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Hemostatic effects of fenofibrate in patients with mixed dyslipidemia and impaired fasting glucose

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Abstract:
Our study aimed to compare the effect of fenofibrate on hemostasis between patients with isolated impaired fasting glucose (IFG) and isolated mixed dyslipidemia and to examine the action of this agent on glucose and lipid metabolism. Twenty-two IFG and 23 mixed dyslipidemic patients were treated for 90 days with micronized fenofibrate (267 mg/day) and were compared with 22 age-, sex- and weight-matched control subjects without lipid and glucose metabolism abnormalities. The lipid profile, fasting and 2-h post-glucose challenge glucose levels, HOMA and glycated hemoglobin as well as the plasma levels/activities of fibrinogen, factor VII and PAI-1 were determined at the beginning and after 30 and 90 days of treatment. Compared to the control subjects, mixed dyslipidemic and IFG patients exhibited increased plasma levels of fibrinogen and PAI-1 as well as increased factor VII activity. Fibrinogen, factor VII and PAI-1 were higher in mixed dyslipidemic than IFG subjects. Not only did fenofibrate improve plasma lipids, but it also increased glucose sensitivity and normalized the IFG- and mixed dyslipidemia-induced changes in coagulation and fibrinolysis. Our study shows that IFG is associated with abnormal hemostasis, which is disturbed to a lesser extent in IFG than in mixed dyslipidemia. Fenofibrate seems to produce a complex beneficial effect on hemostasis in this group of patients.

Key words:
fenofibrate, mixed dyslipidemia, impaired fasting glucose, fibrinogen, factor VII, plasminogen activator inhibitor-I

Abbreviations: HDL – high-density lipoprotein, HOMA – homeostasis model assessment index, IFG – impaired fasting glucose, IGT – impaired glucose tolerance, LDL – low-density lipoprotein, OGTT – oral glucose tolerance test, PAI-1 – plasminogen activator inhibitor-1, PPARα – peroxisome proliferator-activated receptor-α, VA-HIT – Veterans Affairs High-Density Lipoprotein Intervention Trial

Introduction

Peroxisome proliferator-activated receptor (PPAR)α activators (fibrates) have been found to have clinical benefits in the prevention and treatment of cardiovascular disorders (the Helsinki Heart Study and the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT)) [13, 22]. These benefits may be a consequence of the fact that, in addition to normalizing plasma lipids, fibrates produce other so-called pleiotropic effects, which include anti-inflammatory and antioxidant actions as well as improvements in endothelial and adipose tissue function [2, 8, 10]. Moreover, in some [1, 5, 15, 16, 27] but not all [18, 24] studies, PPARα activators reduced procoagulant activity at different stages of the coagulation cascade and activated fibrinolysis.

Prediabetic states known as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are

intermediate glucose metabolism abnormalities between normal glucose tolerance and frank diabetes that differ from each other with respect to the relative contributions of insulin secretory defects and of hepatic and peripheral insulin resistance [19, 26]. The limited overlap between these states explains why the risk of cardiovascular disorders, although increased in both states, is higher in IGT than in IFG [19, 26].

Recently, we found for the first time that micronized fenofibrate administered to IGT patients [17], or to mixed dyslipidemia patients with coexisting IFG or IGT [12], inhibited systemic inflammation and reduced monocyte secretory function. Moreover, when administered to IGT patients, the drug produced anti-thrombotic and profibrinolytic actions [17]. To the best of our knowledge, the effects of PPARα activators on coagulation and fibrinolysis in subjects with IFG have never been assessed. Considering the pathophysiological and prognostic differences between IFG and IGT described above, hemostatic effects of fenofibrate on coagulation and fibrinolysis in this group of patients may be distinct from those observed in IGT patients. Therefore, the present study was undertaken to compare the effects of fenofibrate on hemostasis between subjects with IFG and mixed dyslipidemia, a condition commonly treated with PPARα activators. We determined fibrinogen and PAI-1 levels as well as factor VII coagulant activity, as the increased values of these variables are considered to be cardiovascular risk factors, and even small changes in their concentration/activity remarkably change this risk [6, 11, 23]. Fenofibrate was administered in a micronized form, which is more effective and convenient than its immediate-acting form [7].

Materials and Methods

Patients

Patients (35–65 years old) with recently diagnosed and previously untreated lipid and glucose metabolism abnormalities were eligible for the study if they met the criteria for having primary mixed dyslipidemia (plasma total cholesterol > 200 mg/dl, LDL-cholesterol > 130 mg/dl and triglycerides > 200 mg/dl) or IFG (fasting plasma glucose between 100 mg/dl and 125 mg/dl as well as 2-h post-challenge glucose < 140 mg/dl). These patients, instructed during the first visit to follow the Therapeutic Lifestyle Changes diet, were invited after 90 days of lifestyle modification to repeat the lipid profile and the 75-g oral glucose tolerance test (OGTT). A patient was enrolled in the study only if the second test confirmed the results of the first one. The control group constituted 22 age-, sex- and weight-matched apparently healthy subjects. All patients provided written informed consent. The study protocol was approved by the appropriate local ethical committee and the study was conducted in accordance with the Declaration of Helsinki Principles.

The exclusion criteria included: (1) concomitant presence of mixed dyslipidemia and IFG; (2) isolated hypercholesterolemia or isolated hypertriglyceridemia; (3) diabetes mellitus or IGT; (4) secondary dyslipidemia in the course of autoimmune disorders, nephrotic syndrome, liver and biliary tract diseases, thyroid diseases, chronic pancreatitis or alcoholism; (5) any acute and chronic inflammatory processes; (6) symptomatic congestive heart failure; (7) unstable coronary artery disease, myocardial infarction or stroke within six months preceding the study; (8) moderate or severe arterial hypertension (WHO/ISH grade 2 or 3); (9) impaired renal or hepatic function; (10) malabsorption syndromes; (11) treatment with other hypolipidemic drugs within three months prior to the study; (12) concomitant treatment with other drugs known either to affect plasma glucose or lipid levels or to interact with fibrates; (13) concomitant treatment with drugs that may affect inflammatory processes in the vascular wall (including glucocorticosteroids, nonsteroidal anti-inflammatory drugs, calcium channel blockers and angiotensin-converting enzyme inhibitors) within three months preceding the study; (14) ongoing hormonal replacement therapy or oral contraception and (15) poor patient compliance.

Study design

All of the enrolled patients were treated with micronized fenofibrate, which was administered at a dose of 267 mg once daily for 90 days without any changes in dosage throughout the study. During the entire study, all of the included patients complied with the lifestyle modification. The investigation of possible fenofibrate-induced side effects was performed fortnightly. Compliance was assessed during each visit by tablet counts and was considered satisfactory when the