Atorvastatin Administration after Percutaneous Coronary Intervention in Patients with Coronary Artery Disease and Normal Lipid Profiles: Impact on Plasma Adiponectin Level

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ABSTRACT

Background: There is controversy about the effects of statins on plasma adiponectin, and the impact of percutaneous coronary intervention (PCI) on plasma adiponectin level is still unknown. We investigated the impact of Atorvastatin on plasma adiponectin levels in coronary artery disease (CAD) patients with stable angina and normal lipid profiles after PCI.

Methods: Sixty CAD patients with stable angina and normal lipid profiles scheduled for PCI, and not on statins, were randomly assigned to either no treatment (control group) or the Atorvastatin treatment (Atorvastatin group). Atorvastatin administration was started immediately after PCI. Blood samples were obtained immediately after PCI and again 3 and 6 mo later. Fasting plasma adiponectin concentrations were measured using a radioimmunoassay kit.

Results: After PCI, there were statistically significant decreases in adiponectin levels in the Atorvastatin group at 3 and 6 mo (8.66 ± 0.69 versus 6.87 ± 0.55 and 7.12 ± 0.71 $\mu\text{g/mL}$ at 0, 3, and 6 mo, respectively), despite the anti-inflammation and lipid-lowering effects of Atorvastatin. There were no statistically significant changes in adiponectin levels in the control group. There was significant positive association between baseline plasma adiponectin and high-density lipoprotein (HDL) levels. Changes of adiponectin level were not associated with the changes of high-sensitivity C-reactive protein (hs-CRP) and lipid profiles in the Atorvastatin group.

Conclusions: Our study confirmed the benefits of Atorvastatin on anti-inflammation and anti-atherosclerosis, but we also found that Atorvastatin had a negative effect on the adiponectin system. The anti-inflammatory, anti-atherogenic effects of Atorvastatin are not affected by decreased adiponectin levels.

Key words: atorvastatin, adiponectin, coronary artery disease, percutaneous coronary intervention

Introduction

Adiponectin, a 244-amino acid adipocyte-derived protein accounting for approximately 0.01% of total plasma protein, with concentrations ranging between 4.8 and 34.7 $\mu\text{g/mL}$, was recently revealed to have anti-inflammatory, antidiabetic, and anti-atherogenic properties.^{1–10} Plasma adiponectin concentrations were found to decrease in individuals with obesity, type 2 diabetes mellitus (DM), and coronary artery disease (CAD), while improvement of insulin sensitivity by either weight reduction⁵ or administration of thiazolidinediones was associated with increased adiponectin concentrations.^{11–13} Adiponectin levels have also been found to be lower in adult men than in adult women, and downregulation of adiponectin by androgens, which has been observed in animal models, may explain these differences.⁴ Previous studies showed that plasma

adiponectin levels are negatively correlated with triglyceride and low-density lipoprotein (LDL) cholesterol, and positively correlated with high-density lipoprotein (HDL) cholesterol.^{14,15} Beyond lowering lipid levels, statins have favorable effects on endothelial function via stimulation of nitric oxide (NO) synthase activity and mediate antioxidant effects that result in enhanced NO bioactivity,^{16,17} platelet adhesion,¹⁸ thrombosis,^{19,20} plaque stability, and inflammation,^{21–25} which may improve outcomes after percutaneous coronary intervention (PCI). However, there is controversy about the effects of statins on plasma adiponectin, and the impact of PCI on plasma adiponectin is still unknown. In our study, we investigated the impact of Atorvastatin, a powerful 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor²⁶ on plasma adiponectin levels in patients with CAD and normal lipid profiles after PCI.

Materials and Methods

Patients and Study Protocol

Sixty CAD patients with stable angina and normal lipid profiles scheduled for PCI (balloon angioplasty and stenting), and who were not taking statins were randomly assigned to either no treatment (control group) or to Atorvastatin (10 mg) treatment (Atorvastatin group). No cardiovascular events happened after completion of the treatment, and all patients were recommended to continue with statin treatment. The criteria for CAD was a 75% or greater stenosis of at least 1 segment of a major coronary artery confirmed by quantitative coronary angiography by perpendicular projections. Low dose of Atorvastatin (10 mg) administration was started immediately after PCI in the Atorvastatin group. Patients of both groups were also suggested diet control for dyslipidemia in addition to medical treatment. Blood samples were obtained immediately after coronary intervention, and again 3 and 6 mo later, each sample being acquired after the patient had undergone an overnight fast. The Ethics Committee of the Chung Shan Medical University Hospital approved the study, and all patients gave written informed consent. Patients who took any antihyperlipidemic drugs, thiazolidinediones, angiotensin II receptor blocking (ARB) agents, or angiotensin-converting enzyme inhibitors (ACE-I) were excluded from this study. We used sulfonylurea to control DM.

Laboratory Analysis

Blood samples for the measurement of overnight fasting plasma adiponectin concentrations were drawn into pre-chilled ethylenediamine tetracetic acid (EDTA)-containing tubes and immediately placed on ice. All tubes were centrifuged within 10 min of collection and stored at -70°C until assay. Fasting plasma adiponectin concentrations were measured using a radioimmunoassay kit specific for human adiponectin (HADP-61 HK, LINCO Research, St. Charles, MO, USA) after 1:500 dilution. Samples were analyzed in 2 batches, with an intra-assay coefficient of variation $<5\%$ and inter-assay coefficient of variation $<8\%$ for duplicates over a range of adiponectin concentrations. We used the enzymatic color test (Jaffe method) to measure plasma triglyceride, total cholesterol, HDL, and LDL levels; the scatter-light method to measure fibrinogen; and particle-enhanced immuno-nephelometry to measure plasma high-sensitivity C-reactive protein (hs-CRP) levels.

Statistical Analysis

For constructing a reasonable comparison basis, baseline characteristics of the 2 regimen arms in this trial were statistically examined by chi-square tests for categorical variables and independent *t*-test for continuous variables. Paired *t*-tests were also used for testing the differences before and after Atorvastatin treatment by follow-up periods. Linear regression was used to test whether the changes

of lipid profiles and hs-CRP were related to adiponectin level changes during the 6-mo follow-up period, separately for treatment and control groups. The SPSS 12.0 software for windows was used to perform all the analyses (SPSS Inc., Chicago, Ill., USA). A *p*-value <0.05 was considered statistically significant.

Results

The demographic data for the study patients are presented in Table 1. None of the baseline characteristics was significantly different from each other in our small sample size of both groups. As shown in Table 2, there were statistically significant decreases in total cholesterol and LDL levels, but no statistically significant differences in HDL, triglyceride, and fibrinogen levels in the Atorvastatin group over the 6 mo of the study. In contrast, the control group showed statistically significant increases in LDL and HDL levels, but no statistically significant differences in total cholesterol, triglyceride, and fibrinogen levels. The hs-CRP levels of both groups were decreased, but only levels in the Atorvastatin group decreased significantly, especially 3 mo after treatment. The plasma adiponectin levels decreased significantly in the Atorvastatin group after 3 and 6 mo of PCI and Atorvastatin treatment, whereas in the control group, the plasma adiponectin levels have no significant changes 3 and 6 mo after PCI. As shown in Table 3, there was significant positive association between baseline plasma adiponectin level and baseline plasma HDL level, and there was also a trend of negative association between baseline plasma adiponectin level and baseline plasma hs-CRP level. As shown in Table 4, we tested the associations between changes of plasma adiponectin levels and changes of hs-CRP, triglyceride, total cholesterol, HDL, LDL, and fibrinogen levels during the 6 mo of follow-up, and found that there was no association between changes of the plasma adiponectin levels and changes of other variables in the Atorvastatin group.

Discussion

Plasma adiponection accumulates in the vascular wall when the endothelial barrier is injured.²⁷ It has been reported that adiponectin inhibits monocyte adhesion to endothelial cells and macrophage-derived foam cell transformation, and attenuates tumour necrosis factor (TNF)- α -induced expression of adhesion molecules in endothelial cells, which is the initial step of atherosclerosis.^{2,5,6,28} As we know, the vascular injury from coronary angioplasty and stent placement induces platelet activation, thrombosis, and inflammation within the vessel wall and the distal microvasculature, and it has been demonstrated that the measurement of adiponectin could not predict angiographic restenosis after elective coronary stenting.²⁹

TABLE 1: Baseline characteristics of study subjects randomly assigned to Atorvastatin group (n = 30) and control group (n = 30)

Variable	Number/mean (standard deviation)		p-value ^a
	Atorvastatin (n = 30)	Control (n = 30)	
Gender (male; female)	24; 6	19; 11	0.15
DM (yes; no)	10; 20	9; 21	0.78
Age (ages)	66.13 (11.50)	63.77 (12.73)	0.45
BMI (kg/m ²)	25.86 (2.51)	25.12 (2.48)	0.26
Plasma adiponectin level (μg/mL)	8.66 (3.79)	8.80 (3.74)	0.89
hs-CRP (mg/L)	0.89 (1.16)	0.71 (0.88)	0.50
Triglyceride (mg/dL)	163.57 (123.48)	168.80 (107.70)	0.86
Total cholesterol (mg/dL)	195.13 (36.32)	193.57 (41.31)	0.88
HDL (mg/dL)	40.97 (8.16)	38.77 (8.86)	0.32
LDL (mg/dL)	128.67 (28.80)	123.93 (37.78)	0.59
Fibrinogen (mg/dL)	302.81 (53.67)	330.17 (89.77)	0.16
Medications			
Aspirin (100 mg/day)	30/30	30/30	NS
Clopidogrel (75 mg/day)	30/30	30/30	NS
Beta-blocker	24/30	22/30	NS
Calcium-channel blocker	22/30	19/30	NS
Nitrate	24/30	26/30	NS
Sulfonylurea	10/10	9/9	NS

^aChi-square tests for categorical data and independent *t*-tests for continuous variables. *Abbreviations:* BMI = body mass index; DM = diabetes mellitus; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; NS = nonsignificant.

Atherosclerosis is thought to be a chronic inflammatory disorder and statins are recognized as powerful anti-inflammatory agents that exert beneficial effects beyond their lipid-lowering effect. Improvement of endothelial function is thought to be a primary mechanism responsible for these anti-inflammatory properties.³⁰ It has also been shown by multiple large-scale clinical trials that statin therapy lowers morbidity and mortality in CAD and other atherosclerotic vascular diseases.^{31–34}

Losartan, an angiotensin II antagonist, was shown to increase plasma adiponectin levels and insulin sensitivity

in the treatment of hypercholesterolemic and hypertensive patients.³⁵ However, this beneficial effect of Losartan did not increase further in combination therapy with Simvastatin. On the contrary, Simvastatin alone was shown to decrease plasma adiponectin levels, although not significantly.³⁵ Ramipril alone, an angiotensin-converting enzyme inhibitor, or combined therapy with Simvastatin, were shown to increase plasma adiponectin levels, and this change was significantly greater than in the group treated with Simvastatin alone in patients with type 2 diabetes.³⁶ Fenofibrate alone, or combined therapy with Atorvastatin, were also shown

TABLE 2: Changes of parameters with and without Atorvastatin treatment in patients after PCI

Timing Atorvastatin	Initial		3rd mo		6th mo	
parameters	+	−	+	−	+	−
Adiponectin ($\mu\text{g/mL}$)	8.66 $\pm$ 0.69	8.80 $\pm$ 0.68	6.87 $\pm$ 0.55***	8.93 $\pm$ 0.66	7.12 $\pm$ 0.71**	8.89 $\pm$ 0.64
hs-CRP (mg/L)	0.89 $\pm$ 0.21	0.71 $\pm$ 0.16	0.19 $\pm$ 0.04**	0.49 $\pm$ 0.11	0.21 $\pm$ 0.04**	0.48 $\pm$ 0.13
Triglyceride (mg/dL)	163.57 $\pm$ 22.54	168.8 $\pm$ 19.66	176.00 $\pm$ 33.27	149.13 $\pm$ 12.76	183.10 $\pm$ 45.69	156.77 $\pm$ 16.94
Total cholesterol (mg/dL)	195.13 $\pm$ 6.63	193.57 $\pm$ 7.54	150.57 $\pm$ 4.96***	204.63 $\pm$ 8.19	152.47 $\pm$ 6.14***	204.4 $\pm$ 8.08
HDL (mg/dL)	40.97 $\pm$ 1.49	38.77 $\pm$ 1.62	42.17 $\pm$ 1.57	46.13 $\pm$ 2.18 ⁺⁺	42.77 $\pm$ 1.99	44.57 $\pm$ 1.77 ⁺⁺
LDL (mg/dL)	128.67 $\pm$ 5.26	123.93 $\pm$ 6.90	89.13 $\pm$ 3.81***	136.8 $\pm$ 7.10 ⁺	87.30 $\pm$ 4.20***	137.3 $\pm$ 7.01
Fibrinogen (mg/dL)	302.81 $\pm$ 9.80	330.17 $\pm$ 16.39	303.08 $\pm$ 8.26	316.57 $\pm$ 12.82	302.69 $\pm$ 11.24	316.96 $\pm$ 10.94

Data: mean $\pm$ standard error. Significant differences compared in patients with Atorvastatin were shown as * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$. Significant differences compared in patients without Atorvastatin were shown as + $p < 0.05$ and ++ $p < 0.01$. +: with Atorvastatin treatment. −: without Atorvastatin treatment. Abbreviations: HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.

TABLE 3: The comparison of determinants for baseline plasma adiponectin level by linear regression^a

	Baseline adiponectin level (95% CI)
Baseline hs-CRP (mg/L)	−0.35 (−1.20, 0.51)
Baseline triglyceride (mg/dL)	0.00 (−0.01, 0.01)
Baseline total cholesterol (mg/dL)	0.00 (−0.02, 0.03)
Baseline HDL (mg/dL)	0.10 (0.00, 0.20)*
Baseline LDL (mg/dL)	0.01 (−0.02, 0.03)
Baseline fibrinogen (mg/dL)	−0.00 (−0.01, 0.01)

^aAdjusted by gender, age, and BMI. * p -value < 0.05 . Abbreviations: BMI = body mass index; CI = confidence interval; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.

to increase plasma adiponectin levels, and this change was also significantly greater than in the group treated with Atorvastatin alone in patients with combined hyperlipidemia.³⁷

Treatment with Atorvastatin at a dose of 10 mg/d in kidney transplant recipients for 12 wk does not modify adiponectin, CRP, and TNF- α , despite its hypolipemic effects.³⁸ Pravastatin does not affect the adiponectin levels in healthy nondiabetic patients.³⁹ In Japanese patients with CAD and hypercholesterolemia, 6 mo of treatment with Pravastatin 10 to 20 mg/d was associated with significant increases in serum adiponectin concentrations.⁴⁰ Fluvastatin does not improve plasma adiponectin levels, despite its beneficial effects on lipid levels.⁴¹ From these results, it appears that Simvastatin, Atorvastatin, and Fluvastatin cannot increase plasma adiponectin levels when used in patients with hyperlipidemia, type 2 diabetes, or kidney transplant patients, and the impact of Pravastatin on plasma adiponectin is controversial.

In this study, we found that hs-CRP levels of both groups were decreased, but only levels in the Atorvastatin group decreased significantly, especially 3 mo after treatment, which further confirms the anti-inflammation effect of Atorvastatin. We also found that PCI alone has no effect on plasma adiponectin levels in patients with CAD, whereas administering Atorvastatin to patients who had received PCI decreases plasma adiponectin levels after 3 and

TABLE 4: The comparison of determinants for plasma adiponectin level change from baseline to the sixth mo of follow-up by linear regression^a

Variable level changes	Adiponectin level change 0–3 mo (95% CI)		Adiponectin level change 0–6 mo (95% CI)	
	Atorvastatin	Control	Atorvastatin	Control
hs-CRP (mg/L)	−0.36 (−1.17, 0.45)	−0.68 (−1.12, −0.23)*	−0.49 (−1.40, 0.43)	−0.42 (−1.17, 0.34)
Triglyceride (mg/dL)	0.00 (−0.00, 0.01)	0.00 (−0.01, 0.01)	−0.00 (−0.01, 0.00)	−0.00 (−0.01, 0.00)
Total cholesterol (mg/dL)	0.01 (−0.02, 0.04)	0.01 (−0.00, 0.02)	−0.01 (−0.05, 0.03)	−0.00 (−0.02, 0.02)
HDL (mg/dL)	−0.01 (−0.16, 0.06)	0.04 (−0.01, 0.09)	0.02 (−0.07, 0.12)	0.07 (−0.02, 0.16)
LDL (mg/dL)	0.01 (−0.02, 0.04)	0.02 (0.00, 0.03)*	0.00 (−0.03, 0.04)	0.00 (−0.02, 0.02)
Fibrinogen (mg/dL)	0.00 (−0.02, 0.02)	−0.00 (−0.01, 0.00)	0.00 (−0.01, 0.02)	−0.00 (−0.01, 0.01)

^aAdjusted by gender, age, and BMI. *p-value <0.05. *Abbreviations:* BMI = body mass index; CI = confidence interval; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.

6 mo of treatment, despite the lipid-lowering and anti-inflammatory effects of Atorvastatin. Although the reciprocal association of adiponectin and CRP in CAD patients had been shown before,⁴² we found that changes of plasma adiponectin levels were not associated with the changes of hs-CRP and lipid profiles during 6 mo of follow-up in the Atorvastatin group. Hence, the anti-inflammatory and anti-atherogenic effects of Atorvastatin are probably not affected by decreased adiponectin levels. One animal study revealed that Atorvastatin attenuates adipocyte maturation and impairs glucose tolerance, and these actions of Atorvastatin could potentially affect the control of type 2 diabetes.⁴³ Another animal study also revealed that Pravastatin, but not Atorvastatin, enhances the adiponectin mRNA expression in white adipose tissue that prevents new-onset diabetes.⁴⁴ Our study further confirmed these 2 animal studies that Atorvastatin has a negative effect on the adiponectin system.

In accordance with the results of many prospective statin trials, statin treatment is safe and rescues life-years due to its effects of anti-inflammation and anti-atherosclerosis. To our knowledge, this is the first human study to reveal that Atorvastatin treatment after PCI has a negative effect on the adiponectin system, and the anti-inflammatory and anti-atherogenic effects of Atorvastatin are not affected by decreased adiponectin levels. The beneficial effects of Atorvastatin on anti-inflammation and anti-atherosclerosis could counteract the negative effects on adiponectin.

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