UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulfonylurea–treated type 2 diabetes.

U.K. Prospective Diabetes Study Group.


OBJECTIVE: To assess the efficacy over 3 years of the addition of metformin to maximum sulfonylurea therapy in type 2 diabetes. RESEARCH DESIGN AND METHODS: This multicenter randomized open–controlled trial was conducted in outpatient diabetes clinics in 15 U.K. hospitals. A total of 591 subjects who had already been randomly allocated to sulfonylurea therapy were taking maximum doses with suboptimal glycemic control, i.e., raised fasting plasma glucose (FPG) concentrations of 6–15 mmol/l but no significant hyperglycemic symptoms. The main outcome measures included FPG, glycated hemoglobin, protocol–defined marked hyperglycemia, body weight, blood pressure, fasting plasma lipids, compliance, and hypoglycemia and other side effects. RESULTS: After the addition of metformin, FPG concentrations decreased by mean (95% CI) −0.47 (−0.82 to −0.13) mmol/l over 3 years compared with an increase of 0.44 (0.07–0.81) mmol/l in subjects on sulfonylurea alone (P < 0.00001). Median FPG concentrations at 3 years were 8.6 vs. 9.9 mmol/l, respectively (P < 0.00001), and HbA1c values were 7.5 and 8.1%, respectively (P = 0.006). Adjustment for baseline BMI or FPG concentration did not affect response to therapy. Only 7% of those allocated to sulfonylurea plus metformin developed protocol–defined marked hyperglycemia compared with 36% of those allocated to sulfonylurea alone (P < 0.0001). Fasting plasma lipids, body weight, and blood pressure did not change significantly. The incidence of hypoglycemic episodes did not differ between groups: 4% on sulfonylurea plus metformin and 2% on sulfonylurea alone (NS). CONCLUSIONS: Early addition of metformin improved glycemic control in patients with suboptimal glycemic control while taking maximum sulfonylurea therapy, irrespective of obesity or baseline FPG concentrations.