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Metabolism Clinical and Experimental 54 (2005) 1225–1229

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

The effect of low-dose atorvastatin on circulating monocyte chemoattractant protein–1 in patients with type 2 diabetes complicated by hyperlipidemia

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Received 8 October 2004; accepted 11 April 2005

Abstract

The effect of low-dose atorvastatin on various biomarkers was investigated in patients with type 2 diabetes complicated by hyperlipidemia. At 0 and 12 weeks in both the atorvastatin group (10 mg/d; n = 17) and the no-drug group (n = 10), high-sensitivity C-reactive protein (hsCRP), monocyte chemoattractant protein (MCP)–1, plasminogen activator inhibitor (PAI)–1, and fibrinogen were measured. At baseline, the entire group of diabetic patients (n = 27) had significantly higher values of hsCRP and fibrinogen compared with those in age-matched healthy subjects (n = 29): 0.801 (0.306, 1.760) vs 0.282 (0.143, 0.6505) mg/L, $P = .0042$; 329.1 ± 55.0 vs 212.4 ± 35.9 mg/dL, $P < .0001$, respectively. High-sensitivity C-reactive protein decreased significantly with atorvastatin treatment, from 0.801 (0.243, 1.865) to 0.308 (0.200, 0.804) mg/L ($P = .0191$). Although MCP-1, PAI-1, and fibrinogen did not decrease in the atorvastatin patients overall, the decrease of MCP-1 was significant in women (n = 10; from 241.9 ± 45.8 to 215.4 ± 49.5 pg/mL, $P = .0332$). No correlation was found between changes in the serum lipid concentrations and changes in hsCRP, MCP-1, PAI-1, or fibrinogen in either the atorvastatin or the no-drug group. In conclusion, low-dose atorvastatin (10 mg/d) significantly decreased hsCRP in patients overall, and MCP-1 was also decreased in women. These findings suggest the possibility that atorvastatin provides an anti-inflammatory effect even at a low dose.

1. Introduction

There is evidence that patients with diabetes exhibit elevated serum levels of high-sensitivity C-reactive protein (hsCRP) [1,2], pro-inflammatory cytokines, including interleukin (IL) 6 [3], which stimulate the production of hsCRP in the liver [4], and chemokines such as monocyte chemoattractant protein (MCP)–1 [5,6], which has an important role in atheroma formation, attracting monocytes to atherosclerotic lesions [7,8]. Furthermore, it is known that the plasminogen activator inhibitor (PAI)–1, which regulates fibrinolysis, is also elevated in diabetes [9]. Although the mechanisms for the elevation of these risk factors in the cardiovascular events [5,10] which occur in diabetic patients have yet to be elucidated, because these cytokines and chemokines are mainly regulated by nuclear factor κB (NFκB) [11,12] and hyperglycemia can activate NFκB via oxidative stress [13], the activation of NFκB might be postulated to cause, at least in part, these elevations and the subsequent one of hsCRP.

On the other hand, the statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, antihyperlipidemic drugs) have been reported to inhibit NFκB activation [14] as well as to decrease hsCRP [15,16]. Thus, especially in patients with diabetes complicated by hyperlipidemia, statins might provide a particularly beneficial effect for the inhibition of cardiovascular events in diabetic patients. Very recently it was reported in the Collaborated Atorvastatin in Diabetes Study (CARDS) that a low dose of atorvastatin (10 mg/d) remarkably decreases cardiovascular events, even in type 2 diabetic patients without an elevated serum level of high low-density lipoprotein cholesterol (LDL-C) [17]. Although the beneficial results reported in CARDS do suggest the importance of maintaining LDL-C at very low values,

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doi:10.1016/j.metabol.2005.04.008

simultaneously these beneficial results have been hypothesized to be attributable to pleiotropic effects of statins beyond the known cholesterol-lowering effect.

However, to the best of our knowledge, in patients with type 2 diabetes, there are to date only a few reports that suggest low-dose atorvastatin decreases serum hsCRP [18,19], and no report of atorvastatin effects on serum MCP-1. Therefore, we tested the hypothesis that atorvastatin can reduce MCP-1 as well as hsCRP independently of serum lipid concentrations even at a low dose (10 mg/d) in patients with type 2 diabetes. In addition, the effects of atorvastatin on PAI-1 and fibrinogen were also investigated.

2. Patients and methods

2.1. Patients

At the study outset, 30 type 2 diabetic outpatients with hyperlipidemia were enrolled. Patients with a total cholesterol (TC) of more than 220 mg/dL or triglyceride (TG) of more than 150 mg/dL were defined as having hyperlipidemia, based on the Japanese Atherosclerosis Society guidelines for the diagnosis and treatment of atherosclerotic cardiovascular disease [20].

Three patients treated with atorvastatin were disqualified halfway through the study because of poor compliance on follow-up, leaving a total of 27 patients, 12 men and 15 women. The 17 patients assigned to the atorvastatin group included 7 men and 10 women. In the atorvastatin group, 14 patients had been managed with sulfonylureas (glibenclimide, glimepiride, or gliclazide) and 3 patients kept under observation with dietary modifications. Only 3 patients had been given antihypertensive drugs, with 1 taking an angiotensin-converting enzyme inhibitor and 2 taking a calcium channel blocker.

In the no-drug group, 6 of 10 patients were taking the previously mentioned sulfonylureas and 4 patients were treated with dietary modification. Three patients took antihypertensive drugs, with 1 receiving an angiotensin II receptor blocker and 2 taking a calcium channel blocker in addition to an angiotensin II receptor blocker.

In both groups, any patient exhibiting evidence of liver or renal dysfunction, or findings of infectious or autoimmune disease, was excluded from the study. Any patient already being treated with antilipidemic drugs, including the statins, was also excluded.

In addition, 29 age-matched healthy subjects without diabetes or hyperlipidemia were also examined to obtain clinical features and various biomarkers at baseline.

The characteristics of the 27 diabetic patients (17 in the atorvastatin group and 10 in the no-drug group) and 29 healthy subjects are presented in Table 1.

2.2. Methods

Patients were randomly assigned to the atorvastatin administration group (10 mg/d: initial n = 20) or the no-drug group (n = 10). To minimize the potential effects of bias on the part of physicians who participated in this study, each of the 10 physicians supervised only 3 subjects (2 in the atorvastatin group and 1 in the no-drug group, chosen at random). No change was made in the administration of any drug in any patient during the 12 weeks (3 months) of investigation.

In all patients, blood was sampled in the outpatient department between 8:30 and 9:30 AM after at least 10 hours of overnight fasting. At the time of blood sampling, patients were weighed while wearing only their underwear.

In this study, the degree of change in a variable between 2 time points was defined as the ratio of the value at the second time point to the value at the first time point.

2.3. Serum hsCRP assay

Sera were stored at −70°C until analysis. A BN II N High Sensitivity CRP assay (Dade Behring, Marburg, Germany) was used. The lowest detectable concentration of hsCRP was 0.05 mg/L. The intra- and interassay coefficient of variation (CV) in this assay were 1.72% and 2.80%. In the current study, hsCRP values were logarithmically transformed because of a skewed distribution when the correlations with other variables were considered. To avoid hsCRP values becoming negative upon logarithmic transformation, only in the case that hsCRP was log-transformed, the result was expressed as nanograms per milliliter, not milligrams per liter.

2.4. Serum MCP-1 assay

The same sera in which hsCRP was also measured were used for measurement of MCP-1 using an enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, Minn). The minimum detectable dose of MCP-1 typically was less than 5.0 pg/mL. The intra- and interassay CV for MCP-1 were 4.9% to 7.8% and 4.6% to 6.7%.

2.5. Measurement of plasma PAI-1 and fibrinogen

The plasma concentration of PAI-1 was measured by an enzyme-linked immunosorbent assay (Biopool Immulyse PAI-1; Biopool, Umea, Sweden) that detected both active and latent PAI-1, as well as PAI-1 bound to tissue plasminogen activator. The intra- and interassay CV were 2.26% to 3.77% and 3.57% to 4.76%. Plasma fibrinogen was measured using fibrinogen determination reagents (Dade Behring) based on the von Claus method [21]. The CV was less than 15%.

2.6. Measurement of plasma glucose, hemoglobin A1C, and serum lipid concentrations

Fasting plasma glucose (FPG) was evaluated by an automated glucose oxidase method (Glucose Auto Stat GA1160; Arkray, Kyoto, Japan). Hemoglobin (Hb) A_{1C} was measured by high-performance liquid chromatography (Hi-auto A_{1C}, HA8150; Arkray). With this method, only HbA_{1C} was detected, and the reference range was 4.3% to 5.8%.

Table 1
Clinical characteristics of the age-matched healthy control subjects and diabetic patients

	Nondiabetic patients	Diabetic patients	Atorvastatin	No drugs	P^a	P^b
n (male/female)	29 (12/17)	27 (12/15)	17 (7/10)	10 (5/5)	–	–
Age (y)	60.7 ± 4.7	58.7 ± 8.5	61.3 ± 5.3	54.3 ± 11.3	.2823	.0922
Duration (y)	–	9.0 ± 5.3	9.5 ± 4.9	8.3 ± 6.2	–	.5906
FPG (mmol/L)	5.240 ± 0.705	8.177 ± 1.543	8.021 ± 1.500	8.400 ± 1.700	<.0001*	.5054
HbA_{1C} (%)	4.8 ± 0.2	7.4 ± 1.6	7.4 ± 1.5	7.3 ± 2.0	<.0001*	.8820
TC (mg/dL)	189.6 ± 20.2	253.7 ± 36.2	260.7 ± 40.1	241.6 ± 26.1	<.0001*	.0848
HDL-C (mg/dL)	63.1 ± 16.1	54.6 ± 12.8	57.2 ± 11.2	50.2 ± 14.9	.0351*	.1751
LDL-C (mg/dL)	94.4 ± 20.6	165.6 ± 22.9	170.5 ± 21.7	157.1 ± 23.3	<.0001*	.1438
TG (mg/dL)	88.3 ± 29.2	147.8 ± 91.7	124.6 ± 74.4	187.2 ± 108.3	.0030*	.0868
BMI (kg/m^2)	24.0 ± 2.2	25.1 ± 3.0	24.9 ± 3.1	25.5 ± 3.1	.1197	.6238
IRI (pmol/L)	62.2 ± 25.2	111.0 ± 116.4	84.6 ± 89.4	157.1 ± 122.0	.0700	.1177
SBP (mm Hg)	121.4 ± 7.8	123.5 ± 11.9	124.3 ± 12.2	122.2 ± 11.8	.4478	.6662
DBP (mm Hg)	69.4 ± 4.3	69.5 ± 6.5	70.6 ± 6.4	67.6 ± 6.7	.7636	.2588
MCP-1 (pg/mL)	239.4 ± 30.0	243.6 ± 53.8	251.2 ± 51.9	221.4 ± 54.7	.7219	.1704
PAI-1 (mg/dL)	24.0 ± 5.7	27.3 ± 20.4	24.0 ± 16.9	33.7 ± 24.7	.4241	.2360
Fib (mg/dL)	212.4 ± 35.9	329.1 ± 55.0	337.2 ± 56.9	315.3 ± 51.3	<.0001*	.3262
CRP (mg/L)	0.282 (0.143, 0.6505)	0.801 (0.306, 1.760)	0.801 (0.243, 1.865)	0.739 (0.29025, 2.0625)	.0042*	.3626

Data except for hsCRP are expressed as mean ± SD. Data for hsCRP are expressed as median with interquartile range.
[a] P value for 29 control subjects vs 27 diabetic patients.
[b] P value for 17 patients in the atorvastatin group vs 10 in the non-drug group.
* $P < .05$ is defined as statistical significance.

The plasma insulin concentration was determined by radioimmunoassay. Serum TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), and TG concentrations were measured enzymatically.

2.7. Ethical considerations

All subjects gave informed consent to be included in the present study, which was performed according to the guidelines proposed in the Declaration of Helsinki.

2.8. Statistical methods

All data except for hsCRP are presented as the mean ± SD. Data for hsCRP are expressed with a median and interquartile range (25th and 75th percentiles). The significance of correlations between 2 variables was determined by simple regression analysis. Except for the case of hsCRP, 2 time points for an individual were compared using a paired t test. For hsCRP, Wilcoxon signed rank test as a nonparametric test was used. Comparisons between the 2 groups except for hsCRP were made using an unpaired t test after group normality had been confirmed by a χ^2 test; Student t test or Welch t test was chosen based on the homogeneity of variance calculated by F test. For hsCRP, Wilcoxon rank sum test was used. A P value of less than .05 was accepted as indicating statistical significance.

3. Results

Diabetic patients (17 in the atorvastatin group and in 10 the no-drug group) were found to have high values of hsCRP and fibrinogen compared with these values in 29 age-matched healthy subjects (Table 1). Furthermore, for each measured variable, no significant difference was detected between the atorvastatin and no-drug groups (Table 1). Between each combination of hsCRP, MCP-1, PAI-1, and fibrinogen at baseline and 3 months, no correlations were observed (data not shown).

The 17 patients in the atorvastatin group showed a significant decrease in hsCRP after 3 months of treatment ($P = .0191$). Although the mean MCP-1 did not change overall, a significant decrease in MCP-1 was noted in women ($P = .0332$) (Table 2). Between the hsCRP values after atorvastatin therapy and in healthy subjects, there were no significant differences: 0.308 (0.200, 0.804) vs 0.282 (0.143, 0.6505) ($P = .1398$).

In the no-drug treatment group, no significant change in FPG, HbA_{1C}, TC, LDL-C, HDL-C, TG, body mass index (BMI), immunoreactive insulin (IRI), systolic blood pressure (SBP), or diastolic blood pressure (DBP) was noted during the 3-month observation period. No change occurred in hsCRP, MCP-1, PAI-1, or fibrinogen between the 2 time points in the entire group of 10 subjects, in the case of both men and women (data not shown).

In both the atorvastatin and no-drug treatment groups, the degree of change in log hsCRP, MCP-1, PAI-1, or fibrinogen did not correlate with the degree of change in BMI, FPG, HbA_{1C}, TC, TG, HDL-C, LDL-C, IRI, SBP or DBP, respectively. A significant negative correlation was noted between the degrees of change in MCP-1 and the change in log hsCRP in the group of 17 patients treated with atorvastatin ($r = -0.5222$, $P = .0316$). However, when the patients were classified by sex, the significant correlation was evident in men but not in women ($r = -0.9612$, $P = .0006$; $r = -0.0676$, $P = .8528$, respectively). Furthermore, in the entire 17 patients, the degree of change in log hsCRP was negatively correlated with PAI-1 and positively correlated with fibrinogen ($r = -0.5339$, $P = .0273$; $r = 0.5593$,

Table 2
Changes in various variables at baseline and 3 months after atorvastatin therapy

	Baseline	3 mo	*P*
CRP (mg/L)			
Total (17)	0.801 (0.243, 1.865)	0.308 (0.200, 0.804)	.0191*
Men (7)	0.801 (0.164, 1.090)	0.233 (0.200, 0.826)	.4990
Women (10)	0.631 (0.2745, 2.200)	0.3895 (0.22625, 0.984)	.0284*
MCP-1 (pg/mL)			
Total (17)	251.2 ± 51.9	240.9 ± 53.5	.3880
Men (7)	264.4 ± 60.8	277.4 ± 36.0	.5706
Women (10)	241.9 ± 45.8	215.4 ± 49.5	.0332*
PAI-1 (mg/dL)			
Total (17)	24.0 ± 16.9	26.5 ± 12.5	.4286
Men (7)	20.0 ± 17.1	23.1 ± 13.8	.3559
Women (10)	26.8 ± 17.0	28.9 ± 11.7	.6823
Fibrinogen (mg/dL)			
Total (17)	337.2 ± 56.9	338.9 ± 47.9	.8866
Men (7)	324.1 ± 71.5	314.4 ± 47.9	.6150
Women (10)	346.4 ± 46.1	356.0 ± 42.0	.5306
FPG (mmol/L)	8.021 ± 1.500	8.438 ± 2.198	.2355
HbA_{1C} (%)	7.4 ± 1.5	7.6 ± 1.6	.0758
TC (mg/dL)	260.8 ± 40.1	179.6 ± 25.6	<.0001*
TG (mg/dL)	124.6 ± 74.4	93.2 ± 52.1	.0711
HDL-C (mg/dL)	57.2 ± 11.2	62.1 ± 10.7	.0045*
LDL-C (mg/dL)	170.5 ± 21.7	101.1 ± 30.0	<.0001*
BMI (kg/m^2)	24.9 ± 3.1	25.0 ± 2.8	.3256
IRI (pmol/L)	84.6 ± 107.4	63.6 ± 51.0	.4458

Values in parentheses are the number of the patients. Data except for hsCRP are expressed as mean ± SD. Data for hsCRP are expressed as median with interquartile range. Except hsCRP, MCP-1 PAI-1, fibrinogen, all data are based on total 17 diabetic patients.

* $P < .05$ is defined as statistical significance.

$P = .0195$, respectively). On the other hand, in the 10 no-drug subjects, the degrees of change in log hsCRP did not correlate with those in MCP-1, PAI-1, or fibrinogen (data not shown).

4. Discussion

In the current study, the data show that low-dose atorvastatin (10 mg/d) lowered hsCRP independently of effects on the serum lipid concentration, in agreement with recent reports [18,19]. We also confirmed an elevated hsCRP in diabetic patients compared with those in healthy subjects, which finding is also compatible with those in previous reports [1,2]. Because the data suggested the possibility that in type 2 diabetic patients, atorvastatin decreases the elevated hsCRP to levels near the hsCRP in healthy subjects even at the same low dose used in CARDS, we hypothesized that the beneficial effects of atorvastatin shown in CARDS might be at least partially afforded by the anti-inflammatory effects of the drug. Interestingly, decreases of hsCRP were evident in women. However, because a study with a large number of patients using a high dose of another statin (pravastatin) has shown the statin to also reduce hsCRP in men [16], we speculate that the absence of a decrease in hsCRP in men in the current study was most likely due to the small sample size of the study.

As far as we have been able to determine, this is the first report of the effects of atorvastatin on circulating MCP-1 in patients with type 2 diabetes, although one previous report did mention that atorvastatin reduced circulating MCP-1 in patients with acute coronary syndrome [22]. Monocyte chemoattractant protein–1 in the entire group of patients did not decrease significantly in the current study. However, although it is speculative, because MCP-1 in the diabetic patients studied did not exhibit any significant elevation compared with healthy subjects, which was different from the results of previous reports [5,6], if patients with more strikingly elevated MCP-1 had been included in this study, a more evident decrease of MCP-1 might have been observed. Furthermore, the decrease of MCP-1 did reach statistical significance in women. A recent report has provided evidence that circulating MCP-1 may be a useful predictor of cardiovascular events in middle-aged women [6]. Accordingly, although the exact reason for the sex-related difference cannot be determined, these results suggest the possibility that atorvastatin therapy may afford particular clinical benefit for women. Nevertheless, it must be emphasized that these are tentative findings because of the limitation of the sample size, and additional study will be needed to draw any sort of conclusion.

We also investigated the correlation between the change in hsCRP and that of MCP-1 before and after atorvastatin therapy. It is known that in diabetes, pro-inflammatory cytokines such as IL-6 are elevated, and that there is a subsequent increase of hsCRP, which is at least partially because of the activation of NFκB due to hyperglycemia [3,23]. High-sensitivity C-reactive protein can assist in the induction of MCP-1 or PAI-1 in vascular endothelial cells [24,25]. Furthermore, MCP-1 can also likely increase the expression by the activation of NFκB based on hyperglycemia [12,13], and in addition, the local macrophages attracted by MCP-1 would in turn produce pro-inflammatory cytokines such as IL-6. Thus, because of the possible cellular interaction of these biomarkers and factors, we expected not only to see significant positive associations between these at baseline, but also significant positive associations between the changes in these markers brought about by atorvastatin. However, contrary to our expectation, we found no relationship between these markers at baseline. In addition, although we found a negative, not positive, correlation between the change of hsCRP and that of MCP-1, we should note that the significant relationship disappeared when it was considered only in women, in whom the atorvastatin was effective for the decrease of MCP-1. This may suggest the possibility that happened to be observed because of the small sample size of this study. Furthermore, hsCRP failed to correlate with MCP-1 not only before but also after treatment. Taken together, these results might suggest that the responses of these biomarkers to atorvastatin differ and that their cellular interactions are rather weak in vivo.

In conclusion, in this study, type 2 diabetic patients with the complication of hyperlipidemia administered with 10 mg/d atorvastatin were found to have decreases in their serum hsCRP to levels near to those seen in healthy subjects. Furthermore, in women, atorvastatin also decreased serum MCP-1. These findings suggest that atorvastatin may provide anti-inflammatory effects even at a low dose.

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