□ ORIGINAL ARTICLE □

Early Effects of Smoking Cessation and Weight Gain on Plasma Adiponectin Levels and Insulin Resistance

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Abstract

Background   Tobacco smoking is a major risk factor for atherosclerotic and cardiovascular disease. Studies have found evidence that smoking cessation is associated with weight gain, which is itself a leading cause of cardiovascular disease.

Aim   The present study sought to determine how smoking cessation and associated weight gain affect adiponectin levels and insulin resistance.

Methods   Fifty-two male habitual smokers were treated for 2 months with transdermal nicotine patches, and the 28 subjects who successfully quit smoking were analyzed. Subjects were divided into two sub-groups according to their weight change: weight maintainers and weight gainers. Serum adiponectin levels and the homeostasis model assessment ratio (HOMA-R) were evaluated at the beginning of the study, and at 1 week and 9 weeks after cessation of patch use.

Results   In weight gainers (n=18), serum adiponection levels tended to increase at 1 week after the end of treatment (mean difference 0.4±1.0 μg/mL, p=0.08). Moreover, after 9 weeks, adiponectin levels were significantly decreased in weight gainers (mean difference between 1 week and 9 weeks 0.8±0.9 μg/mL, p=0.002). In weight maintainers, adiponectin levels increased slightly after smoking cessation, but changes were not significant. In weight gainers, HOMA-R index was significantly increased (mean difference between baseline and 9 weeks 0.4±0.7, p=0.01), while in weight maintainers, HOMA-R index showed no differences throughout the study.

Conclusion   Our findings suggest that the adverse effects of weight gain attenuate some of the beneficial effects of smoking cessation.

Key words: smoking cessation, weight gain, insulin resistance, adiponectin

Introduction

Tobacco smoking is a major risk factor for several diseases, including cardiovascular disease (CVD). Long-term smoking is reported to increase insulin resistance, inflammation, lipid peroxidation, and endothelial cell dysfunction (1-3). Cross-sectional studies have demonstrated that smokers are insulin resistant and hyperinsulinemic compared with a matched group of non-smokers (1). Furthermore, few studies have demonstrated that smoking cessation is associated with improvements in insulin sensitivity (4). Adiponectin, the major adipocytokine, is closely associated with anti-atherogenic, anti-inflammatory, and insulin-sensitizing properties. Adiponectin levels in habitual smokers have been reported to be less than those in non-smokers (5, 6). Because adiponectin has anti-atherogenic properties, hypoadiponectinemia in smokers may be one of the causes of

smoking-induced atherosclerotic disease. Although smoking cessation is expected to improve the decreased levels of adiponectin, only a few reports (7, 8) have examined the effect of smoking cessation on adiponectin levels.

Various studies have found that smoking cessation is associated with weight gain, which is itself a leading cause of CVD. Only a few studies have investigated the effects of weight gain after smoking cessation on CVD (9). Wada et al (10) demonstrated that the odds ratio of metabolic syndrome onset for past smokers was higher than that for non-smokers due to the subsequent body weight gain after quitting smoking. Yoon et al (11) demonstrated that weight gainers after smoking cessation had increases in blood pressure and serum levels of total cholesterol, triglycerides, and glucose.

The present study sought to determine how smoking cessation and subsequent weight gain affected adiponectin levels and insulin resistance.

Materials and Methods

Patients

In this study, we defined habitual smokers as current smokers who smoked more than 10 pack-years (calculated as packs per day × smoking years, or as cigarettes per day × smoking years/20). Subjects comprised 52 male habitual smokers (mean age, 48.6±15.6 years; range, 20-74 years). Subjects received no remuneration, but habitual smokers received nicotine patches at no cost.

Habitual smokers were treated for 8 weeks with transdermal nicotine patches (Nicotinell TTS, Novartis Pharma K. K., Tokyo, Japan). They used 52.5-mg patches for 4 weeks, 35-mg patches for 2 weeks, and 17.5-mg patches for 2 weeks. After treatment was started, patients were not allowed to smoke. We discontinued treatment and excluded subjects from the study if they resumed smoking. None of the subjects was being treated with painkillers, antidepressants, hormone drugs, or medicines for the stomach or bowels. Patients with diabetes mellitus, endocrine disease, renal failure, severe obesity (body mass index [BMI] >40 kg/m²), cachexia, or alcohol abuse were excluded from the study. We divided subjects into two sub-groups according to their weight change after quitting smoking: weight maintainers (those who gained <3% in BMI after smoking cessation) and weight gainers (those who gained ≥3% in BMI after smoking cessation). The study protocol was approved by the Medical Ethics Committee of Nagasaki University. Written informed consent was obtained from each subject in accordance with the Helsinki Declaration.

Laboratory investigations

Venous blood samples were collected in the morning after an overnight fast at the beginning of the study, after 2 months of treatment, and after 4 months. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose, serum adiponectin, hyper sensitivity C-reactive protein (hsCRP), tumor necrosis factor α (TNF-α), and interleukin-6 (IL-6) levels were measured (SRL, Tokyo, Japan). The homeostasis model assessment ratio (HOMA-R) index was used to evaluate insulin resistance and was calculated as fasting immunoreactive insulin (μu/mL) × fasting plasma glucose (mg/dL)/405. LDL to HDL cholesterol ratio was used as an evaluation of cardiovascular disease risk and was calculated as LDL-C (mg/dL) divided by HDL-C (mg/dL).

Vascular study

Carotid intima-media thickness (CIMT), cardio ankle vascular index (CAVI), flow-mediated dilatation (FMD), and nitroglycerin-induced dilatation (NID) were measured as risk factors for atherosclerosis. These tests were measured at the beginning of the study, and at 1 and 9 weeks after cessation of the nicotine patch. CIMT was measured using ultra-sonography with a 7.5-Mhz linear array scanner (ALOKA, Tokyo, Japan). CIMT was measured on the far wall of the mid and distal common carotid artery and defined as the distance between the lumen-intima interface and the media adventitia interface using Intima Scope analysis software (SoftMedical Co., Ltd, Tokyo, Japan). CAVI, which assesses the stiffness of arteries, was measured using VaseraVS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan) after at least 10 min rest in the supine position. FMD and NID, which assess the health of the vascular endothelium, were measured in accordance with published guidelines (12) using ultrasonography equipped with a 7.5-MHz liner array transducer (ALOKA, Tokyo, Japan) with a probe-holding device and a rapid cuff inflator (Saraya, Osaka, Japan). Participants took 0.075 mg nitroglycerin (Nippon Kayaku, Tokyo, Japan) by sublingual route after at least 10 min rest following FMD measurements. NID, which assesses vascular smooth muscle dependent vasodilatation, was subsequently measured by way of comparison with endothelium-dependent vasodilatation. BMI was calculated by dividing weight (in kilograms) by the square of height (in meters). Blood pressure was measured in the right brachial artery in a sitting position using automatic hemodynamometer (BP203RVIII, COLIN, Tokyo, Japan). All analyses were carried out without the investigator knowing which group the patient was in.

Statistical analysis

All data are expressed as means ± standard deviation. Differences between groups were examined for statistical significance using the student's *t*-test. $p<0.05$ was considered statistically significant.

Results

Of the 52 smokers, 28 smokers succeeded in quitting until 9 weeks after cessation of patch use, whereas 24 smokers

Table 1.   Changes in Clinical Characteristics after Smoking Cessation

Charastristics	Baseline	1 week after the end of treatment	p¹	9 weeks after the end of treatment	p²	p³
Age	56.3±12.3					
Smoking amount (pack·year)	53.9±26.7					
Body weight (kg)	64.9±11.9	66.8±11.8	<0.01	67.4±11.8	<0.01	<0.01
Body mass index (kg·m⁻²)	23.1±3.4	23.8±3.5	<0.01	24.1±3.4	<0.01	<0.01
LDL cholesterol (mg/dL)	110.4±23.8	110.6±22.8	0.91	113.6±25.3	0.34	0.31
HDL cholesterol (mg/dL)	58.1±11.6	60.9±14.7	0.02	61.5±17.0	0.65	0.07
LDL-C/HDL-C ratio	1.9±0.6	1.9±0.6	0.34	2.0±0.7	0.26	0.79
Triglycerides (mg/dL)	142.4±84.5	150.3±93.9	0.64	155.6±95.8	0.62	0.47
HOMA-R index	1.2±0.9	1.4±1.0	0.64	1.5±1.0	0.11	0.12
hs CRP (ng/mL)	1045±1117	1047±1511	1.00	1354±2214	0.50	0.38
IL-6 (pg/mL)	2.0±1.0	2.0±1.4	0.97	2.3±1.6	0.35	0.29
TNF-α (pg/mL)	1.1±0.5	1.2±0.6	0.24	1.1±0.5	0.67	0.61
Adiponectin (μg/mL)	4.0±1.9	4.3±2.3	0.08	3.9±2.1	0.02	0.61
CIMT (mm)	0.77±0.24	0.75±0.18	0.48	0.77±0.20	0.35	0.96
CAVI	8.5±1.2	8.6±1.3	0.80	8.3±1.1	0.12	0.27
ABI	1.17±0.06	1.14±0.06	0.11	1.15±0.07	0.56	0.30
FMD (%) †	3.7±2.1	4.6±2.0	0.12	4.3±1.9	0.38	0.28

p¹:compared 1 week after the end of treatment with baseline
p²:compared 9 weeks with 1 week after the end of treatment
p³:compared 9 weeks after the end of treatment with baseline
†: n=8

failed to quit (10 smokers succeeded in quitting until 1 week after cessation of patch use, but began smoking again, and the other 14 smokers resumed smoking during patch use). Thus, only data from the 28 subjects who successfully quit smoking were analyzed. Table 1 shows the clinical characteristics at baseline and after smoking cessation. Among all 28 patients, body weight and BMI significantly increased by 1.9±1.7 kg (p<0.001) and 0.7±0.7 kg/m² (p< 0.001) respectively, at 1 week after the end of treatment, and an additional 0.6±1.1 kg (p=0.006) and 0.2±0.4 kg/m² (p=0.005) respectively, at 9 weeks after the end of treatment.

HOMA-R was increased and adiponectin levels were decreased in weight gainers after smoking cessation

Among all subjects, serum adiponection levels were increased at 1 week after the end of treatment, but this change was not significant (mean difference 0.3±0.9 μg/mL, p= 0.08). However at 9 weeks after the end of treatment, adiponectin levels were significantly decreased (mean difference between 1 week and at 9 weeks after the end of treatment 0.4±0.9 μg/mL, p=0.02). HOMA-R index increased gradually after smoking cessation, but this change was not significant. No significant difference was observed among hsCRP, TNF-α, IL-6, or LDL-C/HDL-C.

Next, we compared clinical characteristics between weight gainers (Table 2) and weight maintainers (Table 3). In weight gainers (n=18), serum adiponection levels were increased at the end of 1 week after the end of treatment, but this change was not significant (mean difference 0.4±1.0 μg/ mL, p=0.08). Moreover, at 9 weeks after the end of treatment, adiponectin levels were significantly decreased (mean

difference between 1 week and at 9 weeks after the end of treatment 0.8±0.9 μg/mL, p=0.002). In weight maintainers (n=10), adiponectin increased slightly after smoking cessation, but this difference was not significant.

In weight gainers, HOMA-R index increased gradually after smoking cessation, and the difference between baseline and 9 weeks after the end of treatment was significant (mean difference 0.4±0.7, p=0.01). However, in weight maintainers, HOMA-R index showed no differences between baseline and at 1 week or at 9 weeks after the end of treatment.

Vascular study showed no differences after smoking cessation

Among all patients, CIMT, CAVI, and ABI showed no differences between baseline and at 1 week or at 9 weeks after the end of treatment (Table 1). Even in weight gainers (Table 4) or weight maintainers (Table 5) CIMT, CAVI, and ABI showed no differences between baseline and at 1 week or at 9 weeks after the end of treatment. FMD was measured in a part of all patients and increased at 1 week after the end of treatment, but this change was not significant (mean difference 0.9±1.4%, n=8, p=0.12). This increase was temporal, and at 9 weeks after the end of treatment, FMD decreased, although changes were not significant (mean difference between 1 week and at 9 weeks after the end of treatment 0.3±1.0%, p=0.38) (Table 1).

Discussion

Insulin resistance is key in the pathophysiology of metabolic syndrome. Epidemiologic evidence and experimental studies have suggested that smoking impairs glucose toler-

Table 2. Changes of HOMA-R and Adiponectin in Weight Gainers after Smoking Cessation

Charastristics	Baseline	1 week after the end of treatment	p[1]	9 weeks after the end of treatment	p[2]	p[3]
Age	54.2±12.4					
Smoking amount (pack・year)	53.0±28.0					
Body mass index (kg・m^{-2})	23.1±3.4	24.1±3.6	<0.01	24.5±3.5	<0.01	<0.01
LDL-C/HDL-C ratio	1.9±0.6	1.8±0.6	0.34	1.9±0.7	0.08	0.93
HOMA-R index	1.0±0.6	1.4±1.1	0.07	1.5±1.2	0.43	0.01
hs CRP (ng/mL)	1070±1292	626±436	0.16	1084±1794	0.17	0.74
Adiponectin (μg/mL)	4.2±2.2	4.6±2.6	0.08	3.9±2.3	<0.01	0.34

p[1]:compared 1 week after the end of treatment with baseline

p[2]:compared 9 weeks with 1 weekafter the end of treatment

p[3]:compared 9 weeks after the end of treatment with baseline

Table 3. Changes of HOMA-R and Adiponectin in Weight Maintainers after Smoking Cessation

Charastristics	Baseline	1 week after the end of treatment	p[1]	9 weeks after the end of treatment	p[2]	p[3]
Age	59.4 ± 11.3					
Smoking amount (pack・year)	61.7±26.7					
Body mass index (kg・m^{-2})	23.2±3.8	23.4±3.5	0.29	23.4±3.3	0.78	0.42
LDL-C/HDL-C ratio	2.1±0.6	2.1±0.6	0.50	2.1±0.6	0.56	0.96
HOMA-R index	1.4±1.3	1.3±0.8	0.76	1.3±0.7	0.98	0.77
hs CRP (ng/mL)	798±367	1596±2334	0.38	722±415	0.34	0.63
Adiponectin (μg/mL)	3.3±1.1	3.3±1.2	0.78	3.5±1.6	0.46	0.51

p[1]:compared 1 week after the end of treatment with baseline

p[2]:compared 9 weeks with 1 weekafter the end of treatment

p[3]:compared 9 weeks after the end of treatment with baseline

ance and insulin sensitivity (13). The risk for insulin resistance is also closely linked to the degree of smoking (14). Interestingly, Eliasson et al (15) demonstrated that the degree of insulin sensitivity, measured with the euglycemic hyperinsulinemic clamp technique, is increased after smoking cessation in spite of a modest increase in body weight. Assali et al (4) also demonstrated that insulin sensitivity assessed by minimal model analysis is increased after nicotine withdrawal. Plasma adiponectin concentrations are associated with insulin resistance. Otsuka et al (7) demonstrated the plasma adiponectin levels in Japanese patients with stable angina pectoris were elevated 6 months after smoking cessation. Efstathiou et al (8) also demonstrated that adiponectin levels in healthy Greek smokers were increased 9 weeks after smoking cessation. Nicotine directly inhibits the adiponectin gene expression (8). The consumption of circulating adiponectin also occurs in injured vascular walls (16). Smoking cessation has been suggested to increase the level of adiponectin by reducing the smoking-induced detrimental effects on adiponectin. Although smoking cessation has beneficial effects on CVD morbidity and mortality, it is also associated with weight gain, which is also a strong risk factor for CVD. Weight gain is also associated with a substantial risk for abnormal glucose tolerance and insulin resistance (16). In the present study, we confirmed that smoking cessation increased body weight and BMI and demonstrated that HOMA-R in weight gainers was significantly increased

after smoking cessation, whereas that in weight maintainers was not. We also demonstrated that adiponectin in weight gainers was decreased at 9 weeks after the end of treatment, whereas that in weight maintainers was not. Our findings strongly suggested that the adverse effects of weight gain attenuate some of the beneficial effects of smoking cessation and that interventions to reduce the weight gain that occurs with smoking cessation might be necessary to gain the maximum benefit from smoking cessation. In the present study even in the weight maintainers, HOMA-R and adiponectin showed no significant differences between the baseline and after the smoking cessation. Conflicting results from previous reports (4, 15) may have been due to the length of the period after the cessation, differences in patient characteristics (age, gender, race, underlying disease), or smaller sample number.

The mechanisms of weight gain after smoking cessation include an increase in energy intake, a decrease in energy expenditure, a decrease in physical activity and an increase in lipoprotein lipase activity (10, 18). Recently, our group demonstrated that the rate of gastric emptying was temporally accelerated after smoking cessation (19). As there is a positive correlation between gastric emptying and appetite, the acceleration of gastric emptying may be involved in the increase in energy intake after smoking cessation. Another factor contributing to weight gain is genetic factors. Munafó et al demonstrated that dopamine D4 receptor (DRD4) geno-

Table 4. Vascular Study in Weight Gainers after Smoking Cessation

Charactristics	Baseline	1 week after the end of treatment	p^1	9 weeks after the end of treatment	p^2	p^3
CIMT (mm)	0.72 ± 0.12	0.72 ± 0.14	0.97	0.72 ± 0.15	0.94	0.99
CAVI	8.5 ± 1.3	8.2 ± 0.7	0.35	8.0 ± 1.0	0.36	0.21
ABI	1.16 ± 0.05	1.13 ± 0.06	0.09	1.16 ± 0.08	0.07	0.87

p^1: compared 1 week after the end of treatment with baseline
p^2: compared 9 weeks with 1 week after the end of treatment
p^3: compared 9 weeks after the end of treatment with baseline

Table 5. Vascular Study in Weight Maintainers after Smoking Cessation

Charactristics	Baseline	1 week after the end of treatment	p^1	9 weeks after the end of treatment	p^2	p^3
CIMT (mm)	0.83 ± 0.36	0.77 ± 0.21	0.41	0.82 ± 0.26	0.23	0.98
CAVI	8.7 ± 1.0	8.8 ± 1.0	0.57	8.8 ± 1.2	0.75	0.80
ABI	1.19 ± 0.04	1.15 ± 0.08	0.16	1.14 ± 0.06	0.66	0.08

p^1: compared 1 week after the end of treatment with baseline
p^2: compared 9 weeks with 1 week after the end of treatment
p^3: compared 9 weeks after the end of treatment with baseline

type was significantly associated with BMI, and possession of the -521 C-allele is associated with increased BMI after smoking cessation (20). The DRD4 gene has also been reported to be associated with human personality trait of novelty seeking, which is also associated with obesity and food craving (20).

There are some interventions that have been specifically designed to reduce weight gain after smoking cessation (17). Although behavioral interventions such as general advice are not effective, individualized programs, such as low-calorie diets and cognitive behavioral therapy (CBT), were associated with reduced weight gain (18). Current medications for smoking cessation do not prevent weight gain, although both bupropion and fluoxetine were found to blunt weight gain during treatment (19, 20). Further studies using combination CBT and pharmacotherapy are thus warranted. In the present study one-third of subjects did not gain weight and we could divide the patients into two groups: weight maintainers and weight gainers. If we can predict who will be a weight gainer after smoking cessation, more effective and intensive interventions will be practicable. A genetic approach to know the candidate who will likely be a weight gainer may be useful to tailor the smoking cessation program to prevent the weight gain after cessation in future.

FMD in the brachial artery using ultrasound has been shown to reflect endothelium-dependent vasodilation (21). Endothelial dysfunction represents an early stage in the development of atherosclerosis, which results in CVD. Previous studies (22) have demonstrated that FMD in chronic smokers is significantly lower than that in nonsmokers and that acute smoking impairs endothelial function (23). Although smoking-induced endothelial dysfunction is suggested, few studies have investigated the early effect of smoking cessation on endothelial function. In the largest prospective randomized trial to date, Johnson et al (24) demonstrated that FMD increased after 1 year in those who

quit smoking, but did not change in those who continued to smoke. The present study offers a prospective examination of the early effects of smoking cessation on FMD. We showed that FMD tended to be increased at 1 week after the end of treatment but returned to baseline levels at 9 weeks after the end of treatment. Various studies (9) have found evidence that weight gain is greater during the first 1 - 2 months following smoking cessation. The adverse effects of weight gain after smoking cessation might be also greater at that time and attenuate the beneficial effects of smoking cessation on FMD. We did not have a high enough number of smokers whose FMD was measured to analyze the effect of smoking cessation on sub-groups (that is, weight gainers and weight maintainers). Larger prospective studies in which FMD of weight gainers is compared with that of weight maintainers are essential to clarify how weight gain after smoking cessation affects FMD.

In conclusion, we have demonstrated that HOMA-R in weight gainers was significantly increased after smoking cessation and adiponectin in weight gainers was also decreased at 9 weeks after the end of treatmentt. Our findings strongly suggested that the adverse effects of weight gain attenuate some of the beneficial effects of smoking cessation and that interventions to prevent the weight gain after smoking cessation might be necessary to gain the maximum benefit from smoking cessation.

The authors state that they have no Conflict of Interest (COI).

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