Statin Therapy

Statin Therapy on Insulin Resistance and Plasma Level of Adiponectin in Non-Diabetic, Hypercholesterolemic Patients

Philip Yu-An Ding, Pai-Feng Hsu and Tse-Min Lu

Background: Adiponectin is an adipocyte-derived plasma protein with various anti-atherogenic properties. However, the effect of statins on insulin sensitivity and plasma level of adiponectin remains controversial.

Methods: Forty-eight non-diabetic, hypercholesterolemic patients were enrolled and assigned to statin treatment (atorvastatin 10 or 40 mg) group (n = 27) or no statin treatment group (n = 21). In addition, another 20 age- and sex-matched non-diabetic, normocholesterolemic patients were enrolled as control group. Insulin sensitivity (indicated by HOMA index) and plasma level of adiponectin were determined before and 6 weeks after treatment in all patients.

Results: The HOMA index (1.76 ± 0.81 vs. 1.42 ± 0.57, p = 0.09) and adiponectin level (8.22 ± 2.83 μg/dl vs. 9.23 ± 4.36 μg/dl, p = 0.26) were similar between hypercholesterolemic and normocholesterolemic patients. The treatment with statin did not affect the fasting plasma level of glucose, insulin or HOMA index, suggesting the neutral effects of statins on insulin sensitivity. However, the treatment with statin significantly reduced the plasma level of adiponectin (from 8.6 ± 3.1 μg/ml to 7.8 ± 3.2 μg/ml, P = 0.01). All of these variables did not change in the no statin treatment group.

Conclusion: The result of this study showed that the insulin sensitivity and the plasma level of adiponectin were similar between hypercholesterolemic and normocholesterolemic non-diabetic patients. Although treatment with statins for 6 weeks did not deteriorate insulin sensitivities, the plasma level of adiponectin significantly decreased.

Key Words: Adiponectin • Hypercholesterolemia • Insulin resistance • Statins

INTRODUCTION

Adiponectin, the most abundant adipose-specific protein, is exclusively expressed in and secreted from adipose tissue.[1] Accumulating evidence suggests that this novel adipocytokine possesses several beneficial biofunctions, such as insulin-sensitizing, anti-inflammatory, and anti-atherogenic function. Previous in vitro studies showed that adiponectin suppressed adhesion molecule expression on endothelial cells,[2] reduced vascular inflammatory response by inhibition of endothelial cell NF-κB signaling,[3] and suppressed lipid accumulation in human monocyte-derived macrophages and inhibited macrophage-to-foam cell transformation.[4] Adiponectin knock-out mice developed severe insulin resistance in response to a high-fat diet, and were associated with higher levels of tumor-necrosis factor-α (TNF-α) and increased tissue lipid accumulation.[5] Also, adiponectin-deficient mice are associated with severe neointimal thickening and increased proliferation of vascular smooth muscle cells in mechanically injured arteries.[6]

Received: October 20, 2009 Accepted: November 24, 2009
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In humans, reduced plasma levels of adiponectin have been observed in individuals with obesity,[7] type 2 diabetes mellitus,[8] hypertension,[9] metabolic syndrome,[10] and coronary artery disease.[11] In addition, low plasma concentrations of adiponectin have recently been associated with increased risk of developing type 2 diabetes[12] and myocardial infarction,[13] and related to higher levels of hypersensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6), both inflammatory markers and mediators of increased cardiovascular risk.[14,15] Therefore, it has been suggested that hypoadiponectinemia may be a novel risk factor of atherosclerosis. Although previous studies have demonstrated that adiponectin is closely correlated to triglyceride and high-density lipoprotein cholesterol (HDL-C),[16] the relation of adiponectin and hypercholesterolemia is still controversial. On the other hand, the WOSCOPS study suggested that treatment with hydroxymethylglutaryl-coenzyme A reductase (HMG-CoA reductase, statin) might delay the development of diabetes, and several smaller studies indicated that statins might improve insulin resistance.[17,18] Therefore, it is tempting to hypothesize that statins may beneficially affect the plasma level of adiponectin. In this study, we aimed to investigate the relation between plasma lipid profile and adiponectin level in normocholesterolemic as well as hypercholesterolemic, non-diabetic patients, and further examine the effect of statins on insulin sensitivity and plasma adiponectin level.

MATERIALS AND METHODS

Study patients and protocol

This study was a case-controlled study and enrolled 48 non-diabetic, hypercholesterolemic patients with fasting plasma low-density lipoprotein-cholesterol (LDL-C) level > 160 mg/dl, and triglyceride level < 350 mg/dl after diet control for 6 weeks. During a 6-week dietary run-in period for determining eligibility for the treatments, patients were encouraged to adhere to the American Heart Association step I diet. To examine the relation between plasma adiponectin level and hypercholesterolemia, we enrolled another 20 age- and sex-matched non-diabetic, normocholesterolemic patients as control group. Patients with renal dysfunction (serum creatinine > 2.0 mg/dl), diabetes mellitus, severe hepatic or thyroid disease, chronic or acute inflammation, history of malignancy, uncompensated heart failure and uncontrolled hypertension were excluded. Patients with myocardial infarction or unstable angina in the past 1 month were also excluded. In hypercholesterolemic patients, totally 27 patients were assigned to statin group (atorvastatin 10 or 40 mg) for 6 weeks and the remaining 21 patients were assigned to no statin treatment group. Fasting blood samples were collected before and 6 weeks after treatment in all patients for measurements of plasma biochemistry. Before blood sampling, all medications were withdrawn for at least 12 hours. Cigarette smoking and beverages containing alcohol or caffeine were also avoided for at least 12 hours. This study was approved by local ethics committees, and written informed consents were obtained from all patients before they participated in this study.

Laboratory analysis

The blood samples were centrifuged at 3000 rpm for 10 minutes at 4 °C immediately after collection. The plasma samples were then kept frozen at -70 °C until analysis. Plasma adiponectin level was determined by a commercial human adiponectin ELISA kit (B-Bridge International, Inc., U.S.). The intra-assay and interassay coefficients of variation were 5.76% and 3.18%, respectively. Determination of hs-CRP levels was performed with use of latex-enhanced immunophelometric assays on a BN II analyzer (Dade Behring, Marburg, Germany). The upper normal value of hs-CRP is 0.5 mg/dl in our laboratory. Fasting serum creatinine, total and high-density lipoprotein (HDL) cholesterol, triglyceride, and blood sugar level were determined by an autoanalyzer (Model 747-100, Hitachi, Tokyo). LDL-cholesterol level was calculated according to the Friedewald formula. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Plasma insulin levels were measured with commercial insulin ELISA kits (Mercodia Insulin ELISA, Sweden). Insulin resistance score by homeostasis model assessment (HOMA) was computed with the following formula: HOMA index = [FPG (mmole/L) × fasting plasma insulin (μU/mL)]/22.5. Low HOMA values indicate high insulin sensitivity.[19]

Statistical analysis

All parametric values were presented as mean+/-

standard deviation. Parametric continuous data between hypercholesterolemic and normocholesterolemic patients/statin treatment group and no statin treatment group were compared with unpaired Student's t test and non-parametric data by Mann-Whitney test. Categorical data was compared by means of chi-square test or Fisher's exact test. Baseline data and changes of all plasma variables after treatment at each group were tested by paired t test. Pearson correlation coefficients were calculated to examine possible correlations between continuous variables, and Spearman's rank coefficients were used for variables with non-normal distribution. A stepwise multiple regression analysis was performed to assess the independent determinants of HOMA index and plasma adiponectin levels and the relation between change of plasma adiponectin level and other risk factors. A p value of less than 0.05 (2-tailed) was considered to be statistically significant. The SPSS 15.0 (SPSS Inc., Chicago, Illinois) software package was used for statistical analysis.

RESULTS

Patient characteristics

The baseline characteristics of study patients are summarized in Table 1. The patients' characteristics were similar among the 3 groups except lipid profile, though there were non-significant trends toward higher HOMA index (1.8 ± 0.8 vs. 1.4 ± 0.6, p = 0.09) and lower plasma adiponectin level (8.2 ± 2.8 μg/dl vs. 9.2 ± 4.4 μg/dl, p = 0.26) in hypercholesterolemic patients compared with normocholesterolemics. In addition, β-blocker was more often used in normocholesterolemic patients (p = 0.04), due to there being more cases of coronary artery disease in this group. In the whole population, the HOMA index was closely correlated with BMI and plasma levels of total cholesterol, triglyceride, and adiponectin (BMI: r = 0.45, p < 0.001; total cholesterol: r = 0.25, p = 0.04; triglyceride: r = 0.29, p = 0.02; adiponectin: r = -0.27, p = 0.03). In stepwise multivariate regression analysis, HOMA index was significantly as-

Table 1. Clinical characteristics of study subjects

	Hypercholesterolemic			Normocholesterolemic	
	Statin (n = 27)	No statin treatment (n = 21)	p values	Control (n = 20)	p values*
Age (years)	64.3 ± 11.3	61.4 ± 10.7	0.36	64.0 ± 10.6	0.76
Gender (M/F)	14/13	15/6	0.24	13/7	0.79
Systemic hypertension	13 (48.1%)	13 (61.9%)	0.39	9 (45.0%)	0.60
BMI (Kg/m^2)	25.3 ± 2.6	24.9 ± 2.8	0.58	25.5 ± 2.9	0.61
Diabetes mellitus	0 (0.0%)	0 (0.0%)	1.00	0 (0.0%)	1.00
Established CAD	10 (37.0%)	3 (14.3%)	0.11	9 (45.0%)	0.17
Total cholesterol (mg/dl)	260.9 ± 32.6	260.0 ± 30.9	0.93	171.0 ± 29.9	< 0.001
HDL-cholesterol (mg/dl)	45.6 ± 10.6	49.0 ± 14.0	0.34	50.2 ± 17.7	0.41
LDL-cholesterol (mg/dl)	181.3 ± 30.7	181.9 ± 29.2	0.95	98.9 ± 29.1	< 0.001
Triglyceride (mg/dl)	171.3 ± 82.3	145.7 ± 56.6	0.23	99.6 ± 46.1	0.001
Medications					
Aspirin	5 (18.5%)	5 (23.8%)	0.73	12 (60.0%)	0.004
Nitrate	3 (11.1%)	3 (14.3%)	1.00	4 (20.0%)	0.47
Calcium antagonists	7 (25.9%)	10 (47.6%)	0.14	8 (40.0%)	0.79
ACE-inhibitors/ARBs	8 (29.6%)	7 (33.3%)	1.00	6 (30.0%)	1.00
β-blockers	7 (25.9%)	4 (19.0%)	0.73	10 (50.0%)	0.04
Adiponectin (μg/ml)	8.6 ± 3.1	7.8 ± 2.5	0.35	9.2 ± 4.4	0.26
Insulin (μU/ml)	7.0 ± 3.0	7.00 ± 3.3	0.96	6.3 ± 2.3	0.36
Glucose (mg/dl)	103.7 ± 14.0	100.0 ± 12.6	0.35	92.1 ± 8.0	0.003
HOMA	1.8 ± 0.8	1.7 ± 0.8	0.86	1.4 ± 0.6	0.09
CRP (mg/l)	1.9 ± 2.02	2.6 ± 2.5	0.28	2.1 ± 2.1	0.87

BMI: body mass index; CAD: coronary artery disease; ACE: angiotensin-converting enzyme; ARB: angiotensin-II receptor blocker; HOMA: homeostasis model assessment; CRP: C-reative protein.

* hypercholesterolemic vs. normocholesterolemic.

sociated with BMI and total cholesterol level ($p < 0.001$ and 0.047, respectively). As for the adiponectin level, there was a significant positive correlation with age ($r = 0.27$, $p = 0.03$), and significant negative correlations with triglyceride level, HOMA index, and BMI (triglyceride level: $r = -0.26$, $p = 0.04$; BMI: $r = -0.25$, $p = 0.04$). Only were BMI and age associated with adiponectin level in multivariate regression analysis ($p = 0.018$, 0.025, respectively). There was no correlation among plasma adiponectin, cholesterol levels and hs-CRP.

Effects of statins on plasma adiponectin level

In the hypercholesterolemic patients, finally 27 patients received statin treatment, and 21 patients were assigned to the no statin treatment group. There were no significant differences between the baseline characteristics of the statin treatment group and the no statin treatment group. As expected, treatment with statins for 6 weeks lead to a marked reduction in plasma concentration of total cholesterol, LDL-cholesterol, triglyceride, and an increase of HDL-cholesterol level (Table 2). The treatment with statins did not affect the fasting plasma level of glucose, insulin or HOMA index, indicating the neutral effects of statins on insulin sensitivity. However, compared with the no statin treatment group, the treatment with statin significantly reduced the plasma level of adiponectin (from 8.6 ± 3.1 μg/ml to 7.8 ± 3.2 μg/ml, $p = 0.01$, Figure 1). Moreover, statin treatment also led to a non-significant reduction of hs-CRP (from 1.85 ± 2.02 mg/l to 1.30 ± 1.62 mg/l, $p = 0.10$). All of these variables did not change in the no statin treatment group (Table 2). A stepwise multivariate regression analysis for identifying the factors affecting the reduction of plasma adiponectin level showed that the reduction of adiponectin was not related to the reductions of other variables, including lipid profile, HOMA index and hs-CRP.

DISCUSSION

Major findings

The results of this study showed that the insulin sensitivities and the plasma levels of adiponectin were similar between non-diabetic, hypercholesterolemic and normocholesterolemic patients. Although treatment with statins for 6 weeks did not deteriorate insulin sensitivity, the plasma level of adiponectin significantly decreased.

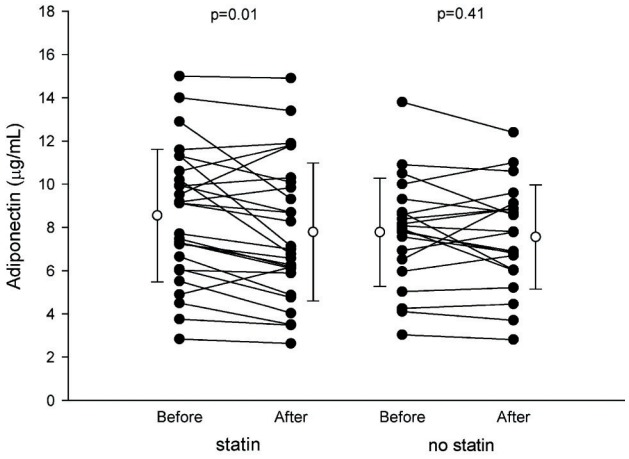

Figure 1. *Comparison of serum adiponectin levels before and after 6 weeks treatment with statins and no statin treatment in hypercholesterolemic non-diabetic patients.*

Table 2. Changes in plasma parameters after treatment with statin or not

	Statin (n = 27)			No statin treatment (n = 21)		
	Before	After	p values	Before	After	p values
Total cholesterol (mg/dl)	260.9 ± 32.6	182.3 ± 35.1	< 0.001	260.0 ± 30.9	269.7 ± 38.0	0.06
HDL-cholesterol (mg/dl)	45.6 ± 10.6	51.5 ± 11.2	< 0.001	49.0 ± 14.0	50.1 ± 11.6	0.58
LDL-cholesterol (mg/dl)	181.3 ± 30.7	102.5 ± 35.6	< 0.001	181.9 ± 29.2	186.2 ± 37.3	0.41
Triglyceride (mg/dl)	171.3 ± 82.3	141.3 ± 67.7	< 0.01	145.7 ± 56.6	167.0 ± 77.5	0.18
Adiponectin (μg/ml)	8.6 ± 3.1	7.8 ± 3.2	0.01	7.8 ± 2.5	7.6 ± 2.4	0.41
Insulin (μU/ml)	7.0 ± 3.0	6.7 ± 2.4	0.54	7.0 ± 3.3	8.6 ± 4.9	0.06
Glucose (mg/dl)	103.7 ± 14.0	99.9 ± 12.1	0.07	100.0 ± 12.6	101.5 ± 16.7	0.47
HOMA	1.8 ± 0.8	1.7 ± 0.7	0.31	1.7 ± 0.8	2.2 ± 1.5	0.08
CRP (mg/l)	1.9 ± 2.0	1.3 ± 1.6	0.10	2.6 ± 2.5	1.8 ± 1.9	0.08

Abbreviations as in Table 1.

Statin treatment and insulin resistance

Several large primary and secondary prevention trials have demonstrated the beneficial effect of statins on reducing cardiovascular events and mortality,[20-22] which have been partly attributed to the various pleiotropic effects of statins, beyond lipid-lowering effects.[23] Intriguingly, the results of WOSCOPS, one of the landmark primary prevention trials, showed that pravastatin treatment resulted in a significant reduction of the risk of becoming diabetetic, which could be attributing to the triglyceride-lowering effect of pravastatin.[21,27] Furthermore, several smaller studies reported that statins may improve insulin resistance, in both patients with type 2 diabetes and non-diabetic dyslipidemic patients.[17,18] This effect may be associated with the statins' insulin-like activation of a series of kinase cascades that involve PIK3 and Akt, thus facilitating glucose uptake.[24] In addition, reduction of plasma triglyceride level by statin may also contribute to the improvement of insulin-mediated glucose uptake, which nevertheless remains controversial.[17,25-27] To the contrary, there also were several studies that failed to demonstrate the insulin-sensitizing effects of statins.[28-30] In addition to studies which were performed on type 2 diabetic patients and showed neutral or even negative effects of statins on insulin resistance, there were 2 studies targeted on the effect of statins on insulin sensitivity in patients with hypercholesterolemia and non-diabetes. Sheu et al. reported that, in patients with hypercholesterolemia (including type IIA and IIB), treatment with pravastatin for 3 months did not improve insulin resistance, relative glucose intolerance or hyperinsulinemia.[29] In another randomized, controlled cross-over trial, Jula et al. demonstrated that 12 weeks' treatment with simvastatin significantly increased serum insulin level and HOMA index, with glucose level remaining unchanged. This insulin-resistance increasing effect of simvastatin may be counteracted by dietary treatment.[30] Moreover, Lamendola et al. showed recently that in insulin-resistant, non-diabetic patients with combined dyslipidemia, treatment with rosuvastatin for 3 weeks did not lower daylong glucose, insulin concentration and steady-state glucose concentration.[31] Our data was similar and showed that although treatment with statins led to a significant reduction of plasma triglyceride, it did not improve insulin resistance. Impairing postreceptor insulin signaling and reducing levels of mevalonate and the derivates of its metabolites, which maybe involved in insulin and IGF (insulin growth factor-1) signaling, have been suggested to be the likely mechanisms of the negative effect of statins.[32,33] Nevertheless, our results need to be confirmed by studies in larger populations.

Statin treatment and adiponectin

The second major finding in our study related to the significant reduction of adiponectin after treatment with statins. Adiponectin, the most abundant protein secreted from fat cells and exerting anti-atherosclerotic effects, is closely associated with insulin resistance. Previous reports have shown that diabetic patients have lower adiponectin levels than do control subjects.[8] Diabetic patients with macroangiopathy also have lower levels of adipoenctin than those without.[34] More recently, hypoadiponectinemia was suggested to be a biomarker of the metabolic syndrome due to its close association with the clinical phenotype of metabolic syndrome.[10,35] Insulin sensitizer, such as peroxisome proliferator-activated receptor γ (PPAR-γ) agonist has been demonstrated to elevate the plasma level of adiponectin in insulin-resistant rodents and humans.[36] Furthermore, reduction in mean body mass index (BMI) was accompanied by a markedly increase in circulating adiponectin level in a recent study.[37] In contrast, pro-inflammatory cytokines, especially TNF-α and IL-6, have been reported to reduce adiponectin concentration.[38,39] Given the evidence that statins may reduce the circulating concentrations of TNF-α and IL-6,[40] it is surprising to find that adiponectin level was decreased in our patients after the 6-week treatment with statins. Previous studies suggested that pravastatin and rosuvastatin could increase adiponectin level after treatments. However, there were no significant increases and even decreased adiponectin levels found in pitavastatin and simvastatin trials.[41,42] Another recent study showed atorvastatin did not affect insulin sensitivity and the adiponectin or leptin levels in hyperlipidemic Type 2 diabetes.[43] No patients with DM or impaired glucose intolerance were included in this study, indicating that our population was relatively insulin-sensitive and theoretically had higher adiponectin level, though the commonly noted correlation still existed among adiponectin, HOMA index and BMI. Thus, the potential beneficial effects of statins on adiponectin level may therefore appear less detectable. In addition,

some of our patients were hypertensive or/and suffered from coronary artery disease, and they were receiving treatment that may potentially influence the insulin sensitivity, such as β-blockers and angiotensin-converting enzyme inhibitors. These factors, combined with the smaller number of our study population, may confound our results. This possible adiponectin-lowering effect of statins warrants elucidation in larger homogenous population.

ACKNOWLEDGMENTS

This study was supported by grants from the National Science Council, Veterans General Hospital Research Program and Pfizer Pharmaceutical Company, Taipei, Taiwan, R.O.C.

The authors are indebted to Ms. Shu-Chuan Lin and Ms. Pui-Ching Lee for their excellent technical and statistical assistance.

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