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The effect of short-term combined treatment with simvastatin and ezetimibe on circulating adipokine levels in patients with isolated hypercholesterolemia

Wpływ krótkotrwałego leczenia skojarzonego simwastatyną i ezetimibem na stężenie adipokin w osoczu pacjentów na izolowaną hipercholesterolemię

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Abstract

Introduction: Although several studies have assessed plasma adipokines in patients treated with hypolipidemic agents, these studies have provided contrasting results.
Material and methods: This study included 19 high-risk patients with elevated total and LDL cholesterol levels treated with simvastatin (40 mg daily) and ezetimibe (10 mg daily). Plasma levels of leptin, adiponectin, visfatin, tumour necrosis factor-α, free fatty acids as well as C-reactive protein were measured before and after 30 days of treatment. High-risk hypercholesterolemic patients were compared with 17 age-, sex- and weight-matched healthy subjects who did not receive any treatment.
Results: Compared to the healthy subjects, hypercholesterolemic patients exhibited lower plasma levels of adiponectin, as well as higher plasma levels of the remaining adipokines. Administration of simvastatin and ezetimibe for 30 days reduced plasma levels of leptin, visfatin, TNF-α, as well as increased plasma levels of adiponectin. The treatment also reduced free fatty acids and C-reactive protein.
Conclusions: High-risk hypercholesterolemic patients with elevated cholesterol levels are characterised by abnormal production of adipose tissue hormones. Short-term treatment with simvastatin and ezetimibe partially restores adipokine production and inhibits low-grade inflammation. **(Endokrynol Pol 2014; 65 (4): 275–280)**

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

Streszczenie

Wstęp: Chociaż w nielicznych badaniach oceniono uprzednio stężenie adipokin w osoczu chorych leczonych lekami hipolipemicznymi, jednak wyniki tych badań nie są zgodne.
Materiał i metody: Badaniem objęto 19 pacjentów należących do grupy zwiększonego ryzyka schorzeń układu sercowo-naczyniowego, u których stwierdzono podwyższone stężenie cholesterolu całkowitego i cholesterolu LDL. U chorych tych zastosowano terapię skojarzoną, obejmującą podawanie simwastatyny (40 mg dziennie) i ezetimibu (10 mg dziennie). Stężenie w osoczu wybranych adipokin (leptyna, adiponektyna, wisfatyna oraz czynnik martwicy nowotworów α), wolnych kwasów tłuszczowych, jak również białka C-reaktywnego oceniano przed i po 30 dniach leczenia. Badani pacjenci byli porównywani z grupą 17 zdrowych ochotników, dobranych pod względem wieku, płci i masy ciała.
Wyniki: W stosunku do grupy kontrolnej, u osób z hipercholesterolemią stwierdzono niższe stężenie w osoczu adiponektyny oraz wyższe stężenie w osoczu pozostałych adipokin. Trzydziestodniowe podawania simwastatyny z ezetimibem zmniejszyło stężenie leptyny, wisfatyny oraz czynnika martwicy nowotworów α, jak również zwiększyło stężenie adiponektyny. Spowodowało również spadek stężenia wolnych kwasów tłuszczowych i białka C-reaktywnego.
Wnioski: Pacjentów należących do grupy wysokiego ryzyka, u których stwierdza się hipercholesterolemię, charakteryzuje nieprawidłowe wytwarzanie hormonów tkanki tłuszczowej. Krótkotrwałe leczenie z zastosowaniem simwastatyny i ezetimibu częściowo przywraca prawidłowe wydzielanie adipokin i hamuje stan zapalny o niewielkim nasileniu. **(Endokrynol Pol 2014; 65 (4): 275–280)**

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

Abbreviations

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

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Introduction

Previous studies carried out in our laboratory have shown that combined therapy with a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) and an inhibitor of a Niemann-Pick C1-Like 1 transporter — ezetimibe — is associated with more pronounced changes in monocyte and lymphocyte cytokine release and in haemostasis than in the case of a statin and ezetimibe administered alone [1-3]. Unfortunately, the results of large clinical trials assessing the effects of the combined treatment with these agents are not so clear-cut. The effect of ezetimibe-simvastatin combination treatment on the carotid intima-media thickness was found in patients at high cardiovascular risk [4], as well as in patients with type 2 diabetes and no prior cardiovascular events [5], but not in patients with ischaemic heart disease or its equivalent [6] nor in patients with familial hypercholesterolemia [7]. Moreover, although in patients with mild-to-moderate, asymptomatic aortic-valve stenosis, simvastatin-ezetimibe combination treatment reduced the incidence of ischaemic cardiovascular events, the treatment had no overall effect on the course of aortic-valve stenosis [8].

The role of abnormal adipokine production in the pathophysiology of obesity, insulin resistance and cardiovascular diseases [9, 10] means that human adipose tissue seems to be an interesting target for hypolipidemic agents. In some studies [11–14], administration of HMG-CoA reductase inhibitors has led to an improvement in adipose tissue function, whereas other studies [15–18] did not find any effect of statins on plasma adipokines. Similarly, some authors have observed ezetimibe-induced changes in plasma adipokines [19, 20], while other authors [16, 21, 22] have not found such a relationship. These results seem to indicate that the effect of statins and ezetimibe, administered alone, is relatively moderate. Our previous *in vitro* studies showed that the relatively weak effect of atorvastatin on adipokine release by cultures of whole adipose tissue [23] and cultures of isolated adipocytes [24] was much stronger if atorvastatin was administered together with fenofibric acid. These findings suggest that the combined hypolipidemic treatment may bring greater benefits to patients than the administration of only one hypolipidemic agent. Therefore, the aim of the present study was to investigate whether combination therapy with simvastatin and ezetimibe has an impact on plasma adipokine levels and low-grade systemic inflammation. Leptin, adiponectin, visfatin and TNF-α were chosen among different adipokines because they are important products of adipose tissue and their presence is found in atherosclerotic plaques, while abnormal levels are associated with an increased risk of atherosclerosis and its complications [25–27]. Also C-reactive protein (CRP), the best known marker of low-grade systemic inflammation, strongly and independently predicts adverse cardiovascular events, including myocardial infarction, ischaemic stroke, and sudden cardiac death [28, 29].

Material and methods

Patients (aged 35–60 years) were enrolled in the study if they met the following criteria: they were at high cardiovascular risk (ischaemic heart disease, SCORE at least 5, peripheral vascular disease and a history of stroke and/or transient ischaemic attacks), had isolated hypercholesterolemia defined as total plasma cholesterol above 200 mg/dL, LDL cholesterol more than 130 mg/dL and triglycerides below 150 mg/dL, and, in the case of women, they were at least 18 months since the last menstruation, hysterectomy or ovariectomy, or used barrier contraception. The exclusion criteria were as follows: any acute or 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 another hypolipidemic drug within the three months prior to the study or with drugs known to interfere with statins or ezetimibe. All participants (n = 19) provided written consent as approved by the ethics committee of the Medical University of Silesia. Each patient meeting the initial inclusion criteria received traditional counselling regarding diet and exercise in the form of printed material based on the National Cholesterol Education Programme diet and lifestyle recommendations. All enrolled patients were treated with simvastatin (40 mg daily) plus ezetimibe (10 mg daily), which were administered once daily for 30 days throughout the study. Our control group included 17 age-, sex- and weight-matched healthy subjects. The daily dose of simvastatin was the same as used in the Heart Protection Study, which is to date the largest study to investigate the use of statins in the prevention of cardiovascular disease [30]. Throughout the entire study period, all patients complied with dietary recommendations. Compliance was assessed during each visit by pill count. Venous blood samples were drawn from the antecubital vein in a quiet, temperature-controlled room (24–25°C) at a regular time each day (between 8:00 and 9:00 a.m.) at least 12 h after the last meal. Blood samples were also taken two hours after

a 75-g oral glucose load. To minimise analytical errors, all measurements were performed strictly according to the manufacturers' instructions in duplicate within a single analytical session, and the final results were averaged. Plasma lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides) were assessed by a colorimetric method using commercial kits (bioMerieux, France). LDL levels were measured directly. Plasma glucose concentrations were determined by a glucose oxidase method (Beckman, Palo Alto, CA, USA). Plasma insulin was measured with a commercial radioimmunoassay kit (Linco Research Inc., St. Charles, MO, USA) that does not cross-react with human proinsulin. The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated from the following equation: fasting plasma glucose (mg/dL) × fasting insulin level (mU/L)/405]. Total non-estrified free fatty acids (FFA) were determined by an enzymatic assay using reagents from Alpha Laboratories (Eastleigh, UK). Plasma levels of C-reactive protein (CRP) were measured using a high-sensitivity monoclonal antibody assay (MP Biomedicals, Orangeburg, NY, USA). Plasma levels of leptin, adiponectin, visfatin and TNF-α were measured with commercial enzyme-linked immunosorbent assay kits obtained from TECOmedical Group (Sissach, Switzerland), Phoenix Pharmaceuticals (Burlingame, CA, USA) and R&D Systems (Minneapolis, MN, USA). 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 interassay coefficients of variation for the assessed markers were less than 5.5 and 8.7%, respectively.

Different groups were compared using the *t* test for independent samples. Pretreatment and post-treatment data within the same group were compared with Student's paired t-test. For categorical variables, χ^2 test was used. Correlations were calculated with the use of Kendall's tau test. P less than 0.05 were regarded as statistically significant.

Table I. *Baseline characteristics of participants*[1]
Tabela I. *Wyjściowa charakterystyka uczestników badania*

	Control group	Combined treatment
Number of patients	17	18
Age [years; mean (SD)]	51.4 (2.7)	53.0 (3.7)
Women (%)	41	44
Smokers (%)	24	28
Body mass index [kg/m^2; mean (SD)]	26.8 (2.9)	27.1 (2.4)
Waist circumference [cm; mean (SD)]	97 (4)	99 (5)
Intima-media thickness [mm; mean (SD)]	0.62 (0.11)	0.99 (0.11)***
Total cholesterol [mg/dL; mean (SD)]	160 (12)	261 (16)***
LDL cholesterol [mg/dL; mean (SD)]	96 (7)	188 (12)***
HDL cholesterol [mg/dL; mean (SD)]	50 (4)	46 (4)
Triglycerides [mg/dL; mean (SD)]	118 (11)	128 (12)
Fasting glucose [mg/dL; mean (SD)]	93 (5)	97 (5)
2-h post-challenge plasma glucose [mg/dL; mean (SD)]	128 (8)	137 (10)
HOMA-IR	1.2 (0.3)	2.6 (0.7)***
Free fatty acids [μmol/L; mean (SD)]	219 (42)	384 (57)***
hsCRP [mg/L; mean (SD)]	1.2 (0.2)	3.8 (0.7) ***
Leptin [ng/mL; mean (SD)]	10.8 (3.4)	25.8 (5.5)***
Adiponectin [mg/L; mean (SD)]	10.9 (1.3)	5.9 (1.1)***
Visfatin [ng/mL; mean (SD)]	10.1 (3.2)	21.8 (3.9)***
TNF-α [pg/mL; mean (SD)]	6.9 (1.6)	16.1 (2.6)***

[1]Only data of subjects who completed the study was included in the final analyses; ***$p < 0.001$ *vs.* control patients

Results

At the start of the study, there was no difference between the treatment and the control groups in terms of sex, weight, age and safety parameters. Plasma levels of adiponectin were lower, while plasma levels of leptin, visfatin, TNF-α, hsCRP and FFA, as well as HOMA-IR were higher, than in the control group. Demographic data and baseline results are shown in Table I. The treatment was well tolerated and, with the exception of one patient who developed abdominal pain and diarrhoea, all patients completed the study. In the control patients, circulating levels of lipids, glucose homeostasis markers, hsCRP and the investigated adipokines remained at a similar level throughout the study. Simvastatin administered together with ezetimibe for 30 days decreased plasma levels of total cholesterol by 39% ($p < 0.001$) and LDL cholesterol by 45% ($p < 0.001$), tended to reduce HOMA-IR (–19%, $p = 0.092$), but did not affect plasma triglycerides, HDL cholesterol, fasting and post-challenge plasma glucose (Table II). This therapy had also no effect on body mass index or waist circumference. Thirty days of the combined therapy decreased plasma levels of leptin by 38% ($p < 0.001$), visfatin by 29% ($p < 0.05$), TNF-α by 32% ($p < 0.001$), hsCRP by 39% ($p < 0.001$) and FFA by 24% ($p < 0.01$), as well as increased circulating levels

Table II. *The effect of simvastatin and ezetimibe treatment on plasma lipids and glucose homeostasis in patients with isolated hypercholesterolemia*[1]

Tabela II. *Wpływ simwastatyny i ezetimibu na stężenie w osoczu lipidów i homeostazę glukozy u pacjentów z izolowaną hipercholesterolemią*

	Control group Mean (SD)	Combined treatment Mean (SD)
Total cholesterol [mg/dL]		
Baseline value	160 (12)	261 (16)***
After 30 days	157 (11)	159 (14)###
LDL cholesterol [mg/dL]		
Baseline value	96 (7)	188 (12)***
After 30 days	95 (7)	102 (8) ###
HDL cholesterol [mg/dL]		
Baseline value	50 (4)	46 (4)
After 30 days	51 (4)	51 (4)
Triglycerides [mg/dL]		
Baseline value	118 (11)	128 (12)
After 30 days	116 (12)	114 (18)
Fasting glucose [mg/dL]		
Baseline value	93 (5)	97 (5)
After 30 days	92 (5)	95 (4)
2-h post-challenge plasma glucose [mg/dL]		
Baseline value	128 (8)	137 (10)
After 30 days	126 (7)	135 (10)
HOMA-IR		
Baseline value	1.2 (0.3)	2.6 (0.7)***
After 30 days	1.3 (0.4)	2.1 (0.5)***

[1]Only data of subjects who completed the study was included in the final analyses; ***p < 0.001 *vs.* control patients; ###p < 0.001 *vs.* baseline value

Table III. *The effect of simvastatin and ezetimibe treatment on free fatty acids, hsCRP and adipokines in patients with isolated hypercholesterolemia*[1]

Tabela III. *Wpływ simwastatyny i ezetimibu na stężenie wolnych kwasów tłuszczowych, hsCRP i adipokin u pacjentów z izolowaną hipercholesterolemią*

	Control group Mean (SD)	Combined treatment Mean (SD)
Free fatty acids [μmol/L]		
Baseline value	219 (42)	384 (57)***
After 30 days	208 (39)	292 (41)***###
hsCRP [mg/L]		
Baseline value	1.2 (0.2)	3.8 (0.7)***
After 30 days	1.3 (0.3)	2.3 (0.5)***###
Leptin [ng/mL]		
Baseline value	10.8 (3.4)	25.8 (5.5)***
After 30 days	10.4 (3.5)	16.0 (3.8)###
Adiponectin [mg/L]	10.9 (1.3)	5.9 (1.1)***
Baseline value	11.2 (1.2)	11.6 (1.3)###
After 30 days		
Visfatin [ng/mL]		
Baseline value	10.1 (3.2)	21.8 (3.9)***
After 30 days	10.3 (2.7)	15.5 (2.9)**#
TNF-α [pg/mL]		
Baseline value	6.9 (1.6)	16.1 (2.6)***
After 30 days	7.0 (1.4)	10.9 (2.4)***###

[1]Only data of subjects who completed the study was included in the final analyses; *p < 0.05; **p < 0.01 ; ***p < 0.001 *vs.* control patients; #p < 0.05; ##p < 0.01; ###p < 0.001 *vs.* baseline value

of adiponectin by 97% (p < 0.001). At the end of the study period, plasma levels of leptin, visfatin, TNF-α, hsCRP and FFA were still higher than in the control group (Table III).

Baseline plasma levels of leptin, visfatin and TNF-α correlated positively with total cholesterol (r values between 0.40–0.52, p < 0.001), LDL cholesterol (r values between 0.43 and 0.58, p < 0.001), HOMA-IR (r values between 0.39 and 0.55, p < 0.001), and hsCRP (r values between 0,31 [p < 0.05] and 0.43 [p < 0.001]), as well as in the case of leptin and TNF-α with body mass index (r = 0.55, p < 0.001 for leptin; r = 0.34, p < 0.05 for TNF-α) and waist circumference (r = 0.49, p < 0.001 for leptin; r = 0.32, p < 0.05 for TNF-α). Circulating adiponectin levels correlated negatively with body mass index, waist circumference, total and LDL cholesterol, HOMA-IR and hsCRP (r values between –0.37 [p < 0.01] and –0.56 [p < 0.001]). The treatment-induced changes in plasma adipokines correlated with the effect of treatment on HOMA-IR (r values between 0.35 [p < 0.01] and 0.43 [p < 0.001]) and FFA (r values between 0.40 and 0.52, p < 0.001). The treatment-induced reduction in plasma TNF-α correlated with the effect of treatment on plasma levels of the remaining adipokines (r values between 0.31 [p < 0.05] and 0.50 [p < 0.001]). There were correlations between the combined treatment-induced reduction in plasma hsCRP and the treatment-induced changes in plasma adipokines (r values between 0.41 and 0.53, p < 0.001). No other correlations were found in either baseline conditions or after treatment.

Discussion

High-risk patients with elevated cholesterol levels were characterised by abnormal hormonal function of adipose tissue, which was parallelled by low-grade systemic inflammation. Taking into account that reduced plasma levels of leptin, visfatin and TNF-α, and increased circulating levels of adiponectin are considered independent risk factors for cardiovascular disease [25–7], enhanced risk in this group of patients may be partially attributed to dysfunction of adipose tissue. Our study did not include high-risk patients with normal plasma lipids. However, the presence of correlations between baseline levels of adipokines and baseline total and LDL cholesterol levels, suggests that adipose tissue dysfunc-

tion in high-risk patients without lipid abnormalities is less expressed than in the assessed population.

The aforementioned changes in plasma adipokines and hsCRP were alleviated by 30-day combined administration of both hypolipidemic agents. This finding indicates that the statin-ezetimibe combination causes early and multidirectional changes in adipose tissue function and reduces systemic inflammation, and that these effects of simvastatin plus ezetimibe are unrelated to lipid lowering. These findings are in line with a recent large clinical trial, which included 9,270 patients with chronic kidney disease with no known history of myocardial infarction or coronary revascularisation, randomised to simvastatin plus ezetimibe or to a placebo [31]. Simvastatin administered together with ezetimibe reduced the incidence of major atherosclerotic events (non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or any arterial revascularisation procedure) in this group of patients.

A partial normalisation of adipose tissue function in our patients cannot be attributed to the combined treatment-induced reduction in body fat content because both body mass index and waist circumference remained unaltered during the treatment. Nor can the changes in adipokine levels be explained by deterioration of kidney function [32] because there were no changes in glomerular filtration rate (data not shown). Therefore, our results most likely reflect the effect of the combined treatment on adipokine production and/or release by adipose tissue.

The observations that plasma adipokine levels correlated with circulating hsCRP levels in both baseline conditions and after treatment shows that the combined treatment-induced improvement in adipose tissue function contributes to the systemic anti-inflammatory effect of this treatment. Interestingly, we have previously observed a similar relationship between the effect of simvastatin and ezetimibe on monocyte cytokine release [1], lymphocyte cytokine release [2] and haemostatic cardiovascular risk factor [3] and their action on plasma hsCRP. Therefore, it may be safely assumed that the combined therapy-induced decrease in low-grade inflammation either is secondary to their action at the levels of various tissues, or that the anti-inflammatory effects of this drug normalise the function of various organs.

At the end of the treatment period, with the exception of adiponectin, plasma adipokine levels, free fatty acids and hsCRP were still different from those observed in the control group, although plasma lipid levels were similar to those observed in the healthy subjects. The obtained results suggest that a treatment period longer than that used in the present study would produce a stronger inhibitory effect on adipose tissue and systemic inflammation, and that a certain minimal period of treatment is required to exhibit the full efficacy of the statin-ezetimibe combination in the prevention and treatment of atherosclerosis-related diseases.

Interestingly, the effect of the treatment on plasma adipokines correlated with the action of simvastatin plus ezetimibe on HOMA-IR. The link between the action of simvastatin and ezetimibe on adipokines and on insulin sensitivity is further supported by finding the correlations between treatment-induced changes in plasma adipokines and in FFA, as well as the correlations between the effect of treatment on leptin, adiponectin and visfatin and on TNF-α. It is worth underlining that FFA [33] and TNF-α [34], by impairing insulin receptor action, are implicated in the development of insulin resistance. These observations may suggest that either adipokines mediate the effect of the combined treatment on insulin sensitivity, or that the normalisation of adipose tissue function is a consequence of a reduction in insulin resistance.

There are several limitations of this study, the most important of which are the small sample size and the lack of a reference group treated only with a statin or ezetimibe. Moreover, we measured only surrogate endpoints. Finally, plasma adipokine levels do not seem to accurately reflect adipokine secretion by different types of adipose tissue.

To sum up, our study has revealed that high-risk patients with isolated hypercholesterolemia are characterised by abnormal adipokine production and the presence of low-grade inflammation. Thirty days of the combined treatment partially reversed adipose tissue dysfunction and reduced systemic inflammation, and therefore the simvastatin-ezetimibe combination may bring some benefits to the investigated population of patients.

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