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Fenofibrate, HDL, and Cardiovascular Disease in Type-2 Diabetes: The DAIS Trial

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Abstract

Background—There are conflicting reports on the role of fibrates in CVD-risk. Several studies indicate beneficial effects of fibrates on CVD risk in type-2 diabetic patients. We tested how fenofibrate changes lipoprotein subfractions and glucose homeostasis in type-2 diabetic patients.

Study design—Selected markers of lipid and glucose homeostasis and inflammation were measured in 204 diabetic patients who participated in the Diabetes Atherosclerosis Intervention Study (DAIS) and were randomly assigned to 200 mg fenofibrate or placebo for a minimum of 3 years.

Results—Triglyceride and remnant-like particle cholesterol (RLP-C) levels decreased significantly, as well as LpPLA2 activity on fenofibrate compared to placebo. HDL-C and apoA-I levels increased on fenofibrate. In contrast to other lipid-modifying drugs that increase HDL-C and the large (α -1) HDL particles; on fenofibrate, the medium and small (α -3 and α -4) HDL particles increased. Although, pre β -1 HDL particle levels decreased significantly from baseline on fenofibrate, they remained elevated compared to normal level (28.6 mg/dl vs. <15 mg/dl). The concentrations of total LDL-C and small dense LDL-C did not change on fenofibrate compared to placebo. On fenofibrate, glycoalbumin levels increased moderately, while insulin and adiponectin levels did not change.

Conclusion—On fenofibrate, lipid homeostasis improved and Lp-PLA2 activity decreased while there was no improvement in glucose homeostasis. Despite of increasing HDL-C and apoA-I levels fenofibrate failed to change the HDL subpopulation profile beneficially.

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Keywords

fenofibrate; lipoproteins; sdLDL-C; HDL particles; CVD risk

INTRODUCTION

The major cause of death in patients with type-2 diabetes is cardiovascular disease (CVD) (1, 2). Diabetic patients, if they are not receiving insulin, often have decreased high-density lipoprotein cholesterol (HDL-C) and elevated triglyceride (TG) levels (3). In the Helsinki Heart Study (HHS) and the Veterans Affairs HDL Intervention Trial (VA-HIT), administration of gemfibrozil, a PPAR- α agonist, caused a concomitant decrease in CVD risk by increasing HDL-C and decreasing TG levels (4, 5). However, in a post-hoc analysis of VA-HIT, Robins *et al.* concluded that the CVD risk-lowering effects of gemfibrozil could not be entirely explained by the modest increase in HDL-C observed in the treatment arm (6). The reduction in CVD was greatest in those individuals who had at least some of the characteristics of the metabolic syndrome both in the HHS and the VA-HIT (4, 5). In the latter, Rubins *et al.* found that the beneficial effects of gemfibrozil on CVD events were greater in patients with either type-2 diabetes or pre-diabetes (7). Moreover, measurement of HDL subpopulations in VA-HIT participants indicated that gemfibrozil decreased the levels of the large, anti-atherogenic α -1 HDL particles; though baseline levels of α -1 HDL were inversely associated with future CVD events (8, 9).

In previous lipid-lowering intervention trials, only post-hoc subgroup analyses on people with diabetes have been presented. The Diabetes Atherosclerosis Intervention Study (DAIS) was the first study specifically designed to investigate whether correcting dyslipidemia in type-2 diabetes mellitus with fenofibrate would reduce coronary artery disease (CAD) as determined by angiography (10). We present an analysis on the effects of fenofibrate on LDL and HDL subpopulations and other emerging CVD risk factors on a subset of the DAIS study.

METHODS

Study design and population

DAIS took place in 11 clinical centers in Canada, Finland, France, and Sweden between 1996 and 1999, as described (10). Eligible participants were patients with dyslipidemia and type-2 diabetes aged 40–65 years, with or without previous coronary intervention. The lipid and diabetes eligibility characteristics were assessed during an 8-week baseline period during which participant were not receiving lipid-lowering medications of any kind but were following an American Heart Association/National Cholesterol Education Program Step 1 diet. The same diet was maintained throughout the treatment period. Lipid entry criteria were: total cholesterol to HDL-C ratio $\geq 4:1$, plus either an LDL-C concentration of 3.5–4.5 mmol/L and TG concentration of ≥ 5.2 mmol/L, or a TG concentration of 1.7–5.2 mmol/L and LDL-C ≥ 4.5 mmol/L. Diabetes entry criteria were: 1) type-2 diabetes as indicated by a fasting plasma glucose concentration without treatment of more than 7.8 mmol/L, or a plasma glucose concentration of 11.0 mmol/L or more 2 h after a 75 g oral glucose load, or

on treatment with glucose-lowering drugs; 2) diagnosis after age 35 years; 3) no history of ketoacidosis; and 4) adequate glycemic control (hemoglobin A1c <170% of laboratory's upper normal limit). DAIS was not a trial of the effects of glycemic control; as such participants' physicians were allowed to adjust the glucose-lowering drug regimen to optimize control in individual patients. Eligible patients were assigned to fenofibrate or placebo with stratification by sex, previous coronary intervention, and clinic center using a permuted blocks randomization procedure. The treatment period was at least 3 years. The protocol was reviewed and approved by each institution's ethics committee, and all participants gave informed consent to take part.

The DAIS analyzed 207 subjects in the fenofibrate and 211 in the placebo arm. Adequate plasma samples for further lipid measurements, including LDL and HDL subpopulation profile determination, were available for 108 subjects (51.2%) in the fenofibrate arm and 96 (45.5%) subjects in the placebo arm. Tufts University IRB committee approval was obtained for measurements and analyses performed at Tufts University.

Laboratory measurements

Fasting plasma samples stored at -80°C were used. Automated chemistries were measured on a Hitachi 911 analyzer. Total cholesterol, TG, and HDL-C were measured using kits from Roche. ApoA-I and highly-sensitive C-reactive protein (hsCRP) were measured using immunoturbidimetric assay kits from Wako Diagnostics (Richmond, VA). Small dense LDLC (sdLDL-C) and LDL-C were measured using kits from Denka-Seiken (Japan). Remnant-like particle cholesterol (RLP-C) was measured using kits from Kyowa-Medex (Japan). Insulin was measured with kits from Kamiya Biomedical (Seattle, WA), glycated albumin was measured with kits from Asahi Kasei Pharma (Japan), adiponectin was measured with kits from Otsuka Pharmaceutical (Japan). Lipoprotein-associated phospholipase A2 (Lp-PLA2) concentration and activity were measured at DiaDexus (San Francisco, CA).

ApoA-I-containing HDL particles were determined by 2-dimensional, non-denaturing gel electrophoresis followed by immunodetection and image analysis as described earlier (11,12). Briefly: in the first dimension, HDL was separated from 4 μl plasma on 0.7% agarose gel by charge into pre β -, α -, and pre α -mobility particles. In the second dimension, each sample was further separated according to size by non-denaturing polyacrylamide gel electrophoresis (on 3-35% concave gradient gels). Gels were electro-transferred to nitrocellulose membranes. ApoA-I was immunolocalized by incubation with monospecific goat human apoA-I antibody for 6 h. After the unbound first antibody was washed off with PBST, membranes were incubated with ^{125}I -labeled secondary antibody. Signals were quantitatively determined by image analysis using a FluoroImager (Molecular Dynamics, Sunnyvale, CA). Ten apoA-I-containing HDL subpopulations were delineated; signals were measured in each area and used for calculating the percent distribution. Concentration of each subpopulations were calculated by multiplying percentiles by total plasma apoA-I concentration.

Data and Statistical Analysis

Percent changes from baseline (visit 4) until a minimum of 3 years on therapy (visit 11) were calculated for all study parameters. Assays which yielded data outside of the measurable level were imputed as the lower or upper limit of detection as appropriate. Missing data secondary to plasma volume insufficiency was imputed using multiple imputation by chained equations (MICE) utilizing all lipid parameters in the MICE model. A burn in of 10 iterations was used to reach converge to produce each of 20 multiple imputations for the final analytical data set. Therefore, all 204 participants were included in the analysis. The normality of percent differences were assessed via a Shapiro-Wilk test, and means and standard deviations were calculated. Intra- and intergroup differences from baseline were analyzed with univariate and bivariate linear regression, respectively. The median and interquartile range of percent changes were reported for parameters which violated the normality assumption, and intra- and inter-group differences were analyzed with median quantile regression. All p values and confidence intervals are reported unadjusted, but the false discovery rate method was employed (13). All analyses were performed using STATA version 12 (StataCorp, TX, USA).

The proposal of this work was reviewed and approved by Tufts University Health Science Campus Institutional Review Board.

RESULTS

Table 1 shows plasma lipid, inflammatory and metabolic parameters in the fenofibrate and placebo groups. LDL-C increased 10.1% ($p=0.01$) in the placebo and 5.5% ($p=0.43$) in the fenofibrate group resulting in no significant difference between the two treatment groups ($p=0.57$). Concentration of sdLDL-C slightly increased in the placebo group (3.5% $p=0.48$) and slightly decreased (−11.8% $p=0.07$) in the fenofibrate group, but the difference between the two groups was not significant ($p=0.60$). TG decreased more in the fenofibrate (−29.1% $p<0.001$) than in the placebo group (−9.4% $p=0.04$) resulting in a significant treatment difference ($p<0.001$). Concomitantly, RLP-C decreased more in the fenofibrate (−31.9% $p<0.001$) than in the placebo (−7.2% $p=0.11$) group with a treatment difference of $p<0.001$. Fenofibrate increased HDL-C more (9.9% $p<0.001$) than placebo treatment (2.0% $p=0.13$) resulting in significant difference between the two groups ($p=0.002$). ApoA-I increased slightly more in the fenofibrate than in the placebo group (5.1% $p=0.002$ vs. 1.2% $p=0.39$), but the difference between the two treatments was not significant ($p=0.07$). Glycated albumin (GA), a marker of diabetes, increased significantly in both the placebo and the fenofibrate arms (5.3% $p=0.01$ and 10.3% $p<0.001$, respectively) with no significant difference between groups ($p=0.07$). Insulin and adiponectin levels did not change significantly in either group. While concentrations of hsCRP and Lp-PLA2 did not change significantly, the activity of Lp-PLA2 decreased significantly in the fenofibrate group (−13.4% $p<0.001$).

Table 2 shows data on apoA-I-containing HDL particles at baseline and on treatment. Concentration of the small pre β -1 HDL particles decreased more on fenofibrate than on placebo (7.8% $p=0.004$ vs. 3.7% $p=0.15$), but there was no significant difference between the two treatments ($p=0.27$). Concentration of the large α -1 particles increased on placebo

treatment by 11.5% ($p=0.03$) while decreased on fenofibrate by -2.0% ($p=0.80$), but no group significant difference between them ($p=0.12$). The medium-sized α -3 HDL particles increased more in the fenofibrate (21.4% $p<0.001$) than in the placebo (3.1% $p=0.33$) group and this difference was significant ($p<0.001$). The small-sized α -4 HDL particles also increased more in the fenofibrate than in the placebo group (17.3% $p<0.001$ vs. 7.5% $p=0.04$) but the difference was not significant ($p=0.08$).

DISCUSSION

The DAIS investigators reported that fenofibrate reduced the angiographic progression of CAD and that the beneficial effects of fenofibrate, at least partially, were due to the correction of lipoprotein abnormalities (10). In a follow-up paper, they reported that changes in LDL size and plasma lipid levels account for part of the antiatherogenic effects of fenofibrate in type-2 diabetes (14). In this sample set, we did not measure LDL size, but measured sdLDL-C concentration, the most atherogenic part of LDL (15, 16). We have seen a slight decrease in sdLDL-C on fenofibrate treatment, however, it was not significantly different from the changes on placebo treatment (group difference $p=0.60$). Therefore, we believe that the effects of fenofibrate on sdLDL-C do not impact CVD risk significantly.

Our findings in this study are similar to our former findings in VA-HIT. In that trial, gemfibrozil increased HDL-C and that was associated with increased levels of medium-sized (α -3) HDL particles but not with large-sized (α -1) HDL particles (8,9). In the present study, fenofibrate increased HDL-C and apoA-I significantly and that was associated with increased levels of the small and medium (α -4 and α -3) not the large (α -1) HDL particles. Although, fenofibrate significantly decreased concentrations of pre β -1 level from baseline, after treatment for three years it was still markedly higher (28.6 mg/dl) than our historic normal level (<15 mg/dl).

In contrast fibrates, statin- and/or niacin-mediated increase in HDL-C and decrease in TG levels are usually accompanied by significant decrease in small-sized pre β -1 and significant increase in large-sized α -1 HDL particles (17-21). Statins decrease TG-rich lipoproteins (TRL) in plasma through decreasing cholesterol synthesis, thereby reducing VLDL production/secretion by the liver. As a result, the concentrations of both major apoB-containing lipoprotein classes, VLDL and LDL, are reduced in plasma. Decreased level of apoB-containing lipoproteins causes lower cholesterol ester transfer protein (CETP) activity. In turn, decreased CETP activity results in increased α -1 and decreased pre β -1 HDL particle levels due to decreased fractional catabolic rate of the large α -1 particles.

In contrast to statins, which decrease synthesis/secretion of TRL from the liver, fibrates reduce plasma TG levels by increasing TRL clearance from plasma (22) by decreasing apoA-V and apoC-III levels [both are lipoprotein lipase (LPL) inhibitors] resulting in increased LPL activity (23-25). In patients with high TG level, LPL increases VLDL catabolism and as a result VLDL to LDL turn over (26). In this case, neither the number of apoB-containing particles nor CETP-mediated exchange of TG for cholesterol ester (CE) between TRL and α -1 HDL change. TG-enriched α -1 HDL particles are good substrates for hepatic lipase, which increases α -1 catabolism into smaller HDL particles (27).

In conclusion, we have verified that, similar to gemfibrozil, fenofibrate significantly increases HDL-C and significantly decreases plasma TG and RLP-C levels, but in our study, had only moderate effects on total LDL-C and sdLDL-C levels. Also, similar to gemfibrozil, fenofibrate-mediated improvements in TG and HDL-C levels were not accompanied with improvement in the HDL subpopulation profile. We believe that fenofibrate decreases CVD risk by ameliorating high plasma TG level by increasing LPL activity and by decreasing inflammation, marked by decreased Lp-PLA2 activity, but not by increasing HDL-C and improving the HDL subpopulation profile. Despite of fenofibrate treatment for three years, DAIS patients did not have normal HDL remodeling, which was indicated by the very low level of the large and the very high level of the small HDL particles.

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Highlights

1. Compared to placebo, fenofibrate significantly decreased TG, but not LDL-C.
2. Compared to placebo, fenofibrate significantly increased HDL-C, but not apoA-I.
3. Despite of decreasing TG and increasing HDL-C, there was no beneficial change in the HDL profile.
4. Fenofibrate's effect was more pronounced on the small HDL particles than on the large ones.

Table 1

Major lipid and metabolic parameters at baseline, on-treatment, and changes (%) during the follow up

Lipid parameters	Placebo (n=96)				Fenofibrate (n=108)			
	Baseline	On-treatment	% (min, max)	p value	Baseline	On-treatment	% (min, max)	p value
Total-C (mg/dl)	245 (45)	239 (41)	-1.0 (-4.7, 2.7)	0.60	239 (37)	222 (41)	-6.3 (-9.4, -3.2)	<0.001
LDL-C (mg/dl)	134 (47)	139 (38)	10.1 (2.5, 17.7)	0.01	130 (42)	133 (33)	5.5 (-8.4, 19.4)	0.43
sdLDL-C (mg/dl)	31.5 (22.4)	37.1 (22.9)	3.5 (-6.4, 13.5)	0.48	31.8 (15.6)	30.8 (21.4)	-11.8 (-24.6, 0.9)	0.07
Triglycerides [†] (mg/dl)	220 (135)	198 (120)	-9.4 (-18.3, -0.5)	0.04	219 (141)	144 (91)	-29.1 (-36.5, -21.5)	<0.001
RLP-C (mg/dl)	21.5 (8.9)	18.6 (8.8)	-7.2 (-16.1, 1.6)	0.11	21.7 (11.1)	13.4 (9.1)	-31.9 (-40.0, -23.7)	<0.001
HDL-C (mg/dl)	39.5 (7.5)	40.2 (9.1)	2.0 (-0.6, 4.7)	0.13	39.2 (8.5)	42.7 (11.3)	9.9 (5.9, 13.9)	<0.001
ApoA-I (mg/dl)	123 (18)	124 (20)	1.2 (-1.5, 3.9)	0.39	124 (19)	130 (27)	5.1 (1.9, 8.3)	0.002
Insulin [‡] (μIU/mL)	8.2 (8.4)	7.9 (8.8)	1.1 (-12.3, 14.4)	0.87	7.4 (9.8)	7.6 (9.0)	-1.7 (-14.7, 11.2)	0.79
Glycoalbumin (%)	19.8 (4.3)	20.4 (4.3)	5.3 (1.3, 9.3)	0.01	19.2 (4.1)	21.0 (4.8)	10.3 (6.6, 13.9)	<0.001
Adiponectin (μg/mL)	7.2 (3.0)	7.2 (2.9)	2.5 (-2.4, 7.4)	0.32	7.4 (3.4)	7.0 (3.1)	-3.0 (-7.7, 1.7)	0.21
hsCRP [‡] (mg/L)	2.2 (4.4)	2.9 (3.6)	10.1 (-7.8, 28.1)	0.26	1.8 (3.7)	2.4 (3.5)	7.1 (-13.2, 25.7)	0.49
Lp-PLA ₂ (ng/mL)	258 (66)	247 (54)	-1.6 (-7.2, 4.1)	0.58	259 (61)	244 (59)	-3.6 (-8.0, 0.7)	0.10
Lp-PLA ₂ activity (nmol/mL/min)	153 (34)	151 (58)	-0.6 (-8.2, 7.0)	0.87	150 (27)	132 (30)	-13.4 (-16.6, -10.2)	<0.001

Data shown as mean (SD) and univariate or multivariate regression of intra- and intergroup differences of percent change.

[‡] Data shown as median (IQR) and median quantile regression of intra- and intergroup differences of percent change.

All data shown are after multiple imputation.

* Significant using FDR after adjusting for all intergroup comparisons.

Table 2

Concentration and changes of apoA-I-containing HDL particles

	Placebo (n=96)				Fenofibrate (n=108)				Group Differences	
	Baseline	On-treatment	% (min, max)	p value	Baseline	On-treatment	% (min, max)	p value	(95% CI)	p value
Pre-β1	32.0 (10.2)	30.2 (9.3)	-3.7 (-8.6, 1.3)	0.15	31.6 (10.7)	28.6 (9.9)	-7.8 (-13.0, -2.7)	0.004	-4.2 (-11.6, 3.2)	0.27
Pre-β2	2.3 (1.4)	2.3 (1.2)	11.1 (-0.1, 22.2)	0.05	2.3 (1.4)	2.3 (1.3)	12.2 (-2.2, 26.6)	0.09	1.2 (-17.2, 19.5)	0.90
α1 [†]	6.8 (5.2)	7.5 (5.4)	11.5 (1.5, 21.4)	0.03	6.9 (5.9)	7.2 (6.3)	-2.0 (-18.2, 14.2)	0.80	-13.5 (-30.5, 3.6)	0.12
α2	32.9 (7.8)	33.4 (9.3)	2.6 (-1.9, 7.0)	0.26	32.7 (8.5)	34.4 (11.4)	6.6 (0.2, 13.0)	0.04	4.1 (-4.1, 12.2)	0.33
α3	24.2 (6.2)	24.2 (6.5)	3.1 (-3.1, 9.2)	0.33	24.5 (7.0)	28.7 (7.8)	21.4 (13.4, 29.3)	<0.001	18.3 (8.4, 28.2)	<0.001*
α4	13.7 (3.7)	14.2 (4.2)	7.5 (0.4, 14.5)	0.04	13.6 (3.9)	15.5 (5.7)	17.3 (8.6, 26.0)	<0.001	9.9 (-1.3, 21.0)	0.08
Pre-α1 [†]	1.5 (1.6)	1.8 (1.8)	16.6 (-3.0, 36.3)	0.10	1.7 (2.0)	1.5 (1.8)	-10.9 (-29.7, 7.9)	0.25	-27.5 (-58.8, -1.2)	0.04
Pre-α2	3.8 (1.5)	4.2 (1.6)	18.6 (8.6, 28.6)	<0.001	4.0 (1.5)	4.3 (1.9)	13.1 (3.2, 22.9)	0.01	-5.5 (-19.6, 8.5)	0.44
Pre-α3	2.8 (1.1)	2.9 (1.2)	8.9 (-0.1, 17.9)	0.05	2.9 (1.2)	3.4 (1.4)	23.4 (14.0, 32.9)	<0.001	14.5 (1.4, 27.7)	0.03
Pre-α4	1.7 (0.7)	1.7 (0.8)	8.1 (-2.3, 18.5)	0.12	1.8 (0.9)	1.9 (0.9)	13.8 (2.6, 24.9)	0.02	5.7 (-10.0, 21.3)	0.47

Data shown as mean (mg/dl) (SD) and univariate or multivariate regression of intra- and intergroup differences of percent change.

[†]Data shown as median (IQR) and median quantile regression of intra- and intergroup differences of percent change.

All data shown are after multiple imputation.

* Significant using FDR after adjusting for all intergroup comparisons.