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Effect of Fenofibrate on Adiponectin and Inflammatory Biomarkers in Metabolic Syndrome Patients

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Adiponectin is an adipose-secreted hormone with anti-inflammatory properties mediated by inhibition of nuclear factor-κB (NF-κB) signaling. This study investigates whether fenofibrate alters adiponectin levels in patients with hypertriglyceridemia and the metabolic syndrome, and examines the association of adiponectin with circulating inflammatory markers and whole blood cytokine production. The effects of fenofibrate (160 mg/day) on adiponectin and other inflammatory markers were investigated in a 12-week randomized, placebo-controlled trial in 55 patients with hypertriglyceridemia (plasma triglycerides ≥1.7 mmol/l and <6.8 mmol/l), central obesity and other characteristics of the metabolic syndrome who were not receiving lipid-altering therapies. In the fenofibrate group, adiponectin levels increased from 4.10 to 4.50 μg/ml (+7.7%); in the placebo group, adiponectin levels increased by 1.8%; (P = 0.0005). In multivariate models including age, gender, and waist circumference, there were inverse correlations between changes in adiponectin and vascular cell adhesion molecule-1 (VCAM-1) (r = −0.54, P < 0.0001) and intercellular adhesion molecule-1 (ICAM-1) (r = −0.57, P < 0.0001), and C-reactive protein (CRP) (r = −0.40, P = 0.0041); lipopolysaccharide (LPS)-stimulated production of tumor necrosis factor-α (TNF-α) (r = −0.30, P = 0.035), interleukin (IL)-1β (r = −0.44, P = 0.0016), monocyte chemotactic protein-1 (MCP-1) (r = −0.46, P = 0.001), and macrophage inflammatory protein-1α (MIP-1α) (r = −0.45, P = 0.0012). Fenofibrate (160 mg/day) raised adiponectin levels in patients with hypertriglyceridemia and the metabolic syndrome. Changes in adiponectin were significantly and inversely associated with changes in multiple inflammatory markers. These data suggest that adiponectin may contribute to the anti-inflammatory effects of fenofibrate.

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INTRODUCTION

Central obesity is an integral component of the metabolic syndrome, and it is associated with increased risk of type 2 diabetes and cardiovascular disease. In addition, the risks of type 2 diabetes and cardiovascular disease are particularly high among patients with metabolic syndrome and high levels of certain inflammatory makers such as C-reactive protein (CRP) (1,2) and low levels of the anti-inflammatory protein adiponectin (3,4).

Visceral fat promotes inflammation through increased secretion of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) (5). These inflammatory cytokines activate the oxidant-stress response transcription factor nuclear factor-κB (NF-κB) that is present in various cell types (6). In hepatocytes, these inflammatory cytokines modulate synthesis of acute phase proteins such as CRP and fibrinogen.

Adiponectin is an adipocyte-derived plasma protein that suppresses TNF-α induced activation of NF-κB in human aortic endothelial cells and aortic smooth muscle cells through inhibition of IκB phosphorylation (7,8). Anti-inflammatory effects of adiponectin include inhibited endothelial adhesion molecule expression, reduced monocyte adhesion, inhibited macrophage-induced cytokine production (9), and reduced CRP expression in human adipose tissue (10).

This study sought to demonstrate whether the fenofibrate-mediated increases in adiponectin levels are associated with reduced circulating levels of inflammatory mediators. In addition, we evaluated whether increases in adiponectin are associated with reductions in *ex vivo* inflammatory cytokine production in whole blood specimens.

METHODS AND PROCEDURES

Selection of patients

The study population consisted of 59 subjects with the metabolic syndrome as previously described (11). Four subjects did not complete the protocol because of withdrawal of consent (n = 2), relocation (n = 1), or gastrointestinal intolerance (n = 1). Therefore, 55 subjects (25 intervention subjects and 30 control subjects) completed the study and

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were included in the final analyses. Male and postmenopausal females >18 years of age with fasting triglycerides ≥1.7 and <6.8 mmol/l were included in the study. Subjects were required to have ≥2 of the following Adult Treatment Panel III (12) criteria of the metabolic syndrome: abdominal obesity (waist circumference >89 cm in females and >102 cm in males); low high-density lipoprotein cholesterol (HDL-C) (<1.3 mmol/l in women and <1.0 mmol/l in men); hypertension (systolic blood pressure ≥130 or diastolic blood pressure ≥85 mm Hg) or current drug therapy for hypertension; and impaired fasting glucose ≥6.1 mmol/l and <7.0 mmol/l. Exclusion criteria included BMI >40 kg/m^2; type 1 or type 2 diabetes; use of lipid-lowering therapies, aspirin >81 mg daily, regular use of nonsteroidal anti-inflammatory agents or cyclooxygenase-2 inhibitors, corticosteroids (oral and inhaled), antioxidants (including multivitamins), herbal or fiber supplements; recent changes in type or formulation of hormone replacement therapy (in the last 6 months); alcohol intake more than three drinks per day; untreated hypothyroidism or recent change (within 2 months) of thyroid replacement therapy; and cigarette smoking (current or within the past 6 months).

The Institutional Review Board approved the protocol of this study. All subjects gave written informed consent before participating in this research trial.

Study design

A registered dietitian counseled subjects on the American Heart Association Step 2 diet, and they were instructed to maintain the diet throughout the study. The dietitian contacted subjects twice during the 6-week dietary lead-in period to obtain 24-h diet recalls. The food recalls were analyzed for fat, calories, fiber, and alcohol intake using the Minnesota Nutrition Data System, version 2.93. At the end of a 6-week run-in period, fasting lipids and glucose were measured to determine study eligibility, and within 1 week subjects returned for randomization. Subjects were randomized to fenofibrate 160 mg/day (TriCor, Abbott Laboratories, Abbott Park, IL) or placebo for the next 3 months. Fasting blood specimens were obtained after a 12-h fast at both randomization and study completion (month 3).

Laboratory studies

Plasma lipids and serum chemistries were analyzed by standard techniques. Lipoprotein subclass profiles were measured with an automated nuclear magnetic resonance spectroscopic assay using a modification of the method described previously (LipoScience, Raleigh, NC) (13).

Chemokines, cytokines, and adhesion molecules were measured in duplicate on plasma samples using monoclonal antibody-based multi-analyte bead immunoassays (Luminex, Linco Research, St Charles, MO). Cytokine and chemokine production was measured on lithium-heparin whole blood specimens that were stimulated with lipopolysaccharide (LPS) (100 ng/ml) for 6 h at 37 °C.

Total plasma adiponectin concentration was measured in duplicate and assayed by an ELISA method (Human Adiponectin/Acrp30 Immunoassay, Quantikine, R&D systems, Minneapolis, MN). The interassay coefficient of variation for this test was <7%. CRP was measured with a high-sensitivity enzyme-linked immunosorbent assay (Life Diagnostics, West Chester, PA). Fibrinogen was analyzed and measured in duplicate by a modified method of Clauss (14). Interassay coefficients of variation were <5% for CRP and fibrinogen, and <12% for the other inflammatory markers.

Statistical analyses

Subject demographic characteristics, as well as fasting lipids and lipoproteins are reported as means ± s.d. (**Table 1**). Person-specific percent changes over the 3-month therapy period in weight, waist circumference, fasting lipids, and lipoproteins, as well as characteristics of inflammatory markers and their respective percent changes are reported as medians and interquartile ranges (IQRs). The IQR gives the 25th and 75th percentile. Wilcoxon rank sum test and Fisher's exact test were

Table 1 Baseline characteristics by study group

Variables	Placebo (*n* = 30)	Fenofibrate (*n* = 25)	*P*
Clinical			
Age, years	55.22 ± 10.01	51.54 ± 9.66	0.088
Sex, male/female	22/8	19/6	0.99
BMI, kg/m^2	33.29 ± 3.50	32.19 ± 4.02	0.25
Waist circumference, cm	109.5 ± 8.9	108.9 ± 8.4	0.63
Systolic blood pressure, mm Hg	133.48 ± 13.46	131.84 ± 12.60	0.71
Diastolic blood pressure, mm Hg	84.97 ± 7.89	82.48 ± 7.81	0.39
Fasting glucose, mmol/l	4.74 ± 0.84	4.70 ± 0.91	0.88
Fasting insulin, μU/l	6.91 ± 5.06	6.88 ± 4.38	0.79
HOMA index	1.48 ± 1.19	1.49 ± 1.10	0.92
Fasting chemical lipids			
Triglycerides, mmol/l	3.10 ± 1.05	3.20 ± 0.98	0.65
Total cholesterol, mmol/l	5.37 ± 1.19	5.54 ± 1.20	0.51
LDL-C, mmol/l	3.46 ± 1.11	3.53 ± 1.02	0.64
HDL-C, mmol/l	0.88 ± 0.29	0.82 ± 0.23	0.44
Non-HDL-C, mmol/l	4.49 ± 1.19	4.72 ± 1.16	0.35
NMR-derived fasting lipoprotein subclasses			
Total VLDL particle, nmol/l	129.58 ± 51.89	154.97 ± 60.06	0.061
Large VLDL particle, nmol/l	12.94 ± 7.77	10.69 ± 7.56	0.32
Medium VLDL particle, nmol/l	75.84 ± 41.83	85.21 ± 41.97	0.37
Small VLDL particle, nmol/l	40.80 ± 30.16	59.07 ± 37.05	0.041
Total LDL particle, nmol/l	1,797.58 ± 588.71	1,813.61 ± 502.68	0.71
Large LDL particle, nmol/l	269.57 ± 239.61	284.56 ± 243.36	0.83
Small LDL particles, nmol/l	1,475.04 ± 561.64	1,476.19 ± 473.23	0.99
OH-FA, μmol/l	1.15 ± 0.34	1.15 ± 0.34	0.74
Characteristics of the metabolic syndrome			
High triglycerides, Yes/No	100/0	100/0	—
Low HDL-C,[a] Yes/No	23/7	19/6	0.99
Central obesity,[b] Yes/No	29/1	23/2	0.49
Elevated blood pressure	20/10	13/12	0.29
Elevated fasting glucose	1/29	1/24	0.99

Data are given as means ± s.d. for continuous variables, frequencies for dichotomous variables. HOMA index was calculated according to the formula: fasting glucose (mmol/l) × insulin (mU/ml)/22.5.
HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; NMR, nuclear magnetic resonance; OH-FA, monohydroxy fatty acids; VLDL, very low-density lipoprotein.
[a]Low HDL cholesterol levels were defined as <1.0 mmol/l in men and <1.3 mmol/l in women. [b]Central obesity was defined as a waist circumference >89 cm in women and >102 cm in men.

used to compare continuous and dichotomous variables, respectively, between treatment groups. Percent change over the treatment phase between adiponectin and inflammatory markers were correlated using Spearman's correlations, and both treatment groups were combined for these correlations. Multivariate Spearman's correlations were calculated as partial correlations on residual ranks. All statistical analyses were performed with SAS package 2003 (SAS Institute, Cary, NC).

This study was an investigator-initiated clinical trial, and was conceived, managed, and analyzed independently of the sponsor. Statisticians (Alfred W. Rademaker and Irene B. Helenowski) employed by Northwestern University performed the statistical analysis based on specific requests of the investigators.

RESULTS

The baseline characteristics of the study populations are described in **Table 1**. This study included predominantly middle-aged men with central obesity, high fasting triglycerides, low levels of HDL-C, and hypertension. Only two subjects had fasting glucose levels ≥6.1 mmol/l. Treatment groups were well balanced with regards to baseline demographics and laboratory values, in particular there were no differences between treatment groups in baseline blood glucose ($P = 0.88$), insulin concentration ($P = 0.79$) or HOMA index ($P = 0.92$).

Aspirin (75–81 mg daily) was used in 50% of placebo-treated subjects and 32% of fenofibrate-assigned subjects ($P = 0.56$). Subjects did not change their intake of dietary fats and calories during the study, and they demonstrated high adherence to study medications, with 97.6% of placebo-treated subjects and 97.1% of fenofibrate-treated subjects returning the correct number of tablets. Weight remained stable in the placebo group (median (IQR), 101.8 kg (96.3, 114.1) vs. 103.2 kg (93.2, 115.5)), and the fenofibrate-treatment group (median (IQR), 105.0 kg (87.3, 113.2) vs. 104.5 kg (86.4, 112.7)); $P = 0.056$). There were no changes in waist circumference between placebo (median (IQR) 46.3 in (41.0, 46.0) vs. 44.0 (40.5, 46.0) and fenofibrate-treatment group (median (IQR), 43.0 in (41.8, 44.3) vs. 43.0 (41.0, 45.0); $P = 0.10$).

Adiponectin and fenofibrate

In the fenofibrate group, median adiponectin levels increased by 0.40 mg/l from 4.10 to 4.50 mg/l (an increase of 7.7%); in the placebo group, median adiponectin levels did not change ($P = 0.0005$ comparing change between groups) (**Table 2**).

Proinflammatory markers and fenofibrate

Subjects assigned to fenofibrate therapy had greater reductions than the placebo group in systemic concentrations of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and CRP (**Table 2**). LPS-stimulated production of monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), and IL-1β were significantly reduced more by fenofibrate therapy than by placebo (**Table 3**).

Correlations between adiponectin and inflammatory markers

In multivariate models that included age, gender, and on-trial weight changes, we demonstrate inverse correlations between changes in plasma adiponectin levels and changes in VCAM-1 ($r = -0.54$, $P < 0.0001$), ICAM-1 ($r = -0.57$, $P < 0.0001$), and

Table 2 Effects of fenofibrate on fasting circulating inflammatory proteins

	Placebo			Fenofibrate			
	Baseline	Treatment	% Change	Baseline	Treatment	% Change	*P* value
Adiponectin, mg/l	4.50 (3.90, 5.40)	4.50 (4.10, 5.40)	+1.8 (−1.6, 2.9)	4.10 (3.70, 4.90)	4.50 (4.10, 5.30)	+7.7 (2.27, 14.63)	0.0005
VCAM-1, µg/ml	517.3 (480.6, 609.4)	514.2 (480.1, 614.7)	−1.5 (−6.3, 1.7)	564.1 (508.9, 602.4)	506.4 (441.2, 516.1)	−10.9 (−14.6, −8.2)	0.0005
ICAM-1, µg/l	414.5 (360.2, 470.1)	415.3 (338.9, 476.9)	0.9 (−7.2, 3.1)	384.3 (345.1, 426.4)	320.5 (284.2, 368.5)	−14.7 (−22.3, −10.1)	<0.0001
CRP, mg/l	2.4 (2.0, 3.2)	2.2 (1.6, 2.7)	−6.5 (−24.5, 1.7)	2.6 (1.4, 3.1)	1.9 (1.1, 2.6)	−24.5 (−31.9, −9.8)	0.02
Fibrinogen, g/l	3.54 (3.13, 3.84)	3.52 (3.1 3.85)	3.1 (−7.0, 12.2)	3.35 (31.0, 3.57)	3.05 (2.67. 3.59)	−5.4 (−17.0, 7.2)	0.054

Data represents LPS-stimulated (100 ng/ml) whole blood production of inflammatory cytokines.
Values are expressed as medians and interquartile ranges (25th, 75th percentile).

Table 3 Effects of fenofibate on lipopolysaccharide-stimulated cytokine production

	Placebo			Fenofibrate			
	Baseline	Treatment	% Change	Baseline	Treatment	% Change	*P* value
MCP-1, ng/l	2,347 (2,205, 2,666)	2,403 (2,186, 2,519)	0.0 (−3.5, 2.9)	2,678 (2,247, 2,847)	2,540 (2,301, 2,716)	−3.4 (−5.0, −0.4)	0.01
MIP-1α, ng/l	16,450 (15,266, 18,755)	16,535 (14,687, 18,397)	−0.2 (−2.6, 1.0)	16,590 (15,423, 17,814)	15,621 (14,726, 17,451)	−3.5 (−4.6, −0.9)	0.01
IL-1β, ng/l	22,380 (19,919, 26,611)	23,027 (19,840, 25,606)	0.6 (−2.5, 2.7)	23,660 (22,540, 25,879)	22,904 (22,045, 24,556)	−2.5 (−4.7, 0.3)	0.044

Values are expressed as medians and interquartile ranges (25th, 75th percentile).
IL-1β, interleukin-1β; MCP-1, monocyte chemotactic protein-1; MIP-1α, macrophage inflammatory protein-1α.

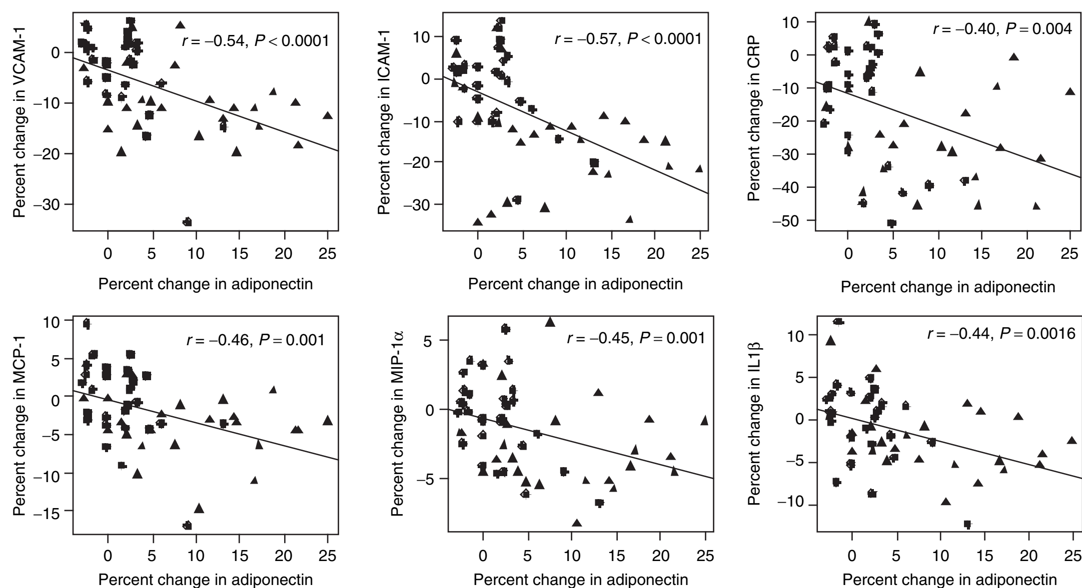

Figure 1 Correlations between adiponectin and inflammatory markers. Inverse association between on-trial adiponectin levels and inflammatory markers. Correlations were adjusted for age, gender, and on-trial weight changes. Circles (or squares), placebo group; triangles, fenofibrate group.

Table 4 Analyses of the associations between adiponectin and inflammatory markers

	VCAM-1		ICAM-1		MCP-1		MIP-1α		IL-1β		CRP		Fibrinogen	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Model 1	–0.55	<0.0001	–0.56	<0.0001	–0.49	0.0002	–0.42	0.001	–0.45	0.0006	–0.42	0.001	–0.22	0.12
Model 2	–0.54	<0.0001	–0.55	<0.0001	–0.49	0.0002	–0.43	0.001	–0.44	0.001	–0.42	0.002	–0.21	0.14
Model 3	–0.54	<0.0001	–0.57	<0.0001	–0.46	0.001	–0.45	0.001	–0.44	0.002	–0.40	0.004	–0.26	0.078

Model 1 represents univariate Spearman correlations between adiponectin and inflammatory markers. Model 2 represents age- and gender-adjusted Spearman correlations between adiponectin and inflammatory markers. Model 3 represents age-, gender-, and weight change–adjusted Spearman correlations between adiponectin and inflammatory markers. Both treatment groups combined for all correlations.

CRP ($r = -0.40$, $P = 0.0041$) (**Table 4**). There were nonsignificant associations between adiponectin and plasma fibrinogen ($r = -0.26$, $P = 0.078$). There were inverse correlations between plasma adiponectin and LPS-stimulated whole blood production of MCP-1 ($r = -0.46$, $P = 0.0010$), MIP-1α ($r = -0.45$, $P = 0.001$), and IL-1β ($r = -0.44$, $P = 0.0016$) in fenofibrate-treated subjects (**Figure 1**). Although, there was a nonsignificant reduction in TNF-α production in the fenofibrate group, TNF-α production was inversely correlated with adiponectin levels ($r = -0.30$, $P = 0.035$). No such correlations were observed in patients treated with placebo.

DISCUSSION

This study demonstrates that short-term (12 week) therapy with fenofibrate increases plasma levels of the adipocyte-secreted anti-inflammatory protein adiponectin, and the increase in adiponectin levels were associated with lower levels of the systemic inflammatory mediators VCAM-1, ICAM-1, and CRP. Because systemic inflammatory markers are derived from multiple sources, it is unclear whether these associations are related to circulating mononuclear cells, tissue macrophages, or adipocytes. In contrast, the inverse association between adiponectin and reduced LPS-stimulated *ex vivo* blood cytokine production of MCP-1, MIP-1α, and IL-1β suggest more that direct involvement of adiponectin and/or adiponectin receptors in circulating leukocytes contribute to the anti-inflammatory effects of fenofibrate. Adiponectin is found in serum an an oligomeric trimer of low molecular weight and a hexamer (two trimers) of high molecular weight (15). The low molecular weight is the predomient isoform in the circulation, whereas the high molecular weight constitutes the major component of intracellular adiponectin. Although both low molecular weight and high molecular weight isoforms of adiponectin activate NF-κB (16), it is possible that fenofibrate has different effects on the different components of adiponectin that may influence the biological activity of increased adiponectin levels; however this study only measured total adiponectin levels.

Although activation of PPAR-α has not been considered a therapy that would increase adiponectin levels, we are aware of two studies that reported an increase in plasma adiponectin with fenofibrate therapy (17,18). In a study among 56 patients with combined hyperlipidemia (total cholesterol ≥5.17 mmol/l and triglycerides ranging from 2.26 mmol/l to 9.03 mmol/l), fenofibrate 8 week therapy increased adiponectin levels by 14% from 3.21 µg/ml to 3.54 µg/ml ($P = 0.05$) (17). In a second adiponectin study, 46 hypertriglyceridemia (≥1.69 mmol/l)

patients, 8 weeks of therapy with fenofibrate increased adiponectin levels by 14 ± 5% ($P = 0.008$) (18). Among a subset of 24 metabolic syndrome patients with triglycerides ≥1.7 mmol/l, fenofibrate increased plasma adiponectin levels by 12 ± 6% from 3.35 mg/l to 3.55 mg/l (18). The authors suggest that restoration of abnormal endothelial function observed in fenofibrate-treated patients may be accompanied by improved insulin sensitivity, increased adiponectin expression and reduced activation of inflammatory pathways (18).

The mechanisms responsible for adiponectin-mediated reduction of inflammatory cytokine reserve in circulating monocytes require further study; however, there are several possible explanations for the anti-inflammatory effects of PPAR-α activation that involve NF-κB mediated inflammatory pathways (15,19). Fibrates have been shown to induce the expression of the inhibitory protein IκB in human aortic smooth muscle cells and primary human hepatocytes (19). Macrophages contained in visceral fat are a rich source of inflammatory cytokines. Activation of PPAR-α by fenofibrate would be expected to inhibit NF-κB-mediated TNF-α signaling pathways in visceral fat and increase expression of adiponectin. Previously, physiological concentrations of adiponectin have been shown to inhibit NF-κB signaling (8) in macrophages (9,20) and endothelial cells resulting in reduced expression of TNF-α and VCAM-1, ICAM-1, and E-selectin (7); and the production of the anti-inflammatory mediators IL-10 and IL-1 receptor antagonist in human leukocytes (21). In visceral fat depots of Otsuka Long-Evans Tokushima fatty rats, fenofibrate-reduced TNF-α expression and increased adiponectin expression (22). Although we did not observe a significant reduction in mononuclear cell TNF-α production, adiponectin mRNA levels have been associated with TNF-α mRNA levels ($r = -0.48$, $P < 0.005$) in adipose tissue of nondiabetes subjects (23).

Recently, two transmembrane proteins that serve as receptors for adiponectin, Adipo R1 and Adipo R2, have been identified in human atherosclerotic plaques (20). Adipo R1 and Adipo R2 are present in monocytes. Expression of these receptors is induced by nuclear receptors for the PPARs α and γ, and for liver X receptors (24). Fenofibrate-induced activation of PPAR-α would provide more binding sites on mononuclear cells for increased circulating adiponectin. Ligation of Adipo1 and Adipo2 on circulating mononuclear cells has been shown to reduce NF-κB activated inflammatory mediators (24). In cultured macrophages and experimental animal models, exogenous administration of adiponectin counteracts increased TNF-α expression. Recombinant adiponectin administration has been shown to inhibit LPS-stimulated TNF-α production and TNF-α mRNA expression in macrophages (20).

Lifestyle and pharmacological therapies that increase adiponectin levels may be valuable in reducing atherosclerotic risk and cardiovascular events particularly among individuals with the metabolic syndrome and type 2 diabetes. Weight loss is accompanied by an increase in adiponectin levels (25). Antidiabetic therapy with thiazolidinediones have been shown to increase adiponectin levels in nondiabetic subjects and in patients with type 2 diabetes through modulation of adiponectin gene expression (26). In patients with type 2 diabetes, rosiglitazone (2 mg twice daily) increased mean plasma adiponectin levels by more than twofold ($P < 0.0005$), whereas no change was observed in the placebo group. In patients with type 2 diabetes, pioglitazone 45 mg daily increased plasma adiponectin levels from 6.73 ± 3.42 mg/l to 17.70 ± 8.76 mg/l ($P < 0.0001$), while glimepiride lowered adiponectin levels (6.45 ± 3. 39 mg/l to 5.96 ± 2.46 mg/l, $P < 0.05$) (27). In the Rimonabant in Obesity–Lipids study, the effects of the selective cannabinoid receptor antagonist rimonabant-1 were investigated in overweight subjects (BMI 27–40 kg/m^2) with untreated dyslipidemia (triglyceride levels >0.73 mmol/l to 3.44 mmol/l, or a ratio of cholesterol to HDL-C of >4.5 among women and >5 among men) (28). In this study, in which 54% of subjects had the metabolic syndrome, rimonabant 20 mg daily increased adiponectin levels by 46.2% (last observation carried forward analysis, $P < 0.001$). Changes in adiponectin levels correlated with changes in HDL-C levels ($r = 0.27$, $P < 0.001$) and apolipoprotein A-I ($r = 0.38$, $P < 0.001$).

The current study explores putative mechanisms for the anti-inflammatory effects of fenofibrate, and these results cannot be extrapolated to cardiovascular outcomes. Further, we included obese metabolic syndrome subjects with adiponectin levels that were substantially lower than average values reported in the Health Professionals Follow-up study. As compared with that study, the adiponectin levels in the current study fell within the lowest quintile (2.4–10.5 mg/l) of the distribution of the adiponectin levels presumably because our study was limited to obese metabolic syndrome patients. Nevertheless, the 0.4 mg/l short-term increase in adiponectin levels in fenofibrate-treated subjects represents about 20% of the difference in adiponectin levels between individuals who experienced an incident myocardial infarction at 6 years vs. those who did not.

In this study, we provide new information regarding the effects of fenofibrate on circulating levels of the adipose-specific cytokine adiponectin as well as whole blood production of inflammatory chemokines and cytokines, and that these changes are inversely correlated. Although the effect of fenofibrate on increasing adiponectin levels is significant, these changes are rather modest when compared to thiazolidinediones. The extent of the biological changes and clinical impact of fenofibrate-mediated changes in adiponectin are uncertain; however, these data suggest a shared biological pathway between visceral adipocyte production of adiponectin and mononuclear cell production of inflammatory cytokines.

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DISCLOSURE

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