

Effect of Glucose and Glycaemic Control

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The number of people world wide with diabetes is predicted to double to 221 million by the year 2010. Diabetes remains the leading cause of blindness, end stage renal disease and lower extremity amputations in the United States and confers a two to four times greater risk of heart disease and strokes. Of the 5102 patients with newly diagnosed type 2 diabetes recruited into the UK Prospective Diabetes Study (UKPDS), 59% of all deaths were from cardiovascular disease. Epidemiological analysis of UKPDS data at diagnosis showed that potentially modifiable risk factors for cardiovascular disease in these patients included hyperglycaemia in addition to a raised LDL cholesterol, a low HDL cholesterol, hypertension and smoking. Elevated glucose levels were also a major determinant of microvascular complications.

The 20-year UKPDS which followed patients with newly diagnosed diabetes in 23 clinical centres confirmed that the life-threatening complications of type 2 diabetes, frequently regarded as inevitable, can be reduced by more intensive management using existing treatments. The study demonstrated that maintaining improved glycaemic control, with sulphonylurea or insulin therapy (median HbA_{1c} 7.0 % *versus* 7.9% over median 10 years), reduced the risk of any diabetes-related endpoint by 12%. The risk of microvascular endpoints was reduced by 25%, the appearance of microalbuminuria by 33% and there was a borderline significant 16% trend to a reduced risk of myocardial infarction ($p=0.052$). Fears that sulphonylurea or insulin therapies may be harmful were allayed as no increase was observed with these agents in the incidence of cardiovascular deaths, myocardial infarction or sudden death. Although neither of these therapies impaired quality of life, both increased the risk of hypoglycaemia and of weight gain. A cost-effectiveness analysis showed that cost savings from the reduction in diabetic complications outweighed the cost of the additional medication required, but not the extra staff costs involved. In overweight patients allocated to metformin as first line therapy, the risk of any diabetes-related endpoint was reduced by 32%, diabetes-related death by 42% and myocardial infarction by 39% with no weight gain, little increase in the risk of hypoglycaemia and a decreased risk of myocardial infarction. A health economic analysis showed metformin to be cost effective as well as clinically beneficial.

Health care professionals and people with diabetes must now adopt new therapeutic strategies if existing pharmacological agents are to be used to best advantage and the benefits of any new treatments are to be maximised. The UKPDS, which was designed primarily as a monotherapy study, showed that there was a marked deterioration in glycaemic over time due to a progressive decrease in beta-cell function with little associated change in insulin resistance. This increasing therapeutic demand occurred irrespective of the differing pharmacological agents used. In practice this means that, in addition to an appropriate dietary and life style strategy, many more patients than at present will need to move rapidly to combinations of oral agents if desirable glycaemic levels are to be achieved. Appropriate consideration needs to be given to both the fasting and the postprandial glucose levels to ensure that HbA_{1c} levels are minimised to the greatest extent possible. Such an approach requires a judicious selection of the pharmacological agents available in order that their differing modes of action can be combined in a complementary fashion. It needs to be recognised also that a major barrier to compliance, apart from pharmacological side effects, is the sheer number of tablets people with diabetes are being asked to take, particularly where they are receiving concomitant therapy for hypertension, dyslipidaemia or other medical conditions. Attention needs to be given to motivational strategies and the possibility of making combined formulations for selected agents. In addition, those affected must be informed that oral glycaemic therapies will need to be increased with time and that insulin therapy will become necessary should glycaemic targets no longer be maintained.

The UKPDS has confirmed that the complications of type 2 diabetes are not an inevitable outcome of a chronic disease, and that the risk can be reduced by appropriate therapy. The challenge now is to implement these findings in everyday clinical practice.