Effects of Cigarette Smoking and Its Cessation on Body Weight and Plasma Leptin Levels

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Smokers weigh less than age-matched nonsmokers, and most smokers gain weight after smoking cessation due to an increase in food intake and a decrease in energy expenditure. Leptin is an endocrine signal thought to regulate body fat stores through hypothalamic control of energy intake and expenditure. To determine whether the "weight-reducing" effects of smoking may be mediated by leptin, we measured plasma leptin concentrations in 22 middle-aged and older male smokers (body mass index [BMI], 28 ± 1 kg/m², mean ± SEM) and 22 nonsmokers matched to the smokers for age (64 ± 1 years) and BMI (28 ± 1 kg/m²). The body weight and leptin concentration were remeasured at 3 and 6 months in 13 of the smokers who successfully stopped smoking. The leptin concentration correlated positively with the BMI in both smokers ($r = .74$, $P < .001$) and nonsmokers ($r = .76$, $P < .001$). However, the intercept of the regression line was higher for smokers versus nonsmokers ($P < .05$), with no difference in the slope. Thus, male smokers have a higher leptin level for a given BMI than nonsmokers. Following 6 months of smoking cessation, body weight increased by 7% (6.0 ± 0.1 kg, n = 13, $P < .01$). Despite this weight gain, the mean leptin concentration did not increase with smoking cessation. On average, leptin levels were 25% lower than would be expected for the amount of weight gained after smoking cessation. These findings suggest that cigarette smoking directly elevates circulating plasma leptin concentrations, and this increase may be one mechanism for the lower body weight of smokers compared with nonsmokers.

CIGARETTE SMOKING is associated with a reduced body weight. Cross-sectional studies show that smokers weigh less than age-matched nonsmokers, while longitudinal data show that most smokers gain weight after smoking cessation.[1-3] This weight gain is the result of an increase in food intake[4,5] and a decrease in energy expenditure[4,6,7] upon cessation of smoking. Moreover, nicotine has a direct effect on adipose tissue metabolism, which diverts fat storage from adipose tissue during smoking and influences the rate of weight gain following smoking cessation.[2,8,9]

After the cloning of the *ob* gene, its protein product, leptin, emerged as a major endocrine signal in the homeostatic control of body weight.[10] Leptin is expressed and secreted by adipocytes and is thought to regulate body fat stores through hypothalamic control of energy intake and expenditure.[11,12] Administration of leptin reduces food intake, increases energy expenditure, and decreases body weight in rodents.[11,13] In humans, both adipose tissue leptin gene expression and circulating leptin concentrations are elevated in the obese state,[14-16] decrease following weight loss,[16,17] and increase again with weight gain.[18]

Since cigarette smoking has profound effects on food intake, energy expenditure, and adipose tissue metabolism, we hypothesized that the "weight-reducing" effects of smoking may be mediated by leptin. This study examines whether plasma leptin concentrations differ between middle-aged and older male smokers and nonsmokers, and whether the plasma leptin level and its relationship to body weight are altered with smoking cessation.

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SUBJECTS AND METHODS

Subjects

Sixty-one men (aged > 50 years) with a smoking history of at least 10 cigarettes per day were recruited for participation in a smoking cessation intervention study through newspaper advertisements and radio announcements from the Baltimore metropolitan area. All subjects underwent an initial screening evaluation that included a medical history, physical examination, fasting blood profile, 12-lead resting electrocardiogram, and pulmonary function test. Patients were excluded if they had a history of cardiac disease (myocardial infarction, congestive heart failure, or peripheral artery disease), were on oxygen therapy, had a seizure disorder, were taking steroids, digoxin, antabuse, or medications for Parkinson's disease, or had cancer. If there was a history of depression or evidence of depression on the Center for Epidemiological Study-Depression Scale, the patient was referred to a psychiatrist for further evaluation to determine whether treatment was needed before acceptance into the program. A total of 34 male smokers met the inclusion criteria, and 22 had blood samples for the measurement of plasma leptin concentrations.

Nonsmokers of a similar age from the Baltimore area were recruited for participation in weight loss and exercise intervention studies that are ongoing at the Geriatric Research, Education and Clinical Center (GRECC) and the University of Maryland, Division of Gerontology. All subjects underwent a similar screening evaluation as the smokers but did not have pulmonary function tests. The nonsmoking men had not smoked for a period of at least 5 years and were healthy, sedentary (<20 minutes of exercise 2 d/wk), and weight-stable (<2.0-kg weight change in the prior year). Data were collected on 22 nonsmoking men matched to the smokers for age and body mass index ([BMI] weight in kilograms divided by height in meters squared). All subjects provided informed written consent to participate in the study according to the guidelines of the University of Maryland Institutional Review Board for Human Research.

Experimental Design

Body weight and height were measured and the BMI was calculated on all subjects at baseline. A venous blood sample was drawn following a 12-hour overnight fast for measurement of the leptin concentration. The smokers then consulted weekly for 2 hours with a registered nurse and behavioral psychologist for a period of 15 weeks for instruction in a cognitive-behavioral approach to smoking cessation. Nicotine replacement patches were optional, and 73% of the subjects (16 of 22) used the patches according to the following recommendations: 21 mg for 4 weeks, 14 mg for 4 weeks, 7 mg for 4 weeks, and then discontinuation. Compliance with smoking cessation was monitored by measurement of expired carbon monoxide prior to each session to validate the self-reported smoking status. We measured body weight and height and collected a fasting blood sample at 3 months and 6 months after the day of smoking cessation.

Leptin Concentrations

Fasting venous blood samples for measurement of the leptin concentration were drawn into chilled tubes containing 1 mg EDTA/mL blood. Plasma was separated by centrifugation at 4°C, and all samples were stored at −70°C until analysis. The leptin level was measured in duplicate using a radioimmunoassay (Linco, St Louis, MO).[13] The interassay and intraassay coefficient of variation for the measurement of leptin is 3.5% and 5.2% in our laboratory, respectively.

Statistical Analyses

Baseline data in smokers and nonsmokers were compared using Student's t test or the Mann-Whitney U nonparametric test (leptin). Differences between smokers for relevant variables at baseline and 3 months and 6 months after smoking cessation were determined using repeated-measures ANOVA. Leptin concentrations were not normally distributed and were transformed using the natural logarithm for regression analyses. Relationships between the logarithm of the plasma leptin concentration and BMI at baseline were determined by linear regression analyses with calculation of Pearson product correlation coefficients. The slope and intercept of the regression lines were compared among smokers, nonsmokers, and ex-smokers using multiple regression analyses. All data are presented as the mean ± SEM, and statistical significance is denoted by a P value less than .05.

RESULTS

Comparison of Smokers and Nonsmokers

The smokers smoked a mean of 29 ± 3 cigarettes per day prior to smoking cessation. The number of cigarettes smoked at baseline did not correlate with the body weight ($r = .10$) or leptin concentration ($r = .11$). The age, body weight, and BMI did not differ between smokers and nonsmokers, but the absolute leptin concentration and leptin per kilogram of body weight were higher in smokers versus nonsmokers ($P < .05$; Table 1).

The relationship of the leptin concentration to the BMI was highly significant in both smokers ($r = .74$, $P < .001$) and nonsmokers ($r = .76$, $P < .001$), and the intercept of the regression line was higher in smokers versus nonsmokers ($P < .05$), with no difference in slope (Fig 1). Thus, middle-aged and older male smokers have approximately 60% higher leptin levels for a given BMI than nonsmokers.

Effects of Smoking Cessation

Of 22 smokers studied at baseline, 18 stopped smoking for 3 months and 13 of these remained cigarette-free for 6 months.

Table 1. Physical Characteristics of Male Smokers and Nonsmokers at Baseline (mean ± SE)

Characteristic	Smokers (n = 22)	Nonsmokers (n = 22)
Age (yr)	62 ± 1	64 ± 1
Body weight (kg)	83.6 ± 2.2	82.9 ± 2.7
BMI (kg/m²)	27.6 ± 0.07	27.6 ± 0.7
Leptin (ng/mL)	8.4 ± 1.3	5.2 ± 0.6*
Log leptin (ng/mL)	0.84 ± 0.06	0.59 ± 0.06†
Leptin/body weight (ng/mL/kg)	0.097 ± 0.013	0.061 ± 0.005*

*$P < .05$ *v* smokers.
†$P < .01$ *v* smokers.

All 13 ex-smokers used the nicotine patch for the first 3 months of smoking cessation. The physical characteristics and leptin data at baseline, 3 months, and 6 months for these 13 men are shown in Table 2. Following smoking cessation, body weight increased by a mean of 4.6 ± 0.7 kg (5%) at 3 months and an additional 1.0 ± 0.2 kg (1%) at 6 months. Despite this weight gain, the mean leptin level did not increase at 3 and 6 months after smoking cessation. Rather, the leptin concentration per kilogram of body weight tended to decrease with smoking cessation (−7% ± 6%); however, this difference did not reach statistical significance ($P = .09$). Changes in body weight did not correlate with changes in leptin levels at 3 months ($r = .30$) or 6 months ($r = .22$), suggesting that changes in leptin levels with smoking cessation are dissociated from changes in body weight.

Figure 2 shows the logarithm of leptin concentrations plotted against body weight at baseline and following 6 months of smoking cessation in 13 men who successfully stopped smoking. In these 13 men, leptin levels were positively correlated with body weight at baseline ($r = .71$, $P < .01$) and after smoking cessation ($r = .75$, $P < .01$). Individually, 12 of 13

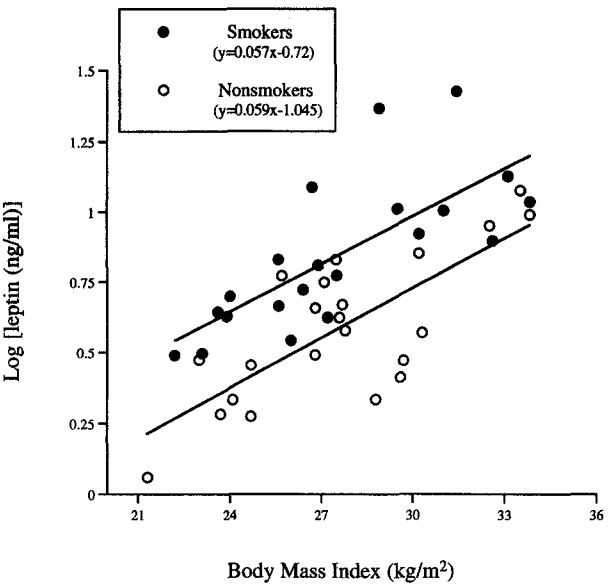

Fig 1. Relationship of the logarithm of plasma leptin to BMI in 22 smokers ($r = .74$, $P < .01$) and 22 BMI-matched nonsmokers ($r = .76$, $P < .01$). The intercepts of the lines differ significantly ($P < .05$).

Table 2. Physical Characteristics of 13 Ex-smokers at Baseline and 3 Months and 6 Months After Smoking Cessation

Characteristic	Baseline	3 Months	6 Months
Body weight (kg)	86.7 ± 3.3	91.3 ± 3.4*	92.3 ± 3.0*
BMI (kg/m²)	28.4 ± 1.1	29.9 ± 1.0*	30.3 ± 0.9*
Leptin (ng/mL)	10.1 ± 2.0	8.6 ± 1.2	8.8 ± 1.2
Log leptin (ng/mL)	0.91 ± 0.08	0.89 ± 0.06	0.90 ± 0.06
Leptin/body weight (ng/mL/kg)	0.112 ± 0.021	0.092 ± 0.012	0.093 ± 0.011

*$P < .01$ *v* baseline.

ex-smokers gained body weight (6.2 ± 0.1 kg) with smoking cessation, but leptin concentrations only increased in seven and decreased in six of these 13 men. On average, leptin levels were 25% lower in these 13 men than would be expected for the amount of weight gained with smoking cessation.

To determine whether smoking cessation eliminated the difference in leptin concentrations between smokers and nonsmokers, we compared the regression lines of the leptin concentration to the BMI at baseline and 6 months in 13 ex-smokers and at baseline in 13 nonsmokers matched by BMI to the 13 smokers (Fig 3). The intercept of the regression line for the smokers was higher than the intercept of the line for nonsmokers ($P < .05$), as previously shown for the 22 men. However, neither the slope ($P = .74$) nor the intercept ($P = .55$) of the line differed for the 13 ex-smokers versus 13 nonsmokers, suggesting that smoking cessation eliminated the difference in leptin concentrations between smokers and nonsmokers.

DISCUSSION

This study examined whether there are differences in plasma leptin concentrations between smokers and nonsmokers, and whether the plasma leptin level and its relationship to body weight are altered with smoking cessation. We found that middle-aged and older male smokers have approximately 60% higher leptin levels for a given BMI than nonsmokers. Upon cessation of smoking, leptin concentrations did not increase despite a 7% increase in body weight. In fact, leptin levels were 25% lower than would be expected for the amount of weight gained with smoking cessation. These findings suggest that cigarette smoking directly elevates circulating plasma leptin concentrations. Thus, the smoking-induced increase in plasma leptin may be one physiological mechanism for the lower body weight of smokers relative to nonsmokers.

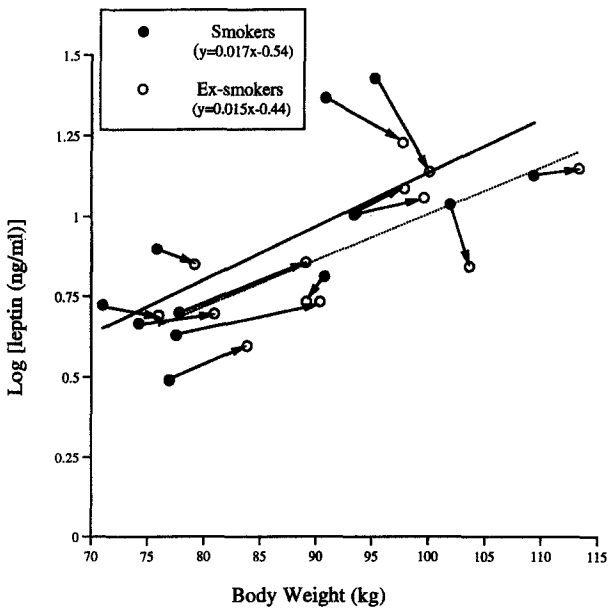

Fig 2. Relationship of the logarithm of plasma leptin to body weight at baseline ($r = .71$, $P < .01$) and 6 months after smoking cessation ($r = .75$, $P < .01$) in 13 men who stopped smoking.

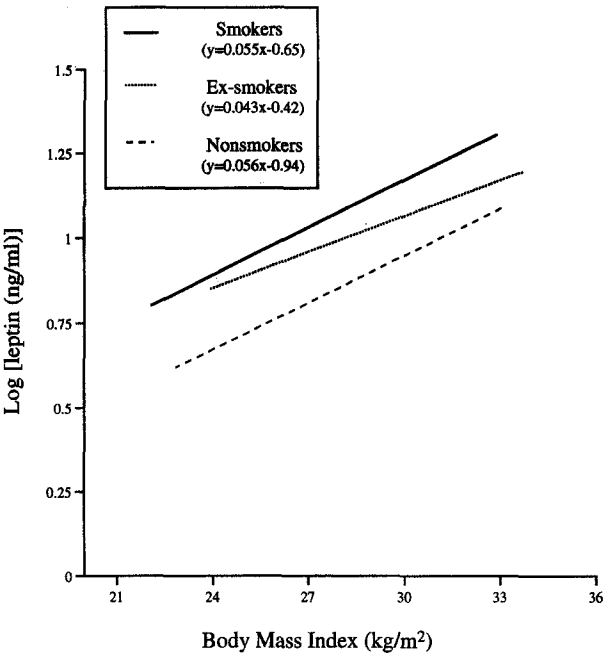

Fig 3. Relationship of the logarithm of plasma leptin to BMI in 13 smokers ($r = .75$, $P < .01$) and ex-smokers ($r = .70$, $P < .01$) who completed 6 months of smoking cessation compared with 13 BMI-matched nonsmokers at baseline ($r = .76$, $P < .01$). Only the intercepts of the lines for smokers and nonsmokers differ ($P < .05$).

The elevated plasma leptin concentrations observed in smokers compared with BMI-matched nonsmokers may be due to a smoking-stimulated increase in adipose tissue leptin secretion or a decrease in leptin clearance. The uptake and degradation of leptin by renal tissue accounts for 80% of leptin removal from the plasma in nonsmokers.[19] Therefore, any effects of smoking on renal leptin removal would result in elevated plasma leptin levels. Alternatively, it is possible that smoking causes an increase in adipose tissue leptin production and secretion, either directly via effects on the adipocyte or indirectly via other hormonal mechanisms. Previous studies document that nicotine increases adipose tissue lipolysis,[9,20] and smokers have elevated fasting adipose tissue lipoprotein lipase activity than weight-matched nonsmokers.[2,8] Whether nicotine also directly increases adipocyte production and secretion of leptin is not known. A hormonally mediated increase in leptin production and secretion by adipocytes also could explain the higher leptin levels in smokers. Cigarette smoking enhances the adrenal release of glucocorticoids,[21] which increase leptin expression in

adipose tissue and elevate plasma leptin concentrations.[22,23] A final possible explanation for the higher leptin levels in smokers may be that smoking induces a decrease in the hypothalamic sensitivity to leptin, resulting in a disruption of the leptin feedback loop and a subsequent increase in adipose tissue leptin production. However, it is unlikely that smokers have a greater leptin resistance than nonsmokers, because they tend to maintain a lower body weight than nonsmokers.

The endocrine action of leptin, as identified in the rodent model, is to decrease food intake via its effects on appetite-regulating neuropeptides in the hypothalamus[12,24] and to increase energy expenditure by elevating sympathetic nervous system activity and upregulating uncoupling proteins.[25-26] Nicotine administration markedly decreases food intake in rats through inhibition of the hypothalamic synthesis of neuropeptide Y (NPY), a powerful appetite-stimulating neuropeptide.[27] This suggests that the nicotine-induced decrease in NPY may be mediated by its stimulatory effect on the leptin concentration. Due to the lack of leptin administration studies in humans, its role in the regulation of energy balance in humans is uncertain. Because the circulating plasma leptin level is proportional to the amount of fat mass,[14,16] it is postulated that obesity in humans is characterized by a resistance to leptin's catabolic actions. If this is the case, smokers may eat less and have a higher rate of energy expenditure because of a higher concentration of circulating leptin. Furthermore, since relatively low plasma leptin levels predicted weight gain in Pima Indians,[28] it is feasible that relatively high leptin levels could underlie the weight-reducing effects of smoking.

Although one study showed no change in plasma leptin concentrations after 2 weeks of smoking cessation in four male Japanese smokers,[29] the present study is the first to report the long-term effects of smoking cessation on leptin levels. Previous cross-sectional studies either found no difference in leptin concentrations between smokers and nonsmokers[29] or found lower leptin levels in smokers compared with nonsmokers.[30,31] The findings of the present study may differ from these results because of ethnic differences among the populations studied or because of differences in study design. Two of the previous studies statistically adjusted for differences in the BMI between smokers and nonsmokers, whereas we matched smokers and nonsmokers for BMI. Furthermore, the studies reported only that the mean leptin concentration is lower in smokers versus nonsmokers, whereas we report that leptin levels are higher in smokers at any given BMI. Our finding that the leptin concentration did not change following smoking cessation despite an increase in body weight supports the hypothesis that smoking elevates plasma leptin levels in middle-aged and older men.

The strengths and limitations of this study warrant comment. The major strength is the longitudinal design that permitted the analysis of changes in plasma leptin concentrations in the same individual before and after smoking cessation. In addition, we eliminated any differences in adiposity between the two groups by individually matching the BMI of nonsmokers and smokers. However, the nonsmokers were not randomly selected, but instead were recruited for weight loss and exercise studies. This may render them different from the smokers in ways other than smoking status. This should be a consideration with regard to our finding that smoking elevates plasma leptin concentrations, and warrants the confirmation of this finding. This study's other limitation is the absence of a direct measurement of adipose tissue mass, the major contributor of plasma leptin concentrations in humans.[14,16] However, the BMI is a reasonable measure of adiposity in men.[32] This study would also be strengthened by measurements of energy intake and expenditure to address whether higher leptin levels in smokers are related to decreased food intake and increased energy expenditure. Finally, since we did not examine the acute effects of cigarette smoking on plasma leptin levels, we cannot determine whether long-term cigarette smoking is necessary to elicit a higher leptin concentration or whether a single cigarette or short-term period of smoking will increase plasma leptin concentrations.

The findings of this study suggest that cigarette smoking increases plasma leptin relative to the levels in nonsmokers, and smoking cessation eliminates this increase in leptin. Future studies are needed to determine the mechanism for this smoking-induced increase in circulating leptin levels, and whether this increase is associated with the reduced food intake and increased energy expenditure of smokers.

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