'. Education is necessary because diabetes does not manage itself between appointments, so that the patient must be in charge and make decisions on a day-to-day basis. For education to be effective it must take into account the patient's beliefs, knowledge, misconceptions and prejudices. Factual information and technical skills can be taught relatively easily, either individually or in group sessions¹⁰ but regular reassessment of knowledge and technical skills¹² is vital to maintain motivation and adequate skill levels. We suggest that purchasers need to ask the following questions: (1) Is there a dedicated area for education? (2) Are the teachers competent, that is, have they been educated about diabetes and teaching methods? (3) Is there a syllabus with clearly defined aims? (4) Is there practical work or is it all theory? (5) Are textbooks available? (6) Is there an exam? (7) Are there refresher courses?

Most of us who passed O-level physics would probably not be able to do so again 5 years later and, with time, diabetic patients also forget much of what they had originally learned and need regular refresher courses. The logistics of doing this are daunting but regular re-education is essential and not provided by most diabetes units.

In addition to education (or re-education), patients with IDDM need motivation and encouragement. The effect of motivation is most readily seen in women whose glycaemic control almost invariably improved during pregnancy. Another sure way of improving metabolic control is to enrol patients in a clinical trial; what the intervention is matters little, because what is virtually always found is that in these self-selected volunteers, control improved more in the run-in period (typically, a fall in GHb of 1–2%) than subsequently with whatever is being tested. For

example, Reeves *et al.*¹³ set out to find if CSII would produce better control than multiple injections, as many at the time believed to be the case. In the event, they found the greatest improvement during the run-in period, with little further gain whether twice, three times daily injections, or CSII were used. What is being seen is the 'Hawthorne effect', a change in performance due to the attention being paid to the subjects who want to help and do the right things, especially if they hold the investigator in high esteem. It is perhaps not surprising that the benefits of entering a trial do not last once patients are no longer being studied. In a well-conducted study of a diabetes education programme, Lennon *et al.*¹⁴ found improved glycaemic control in 31 'educated' patients compared with 25 receiving routine clinic care, but 6 months after the education programme glycaemic control had again drifted back to baseline.

It is self-evident that the patient who takes IDDM seriously and manages it conscientiously must have some 'reward' for following the regimen. The Holy Grail of avoiding complications 30 years' hence may be one but, in the short term, the greatest motivating factor is the attitude of the family and diabetes team.

Another aspect of education is that patients must be empowered to take control of their own treatment. Most people are brought up to believe that doctors are the people who treat you and to be told that you, the patient, are in charge is a culture shock that must be conveyed gently but firmly. Muhlhauser and Berger¹⁵ put it well when they said 'Many physicians still subject their patients to rigid dietary instructions and obedience training, an approach which is mistaken for diabetes education.' It is also important that patients are given explicit goals with feedback about how well they are doing. It is, unfortunately, too often the case that after a visit to the diabetic clinic, a letter is sent to the general practitioner saying what the GHb result was but this information is never conveyed to the patient. One of us has suggested that the answer is to send copy letters to the patient, or even to write directly to the patient, sending a copy to the GP.¹⁶

Diet

Diet is always described as the cornerstone of diabetic management and this may be true for the patient with non-insulin-dependent diabetes. For the patient with IDDM an excessively rigid or peculiar diet (such as one containing 90 g of fibre per day^{17,18}) is self-defeating. One of the advantages of intensified insulin therapy is that it enables the diet to be simplified and liberalized.¹⁹

Over the last decade a consensus has emerged about what people with diabetes should eat²⁰ which

provides a framework on which to base dietary advice. These recommendations are broadly similar to the 'healthy eating' guidelines for the population as a whole and go some way to removing the dietary stigma of diabetes. Few patients, however, achieve even these ideals.²¹ Why is this? Education once again plays a crucial role. Dietary advice must be tailored to the individual social and cultural needs of each patient. Dietary compliance is more likely if small modifications are made than if an entirely new eating pattern is suggested. Many patients find diets based on carbohydrate exchanges or the 'glycaemic index' of different foods difficult to understand, and simple advice is often as effective.^{22,23} An imaginative approach to teaching and evaluation may also help to improve compliance and glycaemic control in the short term²⁴ but the example of the DCCT emphasizes again the need for continued medical input to ensure long-term motivation. Most UK diabetic clinics do not have the dietetic support to see patients even once a year to motivate, monitor and reinforce dietary advice.

Insulin regimens

In health, insulin is secreted as prompt short-lived peaks to dispose of meals with a constant basal insulin delivery rate overnight. Modern insulin regimens (like those in use up to 1935, when the first long-acting insulin was introduced) attempt, with varying degrees of success, to imitate this physiological profile. To the question 'Is there an ideal insulin regimen?', the answer is 'No'. Equivalent control can be obtained in motivated compliant patients using either twice-daily, four-times daily injections, or CSII.²⁵⁻²⁷ Each of these has its advantages and disadvantages, and what is important is that the patient is on a regimen which fits in with their lifestyle and which they feel comfortable with.

Twice-daily insulin

These usually consist of soluble with either isophane (NPH) or lente insulins. There is little to choose between NPH or lente,²⁸ although we think that NPH is better because its absorption is less erratic and it therefore produces more consistent overnight control. Twice-daily regimens should not necessarily be regarded as second class because they were 'conventional' therapy in the DCCT. It is quite possible (and needs testing) that DCCT patients on twice-daily insulin would have done as well as those in the intensive group had they been telephoned every week, seen every month and given feedback on GHb levels. Nevertheless, twice-daily regimens have intrinsic drawbacks; first, and this is

true of multiple injections as well, the delay in absorption of soluble insulin results in a 'mismatch' between the post-prandial increase of blood glucose and insulin levels. Post-prandial hyperglycaemia is the inevitable consequence, with a greater risk of hypoglycaemia between meals. This can be partly overcome by giving insulin 30–60 minutes before a meal,²⁹ but most patients find this inconvenient. An alternative, untested, strategy is to delay carbohydrate absorption with alpha-glucosidase inhibitors.³⁰ Second, no available long-acting insulin achieves the desired 'peaklessness', so that attempts to lower the morning blood glucose by increasing the dose of intermediate-acting insulin before the evening meal often produces hypoglycaemia in the night.³¹ A popular solution to this problem is to delay the injection of intermediate-acting insulin until bedtime.^{32,33} A final disadvantage of twice-daily insulin is inflexibility of lifestyle. Many patients would prefer to have a flexible lunchtime or even no lunch at all but, if they have injected themselves with intermediate-acting insulin in the morning, they cannot 'switch this off' and hence must eat, often more than they want.

Multiple injections

The 'basal/bolus' regimen of soluble insulin before each meal with intermediate-acting insulin last thing at night should produce a more physiological insulin profile. It is remarkably popular with patients who can be persuaded to try it, whether they use a syringe or the more convenient pen injector. It does not necessarily result in better glycaemic control but is liked because patients feel more in control and can vary the times and size of meals.³⁴

Continuous subcutaneous insulin infusion

Insulin is delivered continuously through a subcutaneous needle with pumps which have a (seemingly) infinite variety of programmes. Improved overnight insulin delivery may result in lower fasting blood glucose,²⁷ and the main advantage of CSII is improved glycaemic control at night. However, it is expensive (none of the equipment is available on prescription) and many patients find the pumps bulky and inconvenient. CSII has never been popular in the United Kingdom, partly because of the expense but, more importantly, because patients require considerable medical and educational input together with a 24-hour telephone advice service. Again, one has to ask rhetorically if 'conventional' treatment would work better if patients on it had the same support as those on pumps.

What is the best insulin regimen?

As pointed out earlier, virtually any regimen can give adequate control if the patient is educated and motivated. We believe that insulin regimens must be individualized to meet the lifestyle requirements of the patient and reflect the stage of diabetes. For example, newly diagnosed IDDM patients during the 'honeymoon period' usually find control easy on twice-daily intermediate-acting insulin. Patients who want flexibility with their meals usually prefer a multiple injection regimen. Poor control is not of itself a reason to alter an insulin regimen; it is more important to make a diagnosis of the reason for the high blood sugars. A poorly controlled patient on twice-daily insulin who lives in psychosocial chaos never improves on multiple injections or a change of insulin species. Glycaemic control may actually deteriorate in some patients, especially young women, who transfer from twice-daily to multiple injections.³⁵

Self-monitoring of blood glucose (SMBG)

Optimal glycaemic control relies heavily on the accurate, reliable and regular use of SMBG. There is a wide range of convenient meters which, if correctly used, enable patients to obtain accurate blood glucose measurements.³⁶ Unfortunately, diabetic control does not automatically improve when patients measure their blood sugars. The main reasons are a failure to act on the results and not doing enough tests. Patients in the DCCT intensive therapy group measured their blood sugar at least four times a day every day for up to 10 years, a degree of compliance which is difficult to obtain in the real world; indeed, one might argue that it is pathological. The ideal frequency of SMBG is unknown but to achieve near-normoglycaemia it needs to be more than twice a day.³⁷

Psychosocial factors

The discrepancy between near-perfect control which can be obtained in a trial and poor control under ordinary conditions is most often due to what, for want of a better term, we will call intra-psycho factors in the patient himself.³⁸ This encompasses the whole field of compliance, motivation, perseverance, health beliefs and reaction to stress. In childhood diabetes, investigations of the family as a whole generally show a strong relationship between poor control in the child and defective family functioning and integration³⁹ and the same is true of adolescents and probably most adult diabetics.⁴⁰ Those who are preoccupied with

financial, social and marital problems simply lack the time (and motivation) to manage diabetes. Any solution must take into account the whole family and may require the skills of a psychiatrist, social worker or family therapist. Personality is important as well. A child's temperament (not surprisingly) seems to be one determinant of control. Children described by their parents as never fidgeting, always sitting still and moving slowly, were in the worst control; whereas children who were well organized (regular bedtimes and meals, and keeping their rooms tidy) had the best.⁴¹ In the real world, even the most motivated patients with IDDM suffer eventually from tedium and 'burn out'^{42,43} and need to have their enthusiasm constantly rekindled. Who does this and how is less important than that somebody does it. We have emphasized that one of the aims of diabetes education is to equip patients to manage themselves, but one must be careful not to carry this to such extremes that it is interpreted as rejection. We agree with Ingelfinger⁴⁴ that a certain amount of authoritarianism, paternalism and domination are the essence of the physicians effectiveness. According to Ingelfinger, 'The patient has to believe in the physician and have a conviction that not only can he be trusted but also has some special knowledge that the patient does not possess . . . A physician who merely spreads an array of vendibles in front of the patient and says, "Go ahead and choose, it's your life" is guilty of shirking his duty. . . . He should recommend a specific course of action.'

Dealing with patients with a chronic disease such as IDDM is part of the art of medicine which was brilliantly summarized by Peabody,⁴⁵ who said: 'Disease in man is never exactly the same as disease in an experimental animal, for in man the disease at once affects and is affected by what we call the emotional life. Thus, the physician who attempts to take care of the patient while he neglects this factor is as unscientific as the investigator who neglects to control all the factors that may affect his experiment. The good physician knows his patients through and through and his knowledge is bought dearly. Time, sympathy and understanding must be lavishly dispensed. . . . One of the essential qualities of the clinician is interest in humanity, for the secret of care of the patient is in caring for the patient.'

What about the risks?

Apart from weight gain the major adverse effects of attempting to achieve near-normoglycaemia are likely to be hypoglycaemia and possibly psychological disturbance.

In the DCCT, patients on intensive therapy had

a three-fold increase in the frequency of severe hypoglycaemia. Part of this increased risk may be due to the reduced awareness of hypoglycaemia which often accompanies a 'good' GHb.⁴⁶ This is reversible,⁴⁷ especially in patients with a relatively short duration of diabetes but patients with fixed hypoglycaemic unawareness are unsuitable for intensive therapy. It should be noted that severe hypoglycaemia in the DCCT might well have been more common but for two safeguards; first, after the feasibility study, patients with a history of previous severe hypoglycaemia (and, by implication, unawareness) were excluded. Second, patients measured their blood sugar four times or more each day, and had an unusual amount of medical input. There was no fatality from hypoglycaemia among the study subjects, although a bystander was killed by a car driven by someone on intensive therapy in circumstances leaving little doubt that the driver was hypoglycaemic. We worry about the diabetic salesman who drives 40,000 miles a year on Britain's congested roads who has been told to put his insulin dose up because his last GHb was 'too high'. Whose fault will the pile up on the M1 be? There is also a worry that repeated severe hypoglycaemia will be bad for the brain. In the DCCT no adverse effects on neuropsychological function were seen but follow-up was relatively short and other studies suggest that repeated hypoglycaemia may be harmful.⁴⁸

Like Santiago,⁴⁹ we also see the lack of standardization of GHb assays as a potentially serious risk. The normal range for serum calcium in every hospital in the country is 2.2–2.6 mmol/l but, even within our own region (Trent), the upper limit of normal for GHb varies from 4.8% to 8.5%. Supposing health care providers get the idea that GHb should be below 6.05%, the upper limit of normal for the assay used in the DCCT, but do not realize that the assay in their local hospital has an upper limit of 8.5%. One can imagine what would happen. Is this a slur on the competence of the average doctor or practice nurse? No, because as Santiago points out, 'Most diabetologists know that differences exist, but most diabetic patients and their physicians (in some ways the US equivalent of the general practitioner) do not. Instead, the average patient and health care professional is posed with a dizzying array of HbA1c, total HbA1, total glycated haemoglobin, fructosamine and other measurements'.

Conclusions

Long-term optimal glycaemic control requires a heavy commitment from medical, nursing, and dietetic staff and most of all from the patients themselves. The factors determining glucose con-

rol are complex and interrelated, and the reasons for poor control will vary between patients. A 'diagnosis' of the reasons for poor control must be made before appropriate advice can be given. Not all patients will be suitable (or will want to) improve their glycaemic control, and individual glycaemic targets need to be set for each patient based on an assessment of benefit and risk. The

DCCT, together with the recently published Consensus Guidelines on managing IDDM⁵⁰ provide a framework around which to make such judgements which, apart from scientific knowledge, depend heavily on common sense, a quality with which diabetes nurses sometimes seem to be better endowed than doctors.

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