Effect of Low-Dose Atorvastatin on Plasma Concentrations of Adipokines in Patients with Metabolic Syndrome

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Key Words

Metabolic syndrome • Obesity • Adiponectin • Statins

Abstract

Objective: It has not been conclusively proven whether or not the beneficial effect of statins on the cardiovascular system is mediated through their influence on adipokine secretion. We designed a prospective open-label study to assess the influence of 6 months' atorvastatin therapy on plasma concentrations of some adipokines in patients with metabolic syndrome. **Subjects:** 36 adult patients with metabolic syndrome and serum LDL cholesterol >3.5 mmol/l, previously untreated with statins, were included in the study. **Measurements:** Plasma concentrations of adiponectin, leptin, resistin and insulin were measured before initiation and after 2, 4 and 6 months of atorvastatin therapy (10 mg), and 2 months after treatment cessation. **Results:** Treatment with atorvastatin was followed by a 35.6% decline in LDL cholesterol. Plasma adiponectin concentration decreased by 20.7% after 2 months; however, after 4 and 6 months, this did not differ significantly from the initial values. There was a negative correlation between the initial plasma concentration of leptin and changes in HDL cholesterol ($R = -0.358$; $p = 0.04$). **Conclusions:** Firstly, the long-term effect of atorvastatin

therapy in patients with metabolic syndrome is not mediated by changes in the secretion of adiponectin, leptin and resistin by adipose tissue. Secondly, plasma leptin concentration seems to be a predictor of HDL cholesterol changes during atorvastatin therapy.

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Introduction

Statins lower total and LDL plasma cholesterol concentrations and increase the concentration of the HDL fraction [1]. They also show some pleiotropic actions: anti-inflammatory, immunomodulatory, antithrombotic and fibrinolytic [2–4]. Moreover, statins enhance endothelial function, inhibit platelet activity, lower blood pressure and at least some of them decrease insulin resistance [5–7]. It has not been conclusively proven whether or not the above-listed advantageous actions of statins may be mediated, at least partially, through their influence on the secretion of adipokines, like adiponectin, leptin or resistin [8–10].

Adiponectin enhances metabolism of glucose and fatty acids in the liver and skeletal muscles, and inhibits gluconeogenesis in the liver [11, 12]. It also possesses anti-

atherogenic actions [13]. It has already been found that in patients with metabolic syndrome plasma adiponectin concentration is significantly decreased [14, 15]. Recently, it has been shown that plasma adiponectin concentrations determine HDL cholesterol response to atorvastatin treatment [16].

Another protein produced by adipocytes is leptin. Plasma leptin concentrations are markedly elevated in obese patients, including those with metabolic syndrome [17]. In contrast to adiponectin, leptin exerts (at least in vitro) several proatherogenic effects, such as stimulation of inflammatory processes, oxidative stress, induction of endothelial dysfunction, blood pressure increase, platelet aggregation, hypertrophy and proliferation of vascular smooth muscle cells [18].

Patients with metabolic syndrome are also characterized by elevated plasma resistin concentrations compared to the general population [19]. Unlike adiponectin and leptin, resistin is mainly produced by macrophages of the fat tissue and takes part in obesity-related chronic inflammatory processes [20].

The potential mechanism of statins' influence on adipokine synthesis or biodegradation remains unknown. Regardless, the hypothesis concerning the modulation of adipokine synthesis or secretion in adipose tissue by statins has been tested in a few studies. Many of these did not prove the existence of a significant influence [16, 21–24]. Koh et al. [25] demonstrated an up to 12% decrease in plasma adiponectin concentration after 2 months of simvastatin therapy. In contrast, the opposite effect of atorvastatin was shown by Blanco-Colio et al. [26] in patients at high cardiovascular risk. The authors demonstrated a 9.7% increase in plasma adiponectin concentration in the whole group and a 24.7% increase in patients receiving the highest dose (80 mg) of atorvastatin. Even greater, the 44% increase in plasma adiponectin was found by Miyagishima et al. [27] in a small ($n = 22$) group of patients with ischemic heart disease treated for 3 months with atorvastatin. Recently, Ando et al. [28] and Qu et al. [29] confirmed that atorvastatin increases plasma adiponectin concentration. In the study by Ando et al. [28], in contrast to atorvastatin, pravastatin did not influence plasma adiponectin concentration.

We designed a single-centre prospective open-label study choosing atorvastatin as one of the most potent statins for lowering LDL cholesterol [30] with proven long-term efficacy in cardiovascular risk reduction [31] and pronounced pleiotropic actions [32]. Unlike the others, we selected only patients with metabolic syndrome,

and we followed the therapy with atorvastatin longer than in the majority of previously performed studies (6 months) analyzing its influence on plasma concentrations of adiponectin, resistin and leptin.

Patients and Methods

Thirty-six Caucasians (17 males, 19 females) with metabolic syndrome and newly referred to our outpatient clinic with a total serum LDL cholesterol concentration >3.5 mmol/l, previously untreated with statins, were included into the study. Metabolic syndrome was diagnosed based on NCEP-ATP III criteria [33]. Patients had to match three of the criteria listed below: abdominal obesity (waist circumference: females >88 cm, males >102 cm); serum concentration of triglycerides ≥ 1.7 mmol/l, low HDL cholesterol (<1.3 mmol/l for males and <1.29 mmol/l for females); fasting serum glucose concentration ≥ 100 mg/dl, arterial blood pressure $\geq 130/85$ mm Hg. Patients with a BMI <27 or >40 , elevated glutamic pyruvic transferase (GPT) serum activity, diabetes mellitus type 2, or any chronic disease other than metabolic syndrome and arterial hypertension treated with antihypertensive drugs other than amlodipine (calcium channel blocker) were excluded from the study. The study protocol was accepted by the Local Ethics Committee of Medical University of Silesia. Each patient gave their written consent.

Before the initiation of treatment with 10 mg atorvastatin (Sortis®), anthropometric measurements (body weight, height, waist circumference), whole-body X-ray densitometry DEXA were obtained and blood samples were taken during fasting for the estimation of serum concentrations of glucose, cholesterol and its fractions, triglycerides, GPT activity, and plasma concentration of insulin, adiponectin, leptin and resistin. All patients received a standard 10-mg dose of atorvastatin for 6 months and a low-lipid diet was recommended. The effect of lipid-lowering therapy over 6 months of atorvastatin treatment was monitored by measurement of serum LDL cholesterol levels in 2-month intervals. The protocol specified cessation atorvastatin treatment and exclusion from the study if the GPT activity exceeded twice the upper limit.

Patients received recommendations for a low-fat diet. However, maintenance of a stable body weight during the period of observation was strongly encouraged as its variability makes the interpretation of changes in adiponectin, leptin concentrations and insulin resistance difficult. Therefore, the low-calorie diet and weight reduction were (temporarily) not stressed.

All measurements, except DEXA, were repeated every 2 months, and 2 months after treatment cessation. The second DEXA measurement was performed at the end of the 6-month follow-up period.

All patients with metabolic syndrome suffering from arterial hypertension were treated with amlodipine (5–10 mg/daily). In the previous studies, it has been shown that antihypertensive treatment with amlodipine influences neither plasma leptin nor adiponectin concentrations [34].

Twenty healthy volunteers (11 females, 9 males) served as a control group. All laboratory tests in the control group were performed only once.

Table 1. Characteristics of patients with metabolic syndrome and control group

	Metabolic syndrome (n = 36)	Control group (n = 20)	p
Age, years	51 (42–58)	49 (32–61)	0.77
Gender (males/females)	17/19	9/11	0.87
BMI	29.7 (27.7–32.2)	23.5 (20.9–24.5)	<0.001
Total body fat mass, kg	31.3 (26.0–36.6)	–	–
Trunk fat mass, kg	16.7 (14.0–20.4)	–	–
Waist circumference, cm	103 (91–107)	–	–
Systolic BP, mm Hg	128 (121–142)	126 (120–135)	0.879
Diastolic BP, mm Hg	83 (80–90)	80 (76–85)	0.981
Total cholesterol, mmol/l	6.74 (6.18–7.48)	4.85 (4.60–5.10)	<0.001
HDL fraction, mmol/l	1.29 (1.12–1.50)	1.42 (1.34–1.53)	0.06
LDL fraction, mmol/l	4.92 (4.51–5.94)	3.18 (2.99–3.46)	<0.001
Triglycerides, mmol/l	1.66 (1.38–2.20)	1.15 (0.93–1.30)	<0.001
Glucose, mmol/l	4.91 (4.45–5.37)	4.45 (4.15–4.80)	0.001
Insulin, μ U/ml	9.80 (5.60–11.40)	6.05 (4.55–8.50)	0.003
QUICKY index	0.26 (0.25–0.29)	0.31 (0.28–0.33)	0.001
Creatinine, μ mol/l	80 (72–90)	–	–
Adiponectin, μ g/ml	8.54 (7.09–10.42)	9.83 (8.15–11.78)	0.04
Leptin, ng/ml	12.2 (4.6–21.7)	8.5 (3.7–11.9)	<0.001
Resistin, ng/ml	5.60 (2.50–6.90)	2.90 (1.95–3.50)	0.003

Data are presented as medians with IQR in parentheses. BP = Blood pressure.

Laboratory Measurements

The enzyme immunoassay method was used for the measurement of plasma concentrations of adiponectin (B-Bridge International Inc., San Jose, Calif., USA), resistin (Bio Vendor Laboratory Medicine, Brno, Czech Republic) and insulin (Roche Diagnostics, Mannheim, Germany). An immunoradiometric method was used for the measurement of plasma concentrations of leptin (Linco Research Laboratories, St. Louis, Mo., USA). The other parameters were measured with standard methods.

Insulin sensitivity was calculated as the Quantitative Insulin-Sensitivity Check Index QUICKY index = $1/[\log(\text{plasma insulin level}) + \log(\text{plasma glucose level})]$ [35].

DEXA Measurement

Lunar DPX-L scanner (Lunar Radiation Co., Madison, Wisc., USA) operated by a single experienced technician was used for all body measurements performed in a supine position. This method allows the assessment of total lean mass, total fat mass and fat mass of the trunk.

Statistical Analysis

Statistical analysis was performed using the Statistica 7.0 PL software. Data are presented as medians and IQR. Non-parametric tests (Mann-Whitney U and χ^2) were used to compare the groups. The effects of atorvastatin therapy were analyzed by Friedman's repeated ANOVA on ranks by comparing the relative changes in values in response to treatment. Wilcoxon signed-rank test was used to compare time point values before and after treatment. Correlation coefficients were calculated according to Spearman. Values of $p < 0.05$ were considered as statistically significant.

Results

Patients with metabolic syndrome were characterized by significantly higher mean BMI and serum concentrations of total cholesterol and its LDL fraction, glucose, insulin and HOMA-IR than the control group (table 1). As expected in patients with metabolic syndrome, plasma concentrations of leptin and resistin were about 2 times higher, while plasma adiponectin concentration was 17% lower, than in healthy controls (table 1).

Treatment with atorvastatin was followed by 28.6 and 35.6% declines in total cholesterol and its LDL fraction concentrations, respectively (fig. 1). Two and 6 months after initiation of this therapy, 72 and 61% of patients, respectively, obtained a concentration of LDL fraction within the recommended range (<3.5 mmol/l). Serum triglyceride concentrations also decreased significantly, while the fraction of HDL cholesterol increased slightly, but also significantly (table 2). The above-mentioned values were stable during the 6-month treatment period, and returned to initial values 2 months after discontinuation of the cholesterol-lowering medication.

During the 6 months of atorvastatin treatment in patients with metabolic syndrome, body mass decreased slightly by 1.25 (0.17–2.23) kg, mainly as a consequence

Table 2. Patient data before and after atorvastatin therapy

	Before atorvastatin therapy	After 2 months' atorvastatin therapy	After 6 months' atorvastatin therapy	Wilcoxon test	
				0 vs. 2 months	0 vs. 6 months
Weight, kg	84.1 (79.5–88.7)	83.7 (79.1–88.3)	82.9 (78.2–87.6)	0.01	0.01
Total fat mass, kg	31.8 (29.1–34.5)	–	31.0 (27.9–34.0)	–	0.02
Fat mass of the trunk, kg	17.4 (16.0–18.7)	–	16.8 (15.3–18.3)	–	0.02
Waist circumference, cm	101 (98–104)	–	99 (96–102)	–	0.08
Glucose, mmol/l	4.91 (4.73–5.08)	5.11 (4.88–5.34)	5.09 (4.85–5.32)	0.03	0.07
Triglycerides, mmol/l	1.82 (1.52–2.06)	1.47 (1.20–1.73)	1.51 (1.21–1.81)	<0.01	<0.01
Total cholesterol, mmol/l	6.88 (6.59–7.17)	4.98 (4.66–5.31)	4.91 (4.61–5.21)	<0.01	<0.01
SBP, mm Hg	131 (126–136)	–	132 (126–138)	–	0.56
DBP, mm Hg	85 (82–87)	–	85 (83–87)	–	0.88
IL-6, pg/ml	22.3 (20.7–24.5)	21.2 (18.9–23.2)	21.1 (19.0–23.3)	0.65	0.55
QUICKY index	0.27 (0.26–0.28)	0.27 (0.26–0.28)	0.28 (0.27–0.29)	0.42	0.49

Data are presented as means with 95% CI in parentheses. SBP = Systolic blood pressure; DBP = diastolic blood pressure.

of declining body fat mass (–0.9 kg, including –0.6 kg of trunk fat mass), while the QUICKY index and blood pressure were stable (table 2).

Plasma adiponectin concentration decreased by 20.7% after 2 months of atorvastatin treatment, but later the suppressive effect declined (fig. 1). Thus, after 6 months, plasma adiponectin concentration did not differ significantly from the initial values (table 1).

Treatment with atorvastatin did not significantly influence either plasma leptin or resistin concentrations at any time point in the protocol (fig. 1).

Correlations

There was no correlation between initial plasma concentrations of adiponectin or resistin and changes in LDL and HDL fractions of cholesterol during the 6-month therapy with a standard 10-mg dose of atorvastatin. However, there was a negative correlation between initial plasma leptin concentration and changes in HDL cholesterol ($R = -0.359$; $p = 0.04$; fig. 2), but not for LDL cholesterol during atorvastatin therapy. There was an even stronger correlation between initial body fat mass and changes in HDL cholesterol ($R = -0.419$; $p = 0.01$), but not with changes in LDL cholesterol.

There was no correlation between changes in LDL and HDL fractions during 6-month atorvastatin therapy. We found a strong positive correlation between initial leptinemia and BMI ($R = 0.408$; $p = 0.031$), total fat mass ($R = 0.433$; $p = 0.013$) and trunk fat mass ($R = 0.396$; $p = 0.025$),

Fig. 1. The influence of 6 months' therapy with atorvastatin on serum LDL and HDL cholesterol and plasma adiponectin, leptin, resistin concentration and QUICKY index in patients with metabolic syndrome. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. baseline.

Fig. 2. The correlation between initial (prior to atorvastatin therapy) plasma leptin concentrations and observed changes in HDL concentration during 6 months' therapy with atorvastatin in patients with metabolic syndrome ($R = -0.359$; $p = 0.04$).

and between the same parameters at the end of the study ($R = 0.411$, $p = 0.030$; $R = 0.447$, $p = 0.010$; $R = 0.457$, $p = 0.001$, respectively). We also observed strong negative correlations between initial leptin concentration and total lean mass ($R = -0.421$; $p = 0.016$) and between the same parameters at the end of the study ($R = -0.431$; $p = 0.016$). For adiponectin, we found a negative correlation with total fat mass at the beginning of the study ($R = -0.352$; $p = 0.035$) and at the end of atorvastatin treatment ($R = -0.337$; $p = 0.044$).

Discussion

This study demonstrates that long-term atorvastatin therapy does not influence plasma concentrations of adiponectin, leptin and resistin in patients with metabolic syndrome. Moreover, we found that plasma leptin concentration determines the HDL cholesterol response during therapy with atorvastatin.

Downregulation of adiponectin expression is potentially harmful for the cardiovascular system; however, as we observed only a transient decrease in plasma adiponectin concentration during atorvastatin therapy, the long-term clinical significance of this change is questionable. This observation is in line with results of *in vitro* studies which revealed that atorvastatin directly downregulated expression of adiponectin in adipocytes [36]. Similarly, *in vitro* atorvastatin downregulated expression

of leptin in adipocytes [36] and resistin in 3T3-L1 adipocytes and human preadipocytes and monocytes/macrophages [37]. The potential effect of atorvastatin on adipocyte metabolic pathways remains unknown.

The mentioned *in vitro* experiments were not supported by clinical studies. Blanco-Colio et al. [26] (in patients with high cardiovascular risk) and Miyagishima et al. [27] (in patients with ischemic heart disease) reported an increase in plasma adiponectin concentration after 3 months' therapy with atorvastatin. The exact reason for the discrepancy between our and the above-quoted studies remains unclear. Perhaps differences in the characteristics of studied populations concerning the status of insulin sensitivity and the low dose of atorvastatin (10 mg per day) are the explanations. Only in the current study did all the patients have metabolic syndrome, and therefore presumably lower insulin sensitivity. As claimed by Huptas et al. [38], even a low dose of atorvastatin, as used by us, is able to cause improvement in insulin sensitivity. Unfortunately, we were unable to prove the increase in insulin sensitivity, and perhaps the lack of it may indirectly explain the unaffected concentration of plasma adiponectin.

In our patients, we did not observe a decline in plasma leptin concentration, which was only reported by von Eynatten et al. [39] in a group of patients with type 2 diabetes mellitus after 8 weeks of atorvastatin therapy. Nevertheless, in this study initial and final body weights were not reported, making the interpretation of the obtained results (39.6% reduction in initial plasma leptin concentration) difficult.

Moreover, we did not find any decline in plasma concentration of resistin followed by atorvastatin therapy, which had previously been reported by Shetty et al. [21] and von Eynatten et al. [39]. Such discrepancies are probably related to the low prescribed dose of atorvastatin (10 mg/day) in our study. Shetty et al. [21] used a dose that was twice as high and found a 16% decrease in plasma resistin levels. Interestingly, a similar decline in plasma resistin concentration was found in the group receiving placebo in the above-mentioned study. Thus, this study did not provide strong evidence of a suppressive effect of atorvastatin on resistin secretion.

An interesting finding is the negative correlation between the initial plasma leptin concentration and the extent of the increase in HDL cholesterol concentration after the 6-month atorvastatin therapy. Such an interrelation has not been previously reported. Thus, the marked increase in HDL cholesterol can be anticipated in patients with lower concentrations of leptin. In the current study,

we have not confirmed the recently published data by van Hoek et al. [16] showing a relationship between baseline plasma adiponectin concentration and changes in plasma HDL cholesterol after atorvastatin treatment. In contrast to HDL cholesterol, neither this study nor that by van Hoek et al. [16] demonstrated the predictive role of plasma adipokine concentrations on LDL cholesterol-lowering efficacy of atorvastatin.

The presented study has several limitations. We used a low dose of atorvastatin as the pleiotropic action of statins is probably not related to the dose. However, we could not prove that higher doses of atorvastatin do not influence the secretion of studied adipokines. Moreover, we were unable to prevent the occurrence of changes in body weight in our group of patients. The observed changes were small but significant. The major limitation of the current study is the lack of a placebo group. Therefore, we are not able to prove whether the transient de-

crease in plasma adiponectin is due to treatment or to other causes. This issue should be studied in future randomized controlled trials.

Conclusion

The long-term effect of atorvastatin therapy is not mediated by changes in the secretion of adiponectin, leptin and resistin by adipose tissue. Plasma leptin concentration seems to be a predictor of HDL cholesterol changes during atorvastatin therapy.

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