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Original research article

The effect of fenofibrate on cardiometabolic risk factors in bromocriptine-treated women with mixed dyslipidemia: A pilot study

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ABSTRACT

Background: Elevated prolactin levels are associated with metabolic and hormonal complications. No previous study has investigated the effect of any fibrate on plasma levels of lipids and other cardiometabolic risk factors in patients receiving dopamine agonist therapy.
Methods: The study included 36 premenopausal women with mixed dyslipidemia and slightly increased prolactin levels, 17 of whom had already been treated with bromocriptine (5.0–7.5 mg daily). The included patients received micronized fenofibrate (200 mg daily) for 6 months. Plasma lipids, glucose homeostasis markers, as well as plasma levels of prolactin, uric acid, high-sensitivity C-reactive protein (hsCRP), homocysteine and fibrinogen were determined before and after 12 weeks of fenofibrate therapy.
Results: Insulin sensitivity was more expressed while baseline plasma levels of hsCRP and fibrinogen were lower in patients treated with bromocriptine than in women not receiving dopamine agonist therapy. Although fenofibrate improved plasma lipids and insulin sensitivity, as well as reduced plasma levels of the investigated cardiometabolic risk factors in both groups of patients, its action on HDL cholesterol, triglycerides, insulin sensitivity, hsCRP and fibrinogen was stronger in subjects receiving bromocriptine. Moreover, only in bromocriptine-naïve patients, fenofibrate increased plasma homocysteine.
Conclusions: Our study shows that the effect of fenofibrate on plasma lipids and circulating levels of cardiometabolic risk factors may be potentiated by bromocriptine treatment. They also suggest that hyperprolactinemic women with mixed dyslipidemia and early glucose metabolism abnormalities may receive the greatest benefits from concomitant treatment with a fibrate and bromocriptine.

Introduction

Apart from oligomenorrhea, infertility, galactorrhea, loss of libido and sexual dysfunction, elevated prolactin levels are often associated with weight gain, insulin resistance, hyperinsulinemia, atherogenic dyslipidemia, endothelial dysfunction and subclinical atherosclerosis [1–7]. Bromocriptine and cabergoline, the two most commonly used dopamine agonists, as well as the drugs of choice in the treatment of hyperprolactinemia, were found to reduce fasting plasma glucose [1,8,9], plasma lipids [1,9,10], glycated hemoglobin [9], insulin resistance [1,6,9–11], 2-h post-challenge plasma glucose [10], body mass index [2,12], waist circumference [3], visceral adiposity [9,11], circulating levels of cardiometabolic risk factors [5,6,9,10], as well as the prevalence of metabolic syndrome [11]. These effects were dose-dependent [9], only partially related to a reduction in prolactin levels [10], more pronounced for cabergoline that for bromocriptine [10] and attributed to an increase in dopaminergic neurotransmission in the ventromedial hypothalamus [8,13]. Since 2009 a bromocriptine quick release form has been approved for the treatment of type 2 diabetes mellitus, as an adjunct to diet and exercise [13,14].

Several recent large clinical studies have shown that peroxisome proliferator-activated receptor-α (PPAR-α) activators (fibrates) are effective agents in the prevention and treatment of cardiovascular disorders [15,16]. In the Veterans Affairs High-Density Lipoprotein Intervention Trial, the reduction in cardiovascular events and related mortality was achieved mainly in individuals with insulin resistance [16]. Their clinical effectiveness seems to result not only from lowering lipid levels but also from

Abbreviations: HDL, high-density lipoprotein; HOMA1-IR, the homeostatic model assessment 1 of insulin resistance ratio; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PPAR-α, peroxisome proliferator-activated receptor-α; SD, standard deviation.

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some other, so-called pleiotropic, actions. Fibrates were found to produce anti-inflammatory, antioxidant and antithrombotic properties, to regulate the growth and migration of smooth muscle cells and to improve endothelial function [17,18]. As our previous results suggest, these pleiotropic effects were stronger if fibrates were administered together with other hypolipidemic drugs and metformin. In patients with type 2 diabetes or early glucose metabolism disturbances, fenofibrate administered together with simvastatin produced a stronger effect on lymphocyte secretory function and low-grade systemic inflammation than simvastatin and fenofibrate administered alone [19,20]. Moreover, in patients with impaired glucose tolerance, metformin potentiated the effect of fenofibrate on monocyte and lymphocyte secretory function, low-grade inflammation and hemostasis [21–23].

To the best of our knowledge, no previous study has investigated the safety and effectiveness of PPAR-α activator-dopamine agonist combination therapy. Therefore, the aim of this study was to determine whether bromocriptine treatment plays a role in regulating the strength of fenofibrate action on cardiometabolic risk factors.

Materials and methods

The participants of the study ($n = 17$) were recruited among premenopausal women (aged 20–50 years) treated for at least 6 months with a constant dose of bromocriptine (5.0–7.5 mg daily) because of hyperprolactinemia. To be admitted to the study, they had to meet the following inclusion criteria of mixed dyslipidemia: total cholesterol >200 mg/dL, LDL cholesterol >130 mg/dL, and plasma triglyceride levels between 200 and 500 mg/dL, despite complying with lifestyle intervention for at least 3 months before the beginning of the study. Our control group included 19 age-, weight-, plasma lipid- and plasma prolactin-matched women with mixed dyslipidemia, ineffectively treated with lifestyle modifications but not receiving dopamine agonists. Only women with baseline prolactin levels between 20 and 40 ng/mL were included. We excluded patients with any acute and chronic inflammatory processes, cardiovascular disease, diabetes, thyroid or any other endocrine disorders, impaired renal or hepatic function, fibrate- or bromocriptine-intolerant patients, pregnant and breastfeeding women, as well as patients treated within 6 months preceding the study with other hypolipidemic agents, or with drugs known to interact with bromocriptine and fibrates.

The study was performed in accordance with the Helsinki Declaration. All enrolled patients ($n = 36$) provided written consent as approved by the local ethics committee. Micronized fenofibrate was administered once daily at the daily dose of 200 mg for 12 weeks without any changes in dosage, and throughout the entire study period both groups of patients continued to comply with dietary recommendations (total fat intake <30% of total energy intake, saturated fat intake <7% of energy consumed, cholesterol intake <200 mg per day, an increase in fiber intake to 15 g per 1000 kcal), as well as were encouraged to take moderate to vigorous exercise for at least 30 min per day. Throughout the study, patients received bromocriptine and metformin at the same doses as before the beginning of the study. Patients who were already taking other drugs kept their pharmacologic schedule constant.

Laboratory assays were performed at the beginning of the study and after 12 weeks of treatment. Venous blood samples were drawn from antecubital vein, after a 12-h overnight fast, in a quiet temperature controlled room (24–25 °C) between 8.00 and 9.00 a.m. (to avoid possible circadian fluctuations in the parameters studied). To minimize analytical errors, all assays were carried out in duplicate. Plasma lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides), fasting glucose and plasma uric acid were assayed by routine laboratory techniques (Roche Diagnostics, Basel, Switzerland). To avoid any error resulting from the Friedewald formula, LDL-cholesterol was determined directly. Plasma insulin and prolactin levels were determined by enzyme-linked immunosorbent assay (DRG Instruments GmbH, Marburg, Germany). The homeostatic model assessment 1 of insulin resistance ratio (HOMA1-IR) was calculated by the formula: HOMA1-IR = fasting plasma glucose (mg/dL) × immunoreactive insulin (mU/L)/405. Circulating levels of C-reactive protein were evaluated using a high-sensitivity monoclonal antibody assay (hsCRP) (MP Biomedicals, Orangeburg, NY, USA). Plasma levels of homocysteine were measured by enzyme-linked immunosorbent assay (Diazyme, San Diego, CA, USA). Plasma fibrinogen concentration was determined according to the Clauss method using a commercial enzyme-linked immunosorbent assay kit (bioMerieux, Marcy l'Etoile, France).

The Kolmogorov–Smirnov test was used to analyze the normal distribution of the variables. The differences between the means of variables within the same treatment group were analyzed with Student's paired *t*-test. Comparisons between the groups were performed using the *t*-test for independent samples. Kendall's tau test was used to evaluate the relationship between the measured variables. For categorical variables, χ^2 test was used. The level of significance was set at $p < 0.05$.

Results

At baseline, there were no significant differences between the treatment groups in the age and weight, as well as in plasma lipids, glucose, prolactin and homocysteine (Table 1). Compared to bromocriptine-naïve patients, women receiving dopamine agonist therapy were characterized by lower values/levels of HOMA1-IR, hsCRP and fibrinogen ($p < 0.05$).

Two individuals were withdrawn from the study because of vomiting and diarrhea, and due to due to non-compliance with the study protocol. No significant adverse effects were reported and all laboratory safety tests remained within normal limits throughout the entire treatment period in the remaining participants who completed the study.

Fenofibrate administered for 12 weeks to bromocriptine-naïve patients reduced plasma levels of total cholesterol by 17% ($p < 0.05$), LDL cholesterol by 20% ($p < 0.01$) and triglycerides by 30% ($p < 0.001$), as well as increased HDL cholesterol by 13%

Table 1
Baseline characteristics of participants.[a]

Variable	Fenofibrate	Bromocriptine and fenofibrate
Number of patients	16	18
Age [years; mean (SD)]	36 (7)	34 (6)
Body mass index [kg/m^2; mean (SD)]	28.6 (3.0)	28.3 (3.2)
Smokers (%)	19	22
Hypertension (%)	13	11
Metabolic syndrome (%)	75	72
Asymptomatic atherosclerosis (%)	6	5
Prolactin (ng/mL)	31 (5)	32 (4)
Total cholesterol [mg/dL; mean (SD)]	264 (35)	269 (31)
LDL-cholesterol [mg/dL; mean (SD)]	163 (22)	159 (20)
HDL-cholesterol [mg/dL; mean (SD)]	39 (4)	40 (4)
Triglycerides [mg/dL; mean (SD)]	289 (41)	300 (48)
Glucose [mg/dL; mean (SD)]	99 (8)	96 (7)
HOMA1-IR [mean (SD)]	5.0 (0.8)	4.2 (0.7)[b]
Uric acid [μmol/L; mean (SD)]	406 (47)	380 (39)
hsCRP [mg/L; mean (SD)]	4.0 (0.8)	2.9 (0.6)[b]
Homocysteine [μmol/L; mean (SD)]	32 (9)	31 (8)
Fibrinogen [mg/dL; mean (SD)]	430 (78)	341 (62)[b]

[a] Only data of women who completed the study were included in the final analyses.
[b] $p < 0.05$ *vs.* patients treated with fenofibrate alone.