Journal of Clinical Lipidology (2013) 7, 446–453

Journal of Clinical Lipidology

The influence of fenofibrate on lipid profile, endothelial dysfunction, and inflammatory markers in type 2 diabetes mellitus patients with typical and mixed dyslipidemia

Rohana Abdul Ghani, MMed*, Ismail Bin Yaakob, MMed, Norasyikin Abdul Wahab, MMed, Suehazlyn Zainudin, MMed, Norlaila Mustafa, MD, Norlela Sukor, PhD, Wan Nazaimoon Wan Mohamud, PhD, Khalid Abdul Kadir, PhD, Nor Azmi Kamaruddin, MMed

Department of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur (Ms. Ghani, Mr. Wahab, Ms. Zainudin, Drs. Mustafa and Sukor, and Ms. Kamaruddin); National Heart Institute, Kuala Lumpur (Mr. Yaakob); Institute of Medical Research, Kuala Lumpur (Dr Wan Mohamud); and Department of Medicine, Monash University, Johor Bahru, Johor (Dr. Kadir), Malaysia

KEYWORDS:
Endothelial dysfunction;
Fenofibrate;
High-density lipoprotein cholesterol;
hsCRP;
Low density lipoprotein;
Noninvasive endothelial function assessments;
Triglyceride;
Vascular cell adhesion molecule-1

BACKGROUND: Type 2 diabetes is associated with early development of endothelial dysfunction. Patients present with typical dyslipidemia (predominantly high levels of triglycerides [TG] and low levels of high-density lipoprotein cholesterol [HDL-C]) or mixed hypercholesterolemia (high levels of low-density lipoprotein cholesterol [LDL-C] and TG with low HDL-C). Normal levels include LDL-C $<$ 100 mg/dL, TG $<$ 135 mg/dL, and HDL-C $>$ 40 mg/dL for men and $>$50 mg/dL for women.

OBJECTIVE: To determine the effects of 8 weeks' administration of fenofibrate on inflammatory markers, metabolic parameters, and endothelial dysfunction.

METHODS: We administered micronized fenofibrate (Laboratories Fourneir S.A Dijon, France) daily for 8 weeks to 40 dyslipidemic, type 2 diabetes patients with equal numbers in each arm of the typical or mixed dyslipidemia groups. Noninvasive endothelial function assessments were performed and serum inflammatory markers obtained before and after treatment.

RESULTS: The typical group demonstrated significantly greater TG reduction and HDL-C increment, ie, 56% vs, 21.3% ($P < .005$) and 21% vs. 7.6% ($P = .001$), respectively, compared with the mixed group. There was greater LDL-C reduction within the mixed group compared with the typical group 21.0% vs. 2.2% ($P < .05$). Endothelial dysfunction was present in both groups at baseline. After treatment, the typical group demonstrated significant improvement in resting brachial diameter (3.9 mm [interquartile range {IQR} 3.3-4.7] to 4.2 mm [IQR 3.4-4.8], $P = .001$) compared with no change within the mixed group (3.6 mm [IQR 3.1-5.4] to 3.7 mm [IQR 3.1-5.3], $P = .26$). Flow-mediated diameter improved significantly in both groups. The mixed group had significantly greater levels of hs-CRP at baseline but no changes throughout the study. The mixed group demonstrated an increase in vascular adhesion molecule-1 from 706 ng/mL (IQR 566-1195) to 845 ng/mL (637-1653; $P = .01$), a reduction of tumor necrosis factor-α from 7.0 pg/mL (IQR 1.0-43.5) to 2.5 pg/mL (IQR 1.5-13.5; $P = .04$) throughout the study.

* Corresponding author.
E-mail address: agrohana@gmail.com
Submitted January 4, 2013. Accepted for publication April 22, 2013.

1933-2874/$ - see front matter
http://dx.doi.org/10.1016/j.jacl.2013.04.004

CONCLUSIONS: We effectively compared 8 weeks of fenofibrate therapy in type 2 diabetics with contrasting lipid abnormalities. The typical dyslipidemia group showed significantly greater lipid improvements compared with the mixed dyslipidemia group. Both groups had improvements in endothelial functions that were independent of the lipid levels. We concluded that fibrate therapy in type 2 diabetics is beneficial, especially those with typical dyslipidemia and extends beyond its lipid lowering properties.

Introduction

Type 2 diabetes carries a significantly high risk of cardiovascular disease, with endothelial dysfunction recognized as an important factor contributing to accelerated macrovascular disease and complications. Hypertension and hyperlipidemia further aggravate endothelial dysfunction by increasing oxidative stress and cellular proliferation, leading to atherosclerosis.[1] Endothelial dysfunction is an early feature that even precedes the diagnosis of type 2 diabetes.[2] Thus, it provides a useful surrogate end point to study risk factors for cardiovascular disease. Endothelial dysfunction is associated with increased levels of serum triglycerides (TG) and low levels of high-density lipoprotein cholesterol (HDL-C),[3] the commonest feature of dyslipidemia in type 2 diabetes.[4] It has been shown that although low-density lipoprotein cholesterol (LDL-C) is usually not increased in type 2 diabetes, the LDL particles are present in greater proportions and they are especially atherogenic, smaller, and denser, which means that LDL-C lowering is a primary target in risk reduction of type 2 diabetes.[5]

This may in part, explain the obvious improvement in endothelial function in nondiabetic patients when aggressive lipid-lowering therapy with statins, which aims to lower LDL-C levels, is instituted.[6] Unfortunately, these results were not duplicated within the diabetic population.[7] In contrast, fibrates had demonstrated consistency in improving endothelial function in type 2 diabetes by increasing HDL-C or reducing TG.[8] Fenofibrates also are effective in lowering LDL-C levels to a variable extent but more importantly they change the distribution of LDL-C towards greater and larger particles, which are less atherogenic.[9] The authors of a number of angiographic and clinical trials have confirmed that fibrates slow the progression of atherosclerotic disease and decrease the rate of cardiovascular morbidity and mortality.[10]

Fenofibrate had also been shown to favorably influence the levels of some inflammatory markers, including C-reactive protein (CRP), vascular adhesion molecule-1 (VCAM-1), and cytokine tumor necrosis factor-alpha (TNF-α),[11-13] which had been reported to be significantly higher in diabetic subjects than the healthy non-diabetic population.[14,15] The reductions of these surrogate markers for cardiovascular diseases were shown to be independent of lipid lowering.[16]

This study was therefore designed to examine the influence of fenofibrate on endothelial dysfunction and three inflammatory markers in an exclusively diabetic population. Type 2 diabetics may have the typical diabetic dyslipidemia comprising primarily increased levels of TG, low levels of HDL-C, and normal levels of LDL-C or a mixed combined dyslipidemia consisting of increased LDL-C, increased or normal TG, and normal HDL-C. We therefore hypothesized that these two forms of dyslipidemia may perhaps respond differently to fenofibrate with regards to endothelial dysfunction and inflammatory markers. To our knowledge, this is probably the first study to compare the influence of fenofibrate in endothelial dysfunction and inflammatory markers in type 2 diabetics with contrasting lipid profile; one with typical diabetic dyslipidemia and the other with mixed (combined) dyslipidemia.

Materials and methods

Study population and design

Forty patients with type 2 diabetes and dyslipidemia gave informed consent to participate in the study. Subjects had glylated hemoglobin (A1c) between 7% and 12%; fasting blood sugar of $<$215 mg/dL; body mass index (BMI) $<$30 kg/m^2 and were not on any antilipid therapy, at least a month before the study. We excluded patients with type 1 or secondary diabetes; known ischemic heart disease or cerebrovascular disease; heart failure; liver or renal impairment; uncontrolled hypertension (blood pressure $>$160/90 mmHg); on insulin therapy; current smokers; HIV-infected patients receiving antiretroviral therapy; and those with recent infection or sepsis. Normal levels are as follows: LDL-C $<$ 100 mg/dL, TG $<$ 130 mg/dL, and HDL-C $>$ 40 mg/dL for men and $>$50 mg/dL for women. The participants were divided into two groups, typical diabetic dyslipidemia (defined as high TG and low HDL-C with normal LDL-C) and mixed (combined) hyperlipidemia (defined as high LDL-C; normal or high TG and normal HDL-C). Both groups were administered micronized fenofibrate 160 mg (Lipanthyl-supra 160;Laboratories Fourneir S.A Dijon, France) daily for 8 weeks. Patients received standard diabetic dietary advice and antihypertensive and diabetic treatments. A research nurse counted