Diabetes & Metabolic Syndrome: Clinical Research & Reviews 3 (2009) 17–23

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original paper

Fenofibrate abrogates postprandial blood viscosity among hypertriglyceridemia subjects with the metabolic syndrome

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ARTICLE INFO

Keywords:
Blood viscosity
Rheology
Very-low density lipoprotein
Lipid lowering therapy
Fenofibrate

ABSTRACT

Background: Elevations in blood viscosity have been implicated in the pathogenesis of microvascular disease in patients with diabetes. Recently, fenofibrate has been shown to reduce microvascular complications of diabetes. This study investigates whether fenofibrate lowers fasting and postprandial blood viscosity in patients at high risk for future onset of diabetes.

Methods: Thirty-eight subjects were randomized to fenofibrate (160 mg/d) or placebo in a double-blind controlled clinical trial. A standardized oral fat load was given after a 12 h fast before administration of study medication and after 3 months following the start of therapy. Blood specimens were obtained at fasting, 3.5 h, and 8 h after the test meal. Blood viscosity was measured at 37 °C on fasting and postprandial specimens using a coaxial cylinder microviscometer.

Results: Postprandial blood viscosity was reduced in fenofibrate-treated patients at low and high shear rates. In multivariate models that included conventional risk factors, absolute changes in hematocrit and fibrinogen, there were significant reductions in 8-h postprandial blood viscosity at 100 s^{-1} × 0.13 mPas (95% CI: −0.23, −0.03; $p = 0.0415$), 10 s^{-1} × 0.31 mPas (95% CI: −0.60, −0.01; $p = 0.022$) and at 1 s^{-1} × 1.24 mPas (95% CI: −2.52, 0.05; $p = 0.0083$). Postprandial reductions in blood viscosity were most highly correlated with reductions in VLDL particles (range = 0.305–0.444, p = 0.066–0.018).

Conclusions: Fenofibrate lowers postprandial blood viscosity at low and high shear rates, and this hemorheological effect may contribute to the observed improvement in microvascular disease in patients treated with fenofibrate.

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1. Introduction

Treatment strategies for prevention of microvascular disease have emphasized aggressive glycemic control and blood pressure reduction [1]. Recently, fenofibrate, a highly effective triglyceride-lowering agent, was accompanied by significant reductions in the requirement for laser retinopathy (5.2% vs. 3.6%, for a 30% reduction; $p = 0.0003$) and albuminuria (2.5% absolute reduction and 1.2% regression; $p = 0.002$) in patients with type 2 diabetes enrolled in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study [2,3].

Microcirculatory flow is highly dependent on changes in blood viscosity [4–6]. Triglyceride-containing lipoproteins increase blood viscosity and they have been implicated as a contributor to the microcirculatory abnormalities in diabetes patients [7]. In a cross sectional analysis, elevated fasting triglycerides were associated with hematocrit adjusted blood viscosity values at high ($r = 0.35$, $p < 0.0001$) and low ($r = 0.22$, $p < 0.0001$) shear rates [8]. Further support for the contribution of triglyceride-enriched lipoproteins to elevations in plasma viscosity has been demonstrated from *in vitro* experiments in which there was a concentration-dependent association between chlyomicrons and very low-density lipoproteins (VLDL) and plasma viscosity [9,10].

This study investigates the effects of fenofibrate on fasting and postprandial blood viscosity in subjects with hypertriglyceridemia and the metabolic syndrome, and examines the associations between changes in blood viscosity with lipoproteins and a sensitive measure of oxidized lipids.

2. Methods

2.1. Selection of patients

The study population consisted of 59 subjects with the metabolic syndrome [11], of which data was available on blood viscosity from 41 subjects (17 intervention subjects and 24 control subjects). Due to insufficient blood specimens, blood viscosity measurements were only available in 41 of the 55 subjects who completed the trial.

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doi:10.1016/j.dsx.2008.10.004

We included males and postmenopausal females ≥18 years of age with fasting triglycerides ≥1.7 mmol/L and <6.9 mmol/L and ≥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). Subjects were excluded for type 1 or 2 diabetes, body mass index >40 kg/m^2, use of lipid-lowering therapies, aspirin >81 mg daily, regular use of non-steroidal anti-inflammatory agents or cyclooxygenase-2 inhibitors, corticosteroids (oral and inhaled), anti-oxidants (including multivitamins), herbal or fiber supplements, recent changes in type or formulation of hormone replacement therapy (in the last 6 months), alcohol intake >3 drinks per day, untreated hypothyroidism or recent change (within 2 months) of thyroid replacement therapy, and cigarette smoking (current or within the last 6 months).

The local ethics committee approved the protocol of this study. All subjects gave written informed consent prior to participating in this research trial.

2.2. Study design

Study subjects were counseled by a registered dietitian on the American Heart Association Step 2 diet and were instructed to maintain the diet and their current levels of physical activity throughout the study. At the end of the lead-in period, fasting lipids and glucose were measured to determine study eligibility. Within one week, eligible subjects returned for randomization into the study. After a 12-h fast, baseline blood specimens were collected. A fat challenge was administered as a test meal consisting of a milkshake, which included a standardized fat content (68% of energy) that was adjusted to body surface area (50 g/m^2), and it was comprised of ice cream, cream of coconut and pasteurized egg [13]. After completion of the baseline measurements, subjects had repeat phlebotomies performed at 3.5 h and 8 h. Subjects were provided matching placebo or fenofibrate 160 mg daily, which they were instructed to take in the evening. After 3 months of therapy, repeat laboratory studies were performed on the subjects who completed the study protocol.

2.3. Laboratory studies

Plasma lipids, chemistry panels, and fibrinogen were measured by standard procedures. Lipoprotein subclass profiles were measured with an automated nuclear magnetic resonance (NMR) spectroscopic assay using a modification of the method described previously (LipoScience, Inc., Raleigh, NC, USA) [14]. The following subclass categories were investigated: large very low-density lipoprotein (VLDL) (60–200 nm), intermediate VLDL (35–60 nm), small VLDL (27–35 nm), intermediate-density lipoprotein (IDL) (23–27 nm), large low-density lipoprotein (LDL) (21.2–23 nm), small LDL (18–21.2 nm), large high-density lipoprotein (HDL) (8.8–13 nm), medium HDL (8.2–8.8 nm), and small HDL (7.3–8.2 nm).

Blood viscosity was measured from fasting specimens at 37 °C using a coaxial cylinder rotational viscometer (Contraves LS-40, Greifensee, Switzerland) as previously described [15]. Whole blood samples were measured using a rotational viscometer from shear rates beginning at 100 s^{-1} and terminating at 0.1 s^{-1}. All whole blood viscosity and plasma viscosity measurements were made at 37.0 °C blood viscosity values are reported at shear rates of 100 s^{-1}, 10 s^{-1}, and 1 s^{-1}. Blood viscosity values were adjusted to a hematocrit of 45% by a regression equation [16], and these values are reported as hematocrit-adjusted blood viscosity. The coefficient of variation (CV) for blood viscosity measurements with the rotational viscometer ranged from 2.1% to 7.9% at shear rates ranging from 100 s^{-1} to 0.5 s^{-1}. CV for plasma viscosity was 2.8%. Fibrinogen was analyzed by a modified method of Clauss. The CV was <5%.

Table 1
Baseline characteristics by study group, means ± standard deviation for continuous variables, frequencies for dichotomous variables.

Variables	Placebo (*n* = 24)	Fenofibrate (*n* = 17)	*p*-Value
Clinical			
Age (year)	54.7 ± 10.7	52.0 ± 10.6	0.29
Sex (M/F)	17/7	12/5	0.99
Body mass index (kg/m^2)	33.1 ± 3.7	32.4 ± 3.7	0.60
Waist circumference (cm)	109.6 ± 9.0	110.2 ± 5.2	0.81
SBP (mmHg)	133.2 ± 13.3	134.3 ± 11.5	0.70
DBP (mmHg)	85.0 ± 7.7	82.4 ± 8.3	0.47
Fasting glucose (mmol/L)	4.60 ± 0.86	4.50 ± 0.79	0.93
Fasting insulin (μU/L)	6.52 ± 4.25	7.06 ± 4.80	0.73
HOMA index	1.38 ± 1.03	1.47 ± 1.17	0.89
Fibrinogen (g/L)	3.54 ± 0.59	3.44 ± 0.88	0.20
Hematocrit (%)	41.8 ± 3.6	42.0 ± 2.2	0.86
Characteristics of the metabolic syndrome			
High triglycerides (Yes/No)	24/0	17/0	–
Low HDL-C[a] (Yes/No)	17/7	13/4	0.74
Central obesity[b] (Yes/No)	23/1	17/0	0.99
Elevated blood pressure	17/7	7/10	0.11
Elevated fasting glucose	0/24	0/17	–

Data are expressed as means ± standard deviation for continuous variables, frequencies for dichotomous variables.

[a] Low HDL cholesterol levels were defined as <0.9 mmol/L in men and <1.1 mmol/L in women. High triglycerides were defined as ≥1.69 mmol/L.

[b] Central obesity was defined as a waist circumference ≥88 cm in women and ≥102 cm in men. DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoproteins; LDL-C, low-density lipoprotein cholesterol; NMR, nuclear magnetic resonance; OH-FA, monohydroxy fatty acids; SBP, systolic blood pressure; VLDL, very-low-density lipoproteins. HOMA, homeostasis model. HOMA index was calculated according to the formula: fasting glucose (mmol/L) x insulin (mU/mL) divided by 22.5

2.4. Statistics

Subject demographic characteristics, as well as fasting lipids and lipoproteins are reported as means ± standard deviations (Table 1). Person-specific percent changes over the 3-month therapy period in weight, waist circumference, fasting and postprandial lipids, oxidized fatty acids and blood viscosity and their respective percent changes are reported as means and standard errors and their confidence intervals are provided. Wilcoxon rank sum test and Fisher's exact test were used to compare continuous and dichotomous variables respectively between treatment groups. Percent change over the treatment phase between fasting and post-prandial blood viscosity and lipids, lipoproteins, and oxidized fatty acids, were correlated using Spearman correlations, and both treatment groups were combined for these correlations. Multivariate Spearman correlations were calculated as partial correlations on residual ranks, adjusting for gender, percent change in weight and percent change in hematocrit, All statistical analyses were performed with SAS package 2003 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the 41 study participants with blood viscosity measurements are described in Table 1. This study

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