

Diabetic control and complications

Better control means fewer microvascular complications

Premature mortality and morbidity in insulin dependent diabetes mellitus results from cardiovascular disease, retinopathy, renal failure, and neuropathy. In an attempt to establish definitively the role of chronic hyperglycaemia in the pathogenesis of these complications (and hence our ability to prevent them) the diabetes control and complications trial randomly allocated 1441 patients with insulin dependent diabetes to receive up to 10 years' conventional or intensified treatment. (Intensified insulin treatment aimed for long term near normoglycaemia with at least four home blood glucose assessments a day, three insulin injections a day, and monthly visits to a clinic with telephone contacts in between. Conventional treatment did not mean poor control.)

The trial ended prematurely and last week reported substantially less risk of the development and progression of diabetic retinopathy, microalbuminuria (an indicator of high risk of progression to diabetic renal disease), and abnormal nerve function in patients treated intensively.¹ The results confirm those of earlier smaller trials²⁻⁵ and of a meta-analysis of some of these published earlier this year.⁶ A causal association between chronic hyperglycaemia and microvascular complications in insulin dependent diabetes mellitus now seems established.

The size and high profile of the diabetes control and complications trial have resulted in wide dissemination of its message. The authors suggest that the findings may apply to almost anyone with diabetes, excluding only children and those with advanced diabetic complications. But the costs of the trial were enormous as over 560 health professionals participated. Applying its findings to people with diabetes has substantial implications for the provision of services.

Do the study's findings provide good grounds for such care? The answer is probably yes. Although the most impressive result was the slowing of progression of retinopathy, the risk of sight threatening proliferative retinopathy was also reduced. A previous trial has also suggested that prolonged intensified insulin treatment reduces serious retinopathy and loss of sight.⁵

For nephropathy, the diabetes control and complications trial has again used surrogate end points (microalbuminuria and albuminuria), and the figures suggest retardation rather than absolute prevention of progression to albuminuria, which implies that factors other than hyperglycaemia play a part. Reichard and colleagues, however have previously reported that strict metabolic control provided complete protection over 7.5 years against a fall in glomerular filtration rate

to subnormal values.⁵ Although substantially delaying renal failure and blindness is a valid goal for patients with diabetes and their carers, purchasers of health care services may be less enthusiastic about spending more money on diabetes if savings on renal replacement and photocoagulation are unlikely.

What of the wider application of the trial's results? It contained mainly white patients with insulin dependent diabetes of short duration.

The study of Reichard and colleagues strongly suggests that long duration of diabetes does not negate the benefits of improved glycaemic control, although none of the studies has examined patients with advanced complications.⁵

There are no data on the effect of intensified glucose control in patients with non-insulin dependent diabetes or belonging to ethnic minorities. The pathogenesis of microangiopathy is probably similar in all forms of diabetes so that the same rules for prevention will apply, but the potential risks of intensified treatment may be different in non-insulin dependent diabetes, especially given the possible causal link between hyperinsulinaemia and cardiovascular disease. The intensively treated patients in the diabetes control and complications trial showed a reassuring improvement in low density lipoprotein cholesterol concentration but were too young and at too low a risk for this to have any effect on the incidence of clinical disease.

The UK Prospective Diabetes Study Group, which is based in Oxford, is currently examining the effects of different degrees of diabetic control in non-insulin dependent diabetes.⁷ Until it has reported we should be cautious about applying the results of the diabetes control and complications trial to patients with non-insulin dependent diabetes.

Balancing risks, benefits, and costs

Should we provide in our clinics the high input of professional care provided in this trial? We need to examine not only the financial but also the personal costs of intensified insulin treatment. Patients in the intensively treated group did well, with a high compliance and no worsening on neuropsychological testing or on quality of life scores. But they gained weight and had three times as many episodes of severe hypoglycaemia as the conventionally treated group. Severe hypoglycaemia is a problem for all insulin treated diabetic patients, and other studies have shown an increased risk of severe and sometimes asymptomatic hypoglycaemia with otherwise improved diabetic control.⁵

As a mother of a diabetic child recently pointed out, young people with diabetes are more concerned about losing their driving licences (as a result of severe hypoglycaemia) than the risk of renal failure later. We may therefore be overestimating the impact of the diabetes control and complications trial on our patients' acceptance of stricter control. Certainly we need to pursue better methods of applying good glycaemic control in our diabetic patients and other ways of preventing chronic complications. In the meantime, increased expertise achieves lower rates of severe hypoglycaemia.⁸⁻¹⁰

Undoubtedly, improved glycaemic control is one way of preventing the chronic microvascular complications of diabetes mellitus. The diabetes control and complications trial suggests—at least for retinopathy—that the lower the glycated haemoglobin concentration the lower the risk. So any improvement in diabetic control is worth while and each patient should be helped to achieve the best possible control. But the inverse relation between glycated haemoglobin concentration and risk of severe hypoglycaemia was also a continuum. Patients will need to choose for themselves between the effort and risk of intensified metabolic control and the risks of later microvascular complications. Those who care for them need to be able to help them apply their choice with least harm. The

diabetes control and complications trial offers a firm base on which to make those choices.

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Routine measurement of fibrinogen concentration

Not clinically feasible

The concentration of plasma fibrinogen is a strong independent risk factor for the development of arterial thrombotic disorders.^{1,2} Several carefully designed epidemiological studies have identified fibrinogen as a major risk factor for myocardial infarction,^{3,4} and positive associations with raised fibrinogen concentrations have also been reported for thrombotic stroke, transient ischaemic attacks, peripheral arterial disease, diabetic vascular conditions, angina pectoris, and chronic bacterial infection.

Quantifying other independent risk factors for cardiovascular disease (for example, hypercholesterolaemia, hypertension, and smoking) is relatively easy, but accurate measurement of fibrinogen concentration is neither widely available nor frequently requested as part of general screening programmes in Britain. Should it be? Is measuring fibrinogen concentration a practical, useful, and cost effective laboratory investigation that should be included in future screening programmes?

Several problems, relating both to the fibrinogen assay and to biological variation, need to be considered. Unlike most other haematological variables, fibrinogen must be measured in plasma. It is unstable on storage, and ideally fresh anticoagulated plasma should be analysed. In the Clauss assay, the commonest technique used in routine laboratories, various dilutions of a standard plasma with known fibrinogen concentration and dilute test plasma are clotted with excess thrombin.⁵ The fibrinogen concentration is proportional to the clotting time, which allows the concentration to be quantified. Heparin, fibrinogen degradation products, and abnormal forms of fibrinogen can, however, interfere with the assay.

Most British haematology laboratories have introduced some form of automated coagulometer, which can perform such assays or produce a "derived fibrinogen" value from the prothrombin time test.⁶ The test may be calibrated by testing a standard plasma of known fibrinogen concentration with

each new batch of prothrombin time reagent; however, lipaemia affects the reliability of derived values.⁷ Standardisation is also difficult given the instability of reference materials during lyophilisation and the lack of national and international standard preparations. Although fibrinogen assays are relatively simple, the coefficient of variation from national quality control surveys with more than 350 laboratories participating has ranged from 15% to 20%. This raises the question of the usefulness of a single fibrinogen determination in individual patients at risk of or who have developed a specific clinical thrombotic condition.

Not only are there technical problems with the assay but fibrinogen concentrations are subject to considerable biological variation. Fibrinogen is one of the major acute phase reactant proteins, and increased hepatic synthesis occurs as a physiological response to inflammation and tissue necrosis.⁸ Altered protein catabolism due to intravascular consumption may also influence circulating plasma concentrations. The plasma fibrinogen concentration rises with age, and a considerable gender difference exists.⁹ The concentration is increased in users of the combined oral contraceptive¹⁰ and increases during pregnancy.¹¹ A rise also occurs after the menopause; the effects of hormone replacement therapy are inconsistent.¹²

In well designed research many of these problems can be addressed by use of a single laboratory with specific dedicated equipment, staff, and in house procedures for quality control. But in a busy routine setting it is virtually impossible to control for these numerous variables and thus allow a meaningful clinical decision to be made on a single fibrinogen estimation.

The main therapeutic question is how to lower a raised fibrinogen concentration safely. Although specific defibrinating agents—such as ancrod—are available, they are not a viable clinical option. Secondary drug approaches with fibrates and other lipid lowering drugs, diet, and better diabetic