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Original article

Different effects of fenofibrate on cardiometabolic risk factors in young women with and without hyperprolactinemia

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ABSTRACT

Background: Elevated prolactin levels are associated with increased cardiometabolic risk. No previous study has compared the effect of hypolipidemic therapy on plasma levels of lipids and other cardiometabolic risk factors in patients with and without hyperprolactinemia.
Methods: The study included three age-, weight-, blood pressure- and lipid-matched groups of premenopausal women: 18 women with untreated hyperprolactinemia, 19 women with bromocriptine-treated hyperprolactinemia and 20 drug-naïve women with normal prolactin levels. Because of concomitant atherogenic dyslipidemia, all patients were treated with fenofibrate (200 mg daily) for 12 weeks. Plasma lipids, glucose homeostasis markers, as well as plasma levels of uric acid, high-sensitivity C-reactive protein (hsCRP), homocysteine and fibrinogen were assessed at baseline and at the end of hypolipidemic treatment.
Results: Unlike similar baseline lipid levels, plasma concentrations of the remaining investigated cardiometabolic risk factors were higher in women with elevated prolactin levels than in patients with normal prolactin levels. The impact of fenofibrate on total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels, as well as on uric acid, hsCRP, homocysteine, and fibrinogen was less pronounced in women with untreated hyperprolactinemia than in women with bromocriptine-treated hyperprolactinemia and drug-naïve women with normal prolactin levels.
Conclusions: The results of our study indicate that cardiometabolic effects of fenofibrate depend on plasma prolactin levels.

Introduction

Long-term prolactin excess is often accompanied by numerous metabolic complications, including impaired glucose tolerance, hyperinsulinemia, atherogenic dyslipidemia, subclinical atherosclerosis and endothelial dysfunction [1–6]. Hyperinsulinemia is attributed to prolactin-induced impaired sensitivity of target tissues to insulin [7,8]. Chronic prolactin excess may also be complicated by an increase in body weight, as well as by a higher prevalence of obesity [9,10]. Dopamine agonists, considered the drugs of choice for the treatment of hyperprolactinemia [11], were found to produce multidirectional metabolic effects. Cabergoline and, to a lesser extent, bromocriptine decreased fasting glucose, 2-h postload glucose, glycated hemoglobin and insulin resistance [2,12–15]. Dopaminergic drugs were also found to exert a beneficial effect on waist circumference [4], body mass index [10] and plasma lipids [2,12,15], as well as on the risk of metabolic syndrome [15].

In addition to improving plasma lipids (particularly triglycerides and high-density lipoprotein [HDL] cholesterol), peroxisome proliferator-activated receptor-α (PPAR-α) activators (fibrates), produce numerous pleiotropic effects including anti-inflammatory, antioxidant and antithrombotic properties, an impact on smooth muscle cell growth and migration, as well as an improvement in endothelial function, and hormonal functioning of adipose tissue [16–18]. Subgroup analyses of large lipid trials [19,20] suggest that fenofibrate is of the greatest benefit in decreasing cardiovascular events in patients with atherogenic dyslipidemia. This finding, a similar action on plasma lipids and insulin resistance to dopaminergic agents, as well as the fact that PPAR-α activators are generally well tolerated [16–18] are arguments in favor of their using in subjects with hyperprolactinemia.

Previously, Krysiak et al. [21,22] observed that the effect of statin and fibrate therapy on circulating levels of cardiometabolic

Abbreviations: HDL, high-density lipoproteins; HOMA2-IR, the homeostasis model assessment 2 of insulin resistance index; hsCRP, high sensitivity C-reactive protein; LDL, low-density lipoproteins; PPAR-α, peroxisome proliferator-activated receptor-α; SD, standard deviation.

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risk factors depended on thyroid function. The same authors found that bromocriptine potentiated the effect of fenofibrate on plasma lipids and circulating levels of cardiometabolic risk factors [23]. However, because all participants of that study had elevated prolactin levels, which did not differ between the study groups, the benefits of fenofibrate/bromocriptine combination might have been explained by pharmacokinetic or pharmacodynamic interactions between both drugs. To the best of our knowledge, no previous study has assessed whether the strength of lipid-related and lipid-unrelated effects of hypolipidemic agents is determined by circulating prolactin levels. Therefore, the aim of the present research was to investigate whether the effect of fenofibrate on plasma levels of lipids and other cardiometabolic risk factors in patients differs between women with and without hyperprolactinemia. The study population included subjects with atherogenic dyslipidemia, free of coronary artery disease and with a calculated 10-year risk of a cardiovascular event below 10%, because such patients do not have to be treated with a statin [24].

Materials and methods

Patients

The participants of the study (n = 57) were recruited among 209 premenopausal women (20–50 years old) with recently diagnosed and untreated atherogenic dyslipidemia, defined as HDL cholesterol levels below 50 mg/dL and triglyceride levels at least 150 mg/dL, and a personal history of hyperprolactinemia and/or the presence of at least one of symptoms or signs suggestive of elevated prolactin levels (oligomenorrhea, infertility or empty sella syndrome). These individuals, initially supervised by community-based healthcare providers, were enrolled at the Department of Internal Medicine and Clinical Pharmacology. Based on plasma prolactin levels, assessed on two different occasions, and dopamine agonist treatment, the study population was divided into three age-, weight- and lipid-matched groups. Group A included women with mild or moderate hyperprolactinemia, defined as circulating prolactin levels between 30 and 60 ng/mL (n = 18). Group B consisted of women diagnosed previously with hyperprolactinemia, but effectively treated with bromocriptine (5.0–7.5 mg daily, n = 19). Group C (the control group) included 20 subjects selected among drug-naïve women without hyperprolactinemia (n = 20). Patients belonging to groups B and C were required to have circulating prolactin levels at least 5 mg/dL but less than 30 mg/dL. With the exception of bromocriptine in group B, the participants were drug-naïve.

Patients were excluded if they had type 1 or type 2 diabetes, prolactinoma, mixed pituitary tumors (secreting prolactin and other pituitary hormones), macroprolactinemia, any thyroid disorder, polycystic ovary syndrome, hypopituitarism, primary hypogonadism, impaired renal or hepatic function, coronary artery disease, myocardial infarction or stroke within 6 months preceding the study, symptomatic congestive heart failure, moderate or severe arterial hypertension (European Society of Cardiology/European Society of Hypertension grade 2 or 3). We also excluded subjects having a 10% or greater 10-year risk of developing cardiovascular event, pregnant or breast-feeding women, as well as women poorly tolerating bromocriptine treatment.

Study design

The study protocol was approved by the local ethics committee and each woman gave a written informed consent before participation in the study. Throughout the study, all groups of women were treated with micronized fenofibrate (200 mg daily). The drug was administered once daily in the evening for 12 weeks without any changes in dosage. The participants were required to comply with the lifestyle modification (total fat intake < 30% of total energy intake, saturated fat intake < 7% of energy consumed, cholesterol intake < 200 mg per day, an increase in fibre intake to 15 g per 1000 kcal, moderate to vigorous exercise for at least 30 min per day). Compliance was determined every four weeks by the number of tablets returned and was regarded as satisfactory if the percentage of tablets taken by a patient ranged from 90% to 100%. Blood pressure was measured in a sitting position using standard cuff equipment. They were determined during Korotkoff sounds 1 and 5. All measurements were made on the left arm. The values used in statistical analyses were the means of 3 measurements taken at intervals of at least 5 min, starting 15 min after the patient had sat down. Waist circumference was measured halfway between the lowest rib and iliac crest. The body mass index was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Laboratory assays

Laboratory assays were performed in duplicate (to minimize analytical errors) at baseline and at the end of the treatment period. Venous blood samples were collected from the antecubital vein at 8 a.m. (to avoid possible circadian fluctuations in the parameters studied) after an overnight 12-h fasting. Plasma lipids (total cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides), glucose, uric acid and creatinine were measured with standard methods using commercial kits (Roche Diagnostics, Basel, Switzerland). To avoid any error resulting from the Friedewald formula, LDL cholesterol was determined directly. Plasma prolactin, thyrotropin, insulin, high sensitivity C-reactive protein (hsCRP) and homocysteine levels were assayed by means of a two-site sandwich immunoassay using direct chemiluminometric technology (Advia Centaur XP Immunoassay System, Siemens Healthcare, Warsaw, Poland). Fibrinogen was measured by the Clauss technique in an automated BCS XP analyzer (Siemens Healthcare, Warsaw, Poland). The homeostatic model assessment 2 of insulin resistance (HOMA2-IR) was calculated by from plasma glucose and insulin levels (www.ocdem.ox.ac.uk). Intra- and interassay coefficients of variation were below 5.5 and 8.5%, respectively. The estimated glomerular filtration rate was calculated using the Modification Diet in Renal Disease Study equation.

Sample size calculations

A sample size analysis, performed before the study and based on our previous results [14,21–23,25], showed that, assuming a power of 80% and a significance level of 0.05, at least 16 individuals had to be included in each group to detect a 20% difference in all cardiovascular risk factors assessed in the study. Assuming possible dropouts, the sample size was increased to at least 18 patients per group.

Statistical analysis

Quantitative data without a normal distribution were natural log-transformed to normalize their distributions prior to statistical analysis. Comparisons between the study groups were performed using one-way analysis of covariance followed by the *post hoc* Bonferroni test. Student's paired *t* test was applied to compare pre- and post-treatment data within the same treatment group. For categorical variables, χ^2 test was used. Associations were calculated using Pearson's correlation coefficient (r). The results were considered statistically significant if *p* values were below 0.05.

Results

At the beginning of the study, all groups were comparable with respect to age, smoking, body mass index, waist circumference, blood pressure and the estimated glomerular filtration rate, as well as to plasma levels of glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and thyrotropin. Plasma levels of prolactin, uric acid, hsCRP, homocysteine and fibrinogen, and values of HOMA2-IR were higher in group A than in groups B and C, with no difference between the latter two groups (Table 1). No serious adverse effects were reported during the study period and all patients completed the study protocol.

Fenofibrate reduced plasma triglycerides and HOMA2-IR, as well as increased plasma HDL cholesterol and homocysteine in all study groups. The drug did not exert a significant effect on the body mass index, waist circumference and blood pressure, as well as produced a neutral effect on plasma thyrotropin and on the estimated glomerular filtration rate. In groups B and C, but not in group A, the drug decreased also total and LDL cholesterol, as well as reduced plasma levels of uric acid, hsCRP and fibrinogen. The effect of fenofibrate on circulating levels of total cholesterol, LDL cholesterol, triglycerides, HDL cholesterol, uric acid, hsCRP and fibrinogen was more pronounced in groups B and C than in group A. In turn, the effect on homocysteine was strongest in group A. At the end of the study period, group A differed from the remaining groups in the body mass index, waist circumference, HOMA2-IR, as well as in circulating levels of total, HDL and LDL cholesterol, triglycerides, prolactin, uric acid, hsCRP, homocysteine and fibrinogen (Table 2).

In women with untreated hyperprolactinemia, baseline prolactin levels correlated with baseline levels of thyrotropin ($r = 0.35$, $p < 0.01$), uric acid ($r=0.32$, $p < 0.05$), hsCRP ($r=0.37$, $p < 0.01$), homocysteine ($r=0.30$, $p < 0.05$) and fibrinogen ($r=0.27$, $p < 0.05$). In all study groups, plasma levels of uric acid, hsCRP, homocysteine, and fibrinogen correlated with circulating levels of total cholesterol (r values between 0.24 [$p < 0.05$] and 0.32 [$p < 0.05$]), LDL cholesterol (r values between 0.28 [$p < 0.05$] and 0.35 [$p < 0.01$]), HDL cholesterol (r values between -0.31 [$p < 0.05$] and -0.39 [$p < 0.001$]), and triglycerides (r values between 0.30 [$p < 0.05$] and 0.40 [$p < 0.001$]), as well as with HOMA2-IR (r values between 0.31 [$p < 0.05$] and 0.44 [$p < 0.001$]), the body mass index (r values between 0.26 [$p < 0.05$] and 0.34 [$p < 0.01$]) and waist circumference (r values between 0.23 [$p < 0.05$] and 0.31 [$p < 0.05$]).

In all groups of women, the effect of fenofibrate on homocysteine correlated with baseline prolactin levels (r values between 0.29 [$p < 0.05$] and 0.41 [$p < 0.001$]), while the effect on HDL cholesterol, triglycerides, uric acid, hsCRP and fibrinogen correlated with treatment-induced changes in HOMA2-IR (r values between 0.29 [$p < 0.05$] and 0.41 [$p < 0.001$]). No other correlations were observed.

Discussion

Our study has shown for the first time that hyperprolactinemia prevented beneficial effects of fibrate therapy on both plasma lipids and extra-lipid cardiometabolic risk factors. This unfavorable effect on fenofibrate action in women with atherogenic dyslipidemia was, however, abolished if hyperprolactinemia was effectively managed with dopamine agonists. Moreover, fenofibrate-treated patients with normal prolactin levels were characterized by lower values of waist circumference and the body mass index. The results of our study are in agreement with previous findings showing that the strength of pleiotropic effects of fenofibrate was negatively influenced by untreated subclinical hypothyroidism [22], while extra-lipid effects of atorvastatin were less pronounced in women with subclinical hypothyroidism [21] and vitamin D insufficiency [25]. It should be stressed that in all these studies thyroid hypofunction and hypovitaminosis D were

Table 1
Baseline characteristics of patients.

Variable	Group A[1]	Group B[2]	Group C[3]
Number [n]	18	19	20
Age [years; mean (SD)]	41 (8)	40 (8)	39 (7)
Smokers [%]	28	32	25
Body mass index [kg/m^2; mean (SD)]	28.8 (4.0)	27.8 (3.8)	27.5 (3.5)
Waist circumference [cm; mean (SD)]	97 (7)	95 (6)	94 (6)
Systolic blood pressure [mmHg; mean (SD)]	135 (14)	131 (18)	132 (15)
Diastolic blood pressure [mmHg; mean (SD)]	87 (8)	85 (7)	86 (7)
Glucose [mg/dl; mean (SD)]	93 (7)	90 (8)	89 (7)
HOMA2-IR [mean (SD)]	2.24 (0.62)[b,e]	1.79 (0.46)	1.76 (0.50)
Total cholesterol [mg/dL; mean (SD)]	228 (26)	223 (28)	218 (23)
LDL-cholesterol [mg/dL; mean (SD)]	135 (17)	129 (15)	130 (14)
HDL-cholesterol [mg/dL; mean (SD)]	39 (5)	41 (5)	41(4)
Triglycerides [mg/dL; mean (SD)]	235 (50)	228 (42)	221 (46)
Prolactin [ng/mL; mean (SD)]	45 (8)[c,f]	13 (4)	14 (5)
Thyrotropin [mIU/L; mean (SD)]	2.45 (0.96)	2.23 (0.74)	2.19 (0.83)
Uric acid [mg/dL; mean (SD)]	5.8 (1.7)[a,d]	4.5 (1.5)	4.6 (1.4)
hsCRP [mg/L; mean (SD)]	3.4 (0.8)[b,e]	2.5 (0.5)	2.3 (0.6)
Homocysteine [μmol/L; mean (SD)]	32 (9)[a,d]	26 (8)	25(9)
Fibrinogen [mg/dL; mean (SD)]	442 (88)[a,d]	365 (90)	372 (76)
Estimated glomerular filtration rate [ml/min/1.73 m^2; mean (SD)]	88 (18)	90 (15)	92(18)

HDL - high-density lipoproteins; HOMA2-IR - the homeostatic model assessment 2 of insulin resistance ratio; hsCRP - high-sensitivity C-reactive protein; LDL - low-density lipoproteins; SD - standard deviation.
[1]women with untreated hyperprolactinemia.
[2]bromocriptine-treated women with hyperprolactinemia.
[3]drug-naïve women with prolactin levels within the reference range.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$ *vs.* group B.
[d] $p < 0.05$.
[e] $p < 0.01$.
[f] $p < 0.001$ *vs.* group C.

Table 2
The effect of fenofibrate treatment on body mass index, waist circumference, blood pressure, plasma lipids, glucose homeostasis markers, hormones and plasma levels of the investigated cardiometabolic risk factors in women with and without hyperprolactinemia.

Variable	Group A[1]	Group B[2]	Group C[3]
Body mass index [kg/m^2; mean (SD)]			
At the beginning of the study	28.8 (4.0)	27.8 (3.8)	27.5 (3.5)
At the end of the study	28.9 (3.7)[a,d]	26.6 (3.1)	26.5 (3.2)
Waist circumference [cm; mean (SD)]			
At the beginning of the study	97 (7)	95 (6)	94 (6)
At the end of the study	98 (7)[a,d]	93 (7)	93 (5)
Systolic blood pressure [mmHg; mean (SD)]			
At the beginning of the study	135 (14)	131 (18)	132 (15)
At the end of the study	135 (18)	128 (15)	130 (19)
Diastolic blood pressure [mmHg; mean (SD)]			
At the beginning of the study	87 (8)	85 (7)	86 (7)
At the end of the study	88 (10)	83 (8)	84 (8)
Glucose [mg/dl; mean (SD)]			
At the beginning of the study	93 (7)	90 (8)	89 (7)
At the end of the study	91 (8)	88 (8)	88 (9)
HOMA2-IR [mean (SD)]			
At the beginning of the study	2.24 (0.62)[b,e]	1.79 (0.46)	1.76 (0.50)
At the end of the study	2.22 (0.56)[c,f]	1.47 (0.39)[g,j]	1.48 (0.35)[g,j]
Total cholesterol [mg/dL; mean (SD)]			
At the beginning of the study	228 (26)	223 (28)	218 (23)
At the end of the study	219 (24)[a,d]	200 (30)[g,j]	198 (26)[g,j]
LDL-cholesterol [mg/dL; mean (SD)]			
At the beginning of the study	135 (17)	129 (15)	130 (14)
At the end of the study	130 (16)[b,e]	114 (14)[h,j]	112 (18)[h,j]
HDL-cholesterol [mg/dL; mean (SD)]			
At the beginning of the study	39 (5)	41 (5)	41 (4)
At the end of the study	43 (5)[b,e,g]	48 (6)[i,j]	48 (5)[i,j]
Triglycerides [mg/dL; mean (SD)]			
At the beginning of the study	235 (50)	228 (42)	221 (46)
At the end of the study	203 (41)[a,d,g]	175 (39)[i,j]	169 (48)[h,j]
Prolactin [ng/mL; mean (SD)]			
At the beginning of the study	45 (8)[c,f]	13 (4)	14 (5)
At the end of the study	46 (10)[c,f]	14 (5)	12 (4)
Thyrotropin [mIU/L; mean (SD)]			
At the beginning of the study	2.45 (0.96)	2.23 (0.74)	2.19 (0.83)
At the end of the study	2.52 (0.87)	2.21 (0.83)	2.17 (0.76)
Uric acid [mg/dL; mean (SD)]			
At the beginning of the study	5.8 (1.7)[a,d]	4.5 (1.5)	4.6 (1.4)
At the end of the study	5.9 (1.9)[c,f]	3.5 (0.8)[g,j]	3.7 (0.8)[g,j]
hsCRP [mg/L; mean (SD)]			
At the beginning of the study	3.4 (0.8)[b,e]	2.5 (0.5)	2.3 (0.6)
At the end of the study	3.2 (0.8)[c,f]	1.5 (0.5)[i,k]	1.4 (0.5)[i,k]
Homocysteine [μmol/L; mean (SD)]			
At the beginning of the study	32 (9)[a,d]	26 (8)	25(9)
At the end of the study	43 (10)[a,e,h]	34 (10)[h,j]	32(8)[g,j]
Fibrinogen [mg/dL; mean (SD)]			
At the beginning of the study	442 (88)[a,d]	365 (90)	372 (76)
At the end of the study	435 (74)[c,f]	280 (71)[h,k]	295 (68)[h,k]
The estimated glomerular filtration rate [ml/min/1.73 m^2; mean (SD)]			
At the beginning of the study	88 (18)	90 (15)	92(18)
At the end of the study	87 (20)	93 (16)	89 (15)

HDL – high-density lipoproteins; HOMA2-IR – the homeostatic model assessment 2 of insulin resistance ratio; hsCRP – high-sensitivity C-reactive protein; LDL – low-density lipoproteins; SD – standard deviation.
[1]women with untreated hyperprolactinemia.
[2]bromocriptine-treated women with hyperprolactinemia.
[3]drug-naïve women with prolactin levels within the reference range.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$ *vs.* group B.
[d] $p < 0.05$.
[e] $p < 0.01$.
[f] $p < 0.001$ *vs.* group C.
[g] $p < 0.05$.
[h] $p < 0.01$.
[i] $p < 0.001$ *vs.* baseline value.
[j] $p < 0.05$.
[k] $p < 0.01$ statistically different *vs.* the effect of fenofibrate in group A.

mild and in most subjects were not accompanied by clinical symptoms. All these findings taken together suggest that even small disturbances in endocrine function may markedly impair pleiotropic effects of hypolipidemic agents. This observation is important from a practical point of view because, according to the present recommendations [26–28], mild endocrine abnormalities do not have to be obligatorily treated.

Data about the role of hyperprolactinemia in modulation of cardiovascular risk are unequivocal. In the Framingham Heart Study, serum prolactin levels were not associated with the comprehensive panel of incident cardiovascular disease risk factors [29]. In turn, in the Study of Health in Pomerania, serum prolactin concentrations were independently associated with all-cause and cardiovascular mortality [30]. However, both trials were population-based studies, the participants of which were women with prolactin levels below 30 mg/dL. In studies including only subjects with elevated prolactin levels, increased risk of cardiovascular disease was observed in iatrogenic hyperprolactinemia [31], while all-cause and cardiovascular mortality was increased exclusively in men [32]. In our study, plasma levels of uric acid, hsCRP, homocysteine and fibrinogen were higher in women with untreated hyperprolactinemia than in the remaining two groups of women, in whom prolactin levels were within the reference range. Considering that even discrete differences in these markers are associated with various cardiometabolic risk [33–36], it seems that patients with untreated hyperprolactinemia may be more prone to the development of cardiovascular disease and metabolic complications. It should be stressed that prolactin levels in our patients were only mildly or moderately increased. Because of ethical reasons we excluded subjects with severe hyperprolactinemia (who should be treated with a dopamine agonists [37]), while the included ones were oligosymptomatic.

Dopamine agonists, especially bromocriptine, may result in the appearance of numerous adverse effects, the most common of which are nausea, vomiting, dizziness, postural hypotension and headache [11]. Therefore, unlike severe pituitary tumor-induced hyperprolactinemia, current guidelines recommend neither for nor against the use of these agents in oligosymptomatic patients with mild or moderate non-tumoral hyperprolactinemia [26] In the participants of our study, bromocriptine-treatment did not induce serious adverse effects, a fact which may be explained by excluding women poorly tolerating bromocriptine treatment and no changes in bromocriptine dosage throughout the study. What is more, the lack of serious adverse effects of bromocriptine administered together with fenofibrate during the follow-up suggests that bromocriptine/fenofibrate combination therapy is safe and seems to be well tolerated.

A small sample size limits the generality of the research findings, while the short-term therapy does not fully reflect the reduction in the global cardiovascular risk, even if a positive effect on several biochemical risk factors was found. It seems, however, that fibrate/dopamine agonist add-on therapy may bring clinical benefits to oligosymptomatic women with mildly or moderately elevated prolactin and atherogenic dyslipidemia, preventing the development of cardiovascular and metabolic complications. As post-treatment circulating levels of uric acid, hsCRP and fibrinogen, as well as waist circumference and the body mass index did not differ between women belonging to group B and group C, we may assume that effective treatment of hyperprolactinemia probably reduces cardiovascular and metabolic risk to the level observed in patients without hyperprolactinemia. Moreover, a causative factor for hyperprolactinemia does not seem to determine the strength of pleiotropic effects of fibrates if excessive prolactin secretion is effectively controlled. Finally, the obtained results suggest that measurement of prolactin levels may be helpful in patients with suboptimal response to PPAR-α activators, as well as that fibrate/dopamine agonist combination therapy should be taken into consideration in subjects with elevated prolactin levels who are candidates for treatment with a PPAR-α activator.

According to our expectations [22,23], in all treatment groups, fenofibrate affected homocysteine levels in an unfavorable way. Unlike the remaining cardiometabolic risk factors assessed in our study, changes in homocysteine levels were, however, more pronounced in women with untreated hyperprolactinemia than in the remaining groups of women. This observation is in line with our finding that bromocriptine prevented an increase in homocysteine levels induced by fenofibrate [23]. Taking into account that in hyperprolactinemic women post-treatment homocysteine levels, being a marker of an increased risk of premature cardiovascular disease and diabetes [35], were more than two times higher than the upper limit of normal, fenofibrate use in this group of patients does not seem justified. The obtained results may be partially explained by a negative impact of elevated prolactin levels on the kidneys because hyperprolactinemia was found to decrease urine volume and solute excretion [38]. However, similar baseline and post-treatment values of the estimated glomerular filtration rate seem to contradict this explanation. Alternatively, hyperprolactinemia may potentiate the impact of fenofibrate on creatine-creatinine metabolism and/or on methyl transfer, regarded as main mechanisms responsible for an increase in homocysteine induced by PPAR-α activators [39,40]. Interestingly, the co-administration of folate was found to prevent the fibrate-induced elevation of homocysteine [40] and was associated with a beneficial effect on lipoprotein oxidation and endothelial function [41]. These findings suggest that the unfavorable effect of prolactin excess on fenofibrate action on homocysteine may be mediated by changes in folate metabolism. In line with this hypothesis, prolactin-secreting tumors were associated with a decreased expression of folate receptor gene [42].

Treatment-induced changes in uric acid, hsCRP, and fibrinogen represent pleiotropic effects of fenofibrate and cannot be regarded as secondary to the effect on plasma lipids. However, they seem to result from a fenofibrate-induced improvement in insulin sensitivity because both at entry and during treatment circulating levels of cardiometabolic risk factors correlated with values of HOMA2-IR. Cardiometabolic effects of fenofibrate are probably, at least in part, mediated by free fatty acids [32], which are endogenous ligands for PPAR-α receptors [16,17]. Interestingly, both fenofibrate [43] and prolactin-lowering agents [44] were found to affect free fatty acids. Moreover, in the latter study, prolactin levels correlated with free fatty acids, which may suggest higher baseline levels of free fatty acids in women with untreated hyperprolactinemia than in the remaining groups of women. Differences in prolactin levels, resulting in differences in free fatty acid levels, may make patients with untreated hyperprolactinemia more resistant to fenofibrate action. In agreement with this proposal, cardiometabolic effects of cabergoline were more pronounced than those of bromocriptine, which was paralleled by a stronger effect of cabergoline than bromocriptine on free fatty acids and prolactin [45].

Our study has some limitations which have to be pointed out. Due to a small number of participants, it should be regarded as a pilot study and its results need to be confirmed in a larger clinical trial. Secondly, the study did not investigate clinical outcomes, including morbidity or mortality. Because diabetes belonged to the exclusion criteria, the question whether elevated prolactin levels modulate the impact of fenofibrate on cardiometabolic risk factors in patients with diabetes requires further research. Finally, it cannot be ruled out that the effect of fenofibrate may be different in men, who were not included in our study.

To sum up, the effect of fenofibrate on plasma levels of lipids and other cardiometabolic risk factors was more pronounced in

normoprolactinemic women than in women with elevated prolactin levels. The extent of fenofibrate-induced changes in plasma levels of uric acid, hsCRP and fibrinogen correlated with an improvement in insulin sensitivity and inversely with baseline prolactin levels. The results of our study suggest that prolactin status of a patient may determine the strength of cardiometabolic effects of fenofibrate.

Author contributions

Robert Krysiak conceived of the study, participated in its design, performed the statistical analysis, as well as drafted and edited the manuscript. Witold Szkróbka conducted the literature search, carried out the assays and performed the statistical analysis. Bogusław Okopień participated in its design and coordination, and provided critical input during manuscript preparations. All authors read and approved the final manuscript.

Disclosure statement

The authors declare no conflicts of interest.

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