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Short-Term Fenofibrate Treatment Reduces Elevated Plasma Lp-PLA₂ Mass and sVCAM-1 Levels in a Sub-Cohort of Hypertriglyceridemic GOLDN Participants

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Abstract

Background—High levels of lipoprotein-associated phospholipase A₂ (Lp-PLA₂) are associated with inflammation, atherosclerosis, and CHD events. In addition, Lp-PLA₂ has been linked to classical markers of endothelial activation, including soluble vascular cell adhesion molecule-1 (sVCAM-1). Though treatment with fenofibrate reduces Lp-PLA₂ mass, it is unclear whether fenofibrate reduces sVCAM-1 levels or whether there is an association between any changes observed in Lp-PLA₂ and sVCAM-1.

Methods—Concentrations of Lp-PLA₂ mass and sVCAM-1 levels were measured in plasma at baseline and after 3 weeks of fenofibrate treatment (160 mg/d) in 96 hypertriglyceridemic participants of the Genetics of Lipid-lowering Drugs and Diet Network (GOLDN) study.

Results—Lp-PLA₂ and sVCAM-1 were stratified by tertiles as determined by baseline levels of the respective target. Fenofibrate treatment resulted in increases of 30.1% in Lp-PLA₂ mass (p=0.0003) and 14.7% in sVCAM-1 levels (p=0.0096), but only in tertile 1 of either target. In contrast, Lp-PLA₂ mass was reduced by 35.3 % (p<0.0001) in tertile 3. Soluble VCAM-1 levels were significantly reduced by 7.74% (p=0.0109) and 17.2% (p<0.0001) in tertiles 2 and 3, respectively. No associations were observed between Lp-PLA₂ and sVCAM-1 at baseline or post-treatment.

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Conclusions—In conclusion, fenofibrate treatment in hypertriglyceridemic subjects reduced levels of LpPLA₂ mass and sVCAM-1, but only in those with elevated baseline levels of these biomarkers. The greatest reductions in LpPLA₂ levels were observed in individuals with LpPLA₂ concentrations indicative of increased CVD risk (>200 ng/mL).

Keywords

Fenofibrate; atherosclerosis; VCAM; Lp-PLA; triglyceride; GOLDN

INTRODUCTION

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) is a macrophage derived enzyme from the phospholipase A₂ family and primarily binds low-density lipoproteins (LDL) (1). Lp-PLA₂ activity has been shown to cause inflammation, oxidative stress, and endothelial activation (2, 3)—all well known contributors for increasing disease risk. A recent meta-analysis of over 32 prospective studies investigating the associations of Lp-PLA₂ with risk of disease development observed that both Lp-PLA₂ activity and mass show continuous associations with risk of coronary heart disease (4).

Functionally, LDL-associated Lp-PLA₂ contributes to oxidative stress and inflammation through its hydrolyzation of oxidized LDL (ox-LDL) to oxidized fatty acids and lysophosphatidylcholine (LysPC) (2, 5). LysPC is considered pro-atherogenic as it is a chemotactic attractant for macrophages, lymphocytes, and vascular smooth muscle cells. In addition, both oxidized fatty acids and LysPC have been shown to induce or augment expression soluble vascular cell adhesion molecule-1 (sVCAM-1) (6, 7)—a classical marker of endothelial activation, shed from the endothelium into circulation. Pharmacological therapy that reduces Lp-PLA₂ would thus be expected to reduce sVCAM-1 expression and potentially the risk of CVD.

The PPAR- α agonist, fenofibrate, has been shown to reduce Lp-PLA₂ mass (8) and activity (9-11). Whether the fenofibrate-mediated reduction in Lp-PLA₂ mass is associated with a concomitant decrease in sVCAM-1 has not been thoroughly explored in a larger study population, and indeed, the effect of fenofibrate on sVCAM-1 has proven inconsistent thus far (8, 12-15). It has also been observed that the effect of fenofibrate on a given therapeutic target is strongly associated with the target's baseline concentration. This phenomenon has been observed for traditional therapeutic targets such as serum triglyceride levels, but may have implications for markers of oxidation and endothelial activation as well. It is therefore necessary to test for a similar effect for both Lp-PLA₂ and sVCAM-1. Finally, it has been suggested that LpPLA₂ expression may be stimulated by ox-LDL (16), thus, changes in ox-LDL, LDL particle size, and total number will also be determined.

MATERIALS AND METHODS

Study design

This study is composed of a sub-population of the Genetics of Lipid-lowering Drugs and Diet Network (GOLDN) study. GOLDN is an NIH funded study consisting of families with 3-generation pedigrees seen in two clinical centers (Minneapolis, and Salt Lake City, UT) with predominantly Caucasian populations of European ancestry. The primary aim of the GOLDN study is to investigate the interaction of genetic and environmental factors on individual responses to fenofibrate treatment. The detailed design of the study is described elsewhere (17).

The study participants took part in an initial screening and were asked to suspend their use of lipid-lowering drugs for four weeks. Fasting baseline blood was collected 4 to 8 weeks later on two consecutive days before fenofibrate therapy. Participants were given a 28-day supply of open label 160 mg fenofibrate tablets (TriCor®, Abbott Laboratories, Chicago, IL) and were instructed to take one fenofibrate tablet with breakfast once daily for a minimum of 21 days.

2.2 Study population

Ninety-six participants were selected for elevated baseline triglyceride concentrations (>150 mg/dL). Written informed consent was obtained from each participant at the screening visit. The protocol was approved by the Institutional Review Boards at the University of Minnesota, the University of Utah, and Tufts University.

Biochemical Assays

Ox-LDL was measured in plasma using the ox-LDL ELISA enzyme immunoassay kit from Mercodia AB (Uppsala, Sweden). The ELISA is a two-site enzyme immunoassay using the direct sandwich technique where two antibodies recognize different antigenic determinants on the oxidized apolipoprotein B molecule.

Lipoprotein-Associated Phospholipase A₂: Lp-PLA₂ mass was measured in plasma using the the PLAC Test (Diadexus, San Francisco, CA), a microplate-based enzyme immunoassay. This test format is based on the principle of an ELISA using two highly specific monoclonal antibodies.

(Soluble) Vascular Cell Adhesion Molecule-1: sVCAM-1 was measured in plasma using the quantitative sandwich enzyme technique of the enzyme immunoassay Human sVCAM-1 Quantikine assay from R & D Systems (Minneapolis, MN).

Lipoprotein subclasses

Proton NMR spectroscopy was used to determine HDL and LDL particle sizes and number (Liposcience, Raleigh, NC).

Statistical analyses

The population was stratified into tertiles determined by the baseline values of the respective marker (either Lp-PLA₂ or sVCAM-1). Student t-test was used to determine differences between pre-and post-groups, with statistical significance reached when $P < 0.05$. To test the association of Lp-PLA₂ mass and sVCAM-1, Pearson correlations were used to examine levels at baseline and post-treatment as well as the changes observed following treatment.

RESULTS

Demographic information and baseline levels of HDL-C, LDL-C, and triglycerides (TGs) of the 96 GOLDN participants are listed in Table 1. Fenofibrate treatment resulted in significant increases in HDL-C (4.44 mg/dL, $p < 0.0001$) and LDL-C ($p = 0.0475$) and a significant decrease in TGs (-150.9 mg/dL, $p < 0.0001$).

Lp-PLA₂ mass at baseline and following 3 weeks of fenofibrate treatment (160 mg/day) are shown in Figure 1A. Data were stratified by tertiles according to baseline levels of Lp-PLA₂. Fenofibrate treatment resulted in a 30.1% mean increase in Lp-PLA₂ mass in individuals with the lowest baseline levels ($p = 0.0003$; tertile 1). No significant differences in Lp-PLA₂ mass were observed in tertile 2. In tertile 3, fenofibrate treatment resulted in a 35.3% mean decrease of Lp-PLA₂ mass ($p < 0.0001$).

Soluble VCAM-1 levels at baseline and following 3 weeks of fenofibrate treatment are shown in Figure 1B. As with Lp-PLA₂, sVCAM-1 data were stratified by tertiles according to baseline levels. Fenofibrate treatment resulted in a significant 14.7% mean increase ($p=0.0096$) in individuals with the lowest baseline levels of sVCAM-1 (tertile 1). Decreases in sVCAM-1 levels were observed in tertiles 2 and 3 following fenofibrate treatment—an 7.74% mean decrease was observed in tertile 2 ($p=0.0109$), while the largest mean decrease of 17.2% was observed in tertile 3 ($p<0.0001$).

Pearson correlations revealed no associations between either Δ Lp-PLA₂ mass and Δ sVCAM-1 levels (Figure 2A, $p=0.6804$) or between Δ Lp-PLA₂ mass and Δ ox-LDL concentrations (Figure 2B, $p=0.1086$). Baseline Lp-PLA₂ mass and baseline ox-LDL concentrations were found to be weakly and negatively associated ($\text{corr} = -0.23540$, $p=0.0210$) (Figure 2C). Non-significant correlations were found between change in triglyceride levels and change in either LpPLA₂ mass or sVCAM-1 levels following treatment (data not shown).

Following fenofibrate treatment, NMR analysis revealed a modest but significant decrease in mean HDL particle size (0.124 nm, $p=0.00163$) and increase in mean HDL particle number (4.24 mg/dL, $p<0.0001$). Expectedly, mean LDL particle size was found to increase (0.756 nm, $p<0.0001$), while mean LDL particle number decreased (193.7 nmol/L, $p=0.0001$) (data not shown).

DISCUSSION

As a class of drugs, fibrates are used clinically along with diet to treat hypertriglyceridemia and are intended to reduce the risk of atherosclerosis and CVD events by lowering triglycerides and favorably elevating HDL-C. While fibrates are effective in reducing triglyceride levels, results in the literature have been inconsistent as to whether fibrate treatment decreases CVD risk. The fibrate gemfibrozil was shown to significantly reduce CVD events, although only a portion of the benefits of the drug could be attributed to its effect on triglycerides and cholesterol (18). In contrast, recent studies in trials with diabetic patients such as the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials were unable to demonstrate significant effect on primary CV outcomes; however, secondary endpoint and sub-group analyses did reveal benefits of fenofibrate treatment (19, 20). In view of the widespread use of fenofibrate and the mixed results as to its effectiveness in preventing CVD events, more studies are needed to understand the action of fenofibrate beyond its triglyceride-lowering effect.

Lp-PLA₂ is an independent risk factor for CVD (4, 21, 22), and it has been recommended that patients with levels above 200 ng/mL be considered at increased risk for developing CVD (23). In the present study, we found that fenofibrate treatment resulted in significant reductions of Lp-PLA₂ in tertile 3 (35.3%), comprised of individuals with baseline Lp-PLA₂ levels ranging from 216-504 ng/mL (mean 288.9 ng/mL). The reductions in Lp-PLA₂ in tertile 3 resulted in a mean level below the 200 ng/mL cut point, which may account for a portion of the anti-atherosclerosis benefit of fenofibrate therapy in the subset of individuals with elevated baseline levels.

The means by which fenofibrate lowers Lp-PLA₂ is not completely understood though a number of mechanisms have been proposed. As the bulk of Lp-PLA₂ is associated with LDL fractions 2 and 3 (24), the reduction in Lp-PLA₂ mass and activity has been shown to correspond to the decreases in LDL-C levels and the shift from small to larger LDL particles produced by fenofibrate treatment (9, 12, 25, 26). It has also been suggested that LpPLA₂

may be partially regulated by ox-LDL (16), which is reduced with fenofibrate (27-29). However, we find no evidence to support such a mechanism as no associations were observed between Δ Lp-PLA₂ mass and Δ ox-LDL concentration; on the contrary, a weak, but significant inverse association was found between baseline Lp-PLA₂ mass and baseline ox-LDL.

Soluble VCAM-1 is a well defined marker of endothelial activation and has been associated with atherosclerosis (30-33) and the development of CVD (34). While sVCAM-1 is not a clinical assay target and does not have a reference range, a longitudinal study by Schmidt et al. (2009) showed that levels above 604 pg/mL are predictive of future femoral artery plaque (34). Some benefit may therefore be conferred from pharmacologically lowering elevated sVCAM-1 levels. And though findings have been inconsistent as to whether fenofibrate sVCAM-1 levels (8, 12-15), we report significant reductions in sVCAM-1 in tertiles 2 (mean 660.3 pg/mL) and 3 (mean 922.69 pg/mL)—with the greatest reductions observed in individuals with the highest sVCAM-1 levels. Despite our hypothesis that the reduction in sVCAM-1 may be the result of the corresponding decrease in Lp-PLA₂ and putative decreases in oxidized fatty acids and LysPC, we found no evidence to support such a mechanism. Further investigation over a longer time period is warranted to directly examine whether LysPC and oxidized fatty acids play a role in sVCAM-1 regulation following fenofibrate treatment.

Evidence from cell culture and animal models suggest an alternative signaling mechanism that may account for the observed decrease in elevated sVCAM-1 levels with fenofibrate treatment. In a rat model of heart failure, fenofibrate has been shown to mediate a decrease in NF- κ B and a corresponding reduction in sVCAM-1 expression (35). Furthermore, Rival et al. (2002) showed that fenofibrate reduces nuclear translocation of NF- κ B and concomitantly decreases sVCAM-1 expression in TNF- α stimulated human endothelial cells (36). This fenofibrate-mediated suppression of NF- κ B may be partially due to the observed increase in HDL, reported to suppress activity of this transcription factor (37, 38). Given that NF- κ B has been shown to regulate sVCAM-1 expression by other investigators (39-41), the above reports provide evidence that fenofibrate may decrease sVCAM-1 levels by reducing NF- κ B activity resulting in the repression of sVCAM-1 transcription.

Fenofibrate treatment was shown to modestly but significantly increase both LpPLA₂ mass and sVCAM-1 levels in the lowest tertiles of these targets. Though the mechanism(s) that accounts for the increase in sVCAM-1 is unclear, the increase in LpPLA₂ mass in tertile 1 may be the result of the well-documented increases in HDL as well as HDL-associated LpPLA₂ mass and activity reported with fenofibrate treatment (9, 11, 42). Further studies, including assays that differentiate between LDL and HDL-associated Lp-PLA₂, may demonstrate whether the increase in Lp-PLA₂ mass in such individuals is due to an increase in LDL or HDL-associated Lp-PLA₂. More studies are needed to confirm our finding and determine whether the post-fenofibrate increase of Lp-PLA₂ and sVCAM-1 in individuals with low baseline levels has clinical significance.

The present study has a number of limitations. The 3 week time course for fenofibrate treatment is relatively short compared to the 8 to 12 week time courses of other studies in the literature. While the effect of fenofibrate in reducing triglycerides is comparable to other studies of longer treatment duration, the observed changes in LpPLA₂ and sVCAM-1 may or may not have reached a steady state or be sustained over the long term. In addition, our findings may not extend to the general population, as participants were selected for based on hypertriglyceridemia (TG>150 mg/dL). Finally, the experimental design of the GOLDN study did not include a placebo control, thus we cannot definitively conclude that all changes in LpPLA₂ and sVCAM-1 are due to fenofibrate treatment in this sub-cohort.

In conclusion, the novelty of the present study relies on the observation that fenofibrate is efficacious in reducing relatively *elevated* levels of LpPLA₂ and sVCAM-1. This finding may explain the failure of some studies to show that fenofibrate lowers LpPLA₂ mass and sVCAM-1 levels and why only *sub*-populations in clinical trials show benefits with fenofibrate treatment. Fenofibrate treatment may prove more consistent in affecting clinical outcomes in sub-populations where cardiovascular risk factors, including levels of LpPLA₂ mass, sVCAM-1, ox-LDL, and 8-isoP are elevated. If reductions of these markers of inflammation, endothelial dysfunction, and oxidative stress prove to be dependent on their respective baseline levels, fenofibrate therapy would not be expected to benefit all individuals with elevated serum triglyceride levels equally. The present study may provide the impetus for investigators to run post hoc analyses on past studies or appropriately subdivide cohorts of future clinical trials to confirm or refute these findings.

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Figure 1.

A. Mean Lp-PLA₂ levels at baseline and following 3 weeks of fenofibrate treatment (160 mg/d) are shown in a sub-cohort of the GOLDN study. Results are divided into tertiles determined by baseline values of Lp-PLA₂. In tertile 1, a significant 30.1% increase was found between baseline (89.48 ± 3.2 ng/mL) and post-treatment (128.06 ± 9.83 ng/mL) values ($p=0.0003$). No differences were observed in tertile 2. In tertile 3, mean baseline Lp-PLA₂ levels of 288.94 ± 12.77 ng/mL significantly decreased 35.3% to 193.69 ± 8.26 ng/mL following treatment ($p<0.0001$).

(B) Mean VCAM-1 levels are shown at baseline and following 3 weeks of fenofibrate treatment (160 mg/d) in a sub-cohort of the GOLDN study. Results are stratified into tertiles determined by baseline values of VCAM-1. In tertile 1, a significant increase was observed between baseline (494.48 ± 11.67 pg/mL) and post-treatment (579.69 ± 42.38 pg/mL) values ($p=0.0096$). In tertile 2, mean baseline VCAM-1 levels of 660.32 ± 8.56 pg/mL decreased 7.74% to 609.18 ± 18.77 pg/mL following treatment ($p=0.0109$). In tertile 3, mean baseline VCAM-1 levels of 922.69 ± 26.8 pg/mL significantly decreased 17.2% to 763.68 ± 35.34 pg/mL following treatment ($p<0.0001$). Values are expressed as mean $\pm$ SEM * P value < 0.05 for t-test comparing pre- and post-treatment values.

A **B**

C

Figure 2.

Scatterplots showing the correlation between: (A) the change in LpPLA₂ mass and the change in VCAM-1 levels following 3 weeks of fenofibrate treatment (corr=0.04281, p=0.6804); (B) the change in ox-LDL levels and the change in LpPLA₂ mass following 3 weeks of fenofibrate treatment (corr=-0.16477, p=0.1086); (C) baseline ox-LDL levels vs. baseline LpPLA₂ mass (corr = -0.23540, p=0.0210).

Table 1

Demographics and characteristics of the present GOLDN sub-cohort at baseline and post-treatment, mean $\pm$ SEM

	Baseline	Post-treatment
HDL-C	36.20 $\pm$ 0.877	40.6 $\pm$ 1.11 *
LDL-C	133.6 $\pm$ 3.49	138.8 $\pm$ 3.12 *
TG (mg/dL)	330.4 $\pm$ 13.3	179.5 $\pm$ 7.52 *
N = 96		
Age = 52.3 $\pm$ 1.46		
Female = 33		

* P value < 0.05 for t-test comparing pre- and post-treatment values.