

Combination Therapy With Fenofibrate and Rosiglitazone Paradoxically Lowers Serum HDL Cholesterol

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Thiazolidinediones (TZDs) are insulin sensitizers widely used in the treatment of type 2 diabetes (1). Fibrates are lipid-lowering drugs that lower triglycerides (TGs) and increase HDL cholesterol (2). Individually, fibrates and TZDs generally raise HDL cholesterol. In this study, we report that certain patients treated with a combination of fibrates (fenofibrate) and a TZD (rosiglitazone) show a paradoxical fall in HDL cholesterol levels.

Chart reviews were performed to identify patients on combination therapy with TZDs and fibrates. Information about age, BMI, sex, type of treatment, duration of either single (fibrate) or combination therapy (fibrate + TZD), and blood lipids was collected. There were nine HIV-positive patients who started combination treatment with fenofibrate and rosiglitazone, of whom all experienced a decrease in serum HDL cholesterol concentrations (Table 1). We compared these changes in HDL cholesterol

concentrations with those of HIV-negative patients with type 2 diabetes ($n = 12$) initiating the same combination therapy of fenofibrate and rosiglitazone as well as with HIV-positive patients on fibrate therapy alone ($n = 12$). The patients with diabetes had a significant decrease in HDL cholesterol concentrations, whereas HIV-positive patients on fibrate therapy alone had an expected significant increase in HDL cholesterol concentrations. None of the patients had any other changes from concomitant drugs that are also known to affect HDL cholesterol concentrations (including antiretroviral therapy). On cessation of one of the two drugs (either the fibrate or rosiglitazone), HDL cholesterol concentrations returned to the same level that they were before starting combination therapy. Effect of combination therapy on TG concentrations was variable. Fibrate treatment alone decreased TG concentrations by $27 \pm 40\%$ (\pm SD), while it appeared as if combination treat-

ment increased TG concentrations by $48 \pm 60\%$. There was no major change in serum TGs in the group with diabetes ($-9 \pm 44\%$).

The finding of a decreased serum HDL cholesterol concentration in patients on a combination of fenofibrate and the TZD rosiglitazone is novel and unexpected. One mechanism could be a drug interaction. This appears unlikely; fenofibrates are metabolized primarily by the hepatic cytochrome P450 4A6 (3), while rosiglitazone is metabolized by the cytochrome P450 2C8 (4). Another explanation may be related to the fact that both drugs bind to the peroxisome proliferator-activated receptor (PPAR) family of receptors. The blood lipid improvement by fibrates is activated through ligand binding to PPAR α (5), whereas the effects from rosiglitazone occur through binding to the PPAR γ receptor (1,6). However, because both receptors have a distinct tissue expression, competition at the receptor level seems unlikely. PPAR α is expressed at high levels in the liver, whereas PPAR γ is expressed in many tissues, with the highest concentrations in adipose and skeletal muscle (6).

The observation of a reduced HDL cholesterol level raises some important questions, which we hope will be addressed. First, what is the mechanism behind the paradoxical HDL cholesterol lowering following combination treatment with fibrates and rosiglitazone? Second, how frequent is the reduction in HDL cholesterol following combination treatment in other patient populations? Third, what are the specific characteristics for individuals who respond with decreased serum HDL cholesterol concentrations? The range for the HDL cholesterol change was -4 to -65% in the HIV-positive patients, whereas patients with diabetes had changes between 5 to -50% . Fourth, is the kinetics (turnover) of HDL cholesterol affected by combination treatment, which would be of importance to the potential

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Abbreviations: PPAR, peroxisome proliferator-activated receptor; TG, triglyceride; TZD, thiazolidinedione.

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

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Table 1—Comparison of demographics and lab data between groups A–C

	A (control): HIV ⁺ on fenofibrate	B: HIV ⁺ on TZD + fenofibrate	C: diabetic patients on a TZD + fenofibrate	P
n	12	9	12	—
Age (years)	50.4 ± 7.3	50.1 ± 9.2	57.7 ± 9.3	0.106
Sex (F/M)	—/12	1/8	3/9	0.180
BMI (kg/m ²)	24.1 ± 3.5 ^a	26.0 ± 4.5	30.0 ± 4.1 ^a	0.016
Treatment duration (months)	7 ± 4	6 ± 3 ^a	17 ± 11 ^a	0.043
Blood lipids				
HDL cholesterol				
Initial (mmol/l)	0.91 ± 0.30	0.80 ± 0.20	0.94 ± 0.24	0.466
Treatment (mmol/l)	1.07 ± 0.31 ^{a,b}	0.56 ± 0.25 ^a	0.74 ± 0.32 ^b	0.003
Change (%)	19 ± 13 ^{a,b}	−33 ± 17 ^{a,c}	−20 ± 17 ^{b,c}	<0.001
TG				
Initial (mmol/l)	7.29 ± 2.58 ^a	5.10 ± 2.30	3.24 ± 1.26 ^a	0.002
Treatment (mmol/l)	4.69 ± 1.96	7.25 ± 4.44	3.35 ± 1.39	0.072
Change (%)	−27 ± 40 ^{a,b}	48 ± 60 ^a	−9 ± 44 ^b	0.043

Data are means ±SD. Mean values were compared with Kruskal-Wallis ($P < 0.05$ for significance), with Mann-Whitney used as the post hoc test (results with the same superscripts are significantly different).

atherogenic effect of this combination? Until these questions have been answered, we suggest that combinations of fenofibrate and rosiglitazone be used with caution.

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