Benefits of Strict Glucose and Blood Pressure Control in Type 2 Diabetes
Lessons From the UK Prospective Diabetes Study
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For decades, the treatment of type 2 diabetes has been based more on assumptions than on facts. Even the most crucial question—does a reduction in blood glucose help to prevent long-term complications—has remained unanswered. Now, 4 reports from the United Kingdom Prospective Diabetes Study (UKPDS)1–4 offer useful information on the benefits of treating hyperglycemia and hypertension in this disorder.

Whereas the complications of type 1 diabetes are chiefly microvascular, patients with type 2 diabetes are prone to accelerated atherosclerosis.5 The most important macrovascular complication is coronary heart disease (CHD), which causes almost half the deaths in these patients. Although classic risk factors (ie, high total cholesterol, hypertension, and smoking) play a substantial part in pathogenesis, they do not explain the excess of macrovascular complications in type 2 diabetes. Therefore, the specific risk factors, particularly hyperglycemia, have been given increasing attention. In population-based prospective studies, hyperglycemia has indeed proved to be associated with risk of CHD in type 2 diabetes: a 1% change in glycohemoglobin (HbA1c) signifies about a 10% change in risk of CHD.6,7 Thus, there is potential, albeit modest, for reducing CHD events by lowering blood glucose.

Control of Hyperglycemia
What is the evidence that improvement in glycemic control is beneficial in this respect? The first study aiming to address this question, the University Group Diabetes Program (UGDP), published in the 1970s,8 randomized ~200 patients with type 2 diabetes to phenformin, tolbutamide, a fixed insulin dose, a variable insulin dose, or placebo. With phenformin and tolbutamide, cardiovascular mortality was higher than with insulin or placebo (for which the rates were about the same), and a suspicion that oral hypoglycemic agents are harmful has persisted ever since. The UGDP did not answer the question whether improvement of glycemic control prevents complications.

The UKPDS, which began in 1977, was designed to show whether intensive blood glucose control reduces the risk of macrovascular or microvascular complications and whether any particular therapy is advantageous. In that study, 3867 newly diagnosed patients with type 2 diabetes (median age, 54 years), who after 3 months’ dietary treatment had a fasting plasma glucose of 6.1 to 15.0 mmol/L, were randomly assigned to an intensive-treatment policy (sulfonylurea or insulin, the sulfonylureas being chlorpropamide, glibenclamide, or glipizide) or to a conventional-treatment policy with diet. Over 10 years, HbA1c was 7.0% in the intensive-treatment group and 7.9% in the conventional-treatment group, an 11% difference, although glycemic control deteriorated almost linearly over time in both groups. Compared with the conventional-treatment group, the intensive-treatment group showed the following: any diabetes related end point, 12% reduction (P=0.029); death related to diabetes, 10% reduction (P=0.34); myocardial infarction, 16% reduction (P=0.052); stroke, 11% increase (P=0.52); microvascular disease, 25% reduction (P=0.0099).

All-cause mortality rates did not differ significantly. Chlorpropamide, glibenclamide, and insulin were approximately equivalent in their benefits. There was no evidence of any glycemic threshold for either microvascular or macrovascular complications.

These results leave no doubt that in type 2 diabetes, complication rates are lessened by reduction of blood glucose. Moreover, in obese patients (n=1704), treatment with metformin showed greater advantages over conventional treatment: a 32% reduction of diabetes-related end points (P=0.002), a 42% reduction of diabetes-related deaths (P=0.017), and a 36% reduction of all-cause mortality (P=0.011). Patients taking metformin also had less weight gain and fewer hypoglycemic attacks than those taking insulin or sulfonylureas.

Control of Hypertension
The prevalence of hypertension in type 2 diabetes is >50% (twice that in the nondiabetic population), and subgroup analyses of large trials indicate that the benefits of treatment apply to diabetic patients. The UKPDS is the first large-scale trial to specifically examine the effects of intensive blood pressure lowering on the morbidity and mortality of hypertensive patients with type 2 diabetes. This investigation was
superimposed on the project 10 years behind the glycemia study. Of 1148 patients (mean blood pressure at entry, 160/94 mm Hg), 758 were allocated to tight control (blood pressure <150/85 mm Hg) and 390 to less-tight control. The main treatments were captopril and atenolol. During the 8.4-year follow-up, mean blood pressure in the tightly controlled group was 144/82 mm Hg compared with 154/87 mm Hg in the less-tightly controlled group. The risks in the tightly controlled group were substantially lessened: any diabetes-related end point, 24% reduction ($P=0.0046$); death related to diabetes, 32% reduction ($P=0.019$); myocardial infarction, 21% reduction ($P=0.13$); stroke, 44% reduction ($P=0.013$); microvascular disease, 37% reduction ($P=0.0092$).

As in the glycemia study, all-cause mortality rates showed no significant difference. Captopril and atenolol were equally effective both in lowering blood pressure and in reducing the incidence of diabetic complications; in other words, what matters most is the reduction rather than the nature of the agent prescribed.

**Implications of UKPDS**

From the above results, one might gain the impression that for reduction of all end points, even microvascular disease, blood pressure control is more beneficial than blood glucose control. We should not forget, however, that the number of patients in the hypertension trial was only one third the number in the glycemia trial and that the hypertension trial started 10 years later; therefore, the percentage reductions are not directly comparable. Of great interest are the results for stroke: whereas rigorous antihypertensive treatment lowered the risk as expected, no benefit was seen from blood glucose control. This came as a surprise because earlier prospective studies had indicated that hyperglycemia predicts stroke events more strongly than it does CHD events. Stricter control of blood pressure did not significantly reduce the risk of myocardial infarction, and the reduction achieved with intensive blood glucose control was of borderline significance.

What have we learned from UKPDS? First, it offers powerful support for the “glucose toxicity” hypothesis in type 2 diabetes, viz, that hyperglycemia is causally related to microvascular and macrovascular complications and that intensive control of hyperglycemia is beneficial. However, glucose control deteriorated over time, and the treatment goal (fasting plasma glucose <6 mmol/L) was not achieved. None of the treatment modalities was particularly effective in reducing complications, but the study did remove any residual suspicion that treatment with insulin or sulfonylureas is harmful. The trial offered clear evidence that in hypertensive patients with type 2 diabetes, blood pressure should be controlled rigorously and that therapeutic goals can be reached and maintained. Therefore, the clinicians who have long recommended strict control of blood glucose and blood pressure in type 2 diabetes have been proved right.

What questions are not answered by UKPDS? The study was confined to patients with newly detected type 2 diabetes, aged 25 to 65 years, with mild disease and without symptoms of macrovascular disease. But ≈50% of patients with type 2 diabetes are >65 years old, and 40% have symptoms of CHD or have experienced CHD events; also, blood glucose levels are commonly higher than the 6.1 mmol/L cut-off in the trial. UKPDS does not provide definite answers on how to treat such patients; although insulin and sulfonylureas gave equal benefits in the trial, we cannot be sure that this would be the case in elderly patients, particularly those with macrovascular complications. Moreover, the question whether metformin is superior to other agents in obese patients remains open; metformin was compared with all intensive treatments combined, not separately with insulin and sulfonylureas. An unexpected and unexplained finding was a 96% increase in diabetes-related death ($P=0.039$) in a group that received additional metformin after starting a sulfonylurea. Finally, UKPDS did not clarify the role of all possible combinations of therapy; for example, insulin plus metformin might be advantageous because weight gain is prevented.

An important message from UKPDS and other recent trials is that if one seeks to prevent cardiovascular complications in type 2 diabetes, it is wise to focus on single risk factors. All known risk factors should be attacked simultaneously. Intensive treatment of dyslipidemia and high blood pressure, in addition to hyperglycemia, should now be the rule.

**References**

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