


European Heart Journal (1999) 20, 781–783

The United Kingdom Prospective Diabetes Study — everything you needed to know about diabetes but were afraid to ask?

As risk factors go, diabetes mellitus ranks well below the big three — smoking, cholesterol and hypertension — in most European countries. Yet the population prevalence of around 3–5% belies its importance to cardiologists. In most hospital series, diabetic patients represent around 10–15% of those admitted with myocardial infarction, and up to 20% of those who die[1]. And, despite the potential for major improvements in the outcome of diabetic patients with myocardial infarction (using insulin therapy, aspirin, thrombolysis, beta-blockers and ACE inhibitors[2,3]) important questions remain around primary prevention.

Diabetes is, self-evidently, a hyperglycaemic condition. Moreover, in a number of population studies, the degree of hyperglycaemia predicts the risk of cardiovascular disease, with each 1% increase in glycated haemoglobin increasing risk by around 10%[4]. The United Kingdom Prospective Diabetes Study (UKPDS) was designed, some 20 years ago, to answer the question as to whether improved glycaemic control reduces that risk[5]. Furthermore, by comparing treatment with insulin, sulphonylureas, or (in overweight patients) metformin[6], it also tackled the question of whether any particular therapy might augment, rather than diminish, cardiovascular risk. In particular, the potential effect of sulphphonylureas on the cardiac K$_{ATP}$ channel might adversely affect outcome after myocardial infarction[7]. This has been suggested as potentially responsible for the observations of the University Group Diabetes Program, in which tolbutamide, a sulphonylurea, was suggested to increase cardiovascular mortality in type 2 diabetes[8].

The UKPDS recruited 5102 patients with type 2 diabetes, randomizing patients either to conventional treatment — based initially on diet, with the addition of additional therapy if glycaemia substantially deteriorated — or to intensified treatment — in which oral hypoglycaemic agents or insulin were used to try to maintain fasting plasma glucose concentration under 6 mmol·l$^{-1}$. Over a median follow-up period of 10 years, a mean difference in HbA1C was achieved of just under 1%. This was despite the deterioration in glycaemic control with increased duration of follow-up in both groups, exemplifying how difficult it is to pull out all the glycaemic stops in an ageing population group.

As might be predicted from the results of the Diabetes Control and Complications Trial in type 1 diabetes[9], the UKPDS showed a major impact on microvascular disease — around a 25% reduction[5]. However, for the major large vessel end-point, acute myocardial infarction, the benefit of intensified control just failed to achieve significance — a 16% reduction with a $P$ value of 0.052. With intensified treatment, there was absolutely no evidence for adverse effects on myocardial infarction risk of either insulin or sulphonylureas. In overweight patients, metformin as initial treatment produced substantially greater benefits on risk of myocardial infarction than
other intensified treatment. Curiously, however, addition of metformin to sulphonylureas to achieve normoglycaemia in normal weight patients seemed adversely to affect coronary risk[6].

What is the take-home message for cardiologists? Message one is that glycaemia seems likely to play a direct, albeit weak, aetiological role in atherothrombotic vascular disease. Next is the clear benefit to microvascular disease of reducing glycaemia, regardless of the mode of so doing. And the UKPDS has also clarified the importance of large vessel disease as the major complication in type 2 diabetes: in a population of mean age 52 at diagnosis, over 10 years of follow-up, some 20–25% will suffer an infarct or a stroke, as compared to around 3–4% who become blind in one eye, and less than 1% who develop renal failure. As to coronary heart disease prevention, and a P value of 0·052, are we left with a non-answer after over £23 million and nearly 20 years? Well, at least the Study provides figures to calculate numbers needed to treat, providing the ability to compare potential benefits of improved glycaemia with other strategies for primary prevention. Intensive treatment of 100 patients for 10 years prevented 2·7 infarcts, or 370 person-years of treatment per event. What other strategies are there?

The UKPDS also looked at treatment of blood pressure in these subjects, randomizing 1148 patients with hypertension either to tight control (<150/85), using a beta-blocker or an ACE inhibitor as first line therapy, or to less tight control[10]. The results over 8·4 years were dramatic: tight control, lowering blood pressure by a mean of 10/5 mmHg, reduced diabetes-related deaths by 32% (P=0·019), microvascular endpoints by 37% (P=0·0092), strokes by 44% (P=0·013) and myocardial infarcts by 21% (P=0·13). The reductions in strokes and in total deaths were apparent within 3–4 years, and there were no significant differences in the benefits seen with the two types of therapy[41]. Calculating the benefits of the tight blood pressure control in hypertensive type 2 diabetic patients, it would take 196 person-years of treatment to prevent a stroke, 204 to prevent a myocardial infarct, and 152 to prevent a death. And, while we await the studies of primary prevention with aspirin and statins in diabetic patients, a reduction of 25% in event rate could make these interventions nearly twice as effective as a 1% improvement in glycated haemoglobin, and probably substantially easier to implement[12]. In this regard, it is important to point out that, even without an earlier infarct, a diabetic patient is at the same level of cardiovascular risk as is a non-diabetic who has sustained an infarct[13], suggesting, perhaps, that the type 2 diabetic patient should be managed as if for secondary prevention.

An important question in management decisions is the biological and chronological age of the patient. As age increases, so does the event rate[13]. In addition, so does the importance of large-vessel disease relative to microvascular complications. The newly diagnosed 50-year-old type 2 diabetic patient will probably live 10–15 years with strict glycaemic targets to reduce the incidence of blindness and renal failure. At 70, however, in a newly diagnosed patient, there is a strong likelihood that the macrovascular event will occur before there has been sufficient time for microvascular benefit. And if we add into this equation the problem of initiating intensive glycaemic control policies, especially with insulin and home monitoring, in an elderly patient, the generalizability of the findings becomes questionable.

The UKPDS is a landmark study, which has answered many questions about the role of glycaemia in type 2 diabetes. It has pointed out that intensive blood pressure control in type 2 diabetes saves lives and prevents large- and small-vessel disease. And, while coming across as a powerful message for tight glycaemic control, it has at last enabled the potential benefits of lowered glycaemia and of other risk factor interventions to be compared.

J. S. YUDKIN

Centre for Diabetes and Cardiovascular Risk,
UCL, London, U.K.

References


