Journal of Cardiology (2009) **53**, 219—225

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CARDIOLOGY
Official Journal of the Japanese College of Cardiology

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ORIGINAL ARTICLE

Smoking cessation is associated with increased plasma adiponectin levels in men

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Received 19 August 2008; received in revised form 5 November 2008; accepted 17 November 2008
Available online 20 January 2009

KEYWORDS
Adiponectin;
Angina pectoris;
Insulin resistance;
Smoking cessation

Summary
Objectives: Low levels of adiponectin, an adipocytokine with anti-diabetic and anti-atherogenic properties, are associated with increased risk of future myocardial infarction in men. Previous studies have demonstrated that cigarette smoking is involved in the development of insulin resistance, and current smokers have been shown to have reduced plasma adiponectin levels. However, the influence of smoking cessation on adiponectin levels remains unknown. We sought to assess whether smoking cessation is associated with increased plasma adiponectin levels in men.
Methods: The study includes 72 men (47 non-smokers and 25 current smokers at baseline) with stable angina pectoris who underwent percutaneous coronary intervention and follow-up coronary angiography 6 months later. During the 6-month follow-up period, all 47 non-smokers remained non-smokers, while 15 men of the 25 baseline current smokers successfully quit smoking. We evaluated plasma adiponectin levels at coronary intervention and 6 months later.
Results: Plasma adiponectin levels at coronary intervention were comparable to those after 6 months in non-smokers (4.22 [3.15—6.43] vs. 4.58 [3.03—6.26] μg/mL, $P = 0.124$) and in persistent smokers (4.77 [4.25—10.53] vs. 5.16 [4.11—8.10] μg/mL, $P = 0.721$). Meanwhile, an increase in adiponectin level was observed in patients who quit smoking for 6 months (4.24 [3.30—5.70] vs. 5.50 [4.03—8.00] μg/mL, $P = 0.002$).

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0914-5087/$ — see front matter
doi:10.1016/j.jjcc.2008.11.004

Univariate analysis revealed that the percent increase in adiponectin levels correlated positively with smoking cessation ($P = 0.003$) and negatively with additional use of β-blockers ($P = 0.049$). In addition, increases in adiponectin levels were closely associated with increase in high-density lipoprotein cholesterol ($P = 0.148$), decrease in triglycerides ($P = 0.140$), and additional use of renin–angiotensin system inhibitors ($P = 0.069$). Multivariate analysis demonstrated that smoking cessation was an independent determinant of the increase in adiponectin ($P = 0.036$).
Conclusions: Smoking cessation is associated with increased plasma adiponectin levels in men with stable angina, suggesting that the significance of smoking cessation may be partly explained by the increase in adiponectin level.

Introduction

The adipocyte-derived plasma protein adiponectin is closely associated with insulin sensitivity, and has been identified as a marker of the metabolic syndrome [1]. Adiponectin has anti-atherogenic properties [1], and low levels of adiponectin are known to be associated with coronary artery disease [2] and increased risk of future myocardial infarction (MI) [3]. We have previously reported that plasma adiponectin levels are inversely associated with atherosclerotic burden [4], and that low levels of adiponectin are associated with angiographic coronary lesion complexity, suggestive of coronary plaque instability [5]. Thus, a decrease in adiponectin levels may contribute to the development of atherosclerotic disease including acute coronary syndromes, as well as metabolic syndrome.

Cigarette smoking is a major risk factor for atherosclerotic disease, and cessation of smoking is an important preventive strategy against cardiovascular disease (CVD). Previous studies revealed that cigarette smoking increases inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol [6,7]. In addition, cigarette smoking is known to be associated with insulin resistance [8], and a recent observation in adolescents demonstrated a significant dose–response relationship between tobacco smoke exposure and the incidence of metabolic syndrome [9]. Several cross-sectional studies indicated that smoking habit may be associated with low plasma levels of adiponectin [10,11], suggesting one possible mechanism through which cigarette smoking contributes to the development of atherosclerotic disease. However, the influence of smoking cessation on plasma adiponectin levels remains to be elucidated.

The hypothesis tested in the present study was that cessation of smoking results in increase in plasma adiponectin levels. To investigate this hypothesis, we measured plasma adiponectin levels in men with stable angina pectoris at coronary intervention and 6 months later.

Methods

Study population

The study subjects were 72 men with stable effort angina who underwent percutaneous coronary intervention and follow-up coronary angiography 6 months later at Kumamoto University Hospital. Patients with acute coronary syndromes were excluded from the study, because they are known to have lower levels of plasma adiponectin than patients with stable coronary artery disease, as we have reported previously [5]. We also excluded patients with malignant disease, infectious disease, chronic inflammatory disease, autoimmune disease, and advanced renal disease (serum creatinine level >2.5 mg/dL). None of the patients was taking any type of thiazolidinedione, which is an insulin-sensitizing agent known to increase plasma concentrations of adiponectin [12]. In addition, none of the patients was using any anti-smoking agents such as nicotine patches or varenicline. The group included 47 non-smokers and 25 current smokers at baseline. During the 6-month follow-up period, all 47 non-smokers remained non-smokers, while 15 men of the 25 baseline current smokers successfully quit smoking. Written informed consent was obtained from each patient before participation in the study. The study was performed in accordance with the ethics principles in the Declaration of Helsinki and the study protocol was approved by the ethics committee of our institution.

Blood sampling and measurement of plasma adiponectin

Venous blood samples were obtained in the early morning from all subjects after a 12-h fast. Plasma

Table 1 Baseline clinical characteristics of 72 men with stable effort angina.

	Non-smokers ($n = 47$)	Persistent smokers ($n = 10$)	Quitters ($n = 15$)	P
Age (years)	68.5 ± 9.3	66.5 ± 7.2	68.3 ± 7.0	0.794
BMI (kg/m^2)	24.4 ± 2.7	24.1 ± 3.7	23.2 ± 3.0	0.395
Hypertension	39 (83%)	6 (60%)	12 (80%)	0.266
Diabetes mellitus	21 (45%)	5 (50%)	4 (27%)	0.397
Fasting glucose (mg/dL)	108.1 ± 31.9	105.3 ± 23.6	100.8 ± 27.8	0.712
Hemoglobin A1c (%)	6.2 ± 1.2	5.7 ± 0.6	5.6 ± 0.9	0.181
Total cholesterol (mg/dL)	200.0 ± 40.0	187.0 ± 29.3	188.6 ± 42.7	0.470
HDL cholesterol (mg/dL)	47.3 ± 11.2	42.6 ± 15.0	50.5 ± 27.3	0.500
LDL cholesterol (mg/dL)	133.4 ± 39.4	120.5 ± 18.4	126.5 ± 32.3	0.534
Triglycerides (mg/dL)	131.0 (95.3—153.0)	122.5 (97.0—142.0)	121.0 (75.8—144.8)	0.740
Creatinine (mg/dL)	0.86 ± 0.37	0.93 ± 0.31	1.01 ± 0.40	0.239
CRP (mg/dL)	0.27 (0.05—0.56)	0.16 (0.10—0.22)	0.23 (0.05—0.43)	0.881
Adiponectin (μg/mL)	4.22 (3.15—6.43)	4.77 (4.25—10.53)	4.24 (3.30—5.70)	0.343

Values are mean ± S.D. or median value (25th to 75th percentile range) or n (%). BMI = body mass index; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

samples were immediately stored at −80 °C for subsequent assay of adiponectin levels by enzyme-linked immunosorbent assay (adiponectin ELISA kit, Otsuka Pharmaceutical, Tokyo, Japan) as described previously [4,13]. We measured plasma adiponectin levels at coronary intervention and 6 months later.

Statistical analysis

Results for normally distributed continuous variables are expressed as mean values ± S.D., and those for continuous variables with skewed distributions are expressed as median values (interquartile ranges). Differences between continuous variables were analyzed by one-way analysis of variance followed by Scheffe's test, and the Kruskal—Wallis test, as appropriate. Categorical variables are presented by frequency counts, and intergroup comparisons were analyzed by the χ^2-test. Changes in normally distributed variables were assessed using paired t-test, and those with skewed distribution were assessed by Wilcoxon signed rank test. Correlations between percent change in plasma adiponectin levels and those at baseline variables were first assessed by Spearman two-way test. Multivariate analysis was performed to assess the

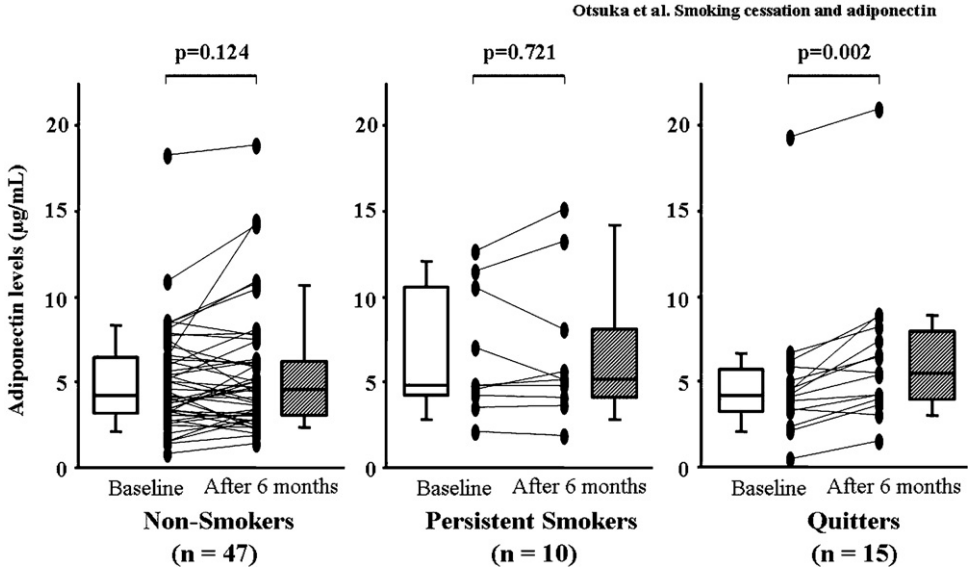

Figure 1 Changes in plasma adiponectin levels in non-smokers ($n = 47$), persistent smokers ($n = 10$), and quitters ($n = 15$). In box-and-whisker plots, the lines within the boxes represent median values; the upper and lower borders of the boxes represent the 75th and 25th percentiles, respectively; and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively.

Table 2 Comparison of variables at baseline and after 6 months in baseline current smokers.

	Persistent smokers ($n = 10$)			Quitters ($n = 15$)		
	Baseline	After 6 months	*P*	Baseline	After 6 months	*P*
Body weight (kg)	64.4 ± 11.5	63.9 ± 7.4	0.803	61.4 ± 8.6	60.5 ± 10.7	0.558
BMI (kg/m^2)	24.1 ± 3.7	24.0 ± 2.5	0.850	23.2 ± 3.0	23.3 ± 3.3	0.814
Fasting glucose (mg/dL)	105.3 ± 23.6	102.4 ± 22.0	0.602	100.8 ± 27.8	97.5 ± 15.4	0.503
Hemoglobin A1c (%)	5.7 ± 0.6	5.9 ± 0.6	0.573	5.6 ± 0.9	5.6 ± 0.5	0.878
Total cholesterol (mg/dL)	187.0 ± 29.3	178.0 ± 20.9	0.301	188.6 ± 42.7	169.4 ± 29.9	0.108
HDL cholesterol (mg/dL)	42.6 ± 15.0	43.3 ± 9.5	0.839	50.5 ± 27.3	47.9 ± 8.4	0.498
LDL cholesterol (mg/dL)	120.5 ± 18.4	120.3 ± 20.5	0.975	126.5 ± 32.3	107.4 ± 26.2	0.014
Triglycerides (mg/dL)	122.5 (97.0—142.0)	126.0 (108.0—158.0)	0.767	121.0 (75.8—144.8)	110.5 (90.0—140.0)	0.851
CRP (mg/dL)	0.16 (0.10—0.22)	0.19 (0.08—0.50)	0.213	0.23 (0.05—0.43)	0.13 (0.07—0.27)	0.168
Adiponectin (μg/mL)	4.77 (4.25—10.53)	5.16 (4.11—8.10)	0.721	4.24 (3.30—5.70)	5.50 (4.03—8.00)	0.002
Medication (%)						
Aspirin	80	100		73	100	
β-Blockers	0	40		20	33	
Calcium antagonists	70	80		73	73	
ACE inhibitors/ARBs	30	40		40	67	
Statins	0	20		27	53	
Nitrates	20	30		53	40	

ACE = angiotensin converting enzyme; ARBs = angiotensin receptor blockers; other abbreviations as in Table 1.

Table 3 Correlation between changes in plasma adiponectin levels and changes in baseline variables.

	Univariate		Multivariate		
	r-Value	*P*	*B* (95% CI)	β	*P*
% Body weight	−0.106	0.603			
% BMI	0.017	0.932			
% Fasting glucose	0.192	0.347			
% Hemoglobin A1c	−0.121	0.552			
% Total cholesterol	0.116	0.579			
% HDL cholesterol	0.302	0.148	0.754 (−0.414 to 1.922)	0.342	0.192
% LDL cholesterol	0.052	0.802			
% Triglycerides	−0.308	0.140	−0.093 (−0.739 to 0.553)	−0.073	0.765
% CRP	−0.079	0.719			
Smoking cessation	0.611	0.003	0.490 (0.035 to 0.945)	0.477	0.036
Additional medications					
Aspirin	0.195	0.340			
β-Blockers	−0.403	0.049	0.031 (−0.544 to 0.605)	0.026	0.912
Calcium antagonists	0.041	0.841			
ACE inhibitors/ARBs	0.371	0.069	0.208 (−0.272 to 0.687)	0.177	0.375
Statins	−0.026	0.899			
Nitrates	−0.061	0.767			

Abbreviations as in Tables 1 and 2. *B* indicates increment of the plasma adiponectin levels for every unit of the independent variable; β value corresponds to the standardized multiple regression coefficient.

independent determinant of percent increase in adiponectin levels during the 6-month follow-up period, and all factors with $P < 0.20$ based on the results of univariate analysis were entered into this multivariate model. Statistical significance was defined as $P < 0.05$. All analyses were performed using Stat View-V software (SAS Institute Inc., Cary, NC, USA).

Results

There were no significant differences in baseline variables between non-smokers ($n = 47$), persistent smokers ($n = 10$), and quitters ($n = 15$) (Table 1). Plasma adiponectin levels at coronary intervention were comparable to those measured 6 months later in non-smokers (4.22 [3.15—6.43] vs. 4.58 [3.03—6.26] μg/mL, $P = 0.124$) and in persistent smokers (4.77 [4.25—10.53] vs. 5.16 [4.11—8.10] μg/mL, $P = 0.721$) (Fig. 1). In contrast, an increase in adiponectin level was observed in quitters (4.24 [3.30—5.70] vs. 5.50 [4.03—8.00] μg/mL, $P = 0.002$) (Fig. 1).

During the 6-month follow-up period, persistent smokers and quitters did not show significant changes in various clinical variables such as body weight, glucose and lipid profiles, and C-reactive protein levels, except that a decrease in low-density lipoprotein cholesterol level was observed in quitters (Table 2). The baseline medications and those after 6 months are shown in Table 2.

We assessed the independent determinants of the increase in plasma adiponectin levels among baseline current smokers (Table 3). Univariate analysis revealed that the percent increase in plasma adiponectin levels correlated positively with smoking cessation ($P = 0.003$) and negatively with additional use of β-blockers ($P = 0.049$). In addition, the percent increase in plasma adiponectin level closely correlated positively with percent increase in high-density lipoprotein cholesterol levels ($P = 0.148$) and additional use of renin—angiotensin system inhibitors ($P = 0.069$), and negatively with percent increase in triglyceride levels ($P = 0.140$), although the difference was not statistically significant. A multivariate analysis including these variables demonstrated that smoking cessation was a significant and independent determinant of the increase in plasma adiponectin levels ($P = 0.036$).

Discussion

In this study, we demonstrated that 6-month smoking cessation was significantly and independently associated with increased plasma levels of adiponectin in men with stable angina pectoris. The present findings suggest that the significance of smoking cessation may be, at least in part, demonstrated by increase in plasma adiponectin, which is known as an anti-atherogenic adipocytokine.

The adipocyte-derived plasma protein adiponectin is associated with insulin sensitivity [1]. Moreover, adiponectin has direct anti-atherogenic properties [1] and a fall in the concentration of this molecule is known to be associated with coronary artery disease [2], restenosis after percutaneous coronary intervention [14], and future incidence of MI [3]. Cigarette smoking is an established risk factor for CVD, while it correlates with insulin resistance and the development of metabolic syndrome [8,9]. Cigarette smoking correlates with low plasma adiponectin levels [10,11], however, there is no information on the correlation between smoking cessation and plasma adiponectin levels.

In the present study, we demonstrated that smoking cessation was significantly associated with increased plasma adiponectin levels. Although the precise mechanisms are unclear, previous studies support the association between smoking habit and reduced adiponectin levels. It has been demonstrated that nicotine directly inhibits the mRNA expression of adiponectin in adipocytes [11]. Smoke exposure is known to increase gene expression of tumor necrosis factor-α [15], which is inversely associated with adiponectin gene expression [16]. Furthermore, it is characteristic of adiponectin to accumulate in injured vessel walls but not in intact vascular walls [17,18], and it is possible that endothelial cell injury caused by cigarette smoking results in increased consumption of circulating adiponectin.

Smoking can potentially contribute to the development of insulin resistance and the metabolic syndrome [8,9], therefore, its cessation could improve insulin sensitivity. On the other hand, smoking cessation sometimes leads to body weight gain [19], which seems to result in deterioration of insulin sensitivity. Weight gain after smoking cessation is largely due to increased body fat, and the mechanism of weight gain includes increased energy intake, decreased physical activity, and increased lipoprotein lipase activity [20—22]. However, despite weight gain after quitting smoking, it was reported that the increase in the waist-to-hip ratio in those who quit smoking was not as much as expected, and conversely, people who re-started smoking after quitting showed significant increase in waist-to-hip ratio in spite of reduction in their body weight [23]. Thus, body fat changes caused by cigarette smoking might differ between abdominal adipose tissue and subcutaneous region (which is represented by hip circumference), and this may account for the apparently discrepant phenomenon after smoking cessation. Indeed, improvement in insulin sensitivity after quitting smoking has been demonstrated regardless of weight gain [24]. Although body weight gain after smoking cessation was not observed in our subjects, the increase in adiponectin levels after smoking cessation may be in line with previous studies.

Smoking cessation is important especially with regard to the prevention of CVD. Previous studies showed that smoking cessation significantly reduced the risk of acute MI and stroke [25], and had beneficial effects on cardiovascular morbidity and mortality [26]. To our knowledge, the present study represents the first report demonstrating that smoking cessation is significantly associated with a rise in plasma levels of adiponectin in men with stable angina. Given the significant association between low adiponectin levels and increased risk of CVD, our results may support the clinical importance of smoking cessation in the prevention of atherosclerotic disease and may help promote smoking cessation in society at large.

This study was limited by the small sample size as well as the specific study subjects who underwent percutaneous coronary intervention. Moreover, several additional medications were used during the follow-up period, although the association between smoking cessation and increase in adiponectin levels was independent of such additional medications. Previous studies have demonstrated that renin—angiotensin system inhibitors increase adiponectin levels, and that high-density lipoprotein cholesterol and triglycerides levels correlate with adiponectin levels [27,28]. In this study, the percent increase in plasma adiponectin level was closely associated with these variables, although the difference was not statistically significant. Further studies in a larger number of subjects including the general population are required to confirm our results.

In conclusion, a 6-month smoking cessation period was significantly associated with increased plasma adiponectin levels in men with stable angina pectoris. Our results suggest that the significance of smoking cessation may be in part demonstrated by the increase in plasma adiponectin concentrations.

Acknowledgments

The authors thank Sachiyo Tanaka for excellent technical support. This study was supported by a Research Grant for Cardiovascular Disease (17C-2) from the Ministry of Health, Labor, and Welfare, Japan, a Grant-in-aid for Scientific Research (B-17390232, C-17590753, and C-18590780) from the Ministry of Education, Science, and Culture, Japan, and the Smoking Research Foundation Grant for Biomedical Research, Japan.

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