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Comparison of the effects of short-term hypolipidaemic treatment on plasma adipokine levels in men and women with isolated hypercholesterolaemia

Porównanie wpływu krótkotrwałego leczenia hipolipemicznego na stężenie adipokin w osoczu kobiet i mężczyzn z izolowaną hipercholesterolemią

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Abstract

Introduction: Hypolipidaemic agents were found to affect plasma adipokine levels, but no previous study has investigated whether this effect is sex-dependent.

Materials and methods: We retrospectively analysed 61 patients participating in our previous studies, who because of isolated hypercholesterolaemia were treated with simvastatin (40 mg daily), ezetimibe (10 mg daily) or simvastatin (40 mg daily) plus ezetimibe (10 mg daily). Plasma levels of leptin, adiponectin, visfatin, tumour necrosis factor-α (TNF-α), free fatty acids (FFA), and high-sensitivity C-reactive protein (hsCRP) were assessed separately for men and women before and after 30 days of treatment.

Results: At baseline, plasma levels of adiponectin and leptin were lower, while plasma levels of TNF-α were higher in men than in women. Administration of simvastatin and statin/ezetimibe combination for 30 days reduced plasma levels of hsCRP, FFA, leptin, visfatin, and TNF-α but increased plasma levels of adiponectin, while the effect of ezetimibe was much more limited. The effect of simvastatin and ezetimibe, administered alone or in combination, on plasma hsCRP, FFA, leptin, adiponectin, visfatin, and TNF-α did not differ between men and women. Irrespectively of sex, the changes in plasma adipokines and systemic-anti-inflammatory effects were more expressed in simvastatin- than in ezetimibe-treated patients and were strongest when both these agents were administered together.

Conclusions: Our results show that sex differences do not determine the effect of hypolipidaemic agents on adipose tissue and low-grade inflammation. **(Endokrynol Pol 2015; 66 (2): 114–120)**

Key words: *sex; simvastatin; ezetimibe; hypercholesterolaemia; leptin; adiponectin; visfatin; tumour necrosis factor-α (TNF-α)*

Abstrakt

Wstęp: Chociaż wykazano związek pomiędzy stosowaniem terapii hipolipemicznej a zmianami stężenia adipokin, nie oceniano czy wpływ ten zależy od płci pacjenta.

Materiał i metody: W badaniu dokonano retrospektywnej analizy wyników 61 pacjentów uczestniczących w poprzednich badaniach autorów, którzy z racji hipercholesterolemii byli leczeni simwastatyną (40 mg dziennie), ezetimibem (10 mg dziennie) oraz terapią skojarzoną (w powyższych dawkach). Stężenie leptyny, adiponektyny, wisfatyny, czynnika martwicy nowotworów-α (TNF-α), wolnych kwasów tłuszczowych (FFA) oraz białka C-reaktywnego (hsCRP) oceniano oddzielnie dla kobiet i mężczyzn przed i po 30 dniach leczenia.

Wyniki: W warunkach wyjściowych stężenie leptyny i adiponektyny w osoczu było wyższe dla kobiet, zaś TNF-α u mężczyzn. Podawanie simwastatyny lub terapii skojarzonej przez 30 dni zmniejszało stężenie w osoczu hsCRP, FFA, leptyny, wisfatyny, TNF-α, jak również podwyższało stężenie adiponektyny, podczas gdy wpływ ezetimibu był ograniczony. Wpływ simwastatyny i ezetimibu, podawanych oddzielnie lub w terapii skojarzonej, na stężenie hsCRP, FFA, leptyny, adiponektyny, wisfatyny oraz TNF-α nie różnił się pomiędzy kobietami i mężczyznami. Niezależnie od płci pacjenta, zmiany stężenia badanych adipokin i nasilenia układowego stanu zapalnego były bardziej wyrażone w grupie leczonej simwastatyną niż ezetimibem i najwyraźniej zaznaczone w grupie stosującej terapię skojarzoną.

Wnioski: Wyniki badania wskazują, iż płeć pacjenta nie warunkuje siły działania ocenianych leków hipolipemicznych na tkankę tłuszczową i układowy stan zapalny. **(Endokrynol Pol 2015; 66 (2): 114–120)**

Słowa kluczowe: *płeć; simwastatyna; ezetimib; hypercholesterolemia; leptyna; adiponektyna; wisfatyna; czynnik martwicy nowotworów-α (TNF-α)*

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Abbreviations

CRP — C-reactive protein
FFA — free fatty acids
HDL — high-density lipoprotein
HMG-CoA — 3-hydroxy-3-methylglutaryl coenzyme A
HOMA-IR — the homeostatic model assessment of insulin resistance ratio
hsCRP — high-sensitivity C-reactive protein
LDL — low-density lipoprotein
TNF-α — tumour necrosis factor-α

Introduction

Coronary artery disease is the leading cause of cardiovascular morbidity and mortality in both men and women [1]. The absolute numbers of women living with and dying of coronary artery disease and stroke exceed those of men, as does the number of hospital discharges for heart failure and stroke [2]. Despite this fact, several lines of evidence suggest that coronary artery disease is treated less aggressively in women than in men. Hypolipidaemic agents, particularly 3-hydroxy-3-methylglutaryl-CoA (HMC-CoA) reductase inhibitors (statins), are among the most important agents in the contemporary therapy of patients with this disorder. Beyond lowering lipid levels, the clinical benefits associated with hypolipidaemic agents may partially result from their extralipid, so-called pleiotropic effects. Very little is known about differences in the strength of action of lipid-lowering agents between men and women. The results of the Action to Control Cardiovascular Risk in Diabetes Lipid (ACCORD Lipid) trial, comparing fenofibrate/simvastatin combination therapy with simvastatin administered alone in patients with type 2 diabetes, showed additional benefits associated with adding fenofibrate to a HMG-CoA reductase inhibitor exclusively in men [3]. Men had a 16% lower primary event rate on fenofibrate, whereas women had a 38% greater primary event rate on fenofibrate.

The various strengths of action of hypolipidaemic agents in men and women may be explained by sex-dependent differences in either their lipid-lowering potential and/or pleiotropic effects. The latter may include their effect on adipose tissue secretory function. This tissue is a highly active metabolic and endocrine organ secreting a range of bioactive peptides with both local and distant actions, known as 'adipokines' or 'adipose tissue hormones, being specific fat-related hormones that are involved in regulating energy homeostasis, carbohydrate and lipid metabolism, and the function of the cardiovascular system [4–6]. Adipose tissue is characterised by gender differences in body distribution and different production of adipokines [4–6]. Therefore, the question of how hypolipidaemic agents affect the hormonal function of human adipose tissue in both sexes requires better understanding. The aim of our study was to compare the effects of 30-day treatment with two hypolipidaemic agents, atorvastatin and ezetimibe, administered alone or in combination, on plasma adipokine levels in men and women with isolated hypercholesterolaemia, participating in our previous studies [7–9]. The results of one study were not taken into consideration because of a longer period of treatment [10]. Leptin, adiponectin, visfatin, and TNF-α were chosen among different adipokines because they are major products of adipose tissue, playing a variety of roles in atherosclerotic plaque development and its clinical sequelae. Their abnormal production contributes to the development of diabetes and insulin resistance as well as atherosclerosis and its complications [6, 11–13].

Material and methods

We retrospectively analysed patients included in our previous studies [7–9]. The study was performed according to the Declaration of Helsinki. All individuals participating in the original studies were fully informed of the purpose and the possible risks. All participants provided written consent as approved by the ethics committee of the Medical University of Silesia. The study population consisted of men and women (35–65 years old) with isolated hypercholesterolaemia, defined as total plasma cholesterol above 200 mg/dL, LDL cholesterol above 130 mg/dL, and triglycerides below 150 mg/dL, despite following the Therapeutic Lifestyle Changes diet for at least three months before the study onset, and who during the study were treated with simvastatin (n = 22) [7], ezetimibe (n = 21) [8], or combination therapy (n = 18) [9]. The exclusion criteria were as follows: any acute and chronic inflammatory processes, untreated stage 2 or 3 hypertension (according to the 2003 European Society of Hypertension–European Society of Cardiology guidelines), symptomatic congestive heart failure, diabetes, autoimmune disorders, thyroid diseases, chronic pancreatitis, impaired renal or hepatic function, body mass index above 35 kg/m^2, and poor patient compliance. No patient had been treated with other hypolipidaemic drugs within three months before the study, or with drugs known to interfere with statins or ezetimibe.

Simvastatin (40 mg), ezetimibe (10 mg), or simvastatin (40 mg) together with ezetimibe (10 mg) were administered once daily at bedtime for 30 days, and no changes in medication dosage were allowed throughout the study. Throughout the study the participants complied with lifestyle modifications, the goals of which were a reduction in weight of 7% or more if necessary, 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, and moderate-to-vigorous exercise for at least 30 minutes per day.

The samples were collected before therapy started and after 30 days of therapy. Venous blood samples were drawn from the antecubital vein in a quiet, temperature-controlled room (24–25°C) in constant daily hours (between 8:00 and 9:00 a.m.) at least 12 hours after the last meal. All assays were carried out in duplicate, and mean values are presented. Total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, triglycerides, glucose, and insulin were assessed by routine laboratory techniques (bioMerieux France; Incstar Corporation, Stillwater, MN, USA; Beckman, Palo Alto, CA, USA; Linco Research Inc, St Charles, MO, USA). LDL levels were measured directly. The homeostasis model of insulin resistance (HOMA-IR) index was calculated as [fasting serum glucose (mg/dL) × fasting serum insulin (μU/mL)/405], with lower values indicating a higher degree of insulin sensitivity. Total non-esterified free fatty acids (FFA) were determined by an enzymatic assay using reagents from Alpha Laboratories (Eastleigh, Hants, UK). Plasma levels of CRP were measured using a high-sensitivity monoclonal antibody assay (hsCRP) (MP Biomedicals, Orangeburg, NY). Plasma levels of leptin, adiponectin, visfatin, and TNF-α were measured with commercial enzyme-linked immunosorbent assay kits obtained from TECOmedical Group (Sissach, Switherland), Phoenix Pharmaceuticals (Burlingame, CA) and R&D Systems (McKinley Place N.E. Minneapolis, MN). The minimum detectable levels for the assessed parameters were: 0.1 mg/L, 7.8 pg/mL, 0.246 ng/mL, 6.1 pg/mL, and 1.6 pg/mL, respectively, for hsCRP, leptin, adiponectin, visfatin, and TNF-α. The intra- and inter-assay coefficients of variation for the assessed markers were less than 5.5 and 8.7%, respectively.

The Shapiro-Wilk test was used to assess the distribution of variables. In the case of variables with non-normal distribution (triglycerides, HOMA-IR, hsCRP, FFA, and adipokines), log transformation was used to fit a normal distribution curve. Comparisons between the groups were made by the *t* test for independent samples. The differences between the means of variables within the same treatment group were analyzed with Student's paired *t*-test. Kendall's τ test was used to evaluate the relationship between metabolic variables and inflammatory mediators. A p-value less than 0.05 was considered significant.

Results

At baseline, the populations of women and men were comparable with respect to age, body weight, medical background, and plasma lipids (Table I). Both popula-

Table I. *Baseline characteristics of the participants*
Tabela I. *Wyjściowa charakterystyka pacjentów*

	Together	Women	Men
Number of patients	61	26	35
Age [years; mean (SD)]	52.1 (1.9)	51.7 (2.4)	52.3 (2.1)
Smokers (%)	25	23	26
Body mass index [kg/m^2; mean (SD)]	26.6 (2.5)	26.0 (2.9)	27.0 (2.7)
Waist circumference [cm; mean (SD)]	96 (4)	92 (5)	99 (4)**
Intima-media thickness [mm; mean (SD)]	0.96 (0.12)	0.94 (0.18)	0.97 (0.15)
Total cholesterol [mg/dL; mean (SD)]	252 (12)	245 (16)	257 (14)
LDL cholesterol [mg/dL; mean (SD)]	180 (10)	173 (15)	185 (13)
HDL cholesterol [mg/dL; mean (SD)]	47 (4)	49 (7)	46 (5)
Triglycerides [mg/dL; mean (SD)]	124 (10)	117 (18)	129 (16)
Glucose [mg/dL; mean (SD)]	95 (5)	94 (6)	95 (5)
HOMA-IR [mean (SD)]	2.8 (0.7)	2.8 (0.9)	2.9 (0.8)
hsCRP [mg/L; mean (SD)]	3.4 (0.5)	3.5 (0.7)	3.4 (0.7)
FFA [μmol/L; mean (SD)]	379 (43)	371 (50)	385 (48)
Leptin [ng/mL; mean (SD)]	24.7 (5.1)	34.6 (3.5)	17.3 (2.3)***
Adiponectin [mg/L; mean (SD)]	5.6 (1.0)	6.9 (0.9)	4.6 (0.8)***
Visfatin [ng/mL; mean (SD)]	21.3 (2.4)	22.1 (2.7)	20.7 (2.5)
TNF-α [pg/mL; mean (SD)]	15.9 (2.3)	13.1 (2.9)	18.0 (2.8)**

**p < 0.01; ***p < 0.001 *vs.* women

Table II. *The effect of 30-day simvastatin treatment on plasma lipids, glucose metabolism markers and circulating levels of high sensitivity C-reactive protein, free fatty acids, and the investigated adipokines in hypercholesterolaemic men and women*

Tabela II. *Wpływ 30-dniowego stosowania simwastatyny na stężenie lipidów, markery gospodarki węglowodanowej oraz stężenie białka C-reaktywnego, wolnych kwasów tłuszczowych i ocenianych adipokin u kobiet i mężczyzn z izolowaną hipercholesterolemią*

	Women (n = 9)	Men (n = 13)
ΔTotal cholesterol [%; mean (SD)]	–28 (7)***	–23 (5)***
ΔLDL cholesterol [%; mean (SD)]	–31 (8)***	–28 (7)***
ΔHDL cholesterol [%; mean (SD)]	2 (4)	6 (5)
ΔTriglycerides [%; mean (SD)]	–11 (8)	–8 (8)
ΔGlucose [%; mean (SD)]	2 (4)	2 (3)
ΔHOMA-IR [%; mean (SD)]	4 (8)	4 (6)
ΔhsCRP [%; mean (SD)]	–23 (5)**	–26 (6)**
ΔFFA [%; mean (SD)]	–19 (4)*	–19 (3)*
ΔLeptin [%; mean (SD)]	–26 (7)*	–29 (6)*
ΔAdiponectin [%; mean (SD)]	29 (7)*	32 (5)*
ΔVisfatin [%; mean (SD)]	–18 (5)	–18 (4)
ΔTNF-α [%; mean (SD)]	–20 (7)*	–23 (5)*

The data show percentage changes from the respective baseline value.
*p < 0.05; **p < 0.01; ***p < 0.001 post-treatment *vs.* baseline value

Table III. *The effect of 30-day ezetimibe treatment on plasma lipids, glucose metabolism markers and circulating levels of high sensitivity C-reactive protein, free fatty acids, and the investigated adipokines in hypercholesterolaemic men and women*

Tabela III. *Wpływ 30-dniowego stosowania ezetimibu na stężenie lipidów, markery gospodarki węglowodanowej oraz stężenie białka C-reaktywnego, wolnych kwasów tłuszczowych i ocenianych adipokin u kobiet i mężczyzn z izolowaną hipercholesterolemią*

	Women (n = 9)	Men (n = 12)
ΔTotal cholesterol [%; mean (SD)]	–24 (7)***	–21 (6)***
ΔLDL cholesterol [%; mean (SD)]	–28 (8)***	–25 (6)***
ΔHDL cholesterol [%; mean (SD)]	4 (4)	0 (6)
ΔTriglycerides [%; mean (SD)]	–9 (12)	–9 (10)
ΔGlucose [%; mean (SD)]	–2 (4)	–2 (4)
ΔHOMA-IR [%; mean (SD)]	–18 (6)	–15 (7)
ΔhsCRP [%; mean (SD)]	–17 (4)	–19 (5)
ΔFFA [%; mean (SD)]	–16 (4)	–15 (4)
ΔLeptin [%; mean (SD)]	–12 (5)	–15 (3)
ΔAdiponectin [%; mean (SD)]	3 (2)	4 (2)
ΔVisfatin [%; mean (SD)]	–17 (5)	–14 (4)
ΔTNF-α [%; mean (SD)]	–12 (5)	–13 (4)

The data show percentage changes from the respective baseline value.
***p < 0.001 post-treatment *vs.* baseline value

tions differed in waist circumference. Plasma levels of adiponectin and leptin were lower, while plasma levels of TNF-α higher in men than in women. No differences between men and women were observed in HOMA-IR, FFA, hsCRP, and visfatin.

Irrespectively of gender, all treatment options decreased total and LDL cholesterol but did not produce any significant effect on HDL cholesterol and triglycerides (Tables II–IV). In both men and women, simvastatin (Table II) and simvastatin/ezetimibe combination therapy (Table IV) reduced plasma levels of hsCRP, FFA, leptin, and TNF-α but increased plasma levels of adiponectin. Simvastatin administered together with ezetimibe, but not administered alone, to hypercholesterolemia women and men reduced additionally plasma visfatin. Irrespectively of sex, ezetimibe administered for 30 days only tended to reduce plasma levels of hsCRP ($p = 0.094$ for women; $p = 0.098$ for men) and did not affect circulating levels of FFA, leptin, adiponectin, visfatin, and TNF-α (Table III).

The effect of simvastatin and ezetimibe, administered alone or in combination, on plasma hsCRP, FFA, leptin, adiponectin, visfatin, and TNF-α did not differ between men and women (Tables I–III). Irrespectively of sex, the effect of simvastatin/ezetimibe combination therapy on plasma lipids, hsCRP, FFA, and all adipokines was stronger than that of simvastatin or ezetimibe alone, while the effect of simvastatin on hsCRP, FFA, leptin, adiponectin, and TNF-α, but not on plasma lipids and visfatin, was stronger than that of ezetimibe (data not shown).

At baseline, in both sexes, plasma adiponectin levels correlated negatively with total cholesterol, LDL cholesterol, as well as with HOMA-IR, FFA, and hsCRP (men: r values between –0.35 [$p < 0.01$] and –0.59 [$p < 0.001$]; women: r values between –0.32 [$p < 0.05$] and –0.55 [$p < 0.001$]). There were positive correlations between plasma levels of the remaining adipokines assessed by our team and total cholesterol, LDL cholesterol, HOMA-IR, FFA, and hsCRP (men: r values between 0.32 [$p < 0.05$] and 0.60 [$p < 0.001$]; women: r values between 0.29 [$p < 0.05$] and 0.58 [$p < 0.001$]).

Irrespectively of gender, the effect of hypolipidaemic treatment on leptin, adiponectin, visfatin, and TNF-α correlated with the reduction in hsCRP (men: r values between 0.42 [$p < 0.001$] and 0.58 [$p < 0.001$]; women: r values between 0.40 [$p < 0.001$] and 0.57 [$p < 0.001$]), FFA (men: r values between 0.43 [$p < 0.001$] and 0.56 [$p < 0.001$]; women: r values between 0.42 [$p < 0.001$] and 0.55

Table IV. *The effect of 30-day simvastatin/ezetimibe combination therapy on plasma lipids, glucose metabolism markers and circulating levels of high sensitivity C-reactive protein, free fatty acids, and the investigated adipokines in hypercholesterolaemic men and women*

Tabela IV. *Wpływ 30-dniowego stosowania simwastatyny wraz z ezetimibem na stężenie lipidów, markery gospodarki węglowodanowej oraz stężenie białka C-reaktywnego, wolnych kwasów tłuszczowych i ocenianych adipokin u kobiet i mężczyzn z izolowaną hipercholesterolemią*

	Women (n = 8)	Men (n = 10)
ΔTotal cholesterol [%; mean (SD)]	–37 (8)***	–40 (8)***
ΔLDL cholesterol [%; mean (SD)]	–44 (10)***	–48 (9)***
ΔHDL cholesterol [%; mean (SD)]	14 (8)	8 (4)
ΔTriglycerides [%; mean (SD)]	–10 (12)	–12 (14)
ΔGlucose [%; mean (SD)]	–2 (3)	–2 (3)
ΔHOMA–IR [%; mean (SD)]	–22 (–15)	–15 (–11)
ΔhsCRP [%; mean (SD)]	–40 (8)***	–45 (9)***
ΔFFA [%; mean (SD)]	–28 (6)**	–24 (5)**
ΔLeptin [%; mean (SD)]	–40 (10)***	–42 (9)***
ΔAdiponectin [%; mean (SD)]	–47 (16)***	–57 (11)***
ΔVisfatin [%; mean (SD)]	–27 (7)*	–32 (5)**
ΔTNF–α [%; mean (SD)]	–38 (10)***	–34 (7)

*** The data show percentage changes from the respective baseline value.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.01$ post-treatment *vs.* baseline value

[$p < 0.001$]), and in the case of ezetimibe or simvastatin/ezetimibe combination therapy with HOMA-IR (men: r values between 0.35 [$p < 0.01$] and 0.49 [$p < 0.001$]; women: r values between 0.37 [$p < 0.01$] and 0.47 [$p < 0.001$]). No correlation was observed between hypolipidaemic treatment on plasma adipokine levels and the effects of this treatment on plasma lipids in either men or women. In both men and women, the effect of simvastatin, ezetimibe, and simvastatin/ezetimibe combination therapy on plasma adipokines correlated with the reduction in TNF-α (men: r values between 0.30 [$p < 0.05$] and 0.50 [$p < 0.001$]; women: r values between 0.29 [$p < 0.05$] and 0.47 [$p < 0.001$]).

Discussion

In this study, we have found for the first time that the effect of treatment with an HMG-CoA reductase inhibitor and ezetimibe on plasma lipid levels and on adipose tissue products does not depend on sex. Strict inclusion criteria and similar clinical and laboratory characteristics of both the men and women included in the analysis minimised the possibility that the obtained findings resulted from the impact of other concurrent diseases or concomitant therapies.

Expectedly [14, 15], baseline levels of leptin and adiponectin were higher in the women than in the men, and these sex differences probably result from the higher fat mass in women, particularly the presence of more subcutaneous adipose tissue, being the most important source of both adipokines, and from differences in oestrogen or androgen concentrations. The opposite relationship was found for TNF-α, produced in adipose tissue predominantly by inflammatory cells (mainly macrophages) [4–6], circulating levels of which were, like in another study [16], higher in men. Interestingly, lymphocyte release of proinflammatory cytokines is sex-dependent and higher in men than women [Krysiak et al., unpublished observations], and if adipose tissue macrophages behave in a similar way, this finding may partially explain the obtained results.

Interestingly, we have not found sex-dependent differences in baseline concentrations of hsCRP, considered a highly sensitive marker of low-grade vascular inflammation and a protein directly involved in atherogenesis [17]. Studies conducted hitherto have provided conflicting results; the obtained results are in line with the findings of some [18, 19] but not other [16] research groups. The authors of the last study [16] explained higher hsCRP levels by a higher percentage of adipose tissue in women than in men. It is possible that the similar hsCRP levels observed by our research team and found previously by other authors [18, 19] reflect either smaller differences in fat content between men and women participating in these studies or may result from higher levels of proinflammatory cytokines stimulating systemic low-grade inflammation. Such a role may be played by TNF-α, and possibly also by interleukin-6, being the most important stimulator of CRP production [20]. These cytokines are produced by inflammatory cells, the function of which, as mentioned, is more impaired in hypercholesterolaemic men than women, while the production of TNF-α and interleukin-6 is inhibited by simvastatin and ezetimibe, administered alone or in combination [21, 22].

Despite sex differences in body fat distribution and systemic sex hormone concentrations, gender had a limited influence on response to lipid-lowering therapies, assessed by percentage changes in circulating levels of the assessed variables. We can only try to explain these findings. Hypolipidaemic agents directly affect adipose tissue adipokine release [23, 24], and therefore their action at the level of adipocytes and other types of cells present in adipose tissue may not differ between both sexes. It should be underlined that both investigated drugs had a neutral impact on body weight (data not shown), and so treatment-induced changes in plasma adipokines reflect rather alternation in secretory function of these cells than a reduction in fat content. Alter-

natively, their indirect effect mediated by sex hormones may be similar. Interestingly, we previously observed that both statin [25, 26] and ezetimibe [Krysiak et al., unpublished observations] therapy reduced androgen levels in both men and women, and their similar effect on oestrogen production cannot be excluded.

Analyses of changes in plasma lipids by sex subgroups have demonstrated that the male and female patients responded similarly to the treatment. This finding is in contrast with the results of some authors [27, 28], who observed that ezetimibe/statin combination therapy and statin monotherapy enabled achievement of significantly greater reduction of total and LDL cholesterol levels in male patients than female patients. These contrasting results may, in our opinion, be attributed to similar baseline concentrations of total and LDL cholesterol in our study, whereas in the observations of other authors, cholesterol levels were higher in women than men.

Irrespectively of gender, the effect of ezetimibe, administered alone or in combination with simvastatin, on plasma TNF-α, leptin, adiponectin, and visfatin was lipid-independent but correlated with drug-induced improvement in insulin sensitivity. This improvement is likely to be a consequence of a similar reduction in plasma levels of FFA and TNF-α, high levels of which play an important role in the development of insulin resistance [29, 30]. In the case of TNF-α, but not FFA, similar percentage changes in plasma levels contrasted with statistically significant differences in baseline plasma levels. Interestingly, in the men and women treated exclusively with simvastatin, the effect on adipokines correlated with the changes in FFA but not with the changes in HOMA-IR. This finding is probably a consequence of the fact that the impact of simvastatin on FFA and TNF-α is counterbalanced by an inhibitory effect of statin-induced inhibition of protein prenylation on glucose transporter 4 activity [31]. This transporter, found primarily in adipose tissue and striated muscle, is responsible for insulin-regulated glucose transport into the cell [32].

There are some important limitations of this study, the most important of which are the small number of participants and the short period of treatment. Secondly, although the original studies were prospective in nature, this study was a retrospective analysis of the obtained results. Finally, the assessment of adipokines in the plasma does not precisely reflect their release by different types of adipose tissue, and therefore we cannot totally rule out some sex-dependent differences in the action of both drugs at the level of local adipose tissue depots.

Conclusions

The obtained results indicate that the effect of simvastatin, ezetimibe, and their combination on plasma adipokine levels and low-grade systemic inflammation is similar in men and in women. Further research in larger populations is needed to confirm our results.

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