Diabetologia (1984) 27: 419

Diabetologia

Letter to the Editor

UK prospective study of therapies of maturity-onset diabetes

Dear Sir,

In a recent letter to the Editor [1], Dr. Sims has queried the design of this Study [2]. Newly presenting maturity-onset diabetic patients are treated by a prudent diet and are seen at monthly intervals. If, after 3–4 months their fasting plasma glucose remains > 6 mmol/l, they are randomly allocated either to continuing diet alone, or with additional tablet therapy or insulin therapy aiming to reduce the fasting plasma glucose to < 6 mmol/l. All patients are seen at the same 3-monthly intervals and continue to receive dietary advice. The diet 'control group' is not seen less frequently as implied by Dr. Sims. This study is thus a properly controlled trial of patients who have a "western" life-style, to determine whether any of the additional therapies are advantageous.

Dr. Sims suggested that there should be an additional randomised control group in which maturity-onset diabetic patients, who remain hyperglycaemic after diet therapy, are requested to alter their life-style with increased exercise and even greater attention to diet. If the completely different means of lowering the fasting plasma glucose, by sulphonylurea, biguanide or insulin, similarly reduce the incidence of the complications of diabetes, then it is likely that reducing glycaemia by altered life-style would also be effective. Whilst, in an ideal world it would be advantageous to include this approach as a separate randomisation group, it is doubtful whether this should be added to the UK multicentre study at present. This is partly because any such study needs to have large numbers of patients in each allocated therapy, and the addition of an extra treatment to be studied would affect recruitment into the current study. In addition, the methods which should be used to encourage a change in life-style are uncertain, as is the degree of adherence which would be obtained. It would not be sensible to include a new treatment group until there has been a satisfactory pilot study first.

In the initial report, it was not feasible to mention all details of the study. In relation to the planned period of follow-up, the first patients were enrolled in 1977, the study was extended from six to 15 centres in 1982 and recruitment of 3,500–4,000 patients will finish in 1988. So far, 1609 patients have been recruited and 1197 have been randomly allocated to diffferent therapies. The study is planned to finish in 1992, although the end points may be reached earlier. The median period of follow-up by 1992 would be 7 years.

Nearly all of the other variables mentioned by Dr. Sims are included in the study. The data base includes family history of diabetes and of vascular diseases, drug therapy of the patients, smoking habits, an assessment of their usual exercise, degree of overweight, serum LDL and HDL cholesterol, triglyceride and fasting plasma insulin. A grant application has been made to fund inclusion of measurement of urine albumen, plasma growth hormone, factor VIII-related antigen and N-acetyl-β-D-glucosaminidase.

Dr. Sims wonders whether a therapy may only be effective in a particular sub-group of patients, and requests that detailed analyses in sub-groups should later be made. Whilst one can do this, it must only be a minor part of the analyses. In view of the very large number of sub-groups of patients which could be examined, the interpretation of any apparently statistically significant result in a particular sub-group will be difficult, as it could be a chance occurrence. The main analysis will be of patients according to their random allocations to diet alone, insulin or sulphonylurea, in relation to pre-determined end-points. Although there will be heterogeneity of patients in each group, the number of patients being studied is such that those in each allocation are expected to be similar populations and to be comparable.

Two major end-points have been chosen: (a) deaths from vascular events, sudden death or renal failure, (b) complication-free interval, including avoidance of death from any cause, heart attack, angina, renal failure, blindness, major stroke or amputation, each variable having strict definitions. These two end-points will be studied (1) between allocation to 'diet' and 'active therapy' (allocation to insulin or sulphonylurea) to determine whether attempting to improve blood glucose control will reduce the complications and (2) between 'insulin' and 'sulphonylurea' allocations to determine whether either has untoward deleterious side-effects. The stopping criterion will be a difference of three standard deviations, approximately $p < 0.01$ in view of eight pre-determined yearly analyses between 1885 and 1992.

Yours sincerely,
R. C. Turner, J. I. Mann and R. Peto

References

1. Sims FAH (1984) The UK study of therapies of Type 2 (non-insulin-dependent) diabetes. Diabetologia 26: 88–89 (Letter)
2. Multi-centre Study (1983) UK prospective study of therapies of maturity-onset diabetes. 1. Effect of diet, sulphonylurea, insulin or biguanide therapy on fasting plasma glucose and body weight over one year. Diabetologia 24: 404–411

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Erratum

Diabetologia, Volume 27, Supplement July 1984. In the article by L. G. Heding et al.: 'Immunogenicity of monocomponent human and porcine insulin in newly diagnosed Type 1 (insulin-dependent) diabetic children', pp 96–98, Reference 8 should read:

Bolli GB, Dimitriadis GD, Pehling GB, Baker BA, Haymond MW, Cryer PE, Gerich JE (1984) Abnormal glucose counterregulation after subcutaneous insulin in insulin-dependent diabetes mellitus. New Engl J Med 310: 1706–1711