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Differential effect of atorvastatin and fenofibrate on plasma oxidized low-density lipoprotein, inflammation markers, and cell adhesion molecules in patients with type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus is associated with elevated plasma triglyceride levels, low high-density lipoprotein cholesterol, and a high incidence of cardiovascular disease. Hydroxymethylglutaryl–coenzyme A reductase inhibitors and fibrates are frequently used in the treatment of diabetic dyslipidemia, but their specific impact on the inflammation processes involved in atherosclerosis remains to be fully characterized. The objective of this 2-group parallel study was to investigate the differential effects of a 6-week treatment with either atorvastatin 20 mg/d alone (n = 19) or micronized fenofibrate 200 mg/d alone (n = 19) on inflammation, cell adhesion, and oxidation markers in type 2 diabetes mellitus subjects with marked hypertriglyceridemia. In addition to the expected changes in lipid levels, atorvastatin decreased plasma levels of C-reactive protein (−26.9%, $P = .004$), soluble intercellular adhesion molecule 1 (−5.4%, $P = .03$), soluble vascular cell adhesion molecule 1 (−4.4%, $P = .008$), sE-selectin (−5.7%, $P = .02$), matrix metalloproteinase 9 (−39.6%, $P = .04$), secretory phospholipase A_2 ($sPLA_2$) (−14.8%, $P = .04$), and oxidized low-density lipoprotein (−38.4%, $P < .0001$). On the other hand, fenofibrate had no significant effect on C-reactive protein levels and was associated with reduced plasma levels of sE-selectin only (−6.0%, $P = .04$) and increased plasma levels of $sPLA_2$ (+22.5%, $P = .004$). These results suggest that atorvastatin was potent to reduce inflammation, oxidation, and monocyte adhesion in type 2 diabetes mellitus subjects with marked hypertriglyceridemia, whereas fenofibrate decreased sE-selectin levels only and was associated with an elevation of $sPLA_2$ levels.

1. Introduction

Atherosclerosis is now considered as a complex and dynamic disease involving inflammatory factors and endothelial dysfunction [1,2]. The formation of plaques is characterized by the accumulation of inflammatory cells and oxidized low-density lipoprotein (oxLDL). C-reactive protein (CRP) is an acute phase inflammatory protein released by the liver in response to any acute injury, infection, or inflammatory stimuli [3]. C-reactive protein has been detected in atherosclerotic plaque and has been shown to recruit macrophages and to mediate the LDL uptake by macrophages [4]. Upon inflammatory activation, endothelial cells increase the expression of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin, increasing monocyte adherence and rolling [5]. Many studies have reported elevated soluble ICAM-1 (sICAM-1), soluble VCAM-1 (sVCAM-1), and sE-selectin levels in patients with cardiovascular disease (CVD); and elevated sICAM-1 levels appear to predict myocardial infarction in healthy individuals [5]. Oxidized LDL is chemotactic for monocytes and is one of the major ligands for type A scavenger receptors and thus directly contributes to foam cell formation. Oxidized LDL is cytotoxic for cultured endothelial cells, inhibits the nitric oxide–mediated vasodilatation, and induces the expression of inflammatory molecules [6]. 8-iso-$PGF_{2\alpha}$ is the product of oxidative modifications of

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arachidonic acid resulting from free-radical attack of cell membranes or LDL. 8-iso-$PGF_{2\alpha}$ is a potent vasoconstrictor and can modify platelet and macrophage functions [7]. Matrix metalloproteinase 9 (MMP-9) is an enzyme involved in the destabilization of plaque by degrading components of extracellular matrix [8]. Elevated MMP-9 levels have been associated to premature CVD [9]. Secretory phospholipase A_2 ($sPLA_2$) is involved in inflammatory processes and has been shown to be an independent CVD risk marker and to promote the formation of small dense LDL particles [10].

In type 2 diabetes mellitus, the commonly associated dyslipoproteinemia is characterized by elevated plasma triglyceride (TG) levels, lowered high-density lipoprotein cholesterol (HDL-C) levels, and the presence of small dense LDL particles, a highly atherogenic state raising CVD risk by 2 to 3 times [11]. The cornerstone of the treatment of type 2 diabetes mellitus and its associated lipoprotein abnormalities remains on lifestyle modifications. However, in most diabetic patients, lipid-modifying drugs are required to achieve significant improvement of lipoprotein profile. Fibrates are peroxisome proliferators–activated receptor α agonists that have been shown to reduce plasma concentrations of atherogenic TG-rich lipoproteins (TRLs), increase HDL-C levels, and reduce LDL density [12]. On the other hand, hydroxymethylglutaryl–coenzyme A reductase inhibitors, or statins, are known to reduce plasma concentrations of apolipoprotein (apo) B–containing lipoproteins, increase HDL-C levels [13], and exert a number of pleiotropic effects [14]. Statins have been shown to decrease atherosclerosis-related morbidity and mortality in diabetic subjects [15-17]. However, the impact of these 2 distinct classes of lipid-lowering drugs on the levels of inflammation, cell adhesion, and oxidation markers has not been systematically examined in type 2 diabetes mellitus patients with associated dyslipidemia. Therefore, the objective of the present study was to compare the effects of atorvastatin and fenofibrate on these markers of CVD risk in type 2 diabetes mellitus subjects with hypertriglyceridemia. We hypothesized that the effects of atorvastatin on these parameters would be greater than those of fenofibrate.

2. Methods

2.1. Subjects

Forty subjects (34 men and 6 women) with type 2 diabetes mellitus and hypertriglyceridemia were included in this study. One subject was excluded after randomization because of poor compliance to the study medication, and another subject was withdrawn because of significant myalgias associated with atorvastatin. Diabetic subjects had to have type 2 diabetes mellitus as defined by the American Diabetes Association [18] and to have a clinical requirement for oral hypoglycemic agent. All diabetic patients were treated with either metformin or a combination of metformin and a sulfonylurea. Twelve subjects received a thiazolidinedione, 5 in the fenofibrate group and 7 in the atorvastatin group. For all subjects, exclusion criteria were history of CVD, microalbuminuria, or genetic condition affecting lipid metabolism (eg, familial hypercholesterolemia, type III hyperlipidemia, LPL deficiency, etc); body mass index (BMI) <18.0 or >35.0 kg/m^2; uncontrolled hypothyroidism; nephrotic syndrome; anorexia nervosa; history of alcohol or drug abuse; persistent elevation of alanine aminotransferase, aspartate aminotransferase, or creatine phosphokinase; uncontrolled endocrine or metabolic disease; poor mental condition; or a positive test for HIV. All diabetic subjects had to receive stable doses of oral hypoglycemic agents for at least 3 months before the study to achieve glycosylated hemoglobin values (HbA_{1c}) less than 9%. Lipid-lowering medications were withdrawn for at least 6 weeks before the study. Upon their entry into the study, subjects met with a dietician and were instructed to maintain their usual nutritional habits throughout the entire intervention. A standardized food frequency questionnaire was also administered to participants to estimate their diet composition, and no significant difference was observed between the 2 groups. The research protocol was approved by the Laval University Medical Center review committee, and written informed consent was obtained from each subject.

2.2. Study design

After a 6-week run-in/washout period, patients were randomly assigned to receive either atorvastatin 20 mg/d or micronized fenofibrate 200 mg/d for 6 weeks. Patients and the study personnel were blinded in regard to the treatment given. Extensive blood testing was performed during the run-in period and before and after the treatment period to ensure the health of the participants and to collect data. Compliance was assessed by pill counting.

2.3. Characterization of fasting plasma lipids and lipoproteins

At each visit, 12-hour fasting venous blood samples were obtained from antecubital vein into Vacutainer tubes (Becton

Table 1
Baseline characteristics of type 2 diabetes mellitus patients according to treatment group

	Atorvastatin treatment (n = 19)	Fenofibrate treatment (n = 19)	*P*
n	19	19	–
Age (y)	55.1 ± 8.6	55.0 ± 7.8	.99
Sex			.99
Men (%)	16 (84.2)	16 (84.2)	
Women (%)	3 (15.8)	3 (15.8)	
BMI (kg/m^2)	29.9 ± 3.8	30.7 ± 4.2	.53
Waist circumference (cm)	101 ± 9	100 ± 9	.68
Smoking			.10
Ever (%)	12 (63.2)	7 (36.8)	
Never (%)	7 (36.8)	12 (63.2)	
Fasting glycemia (mmol/L)	7.5 ± 1.2	8.0 ± 1.9	.37
HbA_{1c} (%)	7.0 ± 0.9	7.0 ± 1.1	.78

Table 2
Fasting lipid/lipoprotein profile of type 2 diabetes mellitus patients before and after treatment with either atorvastatin 20 mg/d or fenofibrate 200 mg/d

	Atorvastatin treatment (n = 19)				Fenofibrate treatment (n = 19)				*P* between baseline	*P* between treated	*P* between Δ%
	Baseline	Atorvastatin	Δ%	*P*	Baseline	Fenofibrate	Δ%	*P*			
Plasma											
C (mmol/L)	6.24 ± 1.02	3.89 ± 0.82	-37.7	<.0001	6.13 ± 1.08	5.46 ± 1.03	-10.9	.0001	.74	<.0001	<.0001
TG (mmol/L)	5.40 ± 2.11	3.37 ± 1.38	-37.6	<.0001	5.02 ± 2.70	2.94 ± 1.71	-41.4	.0002	.63	.39	.99
Apo B (g/L)	1.39 ± 0.30	0.79 ± 0.24	-43.2	<.0001	1.31 ± 0.33	1.18 ± 0.29	-9.9	.01	.42	<.0001	<.0001
TRL											
C (mmol/L)	2.13 ± 0.84	1.19 ± 0.65	-44.1	<.0001	1.99 ± 1.17	0.94 ± 0.65	-52.8	<.0001	.67	.23	.57
TG (mmol/L)	4.47 ± 1.75	2.82 ± 1.52	-36.9	<.0001	4.58 ± 2.64	2.46 ± 1.74	-46.3	.0002	.89	.49	.59
Apo B (g/L)	0.29 ± 0.06	0.25 ± 0.09	-13.8	.04	0.27 ± 0.10	0.23 ± 0.02	-14.8	.02	.48	.24	.93
LDL											
C (mmol/L)	2.70 ± 1.13	1.54 ± 0.62	-43.0	<.0001	2.83 ± 1.17	3.28 ± 0.83	+15.9	.04	.71	<.0001	.0004
Apo B (g/L)	0.82 ± 0.30	0.47 ± 0.15	-42.7	<.0001	0.78 ± 0.33	0.89 ± 0.34	+14.1	.14	.77	<.0001	.004
HDL											
C (mmol/L)	0.67 ± 0.17	0.79 ± 0.21	+17.9	.001	0.79 ± 0.19	0.86 ± 0.22	+8.9	.05	.06	.29	.32
Apo A-I (g/L)	0.68 ± 0.17	0.75 ± 0.20	+10.3	.004	0.78 ± 0.17	0.82 ± 0.17	+5.1	.11	.10	.27	.56
Ratios											
Plasma C/HDL-C	10.82 ± 8.09	5.45 ± 2.69	-49.6	.0003	8.14 ± 1.93	6.77 ± 2.20	-16.8	.0004	.17	.11	<.0001
LDL-C/HDL-C	4.59 ± 3.86	2.19 ± 1.59	-52.3	.0002	3.65 ± 1.50	4.06 ± 1.54	+11.2	.11	.33	.0007	.0002
Plasma apo B/A-I	1.29 ± 0.58	0.77 ± 0.37	-40.3	<.0001	1.07 ± 0.29	0.95 ± 0.27	-11.2	.01	.15	.10	<.0001

Δ% represents the percentage change between baseline and posttreatment values.

Dickinson, Franklin Lakes, NJ) containing EDTA (0.1% final concentration). Samples were then immediately centrifuged at 4°C for 10 minutes at 3000 rpm to obtain plasma and were stored at 4°C until processed. Plasma very low-density lipoprotein (density <1.006 g/mL) was isolated by preparative ultracentrifugation, and the HDL fraction was obtained after precipitation of LDL in the infranatant (density >1.006 g/mL) with heparin and $MnCl_2$. The cholesterol (C) and TG contents of the infranatant fraction were measured before and after the precipitation step. The C and TG levels were determined using an Olympus AU400[e] analyzer (Melville, NY) using reagents and calibrators provided by the manufacturer. Apolipoprotein B concentrations were measured by nephelometry (Dade Behring, Mississauga, Ontario, Canada) in plasma and in TRL and LDL fractions using reagents and calibrators provided by the manufacturer. The HDL apo A-I levels were measured by nephelometry (Dade Behring).

2.4. Inflammation and adhesion molecules

C-reactive protein was measured in plasma using a Dade Behring BN ProSpect autoanalyzer (Deerfield, IL), using reagents and calibrators provided by the manufacturer. The following molecules were all measured using commercial enzyme-linked immunosorbent assay kits: sICAM-1, sVCAM-1, and sE-selectin (R&D Systems, Minneapolis, MN); MMP-9 (General Electric Biosciences, formerly Amersham Biosciences, Piscataway, NJ); $sPLA_2$ concentration (Cayman Chemical, Ann Arbor, MI); oxLDL (Mercodia, Uppsala, Sweden); and 8-iso-$PGF_{2\alpha}$ (Assay Designs, Ann Arbor, MI).

2.5. Statistical analysis

Data from the 2 groups were compared using χ^2 tests for categorical measures and analysis of variance tests for continuous variables. Changes within the 2 treatment groups

Table 3
Plasma levels of inflammation, cell adhesion, and oxidation markers in type 2 diabetes mellitus patients before and after treatment with either atorvastatin 20 mg/d or fenofibrate 200 mg/d

	Atorvastatin treatment (n = 19)				Fenofibrate treatment (n = 19)				*P* between baseline	*P* between treated	*P* between Δ%
	Baseline	Atorvastatin	Δ%	*P*	Baseline	Fenofibrate	Δ%	*P*			
CRP (mg/L)	1.56 ± 0.97	1.14 ± 0.91	-26.9	.004	2.97 ± 3.29	2.86 ± 3.58	-3.7	.44	.08	.05	.07
sICAM-1 (ng/mL)	305 ± 93	289 ± 76	-5.4	.03	314 ± 92	312 ± 101	-0.6	.42	.77	.42	.32
sVCAM-1 (ng/mL)	637 ± 131	609 ± 139	-4.4	.008	710 ± 167	733 ± 155	+3.2	.09	.14	.01	.004
sE-selectin (ng/mL)	50 ± 28	48 ± 22	-5.7	.02	53 ± 28	50 ± 26	-6.0	.04	.76	.78	.68
MMP-9 (ng/mL)	21.8 ± 20.4	13.2 ± 3.5	-39.6	.04	12.6 ± 3.7	14.9 ± 7.5	+17.4	.14	.06	.38	.05
$sPLA_2$ (ng/mL)	4.1 ± 1.8	3.5 ± 2.0	-14.8	.04	3.0 ± 1.4	3.6 ± 1.7	+22.5	.004	.03	.83	.01
oxLDL (U/L)	74 ± 18	46 ± 12	-38.4	<.0001	72 ± 27	66 ± 20	-8.8	.09	.83	.0005	<.0001
8-iso-$PGF_{2\alpha}$ (pg/mL)	1518 ± 2530	576 ± 325	-62.1	.06	3068 ± 8564	815 ± 682	-73.4	.14	.45	.18	.22

Δ% represents the percentage change between baseline and posttreatment values.

were tested for significance using paired *t* tests. Associations between changes in variables were quantified with Pearson correlation coefficients. Plasma TG levels were log-transformed to normalize their distribution. All analyses were performed using JMP Statistical Software (version 6.03; SAS Institute, Cary, NC). A total of 38 patients entered this 2-treatment, parallel-design study. A conservative power calculation indicates that the probability is 85% that this study detects a treatment difference at a 2-sided 5% significance level if the true difference between treatments (atorvastatin vs fenofibrate) is 5%. This is based on the assumption that the standard deviation of the difference between treatments is as important as the difference between treatments per se.

3. Results

Table 1 shows baseline characteristics of the study participants according to treatment group. There was no significant difference in age, sex distribution, BMI, waist circumference, smoking habits, fasting glycemia, and HbA_{1c} between the 2 treatment groups.

Table 2 shows fasting lipid and apo levels before and after treatment with either atorvastatin 20 mg/d (n = 19) or fenofibrate 200 mg/d (n = 19). At baseline, no difference was observed between the 2 groups for any of the variables listed.

Treatment with atorvastatin had significant impact on plasma C (−37.7%, $P < .0001$), plasma TG (−37.6%, $P < .0001$), plasma apo B (−43.2%, $P < .0001$), TRL-C (−44.1%, $P < .0001$), TRL-TG (−36.9%, $P < .0001$), TRL apo B (−13.8%, $P = .04$), LDL-C (−43.0%, $P < .0001$), LDL apo B (−42.7%, $P < .0001$), HDL-C (+17.9%, $P = .001$), and HDL apo A-I levels (+10.3%, $P = .004$). On the other hand, treatment with fenofibrate was associated with a significant decrease in plasma C (−10.9%, $P = .0001$), plasma TG (−41.4%, $P = .0002$), plasma apo B (−9.9%, $P = .01$), TRL-C (−52.8%, $P < .0001$), TRL-TG (−46.3%, $P = .0002$), and TRL apo B (−14.8%, $P = .02$) and a significant elevation in LDL-C (+15.9%, $P = .04$) and HDL-C (+8.9%, $P = .05$). There were significant differences in the percentage changes of plasma C, plasma apo B, LDL-C, and LDL apo B between the 2 treatment groups. In contrast, no significant difference in the percentage in changes of plasma TG was observed between the 2 treatments.

Table 3 shows values for inflammation, cell adhesion, and oxidation markers before and after treatment with atorvastatin or fenofibrate. No significant difference in these parameters at baseline was observed between the 2 groups except for $sPLA_2$ levels. Treatment with atorvastatin significantly decreased plasma levels of CRP (−26.9%, $P = .004$), sICAM-1 (−5.4%, $P = .03$), sVCAM-1 (−4.4%, $P = .008$), sE-selectin (−5.7%, $P = .02$), MMP-9 (−39.6%, $P = .04$), $sPLA_2$ (−14.8%, $P = .04$), and oxLDL (−38.4%, $P < .0001$). We also observed a tendency toward decreased 8-iso-$PGF_{2\alpha}$ levels (−62.1%, $P = .06$). On the other hand, fenofibrate significantly decreased sE-selectin levels only (−6.0, $P = .04$) and was found to increase $sPLA_2$ levels (+22.5%, $P = .004$).

The relationships between changes in plasma lipid levels and changes in plasma levels of inflammation, cell adhesion, and oxidation markers were then investigated using Pearson correlation. Under atorvastatin treatment, the percentage change in LDL-C levels correlated with the percentage change in plasma levels of sICAM-1 ($r = 0.48$, $P = .04$). However, there was no significant correlation between LDL-C response to atorvastatin and the percentage change in plasma levels of oxLDL ($r = 0.33$, $P = .16$), sVCAM-1 ($r = −0.10$, $P = .69$), sE-selectin ($r = −0.11$, $P = .65$),

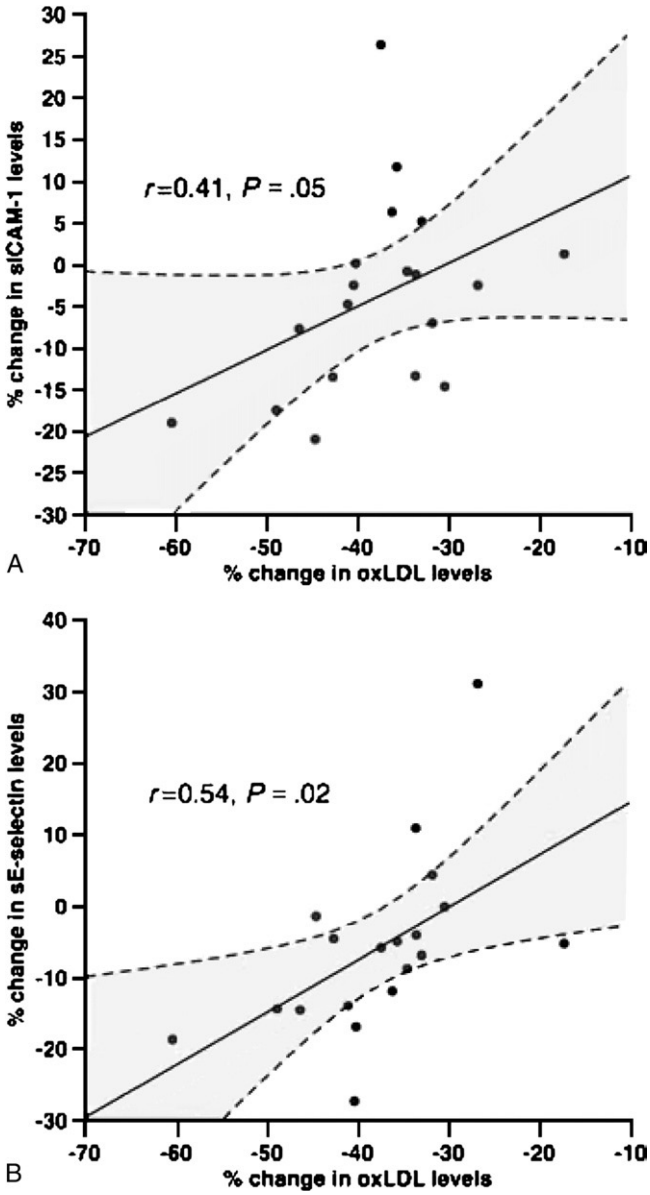

Fig. 1. Correlation between change in plasma levels of oxLDL and (A) sICAM-1 levels and (B) sE-selectin levels in patients treated with atorvastatin.

MMP-9 ($r = -0.22$, $P = .37$), $sPLA_2$ ($r = -0.17$, $P = .48$), CRP ($r = 0.02$, $P = .93$), and 8-iso-$PGF_{2\alpha}$ ($r = -0.51$, $P = .11$). Correlations between plasma oxLDL response to atorvastatin and the percentage change in sICAM-1 ($r = -0.41$, $P = .05$) and sE-selectin levels ($r = 0.54$, $P = .02$) are shown in Fig. 1. Under fenofibrate treatment, we observed that the percentage change in plasma levels of oxLDL was directly correlated with LDL-C response ($r = 0.60$, $P = .006$) and the percentage change in sE-selectin levels ($r = 0.64$, $P = .003$). Finally, in both treatment groups, there was no significant correlation between HDL-C response and the percentage change in plasma levels of inflammation, cell adhesion, and oxidation markers.

4. Discussion

The objective of the present study was to compare the effects of atorvastatin and fenofibrate on the plasma levels of inflammation, cell adhesion, and oxidation markers in type 2 diabetes mellitus subjects with hypertriglyceridemia. Atorvastatin was found to decrease plasma levels of total C, TG, apo B, and LDL-C and to increase HDL-C. On the other hand, fenofibrate reduced plasma levels of total C, apo B, and TG but was associated with a significant increase in LDL-C in these patients. In addition to the expected changes in lipid values, the present study showed that atorvastatin was potent to reduce inflammation, cell adhesion, and oxidation markers, whereas fenofibrate had little effects on these markers. Specifically, atorvastatin significantly reduced plasma levels of CRP, sICAM-1, sVCAM-1, sE-selectin, MMP-9, $sPLA_2$, and oxLDL, whereas fenofibrate decreased sE-selectin only. Importantly, there was a significant correlation between oxLDL-C response to atorvastatin and the percentage change in plasma levels of sICAM-1 and sE-selectin.

Hydroxymethylglutaryl–coenzyme A reductase inhibitors, or statins, are well known to exert so-called pleiotropic effects independent of their lipid-lowering effects. Indeed, a number of studies have shown that statins decrease CRP levels [19], decrease oxidation susceptibility of LDL particles [20-22], decrease scavenger receptor expression in macrophages [23], decrease CRP levels [24], and increase plaque stability by lowering metalloproteinases [25]. On the other hand, the effects of fenofibrate on inflammation [26], oxidation, and monocyte adhesion remain controversial and vary based upon the model studied. Nonetheless, recent studies have shown that fibrates can modulate a number of factors and genes involved in various steps of the development of atherosclerosis, including oxidative stress and monocyte adhesion (reviewed by Marx et al [27]).

Previous studies examined the impact of statins and fibrates on plasma levels of cell adhesion molecules in dyslipidemic subjects. Calabresi et al [28] reported that treatment with fenofibrate was associated with an elevation in HDL-C levels and a significant reduction in plasma levels of sICAM-1 and sE-selectin levels in patients with low HDL-C levels. The authors also reported a strong correlation between changes in HDL-C and changes in sICAM-1 and sE-selectin, suggesting that increased cell adhesion molecule expression may be a mechanism by which a low plasma HDL level promotes atherogenesis and causes acute atherothrombotic events. However, these results contrast with the findings of the present study showing no correlation between HDL-C response to fenofibrate or atorvastatin and the percentage change in plasma levels of cell adhesion molecules. Our results, however, support a recent study by Empen et al [29] that examined the impact of a treatment with either fenofibrate or atorvastatin on sVCAM-1, sICAM-1, and sE-selectin levels in 11 subjects with type 2 diabetes mellitus and hypertriglyceridemia. In addition to expected changes in lipid values, the authors observed a decrease in sVCAM-1 levels under atorvastatin treatment and a decrease in sE-selectin levels under fenofibrate treatment. Another recent study [30] with 10 controls and 10 nondiabetic subjects with high LDL-C levels showed that both simvastatin and fenofibrate were potent to reduce sICAM-1 levels by 10% and 17%, respectively. Interestingly, the authors also demonstrated that a restriction in dietary lipids with no pharmacologic treatment was associated with parallel reductions in LDL-C (−15%) and sICAM-1 levels (9%), suggesting that drug-induced decrease in lipid levels, but not a direct action of the drugs on endothelial cells, smooth muscle cells, or macrophages, leads to a reduction in the levels of cell adhesion molecules. These data are consistent with the results of the present study showing that LDL-C response to atorvastatin was correlated with the magnitude of change in plasma levels of sICAM-1. Further studies are required to assess the mechanisms underlying the association between changes in LDL-C and plasma levels of cell adhesion molecules in humans.

Elevated circulating concentrations of oxLDL are considered to be relevant markers of oxidative stress that are thought to favor the development of CVD [31]. As oxLDL is not recognized by the LDL receptor but rather by scavenger receptors at the surface of subendothelial resident macrophages, LDL oxidation favors the unrestricted uptake of cholesterol leading to the formation of foam cells, which is the first step in the formation of the earliest atherosclerotic lesions known as *fatty streaks* [32]. In the present study, the percentage change in plasma oxLDL levels after atorvastatin treatment was positively correlated with the percentage change in sICAM-1 and E-selectin levels, suggesting that oxLDL could influence the production rate of cell adhesion molecules. In fact, the most extensively characterized pathway for cell adhesion molecule production involves the activation of the nuclear factor κB (NF-κB), which is able to regulate the transcription of numerous genes including adhesion cell molecules [31]. A recent study by Devaraj et al [33] showed that simvastatin treatment in insulin-resistant

subjects was able to significantly decrease NF-κB levels. Although NF-κB levels were not assessed in the current study, our observations are somewhat supportive of oxLDL-induced production of ICAM-1 and E-selectin.

In the present study, fenofibrate was associated with significant reductions in plasma sE-selectin levels, a finding previously reported by others [28,29]. In contrast with previous studies, however, changes in HDL-C levels were not correlated with changes in sE-selectin levels, suggesting that the impact of fenofibrate on HDL-C is independent of its effect on E-selectin. The beneficial impact of fibrates on inflammatory biomarkers remains controversial, and we cannot exclude that the lack of effect of fenofibrate on CRP levels in the current study could be due to the relatively small number of participants and a type II error. Additional studies are required to elucidate the molecular mechanisms responsible for the differential effects of statins and fibrates on inflammation, cell adhesion, and oxidation and to relate these effects to the development of atherosclerosis in patients with type 2 diabetes mellitus.

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