0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(5):1770–1778
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doi: 10.1210/jc.2005-1615

Effects of Short-Term Fenofibrate Treatment on Circulating Markers of Inflammation and Hemostasis in Patients with Impaired Glucose Tolerance

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Context: Apart from lowering lipid levels, peroxisome proliferator-activated receptor (PPAR) α activators (fibrates) produce many other favorable effects that may contribute to their clinical effectiveness in dyslipidemic and diabetic patients.

Objective: The objective of this study was to compare the impact of a short-term treatment with fenofibrate and the American Heart Association (AHA) step 1 diet on systemic inflammation, hemostasis, and monocyte secretory function in relationship with their metabolic actions.

Design, Setting, Participants, and Interventions: This was a prospective, randomized, placebo-controlled trial involving the group of 91 ambulatory patients with impaired glucose tolerance (IGT) (diagnosed on the basis of the American Diabetes Association criteria), randomly divided into three groups, simultaneously treated for 30 d with the AHA step 1 diet (n = 30), micronized fenofibrate (267 mg/d, n = 31), or placebo (n = 30). The control group included 34 age-, sex-, and weight-matched subjects with normal glucose tolerance. Eighty-six (95%) patients and all control subjects completed the study.

Main Outcome Measures: Plasma markers of inflammation and hemostasis and monocyte release of proinflammatory cytokines were measured.

Results: Compared with subjects with normal glucose tolerance, IGT patients exhibited higher plasma levels/activities of fibrinogen, factor VII, plasminogen activator inhibitor-1, high-sensitivity C-reactive protein, and oxidized low-density lipoproteins. Lipopolysaccharide-activated monocytes from IGT patients released significantly more TNF-α, IL-1β, IL-6, and monocyte chemoattractant protein-1 in comparison with monocytes from control subjects. Thirty-day treatment with fenofibrate but not with the AHA step 1 diet: 1) improved lipid/lipoprotein profile and glucose metabolism, and 2) reversed or alleviated all the above-mentioned abnormalities. The favorable effects of fenofibrate on plasma high-sensitivity C-reactive protein and on monocyte release of TNF-α, IL-1β, IL-6, and monocyte chemoattractant protein-1 did not correlate with its action on plasma lipids but was related to the improvement in insulin sensitivity and weakly to free fatty acid-lowering action.

Conclusions: Our study is the first to show that relatively small disturbances in glucose metabolism are associated with marked and multidirectional abnormalities in plasma markers of inflammation and hemostasis and in monocyte secretory function. Moreover, fenofibrate may exhibit early pleiotropic effects in patients with IGT. (***J Clin Endocrinol Metab* 91: 1770–1778, 2006**)

THE RESULTS OF recent studies have shown that peroxisome proliferator-activated receptor-α (PPARα) activators (fibrates) not only reduce lipid levels but also exhibit antiinflammatory, antioxidant, and antithrombotic properties and improve endothelial function (1, 2). Fibrates have been shown to decrease the production of TNF-α (3, 4), IL-6 (3, 5, 6), vascular cell adhesion molecule-1 (6), monocyte chemoattractant protein (MCP)-1 (7), interferon-γ (8), IL-2 (8), and 6-keto-prostaglandin $F_{1\alpha}$ (5). Moreover, in some (9–12) but not all (13, 14) studies, PPARα activators diminished procoagulant activity at different stages of the coagulation cascade and stimulated fibrinolysis. Via their antiinflammatory action, fibrates reduce the plasma levels of inflammation and hemostatic markers, including those regarded as cardiovascular risk factors [C-reaction protein (CRP), IL-6, fibrinogen, and plasminogen activator inhibitor-1 (PAI-1)] (3, 5, 15–17).

Some studies have revealed that impaired glucose tolerance (IGT), a condition associated with an increased risk of type 2 diabetes mellitus and cardiovascular disease (18), may be related to the enhanced low-grade inflammation and disturbed hemostasis. In these studies, serum levels of IL-6, TNF-α, CRP, MCP-1, serum amyloid A protein, fibrinogen, and PAI-1 of IGT patients were found to be higher than in healthy subjects (19–22). However, other authors (20, 23) did not confirm the above-mentioned results. When interpreting clinical trials, one should remember that their contrasting results may be the consequence of the fact that patients included in these studies differed from healthy subjects not only by the presence of IGT but also by the occurrence of concomitant disorders. Some of them, especially dyslipidemia and arterial hypertension (7, 8, 11, 24, 25), which are frequently observed in patients with metabolic syndrome, may contribute to the increased production of proinflammatory cytokines, enhanced coagulation, and impaired fibrinolysis found in some trials. Moreover, plasma levels of these factors may not be good markers of local inflammation.

Therefore, this prospective, partially double-blind, place-

First Published Online February 21, 2006

Abbreviations: CRP, C-reactive protein; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; hsCRP, high-sensitivity CRP; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; MCP, monocyte chemoattractant protein; OGTT, oral glucose tolerance test; PAI-1, plasminogen activator inhibitor-1; PPAR, peroxisome proliferator-activated receptor.

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bo-controlled randomized trial was aimed to determine whether IGT itself is associated with the changes in both plasma levels of cardiovascular risk factors and monocyte release of proinflammatory cytokines. Furthermore, because recent trials have provided arguments that fibrates may produce a beneficial effect in the prevention and treatment of the early stages of carbohydrate metabolism disorders (26–28), we investigated which of the two options, fenofibrate or a dietary intervention, is superior in normalizing IGT-related changes in the studied parameters of inflammation and hemostasis and monocyte secretory function. Thirty days was used as a treatment period because it was the shortest time after which, in our previous study, fenofibrate affected cytokine release in dyslipidemic patients (7). In line with these results, in our pilot study (our unpublished observations), we have not found any changes in the inflammation and hemostasis markers and in monocyte release of the studied cytokines after 7 and 15 d of treatment. The short period of treatment and using the group of placebo-treated patients reduced also the possible impact of seasonal variations on the levels of factors studied, particularly of fibrinogen (29).

Patients and Methods

Study population

A total of 356 individuals (35–65 yr old) with at least one risk factor for diabetes mellitus (overweight, family history of diabetes, previous gestational diabetes, or previous high blood glucose) were screened for enrollment at the Department of Clinical Pharmacology of the Medical University of Silesia. The patients were eligible for the study if they met the following American Diabetes Association criteria of IGT: 1) fasting plasma glucose less than 126 mg/dl (7.0 mmol/liter); and 2) plasma glucose concentration 2 h after a 75-g oral glucose load at least 140 mg/dl (7.8 mmol/liter) but less than 200 mg/dl (11.1 mmol/liter).

The exclusion criteria were as follows: 1) diabetes mellitus [fasting plasma glucose at least 126 mg/dl (7.0 mmol/liter) or plasma glucose concentration 2 h after a glucose load at least 200 mg/dl (11.1 mmol/liter)]; 2) impaired fasting glycemia [fasting plasma glucose at least 100 mg/dl (5.6 mmol/liter) but less than 126 mg/dl (7.0 mmol/liter) and 2-h postchallenge glucose level less than 140 mg/dl (7.8 mmol/liter)]; 3) other than mild forms of primary dyslipidemia [total cholesterol above 230 mg/dl (6.0 mmol/liter) and/or triglycerides above 230 mg/dl (2.6 mmol/liter)][1]; 4) whichever type of secondary dyslipidemia; 5) obesity (body mass index > 30 kg/m^2); 6) any acute and chronic inflammatory processes; 7) symptomatic congestive heart failure; 8) unstable coronary artery disease, myocardial infarction, stroke, transient ischemic attacks, or intermittent claudication within 6 months preceding the study[2]; 9) any form of arterial hypertension; 10) impaired renal or hepatic function; 11) gallbladder diseases; 12) malabsorption syndromes; 13) treatment with other hypolipemic drugs within 3 months before the study; 14) concomitant treatment with other drugs known either to affect plasma lipid levels or to interact with fibrates; 15) concomitant treatment with drugs known to interfere with glucose tolerance (including glucocorticosteroids); 16) concomitant treatment with drugs that may affect inflammatory processes in the vascular wall (including nonsteroid antiinflammatory drugs and angiotensin-converting enzyme inhibitors) within 3 months preceding the study; 17) ongoing hormonal replacement therapy or oral contraception; and 18) poor patient compliance.

Study design

The study complied with the principles of the Declaration of Helsinki, and its protocol was approved by the Bioethical Committee of the Silesian University School of Medicine. All patients gave their written informed consent for the investigation after detailed explanation of possible adverse effects of the treatment. Subjects with a risk for IGT were invited to undergo a screening 75-g oral glucose tolerance test (OGTT). Those with 2-h plasma glucose concentrations in the IGT range (n = 97) were invited to repeat the OGTT. Only patients in whom the second OGTT confirmed IGT (n = 91) were included in the study.

All the enrolled patients were divided in a ratio (1:2) into one of the two major groups according to a computer-generated randomization procedure. The patients from the first group (n = 30) were instructed and followed the American Heart Association step 1 diet.[3] The diet was isocaloric and consisted of no more than 30% of total calories as fat (less than 10% as saturated fat), about 50% as carbohydrate with an emphasis on complex carbohydrates (starch), and about 20% as protein, giving less than 300 mg cholesterol daily. Dietary intake was prescribed individually according to data obtained from dietary questionnaires to maintain the initial caloric intake and nutrient proportions constant throughout the study. The patients randomized to the second group (n = 61) received brief information about the beneficial effects of a healthy diet but were not prescribed any special dietary recommendations. These patients were randomly assigned in a double-blind fashion to fenofibrate (267 mg daily; n = 31) or placebo (n = 30). For fenofibrate, a micronized form was used, which is more effective and convenient than its immediate-acting form (30). Both fenofibrate and placebo were administered once daily at bedtime for 30 d. No changes in the therapy were made during the study. Patients with IGT were compared with the control group including 34 age-, sex-, and weight-matched subjects with normal glucose tolerance at the initial visit, confirmed by a negative result of the second OGGT [normal glucose tolerance was defined on the basis of the American Diabetes Association criteria as fasting plasma glucose level less than 100 mg/dl (5.6 mmol/liter) and a 2-h postchallenge glucose level less than 140 mg/dl (7.8 mmol/liter)]. Like patients randomized to fenofibrate and placebo, the control subjects were briefly informed about the benefits of a healthy diet. All the subjects participating in the study were encouraged to increase their physical activity to at least 30 min of moderate physical activity a day for at least 5 d/wk. The investigation of possible fenofibrate-induced side effects was performed every 2 wk. Compliance was assessed during each visit by tablet counts and was considered satisfactory when the number of tablets taken by a patient ranged from 90–110%.

Laboratory assays

An OGTT was performed after a 10-h overnight fast three times during the study: on the day of the screening visit, the day of randomization and after 30 d of treatment. The result of the second OGTT was considered the baseline value.

Lipid/lipoprotein profile, fasting plasma glucose, plasma insulin, glycated hemoglobin (HbA_{1c}), high-sensitivity CRP (hsCRP), factor VII, fibrinogen, PAI-1, and monocyte cytokine production were determined twice before and after 30 d of treatment. Blood samples were taken 12 h after the last meal in a quiet, temperature-controlled room (24–25 C) between 0800 and 0900 h. The samples were immediately coded so that the person performing laboratory assay was blinded to subject identity and study sequence. All the tests were performed in triplicate according to manufacturers' instructions.

Plasma glucose concentrations were measured by a glucose oxidase method (Beckman, Palo Alto, CA). Plasma insulin was measured with a commercial RIA kit (Linco Research Inc., St Charles, MO). This assay does not cross-react with human proinsulin. Fasting plasma glucose and insulin levels were used to calculate the homeostatic model assessment (HOMA) index [fasting serum glucose (millimoles per liter) × fasting

[1] There is no one generally accepted classification of severity of dyslipidemia. Plasma level of 230 mg/dl as cut-off for both triglycerides and cholesterol was chosen arbitrarily on the basis of the distribution of plasma cholesterol and triglyceride levels in the Polish population.

[2] Stable coronary artery disease and cerebrovascular disease did not exclude a patient from the trial, nor did unstable coronary artery disease, myocardial infarction, stroke, transient ischemic attacks, or intermittent claudication if the event occurred more than 6 months before the beginning of the study.

[3] Dietary recommendations have changed slightly since the study was done. Presently, patients with dyslipidemia are recommended to follow the Therapeutic Lifestyle Changes diet.

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insulin level (microunits per milliliter)/22.5]. HbA_{1c} was determined in fasting plasma samples using a DCA 2000 analyzer (Bayer Ames Technicon, Tarrytown, NY). The serum levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides were determined colorimetrically using commercial kits (bioMerieux, Marcy l'Etoile, France). Total nonestrified fatty acids were assessed by an enzymatic assay (Alpha Laboratories, Eastleigh, Hants, UK). Levels of apoprotein A-I and apoprotein B were measured by immunoturbidimetry using reagents from Incstar Corp. (Stillwater, MN). Oxidized LDL-cholesterol levels were determined by an ELISA method (Mercodia, Uppsala, Sweden). Plasma levels of CRP were measured using a high-sensitivity monoclonal antibody assay (MP Biomedicals, Orangeburg, NY). The lower limit of sensitivity of this method was 0.1 mg/liter. Both fibrinogen and factor VII were assessed by a semiautomated blood coagulation analyzer OPTION 2 Plus using reagents obtained from bioMerieux. Fibrinogen levels were determined by the Clauss method, whereas factor VII activity was assessed by a one-step method using factor VII-deficient plasma. PAI-1 antigen levels were assessed by a commercially available ELISA method (Asserachrom, Diagnostica Stago, Asnieres, France).

Cytokine release from blood monocytes stimulated with lipopolysaccharide was measured as described previously (7). TNF-α, IL-1β, IL-6, and MCP-1 levels were estimated using commercial ELISA kits (R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. The minimum detectable levels for the assessed cytokines were: 4.4, 1.0, 3.9, and 5.0 pg/ml, respectively, for TNF-α, IL-1β, IL-6, and MCP-1.

The intra- and interassay coefficients of variation in our laboratory were as follows: fibrinogen, 3.6 and 2.3%; factor VII, 4.3 and 3.2%; PAI-1, 8.7 and 5.0%; hsCRP, 4.3 and 5.9%; oxidized LDLs, 4.0 and 7.4%; insulin, 4.0 and 6.0%; HbA_{1c}, 1.1 and 2.3%; TNF-α, 4.4 and 8.7%; IL-1β, 3.4 and 4.1%; IL-6, 2.5 and 5.9%; and MCP-1, 4.0 and 4.8%.

Statistical analysis

All data are expressed as the mean ± SEM. First, the distribution of the variables was analyzed. Outcomes for TNF-α, IL-1β, IL-6, MCP-1, HOMA, fibrinogen, factor VII, PAI-1, and hsCRP were natural-log transformed to satisfy assumptions of normality and equal variance. Because lipid, lipoprotein, free fatty acid, carbohydrate, and after logarithmic transformation, also, the other values were normally distributed, parametric tests were used for statistical analysis. Comparisons between the groups were performed using one-way ANOVA followed by Bonferroni's Multiple Comparison test. Student's paired *t* test was used to compare differences between the means of variables within the same treatment group. For categorical variables, χ^2 test was used. $P < 0.05$ was regarded as statistically significant. In addition, to verify the correctness of statistical analysis for TNF-α, IL-1β, IL-6, MCP-1, HOMA, fibrinogen, factor VII, PAI-1, and hsCRP, their median values on the original scale were recalculated using nonparametric tests (the Kruskal-Wallis test followed by the Mann-Whitney *U* test and the Wilcoxon matched paired test). Because the results of this analysis are consistent with the ones obtained after using parametric tests, they are not placed in the text. Correlations were calculated with the Kendall tau test. Statistical analysis was performed using GraphPad Prism 2.01 software (GPA-26576-117, GraphPad Software Inc., San Diego, CA) and Statistica 6.1 (axxp308a903804ar, StatSoft, Tulsa, OK).

Results

Baseline characteristics (Table 1)

At study entry, there was no difference between the control and IGT groups relative to sex, weight, age, medical history, clinical characteristics, lipid/lipoprotein profile, and safety parameters. At entry, patients with IGT exhibited higher plasma levels/activities of oxidized LDLs, hsCRP, fibrinogen, factor VII, and PAI and the higher value of HOMA index. Unstimulated monocytes of both control and IGT patients released hardly detectable amounts of TNF-α, IL-1β, and IL-6. In turn, MCP-1 release by unstimulated monocytes exhibited marked interpersonal differences and therefore only tended to be higher in IGT patients than in control subjects ($P = 0.09$) (data not shown). Compared with control, lipopolysaccharide-activated monocytes of IGT patients produced larger amounts of TNF-α, IL-1β, IL-6, and MCP-1.

Adverse effects

Neither significant adverse effects nor any other complications were reported throughout the study. All laboratory safety parameters remained within normal limits. Two subjects randomized to the diet group dropped out because of acute infections of the upper respiratory tract. Three other patients, two subjects who received placebo and one treated with fenofibrate, were withdrawn from the trial due to noncompliance with the study regimen. Baseline characteristics of the five subjects who left the study did not differ from the 86 completing the trial (data not shown).

Control subjects and placebo-treated patients (Table 2 and Figs. 1–3)

In both control subjects and placebo-treated IGT-patients, lipid/lipoprotein profile, HbA_{1c}, HOMA index, 2-h postglucose load plasma glucose, plasma levels/activity of oxidized LDLs, hsCRP, fibrinogen, factor VII, PAI-1, and cytokine release by lipopolysaccharide-stimulated monocytes remained at the similar level throughout the study.

Fenofibrate-treated patients

As expected, fenofibrate significantly changed lipid/lipoprotein profile (Table 2). After 30 d of therapy, the drug reduced 2-h postchallenge plasma glucose levels by 14.2% ($P < 0.01$), HOMA index by 39.1% ($P < 0.001$), HbA_{1c} by 12.7% ($P < 0.05$), and oxidized LDLs by 30.4% ($P < 0.001$) (Fig. 1). It also decreased plasma levels of fibrinogen by 16.7% ($P < 0.01$), factor VII activity by 18.6% ($P < 0.01$), PAI-1 by 25.7% ($P < 0.001$), and hsCRP by 25.0% ($P < 0.001$) (Fig. 2). Moreover, fenofibrate reduced the release of all studied proinflammatory cytokines by activated monocytes: TNF-α by 32.1% ($P < 0.001$), IL-1β by 35.4% ($P < 0.001$), IL-6 by 22.3% ($P < 0.001$), and MCP-1 by 17.0% ($P < 0.01$) (Fig. 3).

After 30 d of treatment, plasma oxidized LDLs, 2-h postchallenge glucose levels, plasma PAI-1 and hsCRP levels, and monocyte release of MCP-1 release were still higher than in the control group.

American Heart Association step 1 diet-treated patients (Table 2 and Figs. 1–3)

No significant changes in lipid/lipoprotein profile, plasma glucose in OGTT, HbA_{1c}, HOMA index, oxidized LDLs, and the studied parameters of systemic inflammation, hemostasis, and monocyte secretory function were observed after 30 d of the dietary intervention.

Correlations

At baseline, none of the groups showed any correlations between the studied plasma markers or monocyte cytokine release and plasma lipid/lipoprotein levels. Pretreatment

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TABLE 1. Baseline characteristics of patients

	Control group	Patients with IGT		
		Placebo	Fenofibrate	Diet
No. of patients	34	30	31	30
Age [yr (range of age)]	47.0 ± 1.5 (37–62)	48.3 ± 1.4 (36–64)	48.8 ± 1.6 (37–63)	47.4 ± 1.0 (36–62)
Female/male	12/24	11/19	11/20	10/20
BMI (kg/m^2)	26.7 ± 0.5	27.7 ± 0.3	27.3 ± 0.4	27.9 ± 0.4
Smokers (%)	12 (35.3)	12 (40.0)	12 (38.7)	11 (36.7)
Stable coronary artery disease (%)	4 (11.8)	5 (16.7)	4 (12.9)	4 (13.3)
Stable cerebrovascular disease (%)	2 (5.9)	3 (10.0)	2 (6.5)	2 (6.5)
Previous atherosclerotic clinical events[a] (%)	2 (5.9)	1 (3.3)	2 (6.5)	1 (3.3)
Medications				
β_1-Adrenergic blockers (%)	3 (8.8)	3 (10.0)	3 (9.7)	3 (10.0)
Long-acting nitrates (%)	2 (5.9)	3 (10.0)	2 (6.5)	4 (13.3)
Long-acting calcium channel blockers (%)	2 (5.9)	2 (6.7)	2 (6.5)	2 (6.7)
Thienopyridines	2 (5.9)	3 (10.0)	2 (6.5)	3 (10.0)
Total cholesterol (mg/dl)	210.5 ± 4.3	218.4 ± 6.8	219.3 ± 4.6	212.7 ± 6.7
LDL-cholesterol (mg/dl)	124.8 ± 4.1	127.9 ± 3.2	130.9 ± 4.3	126.5 ± 3.7
HDL-cholesterol (mg/dl)	44.6 ± 1.3	44.1 ± 2.1	44.9 ± 1.2	44.3 ± 2.1
Triglycerides (mg/dl)	201.6 ± 10.8	207.5 ± 10.1	212.1 ± 12.0	200.1 ± 12.5
Oxidized LDLs (U/liter)	36.5 ± 3.7	68.1 ± 6.1[b]	71.5 ± 6.2[b]	69.9 ± 5.7[b]
Free fatty acids (μmol/liter)	433.1 ± 21.3	472.7 ± 32.9	475.4 ± 28.2	485.8 ± 36.6
Apoprotein A-I (mg/dl)	132.3 ± 12.9	125.8 ± 16.9	123.9 ± 14.0	122.1 ± 13.1
Apoprotein B (mg/dl)	134.2 ± 14.1	148.1 ± 12.1	151.0 ± 12.4	146.7 ± 14.4
Fasting glucose (mg/dl)	88.3 ± 3.3	91.6 ± 3.2	90.6 ± 2.3	92.1 ± 2.0
2-h Postchallenge plasma glucose (mg/dl)	112.8 ± 4.4	169.2 ± 5.1[b]	164.3 ± 4.6[b]	172.3 ± 4.3[b]
HOMA index	2.3 ± 0.2	3.9 ± 0.3[b]	4.0 ± 0.4[b]	4.2 ± 0.3[b]
HbA_{1c} (%)	5.0 ± 0.2	5.3 ± 0.2	5.5 ± 0.2	5.2 ± 0.2
Fibrinogen (g/liter)	3.3 ± 0.1	4.2 ± 0.1[b]	4.1 ± 0.2[c]	4.3 ± 0.1[b]
Factor VII activity (%)	105.9 ± 3.7	147.2 ± 5.6[b]	142.9 ± 7.8[c]	154.1 ± 5.3[b]
PAI-1 (ng/ml)	42.4 ± 4.9	97.8 ± 8.3[b]	102.0 ± 9.2[b]	93.6 ± 5.4[b]
hsCRP (mg/liter)	1.0 ± 0.1	2.7 ± 0.3[b]	2.6 ± 0.3[b]	2.6 ± 0.2[b]
TNF-α release (ng/ml)	0.8 ± 0.1	1.4 ± 0.1[b]	1.4 ± 0.1[b]	1.3 ± 0.1[b]
IL-1β release (pg/ml)	78.0 ± 10.8	135.2 ± 17.1[b]	136.3 ± 15.5[b]	131.7 ± 16.0[b]
IL-6 release (ng/ml)	6.1 ± 0.2	7.9 ± 0.8[b]	7.8 ± 0.8[b]	7.9 ± 0.4[b]
MCP-1 release (ng/ml)	11.0 ± 1.8	19.2 ± 2.2[b]	18.8 ± 2.2[b]	18.4 ± 2.3[b]

Each value represents the mean ± SEM.

[a] Unstable coronary artery disease, myocardial infarction, stroke, transient ischemic attacks, or intermittent claudication if occurred more than 6 months before the beginning of the study.

[b] $P < 0.001$ *vs.* control group.

[c] $P < 0.01$ *vs.* control group.

TABLE 2. Effect of fenofibrate and diet on lipid profile in patients with IGT

	Control group (n = 34)	Patients with IGT		
		Placebo (n = 28)	Fenofibrate (n = 30)	Diet (n = 28)
Total cholesterol (mg/dl)				
Baseline	210.5 ± 4.3	215.2 ± 6.9	219.1 ± 4.5	212.4 ± 6.8
After 30 d	214.1 ± 4.5 (+1.7%)	210.3 ± 6.5 (−2.3%)	187.4 ± 4.1 (−14.5%)[a]	195.0 ± 4.5 (−8.2%)
LDL-cholesterol (mg/dl)				
Baseline	124.8 ± 4.1	128.2 ± 3.2	130.8 ± 4.2	126.2 ± 3.8
After 30 d	128.9 ± 3.3 (+3.3%)	125.0 ± 3.5 (−2.5%)	110.1 ± 4.8 (−15.8%)[a]	114.1 ± 5.5 (−9.6%)
HDL-cholesterol (mg/dl)				
Baseline	44.6 ± 1.3	43.9 ± 2.2	43.7 ± 1.1	44.2 ± 2.1
After 30 d	43.5 ± 2.2 (−2.5%)	44.4 ± 1.6 (+1.1%)	49.2 ± 1.2 (+12.6%)[a]	46.7 ± 2.9 (+5.6%)
Triglycerides (mg/dl)				
Baseline	201.6 ± 10.8	205.9 ± 10.2	210.1 ± 12.1	199.3 ± 12.3
After 30 d	209.5 ± 8.0 (+3.9%)	214.1 ± 12.1 (+4.0%)	165.6 ± 10.7 (−21.2%)[a]	187.1 ± 15.8 (−6.1%)
Free fatty acids (μmol/liter)				
Baseline	433.1 ± 21.3	472.7 ± 32.9	475.4 ± 28.2	485.8 ± 36.6
After 30 d	422.6 ± 20.9 (−2.6%)	451.9 ± 29.1 (−4.4%)	400.8 ± 19.3 (−15.7%)[a]	442.0 ± 22.4 (−9.0%)
Apoprotein A-I (mg/dl)				
Baseline	132.3 ± 12.9	125.8 ± 16.9	123.9 ± 11.0	122.1 ± 13.1
After 30 d	137.1 ± 13.5 (+3.6%)	127.2 ± 15.1 (+1.1%)	142.6 ± 10.7 (+15.1%)[a]	130.2 ± 12.5 (+6.6%)
Apoprotein B (mg/dl)				
Baseline	134.2 ± 14.1	148.1 ± 12.1	151.0 ± 12.4	146.7 ± 14.4
After 30 d	138.2 ± 3.0 (+3.0%)	145.3 ± 13.4 (−1.9%)	127.9 ± 14.4 (−15.3%)[a]	139.8 ± 12.5 (−4.7%)

Each value represents the mean ± SEM. Values in *parentheses* represent percent changes from baseline values.

[a] $P < 0.05$ *vs.* pretreatment values.

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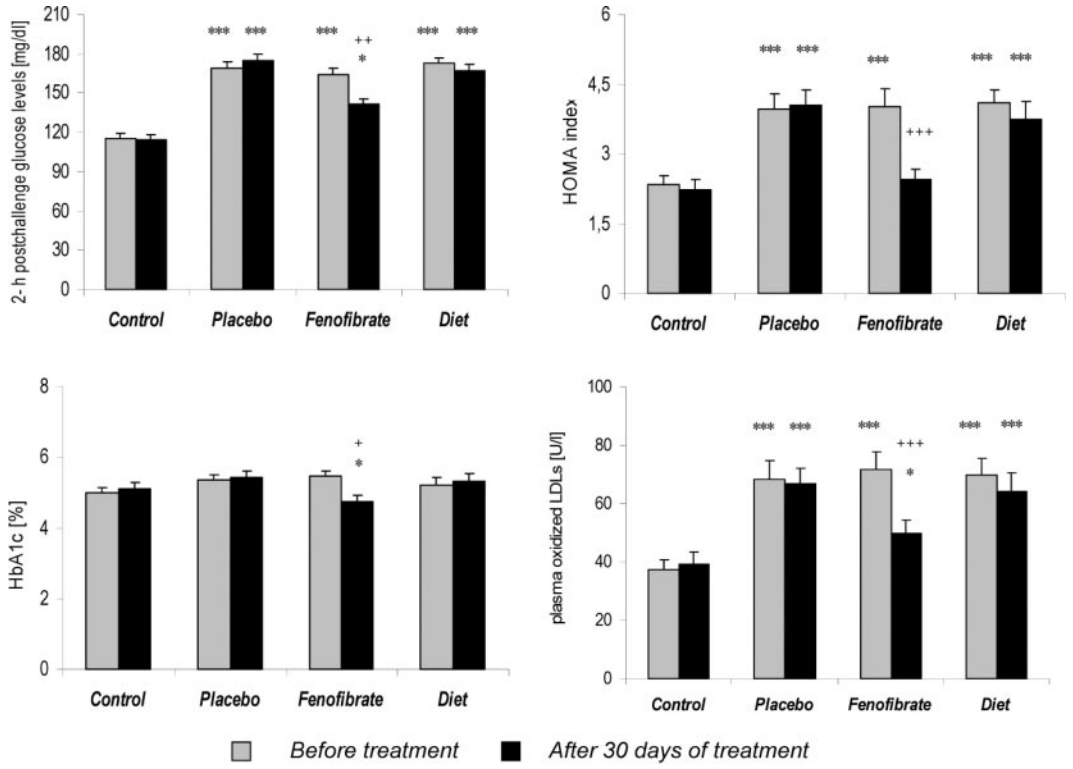

FIG. 1. Effect of fenofibrate and diet on 2-h postchallenge plasma glucose levels, HOMA index, HbA_{1c}, and oxidized LDLs in patients with IGT. Data represent the mean ± SEM. *, $P < 0.05$; ***, $P < 0.001$ *vs.* control group. +, $P < 0.05$; ++, $P < 0.01$; +++, $P < 0.001$ *vs.* baseline values.

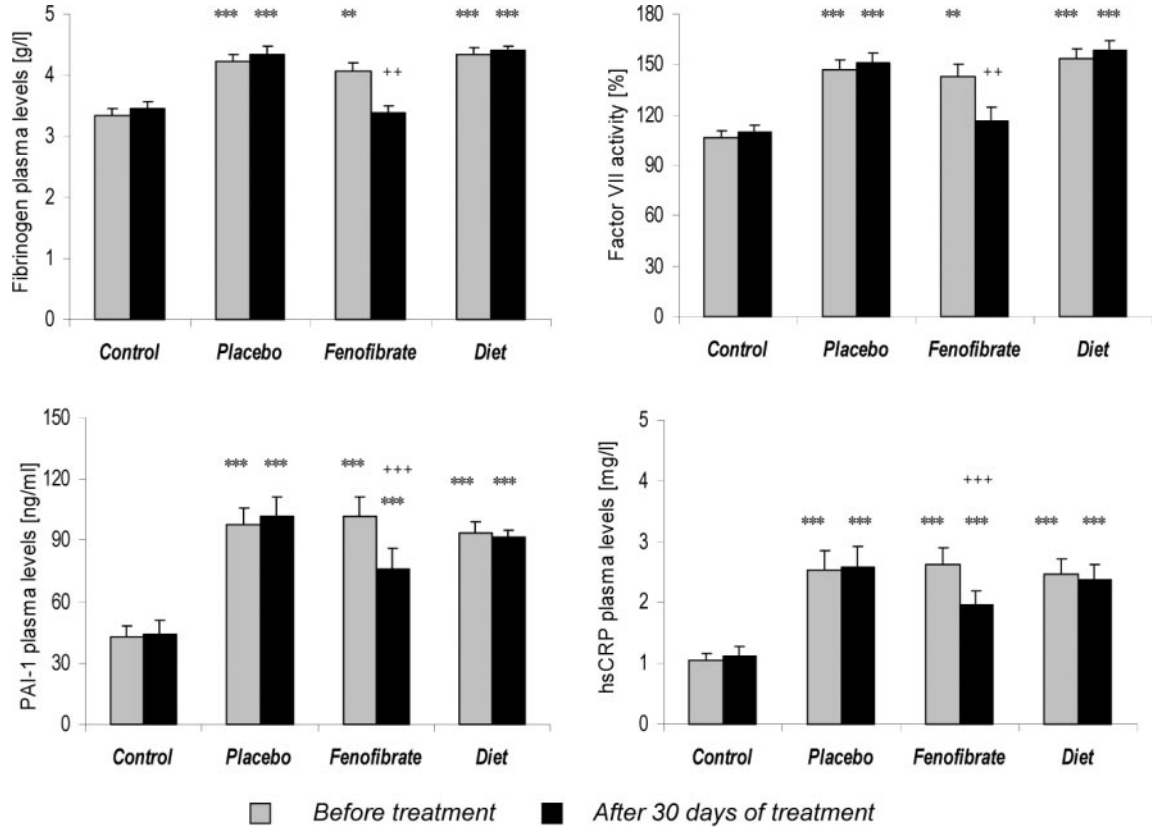

FIG. 2. Effect of fenofibrate and diet on plasma markers of hemostasis and low-grade inflammation in patients with IGT. Data represent the mean ± SEM. **, $P < 0.01$; ***, $P < 0.001$ *vs.* control group. ++, $P < 0.01$; +++, $P < 0.001$ *vs.* baseline values.

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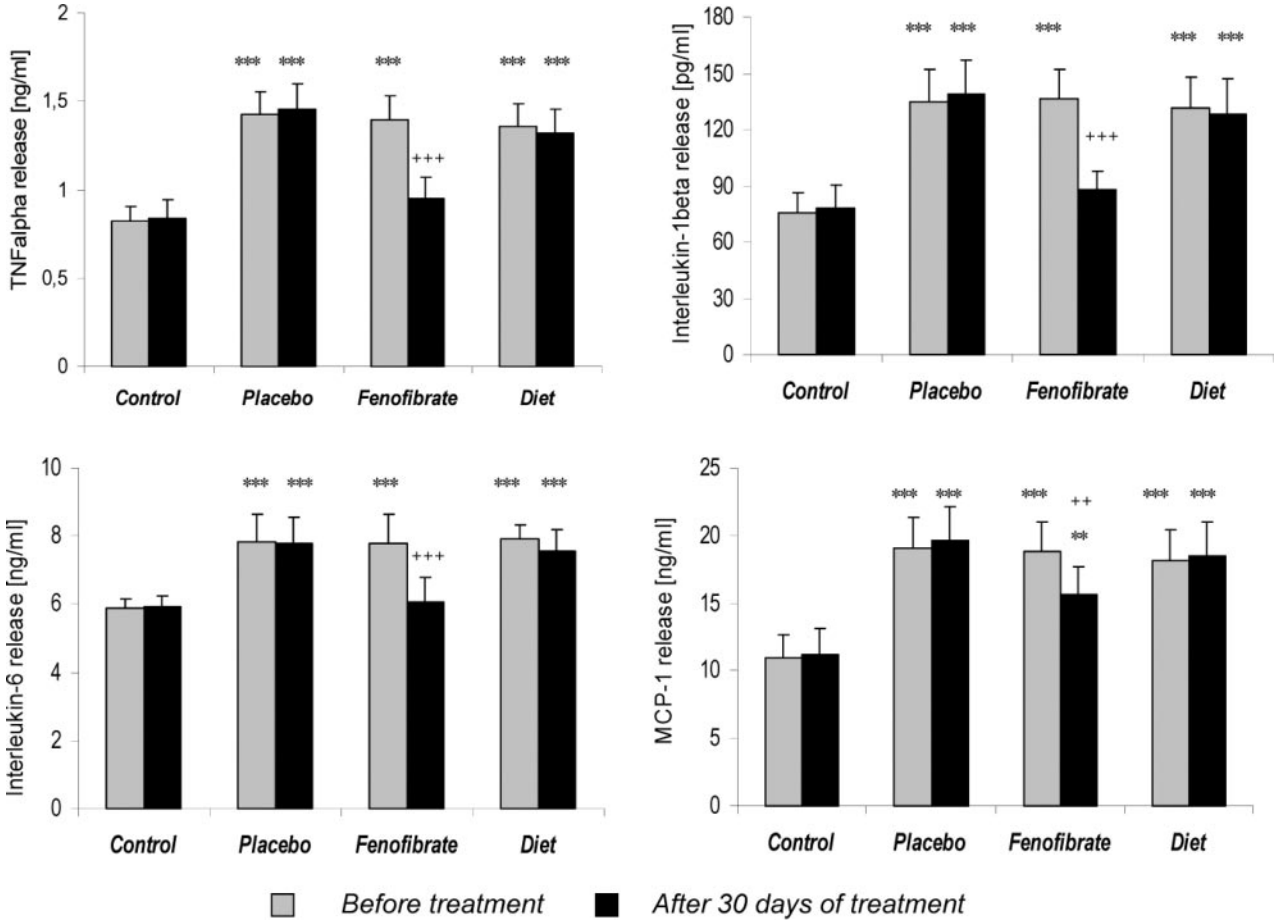

FIG. 3. Effect of fenofibrate and diet on cytokine release by lipopolysaccharide-stimulated monocytes in patients with IGT. Data represent the mean ± SEM. **, $P < 0.01$; ***, $P < 0.001$ *vs.* control group. ++, $P < 0.01$; +++, $P < 0.001$ *vs.* baseline values.

plasma hsCRP levels correlated weakly with baseline release of TNF-α (r = 0.45; $P < 0.001$), IL-1β (r = 0.40; $P < 0.001$), IL-6 (r = 0.49, $P < 0.001$), and MCP-1 (r = 0.42, $P < 0.001$). Baseline insulin sensitivity correlated with plasma hsCRP (r = 0.75, $P < 0.001$ between HOMA and hsCRP), fibrinogen (r = 0.67, $P < 0.001$ between HOMA and fibrinogen), factor VII (r = 0.70, $P < 0.001$ between HOMA and factor VII), PAI-1 (r = 0.71, $P < 0.001$ between HOMA and PAI-1), and monocyte cytokine release (r = 0.72, $P < 0.001$ between HOMA and TNF-α; r = 0.69, $P < 0.001$ between HOMA and IL-1β; r = 0.66, $P < 0.001$ between HOMA and IL-6; and r = 0.73, $P < 0.001$ between HOMA and MCP-1). No other correlations between baseline values were found.

There was no correlation between the studied plasma markers and cytokine release and lipid/lipoprotein profile in terms of their response to fenofibrate (r values from 0.12–0.28; all nonsignificant). There was a weak correlation between hsCRP and cytokine release during treatment with fenofibrate (r = 0.48, $P < 0.001$ between ΔTNF-α and ΔCRP; r = 0.42, $P < 0.001$ between ΔIL-1β and ΔCRP; r = 0.46, $P < 0.001$ between ΔIL-6 and ΔCRP; and r = 0.53, $P < 0.001$ between ΔMCP-1 and ΔCRP). The reduction of monocyte cytokine release and plasma hsCRP, fibrinogen, factor VII, and PAI-1 correlated with the degree of improvement in insulin sensitivity (r values between 0.69 and 0.74, $P < 0.001$; Fig. 4), with 2-h postchallenge glucose levels (r values between 0.63 and 0.72, $P < 0.001$), and weakly with the changes in free fatty acids (r values between 0.41 and 0.54, $P < 0.001$). There were no correlations between the effects of fenofibrate on monocyte cytokine release and on plasma markers of hemostasis or oxidized LDLs.

Discussion

This study has shown that patients with relatively early changes in glucose metabolism experience multidirectional unfavorable shifts in plasma markers of systemic inflammation and hemostasis. Moreover, we have found for the first time that monocytes coming from IGT subjects release greater amounts of proinflammatory cytokines than monocytes of control subjects. All these abnormalities have been reversed or attenuated by a short-term treatment with fenofibrate but not with the dietary intervention.

We observed that patients with IGT had increased plasma levels of all studied factors and released the enhanced amounts of all measured monocyte-derived cytokines. To minimize the impact of concurrent diseases and concomitant therapies, we used very strict inclusion criteria in this study. First of all, we excluded all the patients suffering from moderate and severe dyslipidemia and any form of arterial hy-

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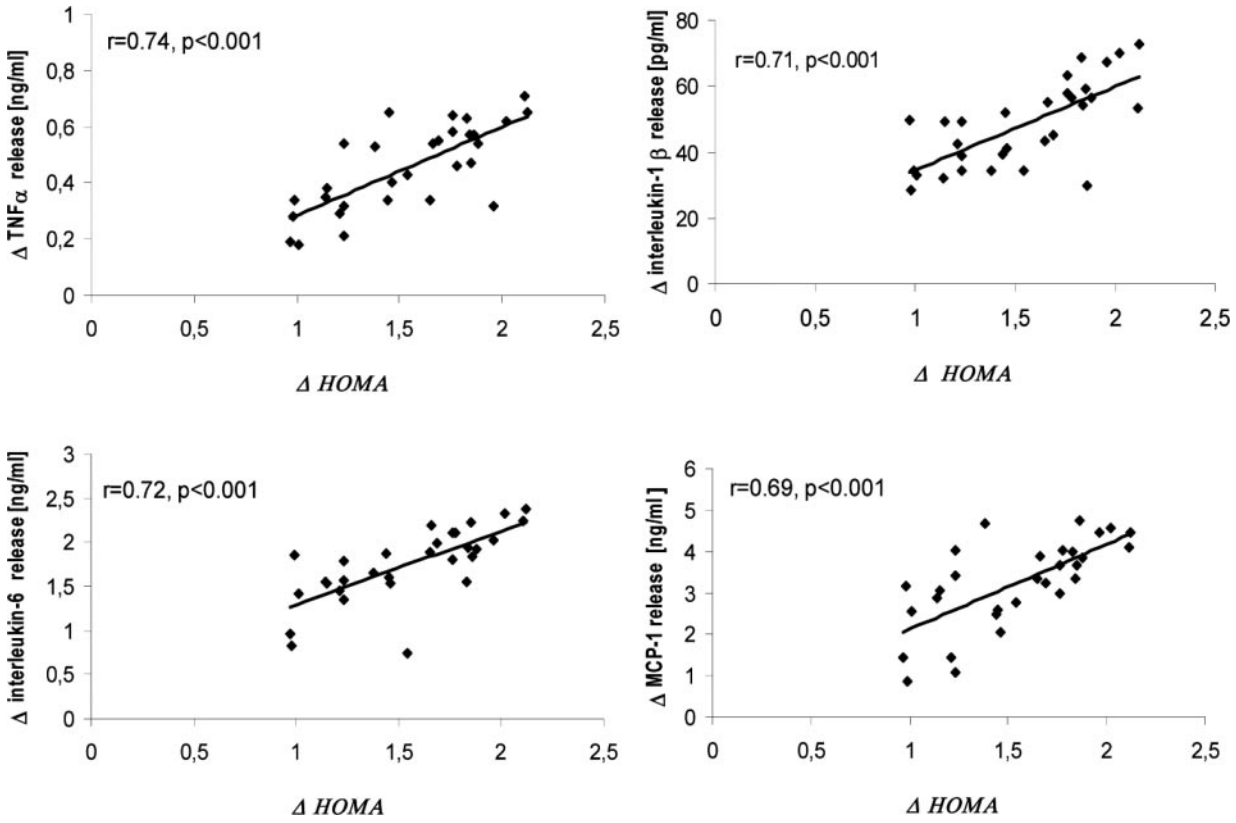

FIG. 4. Relationship between changes in HOMA index and changes in monocyte cytokine release. The *line* shows the predicted regression line.

pertension, both of which in our previous studies were strongly associated with the increased plasma levels of oxidized LDLs, MCP-1, fibrinogen, factor VII, and PAI-1 and with enhanced monocyte release of TNF-α, IL-1β, and MCP-1 (7, 8, 11, 24, 25). We also excluded subjects with recent atherosclerotic clinical events that at least potentially might affect the results. The presence of other concomitant disorders (stable coronary artery disease, cerebrovascular disease) in IGT patients does not seem to be responsible for the observed changes in the factors studied because these disorders occurred in the minority of patients, were also found in control subjects, and were not advanced and effectively treated. The existence of the correlation between all the studied parameters and HOMA index indicate that their abnormal levels and release were at least partially related to decreased insulin sensitivity, resulting from insulin resistance and/or leading to its development.

Although several studies assessed the effects of PPARα activators on glucose tolerance, their results are inconsistent. In some studies, fibrates reduced 2-h postchallenge plasma glucose levels and increased insulin sensitivity (12, 27, 28), whereas in the others, they did not produce these effects (31, 32). In our study, short-term treatment of IGT patients with micronized fenofibrate was enough to reduce postglucose load glucose levels, HOMA index, and HbA_{1c}. In opposition to most previously conducted trials, the strength of our study is that the population is a relatively homogeneous group of patients. The fact that fenofibrate but not the diet produced early and favorable effects on glycemic control may make this drug particularly suitable for treatment of the early stages of carbohydrate metabolism disorders.

Probably the most important finding resulting from our study is that fenofibrate was superior to the dietary intervention in reducing IGT-related changes in plasma markers of inflammation, hemostasis, and monocyte secretory function. The beneficial effects of fenofibrate cannot be explained by its lipid-lowering action because treatment-induced changes in lipid profile and apoproteins did not correlate with plasma levels/monocyte release of the studied markers. This pleiotropic action of fenofibrate may contribute to the positive effect of fibrates on the incidence of cardiovascular events, reported previously in some large clinical trials, especially the Veterans Affairs HDL Intervention Trial (VA-HIT). In the last, the changes in major lipids or lipoproteins accounted only for less than 25% of the benefit of gemfibrozil therapy (33). Interestingly, our findings that changes in plasma markers of inflammation, hemostasis, and monocyte secretory function were associated with the improvement in insulin sensitivity may explain why in the Veterans Affairs HDL Intervention Trial the reduction in coronary heart disease events and related mortality was achieved mainly in individuals with diabetes or in nondiabetic patients with hyperinsulinemia (33). A recently published study (FIELD) has provided mixed results on the effects of fenofibrate in individuals with type 2 diabetes (34). The drug significantly reduced total cardiovascular disease events, mainly through the prevention of nonfatal myocardial infarctions and coronary revascularizations, and also reduced microvascular-

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associated complications. The greater use of statins in placebo-allocated patients may, at least in part, explain why fenofibrate caused only a nonsignificant reduction in the primary outcome of first myocardial infarction or coronary heart disease death (34).

To factors linking restoration of insulin sensitivity and pleiotropic effects of fenofibrate may belong free fatty acids. Our findings that the correlation between the changes in free fatty acids and studied factors was weak indicate, however, that monocyte cytokine production, systemic inflammation, and hemostasis are regulated additionally by other factors and that the plasma free fatty acid content does not reflect precisely the pleiotropic effect of fenofibrate.

Our findings that plasma levels of hsCRP were positively correlated with the monocyte release of TNF-α, IL-1β, IL-6, and MCP-1 in both baseline conditions and after treatment are in line with the previous *in vitro* and animal studies that showed that proinflammatory cytokines stimulated CRP production and that this effect was prevented by fibrates (35, 36). These results suggest that IGT-induced stimulation of monocyte cytokine release contributes to systemic inflammation expressed by the increased CRP production in IGT patients and that a fenofibrate-induced reduction in the monocyte secretory function may be involved in the CRP-lowering effect of this drug.

Our results show that fibrates might produce the early pleiotropic effect on coagulation and fibrinolysis in IGT patients. Thirty-day treatment with fenofibrate was enough to affect plasma fibrinogen and PAI-1 levels and factor VII activity. Taking into consideration that fibrinogen, PAI-1, and factor VII belong to cardiovascular risk factors and that even small differences in fibrinogen level among the population alter the risk of coronary artery disease and its complications (29), these actions of fenofibrate may be clinically relevant. Furthermore, the favorable action of fenofibrate on hemostasis may be additionally indirect because the drug reduced oxidized LDLs that stimulate macrophage tissue factor expression, interfere with endothelial thrombomodulin expression, and inhibit fibrinolysis (37).

After 30 d of treatment, hsCRP and PAI-1 plasma levels, oxidized LDLs and 2-h postchallenge glucose levels, and monocyte secretion of MCP-1 release still exceeded the control values, despite the marked decrease observed at the end of the study. The lack of complete normalization of these factors suggests that longer treatment may be necessary to produce the full effect of fenofibrate on hemostasis and inflammatory processes.

The most probable molecular explanation for the ability of fenofibrate to produce its pleiotropic action is its effect on PPARα. That PPARα regulates a number of genes involved in lipid metabolism including those encoding for apoprotein A-I, apoprotein A-I, apoprotein C-III, and lipoprotein lipase (30) may explain why fenofibrate decreased triglycerides and apoprotein B and increased HDL cholesterol and apoprotein A-I levels. The early and pronounced changes in lipid/lipoprotein profile may result from full agonism of fenofibrate for PPARα (38). The fact that the effect of fenofibrate on plasma markers of inflammation and hemostasis and on monocyte secretory function correlated with its action on free fatty acids, which are the endogenous ligands for PPARα (30), provides some arguments that also nonlipid-related effects of this drug may be mediated by PPARα. This hypothesis is in line with the results of *in vitro* and animal studies that showed that pirinixic acid (Wy-14643), a selective PPARα agonist, exhibited a marked and similar to fibrates antiinflammatory effect (5, 36), reversed basal and glucose-stimulated insulin hypersecretion (39), and inhibited the initiation of coagulation cascade (40). Taking into account that PPARα is involved in atherogenesis since its early stages and expressed on many various types of inflammatory cells (endothelial cells, smooth muscle cells, macrophages), our study suggests that both lipid and nonlipid-related PPARα-mediated events may be relevant for the success of fibrate therapy.

In summary, our trial has revealed for the first time that IGT patients experience pronounced and multidirectional disturbances in plasma markers of inflammation, hemostasis, and in monocyte secretory function. All these abnormalities were alleviated by a short-term treatment with fenofibrate, whereas a diet remained without any significant effect. The results of our trial have shown that proinflammatory state and the increased procoagulant activity may contribute to the development and progression of IGT, support previous findings of the antiinflammatory effect of fibrates, and indicate that fenofibrate may be an effective agent in the prevention and treatment of IGT and its complications.

Acknowledgments

Received July 20, 2005. Accepted February 13, 2006.

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This work was supported by Statutory Grant NN-1-038/03 of the Medical University of Silesia. The experiments comply with the current law of Poland.

Disclosure Statement Summary: B.O., R.K., and Z.S.H. have nothing to declare.

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