Journal of Diabetes Science and Technology
Volume 2, Issue 6, November 2008

EDITORIAL

United Kingdom Prospective Diabetes Study Follow-Up Studies Establish a Legacy Effect of Therapy for Hyperglycemia but Not Hypertension

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In type 2 diabetes, early intervention with intensive glucose control has long-lasting effects, according to 10-year follow-up data on a cohort of patients with type 2 diabetes enrolled in the United Kingdom Prospective Diabetes Study (UKPDS). This was the conclusion of the 10-year follow-up study of the UKPDS, which was presented on September 19, 2008, at the 44th Annual Meeting of the European Association for the Study of Diabetes in Rome, Italy.[1,2] I attended this meeting, and the UKPDS follow-up data were among the most discussed topics there.

Treatment of Hyperglycemia

The UKPDS was a randomized, prospective, multicenter trial of intensive glucose therapy in subjects with newly diagnosed type 2 diabetes mellitus.[3] The study was conducted in the United Kingdom from 1977 to 1997 and was one of the most complicated diabetes trials ever conducted, in terms of number of subjects and study duration. The intensive intervention was associated with a significantly reduced risk of clinically evident microvascular complications and a nonsignificant reduction in the risk of myocardial infarction and other macrovascular complications.[4] A relative risk reduction for myocardial infarction of 16% was observed with a nonstatistically significant p value of 0.052. In a subset of study subjects whose body weight was greater than 120% of their ideal weight and who primarily received metformin, reductions in the risk of myocardial infarction and death from any cause were observed.[5]

In the original study of 5102 subjects with newly diagnosed type 2 diabetes, 4209 were randomly assigned to receive either conventional therapy (dietary restriction) or intensive therapy (either sulfonylurea or insulin or, in overweight subjects, metformin) for control of glycemia. In the posttrial monitoring part of the study, 3277 subjects were asked to attend annual UKPDS clinics for 5 additional years, but no attempts were made to maintain their previously assigned therapies. Funding limitations did not permit direct follow-up after 5 years. Annual questionnaires were used to follow the subjects who were unable to attend the clinics. All subjects in years 6–10 were assessed through questionnaires. Seven aggregate clinical outcomes from the UKPDS were studied on an intention-to-treat basis, including (1) any diabetes-related end point; (2) diabetes-related death; (3) death from any cause; (4) myocardial infarction; (5) stroke; (6) peripheral vascular disease; and (7) microvascular disease. The UKPDS follow-up study investigated whether postinterventional follow-up of the UKPDS survivor cohort at 10 years demonstrated a continued microvascular benefit from earlier improved glucose control and whether such intensive therapy had a long-term effect on macrovascular outcomes.

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Abbreviation: (UKPDS) United Kingdom Prospective Diabetes Study

Keywords: diabetes, hyperglycemia, hypertension, legacy, therapy, UKPDS

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J Diabetes Sci Technol 2008;2(6):922-924

Between-group differences in glycemic control were lost after the first year following closure of the trial. At 10 years, subjects assigned to intensive control with sulfonylurea and insulin had significantly reduced risks for microvascular disease (24%), myocardial infarction (15%), death from any cause (13%), and any diabetes-related end point (9%) compared with subjects assigned to conventional therapy. Subjects assigned to metformin therapy experienced significant risk reductions for myocardial infarction (33%), death from any cause (27%), and any diabetes-related end point (21%) compared with controls.

Despite an early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during the 10 years of posttrial follow-up. A continued benefit after metformin therapy was evident among overweight patients.

Treatment of Hypertension

In a separate UKPDS follow-up study, which was also reported in Rome at the same time as the first follow-up study, posttrial monitoring of UKPDS subjects assessed whether risk reductions for microvascular and macrovascular disease, achieved with the use of improved blood pressure control during the trial, would be sustained.[2]

Among 5102 UKPDS subjects with newly diagnosed type 2 diabetes mellitus over a 4-year period beginning in 1987, 1148 subjects with hypertension were assigned to either tight control (with a goal of no more than 150/85 using angiotensin converting enzyme inhibitors and beta blockers) compared with conventional control (with a goal of no more than 200/105) over a median time span of 8.4 years. The 884 subjects out of this group who underwent posttrial monitoring were asked to attend annual UKPDS clinics for the first 5 years, but no attempt was made to maintain their previously assigned blood pressure therapies. Questionnaires were completed each year by subjects and general practitioners in order to follow the subjects who were unable to attend the clinic in years 1–5. Later, during years 6–10, questionnaires were used for all subjects. Seven aggregate clinical outcomes from the UKPDS were studied on an intention-to-treat basis, including (1) any diabetes-related end point; (2) diabetes-related death; (3) death from any cause; (4) myocardial infarction; (5) stroke; (6) peripheral vascular disease; and (7) microvascular disease.

Differences in blood pressure between the two treatment groups, which were differentiated during the trial, disappeared within 2 years after termination of the trial. In fact, 51% of the trial participants had died by the time the 10-year posttrial monitoring period ended in 2007. The significant relative risk reductions that were found during the trial for any diabetes-related end point, diabetes-related death, microvascular disease, and stroke in the group receiving tight, as compared with less tight, blood pressure control were not sustained during the posttrial follow-up. No risk reductions were seen during or after the trial for myocardial infarction or death from any cause, but a risk reduction for peripheral vascular disease associated with tight blood pressure control became significant.

Legacy Effects of Therapy

The investigators concluded that the benefits of previously improved blood pressure control were not sustained when between-group differences in blood pressure were lost. Early improvement in blood pressure control in subjects with both type 2 diabetes and hypertension was associated with a reduced risk of complications, but it appears that good blood pressure control must be continued if the benefits are to be maintained.

Based on the findings of these two UKPDS follow-up studies, with glucose control, it matters both how well a patient is treated now and how well the patient was treated in the past; but with blood pressure, it seems to be related only to current therapy. These findings underscore the importance of consistently maintaining good blood pressure levels over time in order to minimize the risk of diabetic complications in type 2 diabetes.

The prolonged benefits of good glucose control are referred to as a legacy effect of therapy. This effect is likely related to the vascular damage that can occur from the insult of a metabolic abnormality. On the other hand, the adverse consequences of elevated blood pressure appear to be due to a pressure effect on the walls of blood vessels. Therefore, with two different pathophysiologic models responsible for vessel wall disease, the adverse effect of either of these states (hyperglycemia or hypertension) is, not surprisingly, affected differently by past good control. Good blood glucose control is thus associated with a lasting improvement in vascular outcomes, but tight control of blood pressure is not associated with a legacy effect of therapy in type 2 diabetes.

Conclusions

The clinical lesson from the UKPDS follow-up studies is that, although the risks of complications of hypertension might be mitigated with initiation of treatment even after a prolonged elevation of blood pressure, it is particularly necessary to treat hyperglycemia appropriately from the outset of type 2 diabetes.

In the UKPDS, whereas early improvement in blood pressure control in type 2 diabetes patients with hypertension was associated with fewer complications, it was necessary to continue with good blood pressure control to preserve this benefit. However, early improvement in glycemic control in type 2 diabetes patients was associated with a continued reduction in micro- and macrovascular events even after the early improvement in glycemic control was lost.

Therefore, according to the results of the UKPDS follow-up study, it is not appropriate to delay treatment of glycemia until complications occur.

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