Troglitazone Directly Increases HDL Cholesterol Levels

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Hyperglycemia in patients with type 2 diabetes is caused by peripheral insulin resistance, increased endogenous glucose production, and inadequate pancreatic insulin secretion (1). Poorly controlled type 2 diabetic patients frequently develop dyslipidemia, characterized by elevated triglyceride levels and reduced HDL cholesterol levels. Troglitazone has been shown to improve insulin resistance in type 2 diabetic patients, resulting in beneficial effects on their lipid metabolism. However, its precise mechanism has not yet been identified.

In the present study, we evaluated the effects of 24-week treatment with troglitazone (400 mg/day) in 282 consecutive patients with type 2 diabetes (154 men and 128 women, mean age 59 years, BMI 23.9 ± 4.0 kg/m^2). Of these, 146 patients were treated with a combination of sulfonylureas, and the remaining 136 patients were treated with troglitazone alone.

Mean levels of fasting plasma glucose significantly decreased from 152 ± 48 mg/dl (mean ± SD) at baseline to 126 ± 30 mg/dl (−17%) at week 24. Mean levels of plasma HbA_{1c} also decreased from 6.9 ± 1.4% at baseline to 6.1 ± 1.0% (−11.6%) at week 24. Throughout the study period, there were no significant alterations in body weight, systolic and diastolic blood pressures, or mean levels of serum and LDL cholesterol, as estimated by Friedewald's formula. In contrast, mean levels of serum triglyceride significantly decreased, and those of HDL cholesterol significantly increased. At week 24, triglyceride levels had decreased from 130 ± 73 mg/dl at baseline to 96 ± 46 mg/dl (−26%), and HDL cholesterol levels had increased from 54 ± 18 to 66 ± 21 mg/dl (+22%). These significant changes in both triglyceride and HDL cholesterol levels could be observed again, even in the case of treatment with a combination of sulfonylureas. To investigate the relationship between the effects of troglitazone on glucose and lipid metabolism, we divided patients into two groups according to the effects of troglitazone on fasting plasma glucose levels at week 12. Among 173 patients (88 men and 85 women) who showed reduced glucose levels, triglyceride levels had significantly decreased (−42 mg/dl, −29%) and HDL cholesterol levels had significantly increased (+10 mg/dl, +18%) at week 24. Unexpectedly, in 53 patients (36 men and 17 women) who did not show any reduction in their fasting glucose levels, HDL cholesterol levels also increased significantly (+21 mg/dl, +41%), even though triglyceride levels in these patients showed small and insignificant reductions.

Troglitazone alone or in combination with a fixed dose of sulfonylureas consistently reduced triglyceride levels significantly when compared with the placebo group (2–4) or baseline values (5–8). In addition, HDL cholesterol levels slightly but significantly increased in two (6,7) of these seven trials (2–8). Ghazzi et al. (9) have reported the largest increase in HDL cholesterol level (+0.16 mmol/1, +16%) as a result of troglitazone administration in association with a significant decrease in triglyceride levels (−1.01 mmol/1, −32%) compared with baseline levels (9). However, a causal relationship among the changes in glucose, triglyceride, and HDL cholesterol levels has not been fully established. The findings of the present study, that significant increases in HDL cholesterol levels were observed even when plasma glucose levels did not improve, suggest the possibility that troglitazone might have a direct effect on HDL metabolism.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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