HIGH INCIDENCE OF REDUCED SERUM HDL CHOLESTEROL IN DIABETIC PATIENTS TREATED WITH ROSIGLITAXONE AND FIBRATE

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Abstract:
To evaluate the effect of rosiglitazone, fenofibrate, or their combined use on plasma lipids in normoglycemic healthy adults. Methods and Results. Subjects were randomized in a double-blind fashion to rosiglitazone + placebo, fenofibrate + placebo, rosiglitazone + fenofibrate, or matching double placebo. The between-group difference in the change in fasting TG, high-density lipoprotein cholesterol (HDL-C), LDL-C, and plasma apolipoproteins A-I, A-II, and C-III level were compared after 12 weeks of treatment.
A total of 548 subjects were screened and 41 met the inclusion criteria. After 12 weeks of therapy, the median change in the triglyceride levels showed a significant reduction ranging from 47 to 55 mg per deciliter in the fenofibrate only and rosiglitazone/fenofibrate groups compared with placebo ($P = 0.0496$).
However, the rosiglitazone only group did not show significant change in triglyceride level. The change in the Apo AII showed increase in all the treatment groups compared with placebo ($P = 0.009$). There was also significant change in the Apo CIII that showed reduction of its level in the fenofibrate only and rosiglitazone/fenofibrate groups ($P = 0.0003$). Rosiglitazone does not appear to modulate hypertriglyceridemia in patients with elevated triglycerides independent of glucose metabolism.
Keywords: *Reduced Serum HDL; Rosiglitaxone; Fibrate*

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INTRODUCTION:

The thiazolidinediones (TZDs), which include troglitazone, rosiglitazone, and pioglitazone, correct hyperglycemia in diabetic patients by increasing insulin sensitivity in both the liver and skeletal muscles. The mechanism involved in the plasma lipid and lipoprotein changes induced by thiazolidinediones (TZDs) remains unclear. It is possible that these agents indirectly alter plasma lipid and lipoprotein levels indirectly by improving insulin sensitivity and glycemic control or directly by influencing lipoprotein synthesis and/or catabolism. The intent of this study is to assess whether rosiglitazone affects lipids independent of glycemic control by testing the hypothesis in normoglycemic patients with elevated TG. The presence of synergistic effect when combined with fenofibrate will be evaluated as well.

Clinical trials using TZDs in type 2 diabetic subjects have observed that these agents also favorably impact plasma lipid and apolipoprotein concentrations. Following eight weeks of treatment with rosiglitazone (4 mg, twice daily) in 243 type 2 diabetic patients, the mean HDL-C increased by 6% and TG by 2%. The increase in the LDL-C concentration (9%) was accompanied by a shift in small, dense LDL to large, buoyant LDL in 52% of the treated subjects. The shift in LDL size occurred independent of a significant triglyceride reduction, which is in contrast to several studies reporting that increases in LDL size are significantly correlated with a decrease in the plasma concentrations of total and very-low-density lipoproteins (VLDL) and triglycerides. The mechanism involved in the plasma lipid and lipoprotein changes induced by TZDs remains unclear. It is possible that these agents indirectly alter plasma lipid and lipoprotein levels indirectly by improving insulin sensitivity and glycemic control or directly by influencing lipoprotein synthesis and/or catabolism.

Three distinct peroxisome proliferator-activated receptors (PPARs), termed alpha, beta, and gamma, modulate intracellular lipid and glucose metabolism through controlling gene expression when activated. Activation of PPAR-alpha leads to decrease production of ApoC-III, which in turn increases the synthesis of lipoprotein lipase, and triglyceride catabolism. Gene expression for the synthesis of ApoA-I and ApoA-II is also enhanced by activation of PPAR-alpha, resulting in increase in HDL concentration. Fibric acid derivatives (gemfibrozil and fenofibrate) reduce triglycerides and increase HDL-C by binding to the PPAR-alpha nuclear receptor. Theoretically, TZDs given to nondiabetic individuals should not modulate lipid through its effect on PPAR-gamma, and any change would be anticipated to be due to binding to PPAR-alpha. Thus, it would result in decrease in the plasma concentration of ApoC-III and an increase in ApoA-I and ApoA-II, with a subsequent rise in HDL-C and reduction in triglyceride concentration.

The Rosiglitazone and Fenofibrate Additive Effects on Lipids (RAFAEL) trial was designed to evaluate the effect of rosiglitazone when combined with fenofibrate on the plasma lipid and lipoprotein concentrations assuming direct influence on the synthesis of the apolipoproteins that are responsible for VLDL and HDL metabolism in normo-glycemic individuals with elevated TG as well as the mechanism of action of rosiglitazone.

METHODS:

Oversight

High Incidence of Reduced Serum HDL Cholesterol in Diabetic Patients Treated with Rosiglitaxone and Fibrate protocol was reviewed and approved by concerned authorities.

Population

All patients provided written informed consent to participate in the study. Patients were eligible if they were 18 years of age or older, had a fasting glucose <100 mg/dL, fasting LDL-C <160 mg/dL, and a triglyceride <400 mg/dL. Patients taking any cholesterol lowering medication prior to entering the study underwent a "wash-out" period of two weeks.

Inclusion and Exclusion Criteria

Patients were excluded if they had a history of congestive heart failure, evidence of renal impairment (Cr > 1.4 mg/dL), history of liver disease (ALT and/or AST above the upper level of normal), known diabetes mellitus or impaired fasting glucose (fasting glucose > 100 mg/dL), pregnant or breast feeding, prior history of an acute coronary syndrome, myocardial infarction, or coronary revascularization, life-threatening disease with an estimated survival of less than 3 years, or inability to take rosiglitazone and/or fenofibrate.

Design of Study

At the beginning of the trial, candidates were instructed to fast for 12 to 15 hours for the initial visit. Baseline fasting lipid profile with direct LDL-C measurement, fasting glucose, hepatic function and plasma concentrations of apolipoproteins A-I, A-II, and C-III were drawn at the initial visit. Based on the

concentration of total cholesterol, triglyceride, and glucose, eligible subjects were randomized within 7 days of providing the initial blood sample.

Subjects, who met the inclusion criteria, were then randomized to one of 4 groups: rosiglitazone (dose 8 mg daily) plus placebo; fenofibrate (145 mg daily) plus placebo; fenofibrate (145 mg daily) plus rosiglitazone (dose 8 mg daily); or double placebo for a total of 12 weeks. At the mark of 12 weeks (final visit), the initial laboratory collections were repeated to assess the difference in concentration of fasting glucose, insulin, hepatic transaminases, fasting lipid profile, apolipoproteins, HDL size, LDL size, and statistical difference from baseline.

Statistical analysis

The null hypothesis was that there will be no difference in the serum triglyceride level between treatments. The alternative hypothesis is that there will be at least a 20% decrease in the serum triglyceride level in the fenofibrate, rosiglitazone, fenofibrate, and rosiglitazone treatment groups relative to the placebo group. The sample size was determined to be 16 subjects in each arm (64 subjects total) based on eight comparisons between groups before and after treatment with 80% power and a 95% level of confidence.

RESULTS:

A total of 548 patients were screened at one centre. Of the 548 patients who were screened, a total of 41 patients met the inclusion criteria and were randomly assigned one of the pre-specified study groups. With ascertainment of end points, was completed in 73% of the patients in the study. There were seven (17%) patients that did not complete the study due to either loss of follow up or adverse events that make them to withdraw from the study. The baseline characteristics of the patients who were enrolled in the study are shown in Table 1. The mean age was 56 years; 48% of the patients were male, and 39% of the patients were treated for hypertension. At baseline, the mean total cholesterol was 214 mg per deciliter, mean HDL cholesterol was 48 mg per deciliter, mean LDL cholesterol was 121 mg per deciliter, and mean triglyceride was 240 mg per deciliter.

Table 1: Baseline characteristics and laboratory findings with posttreatment changes.

Group	Placebo N = 10 Mean ± SD	Fenofibrate N = 9 Mean ± SD	Rosiglitazone N = 8 Mean ± SD	Combined N = 7 Mean ± SD	ANOVA Rank P-value
Age	57.4 ± 11.1	61.2 ± 11.6	57.3 ± 8.4	54.7 ± 9.5	
M : F	6 : 4	3 : 6	5 : 3	3 : 4	
Pre-TG	206 ± 65	278 ± 126	234 ± 58	239 ± 73	
Post-TG	202 ± 53	192 ± 64	240 ± 115	172 ± 27	P = 0.212
(%Δ)	(7.6% ± 51.0%)	(−2.2% ± 26.0%)	(7.4% ± 48.9%)	(20.0% ± 36.5%)	
Pre-HDL-C	48 ± 9	41 ± 8	52 ± 19	52 ± 14	
Post-HDL-C	48 ± 9	47 ± 7	50 ± 17	53 ± 9	P = 0.342
(%Δ)	(1.7% ± 10.5%)	(14.5% ± 21.6%)	(1.9% ± 24.6%)	(5.8% ± 16.4%)	
Pre-LDL-C	124 ± 46	111 ± 40	145 ± 24.6%	106 ± 41	
Post-LDL-C	128 ± 39	118 ± 32	140 ± 41	102 ± 31	P = 0.692
(%Δ)	(13.7% ± 47.8%)	(2.6% ± 29.3%)	(−.5% ± 27.4%)	(37.3% ± 141.6%)	
± pre-Tot C	204.4 ± 57.9	213.6 ± 39.0	238.4 ± 39.5	215.7 ± 36.6	
Post-Tot C	227.4 ± 37.2	199.0 ± 51.2	230.9 ± 52.2	201.1 ± 36.5	P = 0.372
(%Δ)	(25.8% ± 70.2%)	(−7.7% ± 26.1%)	(−2.3% ± 21.3%)	(−5.0% ± 21.6%)	

After 12 weeks of therapy, the change in the triglyceride levels showed a significant reduction ranging from 47 to 55 mg per deciliter in the fenofibrate only and rosiglitazone/fenofibrate groups compared with placebo ($P = 0.0496$) as mentioned in below Figure 1. However, the rosiglitazone only group did not show significant change in triglyceride level. There was also a significant reduction in the HDL levels showing a significant reduction ranging from 20 to 22 mg per deciliter compared with placebo ($P = 0.0152$) as mentioned in below Figure 1. There was no significant difference in the median change in the total cholesterol or LDL cholesterol between the groups as mentioned in below Figure 1. In regards to the apolipoproteins, the median change in the Apo AII showed a significant increase in all the treatment groups compared with placebo ($P = 0.009$) as mentioned in below Figure 2. There was also significant median change in the Apo CIII that showed reduction of its level in the fenofibrate only and rosiglitazone/fenofibrate groups ($P = 0.0003$) as mentioned in below Figure 2. There was no difference in median change in Apo AI as mentioned in below Figure 2.
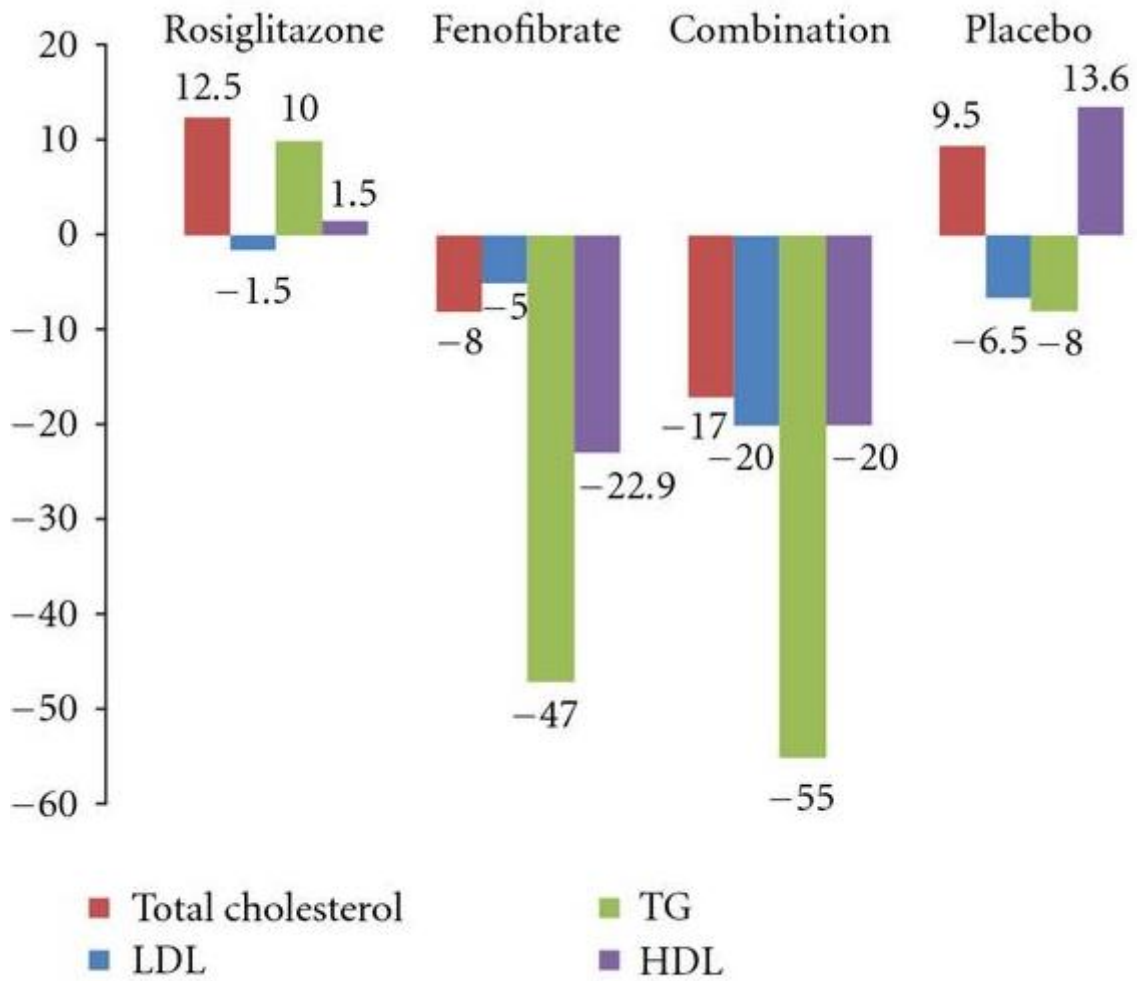
Figure 1: Median change in lipid profile after treatment.
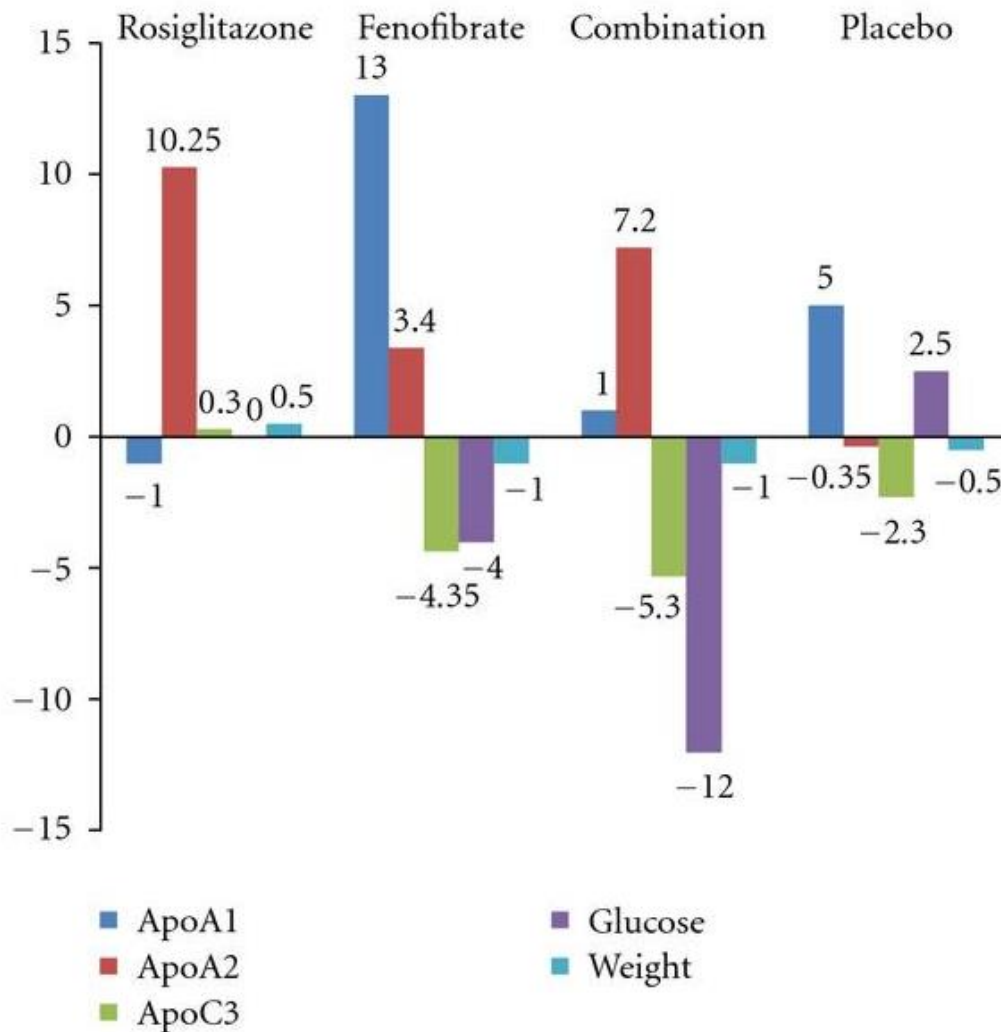
Figure 2: Median change before and after treatment in Apo subparticle, blood sugar, and weight.

DISCUSSION:

Clinical trials have shown that the use of thiazolidinedione in type 2 diabetic patients has shown favorable impact in plasma lipid and lipoprotein concentrations in addition to glycemic control. The mechanism involved in the plasma lipid and lipoprotein concentration changes in type 2 diabetics by thiazolidinedione remains unclear. The high incidence of reduced serum HDL cholesterol in diabetic patients treated with rosiglitaxone and fibrate trial is the first study performed in the literature to evaluate the effect of thiazolidinedione to plasma lipid and apolipoprotein concentration in normoglycemic population to assess mechanism of action. After 12 weeks of therapy, the median change in the triglyceride level was only significant in the group that received fenofibrate as expected due to its

known mechanism of action. We also saw significant changes in the fenofibrate/rosiglitazone group which were most likely due to the fenofibrate alone since it was very similar change compared to the fenofibrate alone. In addition, the rosiglitazone group did not show a significant change in the triglyceride level. Therefore, combination therapy of rosiglitazone and fenofibrate did not show trend towards additive reduction in triglyceride levels.

In regards to the apolipoproteins, all treatment groups showed significant increase in the median change of Apo AII compared to placebo. Also, median change of Apo CIII showed significant reduction of its level in the fenofibrate only and fenofibrate/rosiglitazone groups. However, this change was not seen in the rosiglitazone group only. As a result, rosiglitazone

does not affect Apo CIII levels and subsequently lipoprotein lipase activity as anticipated. However, rosiglitazone increases Apo AII levels without observed change in HDL-C in patients with type 4 hyperlipidemia with normoglycemia. Fibrates impact on TG reduction is known to correlate with its reduction of Apo CIII in animal models. The absence of impact on ApoC III and TG simultaneously by Rosi does not negate the fact that it might bind to PPAR alpha and therefore affecting ApoAII, but it negates its independent impact on lipid metabolism as a PPAR-alpha strong agonist independent of glucose metabolism.

CONCLUSION:

In conclusion, the results from our study suggest the favorable effects of rosiglitazone on plasma lipid and lipoprotein concentrations in diabetic patients noted in prior studies are not independent of glucose control as noted in our normoglycemic cohort of subjects.

REFERENCES:

1. B. Staels, N. Vu-Dac, V. A. Kosykh et al., "Fibrates downregulate apolipoprotein C-III expression independent of induction of peroxisomal acyl coenzyme A oxidase. A potential mechanism for the hypolipidemic action of fibrates," Journal of Clinical Investigation, vol. 95, no. 2, pp. 705–712, 1995.
2. C. D. Gardner, S. P. Fortmann, and R. M. Krauss, "Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women," Journal of the American Medical Association, vol. 276, no. 11, pp. 875–881, 1996.
3. C. M. O'Rourke, J. A. Davis, A. R. Saltiel, and J. A. Cornicelli, "Metabolic effects of troglitazone in the Goto-Kakizaki rat, a non-obese and normolipidemic rodent model of non-insulin-dependent diabetes mellitus," Metabolism, vol. 46, no. 2, pp. 192–198, 1997
4. J. Coresh and P. O. Kwiterovich, "Small, dense low-density lipoprotein particles and coronary heart disease risk: a clear association with uncertain implications," Journal of the American Medical Association, vol. 276, no. 11, pp. 914–915, 1996.
5. M. J. Stampfer, R. M. Krauss, J. Ma et al., "A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction," Journal of the American Medical Association, vol. 276, no. 11, pp. 882–888, 1996.
6. M.-K. Lee, P. D. Miles, M. Khoursheed et al., "Metabolic effects of trogiltazone on fructose-induced insulin resistance in the rat," Diabetes, vol. 43, pp. 1435–1439, 1995.
7. T. P. Ciaraldi, A. Gilmore, J. M. Olefsky, M. Goldberg, and K. A. Heidenreich, "In vitro studies on the action of CS-045, a new antidiabetic agent," Metabolism, vol. 39, no. 10, pp. 1056–1062, 1990
8. Troglitazone Study Group, "The metabolic effects of troglitazone in non-insulin dependent diabetes," Diabetes, vol. 46, supplement 1, p. 149A, 1997