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

U.K. Prospective Diabetes Study Group.

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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.