Weight Gain and Insulin Resistance during Nicotine Replacement Therapy

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Summary

Background: Although the cessation of smoking reduces the increased risk for ischemic heart disease, it is associated with marked weight gain and presumably insulin resistance, both of which heighten the risk of coronary heart disease.

Hypothesis: We investigated the isolated effect of nicotine on body weight and insulin resistance during smoking cessation.

Methods: Eleven healthy, middle-aged heavy smokers were studied. Insulin sensitivity was assessed by an insulin-enhanced, frequently sampled intravenous glucose tolerance test with minimal model analysis. The subjects were studied at baseline (last day of smoking) (phase 1), at the end of the 6-week nicotine replacement program (phase 2), and after 8 weeks without smoking or nicotine replacement (phase 3).

Results: The subjects started to gain weight during nicotine replacement (phase 2) (0.3 ± 0.2 kg/week, mean $\pm$ standard deviation) and continued to do so at a steady rate after nicotine replacement was stopped (0.2 ± 0.2 kg/week) ($p = 0.3$). Insulin sensitivity decreased by $14 \pm 2.6\%$ during nicotine replacement but increased by $16 \pm 5.1\%$ (compared with phase 2) during phase 3, even though the weight gain continued ($p = 0.047$; 95% confidence interval: 0.05–5.73).

Conclusions: Smoking cessation is associated with weight gain and improvement in insulin resistance. Nicotine is the main ingredient in cigarette smoke causing insulin resistance,

but the withdrawal of another, unknown ingredient in cigarette smoke is responsible for the weight gain associated with smoking cessation.

Key words: insulin resistance, nicotine, smoking

Introduction

Smoking is a major risk factor for atherosclerotic cardiovascular disease, cancer, and lung disease.¹ Insulin-resistance syndrome is associated with visceral obesity, elevated plasma insulin, elevated blood pressure, dyslipidemia, decreased fibrinolysis, and premature atherosclerosis;^{2,3} recent studies have found that it is also related to smoking.^{4–6} Cigarette smokers as a group are leaner and are insulin resistant compared with non-smokers.^{5,7,8} Although the cessation of smoking reduces the increased risk of ischemic heart disease, it tends to lead to marked weight gain and an increase in waist-to-hip ratio,^{8,9} both risk factors for cardiovascular disease. The components of tobacco smoke responsible for these opposing effects have not been identified, although nicotine has been implicated by some authors.^{5,7,9–11}

Temporary nicotine substitution by rate-controlled transdermal application has been shown to be effective in assisting individuals to stop smoking.¹² In this study, we took advantage of the temporary use of transdermal nicotine replacement in a group of heavy smokers to investigate the isolated effect of nicotine on weight gain and insulin resistance and thereby differentiate its effects from those of other ingredients of inhaled cigarette smoke.

Methods

Subjects

Seventeen healthy, middle-aged smokers (> 20 cigarettes/day for more than 5 years) were recruited by advertisement on the hospital bulletin board. None had a history of heart, liver, kidney, metabolic, hematologic, pulmonary, gastrointestinal, or neurologic disease, nor detectable abnormalities on physi-

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cal examination or laboratory testing. They were all normotensive (blood pressure < 140/90 mmHg) and took no regular medications. The study was approved by the hospital Ethics Committee, and all subjects gave informed consent to participate in the study.

Dietary habits were confirmed by weekly dietary recall and interviews. Subjects were encouraged not to change their dietary habits or physical activity during the study period. Two weeks after stabilization of smoking and dietary habits, the subjects stopped smoking and started replacement therapy with Nicotinel TTS® patch (Ciba-Geigy AG, Basel, Switzerland). The patches were taped daily at 8 A.M. for 24 h. All subjects used 30 cm² patches (providing 21 mg of nicotine over 24 h) for the first 2 weeks, followed by 20 cm² patches (14 mg/24 h) for 2 weeks, and then 10 cm² patches (7.7 mg/24 h) for the last 2 weeks. Body weight was recorded weekly, and, using a nonelastic tape with the subjects standing, waist and hip circumferences were measured according to the World Health Organization criteria.¹³

Plasma cholesterol, triglyceride, and high-density lipoprotein (HDL) levels were determined by enzymatic methods (Boehringer-Mannheim, Mannheim, Germany) after a 12-h overnight fast. Plasma lipoproteins were determined by the beta-quantification method designed for the Lipid Research Clinics protocol.¹⁴ Insulin sensitivity (SI) was assessed by an insulin-enhanced, frequently sampled intravenous glucose tolerance test (FSIGT) with minimal model analysis.¹⁵ The FSIGT was conducted after an overnight fast and 30 min recumbency. An intravenous line was inserted into each antecubital vein, one for glucose and insulin administration and one for sampling. Glucose (0.3 g/kg) and insulin (0.03 U/kg) were injected intravenously at 0 and 20 min, respectively, and blood samples for glucose and insulin determination were collected at -5, -1, 2, 4, 6, 8, 10, 12, 14, 16, 19, 22, 23, 25,

27, 30, 40, 50, 60, 90, 120, and 180 min. Blood glucose was determined by the glucose-oxidase method (Boehringer, Mannheim) and serum insulin by radioimmunoassay (Sorin, Biomedica, Saluggia, Italy).

The subjects were studied at baseline, on the last day of smoking (phase 1), at the end of nicotine replacement therapy (phase 2), and 8 weeks without smoking or nicotine replacement (phase 3). Due to the effects of the menstrual cycle on plasma lipids and insulin sensitivity,^{16,17} the studies in women were synchronized on the same day $\pm$ 2 days of the menstrual cycle.

Statistical Analysis

Data are presented as mean $\pm$ standard deviation (SD). Significance of differences between phases were evaluated by Student's *t*-test for paired data. Repeated measures analysis of variance (ANOVA) was used to compare the different periods, and Pearson correlation coefficient was used to study the degree of association between changes in SI and weight. A *p* value of $\leq$ 5% was considered significant.

Results

Of the 17 subjects enrolled in the study, 6 did not comply with the study protocol and were excluded from the analysis (5 resumed smoking and 1 had a skin allergy to the nicotine patches). The baseline characteristics of the remaining 11 subjects (6 men and 5 women) are shown in Table I. The number of cigarettes smoked daily was 24 ± 6 and the duration of smoking was 31 ± 12 years (mean $\pm$ SD).

TABLE I Baseline characteristics of the study group (phase 1) (mean $\pm$ SD)

	Men	Women
No. of subjects	6	5
Age (years)	40.8 $\pm$ 6.7	43.2 $\pm$ 8.1
Weight (kg)	80.5 $\pm$ 18.7	61.5 $\pm$ 7.0
BMI (kg/m ²)	27.7 $\pm$ 5.2	23.05 $\pm$ 2.4
Waist-hip ratio	0.96 $\pm$ 0.07	0.87 $\pm$ 0.05
Smoking (pack $\times$ years)	36.7 $\pm$ 20.6	36.8 $\pm$ 12
Fasting glucose (mg/dl)	89.7 $\pm$ 14.5	85.4 $\pm$ 5.2
Fasting insulin (μ U/ml)	10.1 $\pm$ 7.6	8.8 $\pm$ 2.5
Insulin sensitivity index ($10^{-4} \times \text{min}^{-1}/(\mu\text{U}/\text{ml})$)	7.6 $\pm$ 5.5	10.4 $\pm$ 5.7
Serum cholesterol (mg/dl)		
Total	213.2 $\pm$ 29.1	184.0 $\pm$ 19.0
HDL	33.5 $\pm$ 3.9	42.4 $\pm$ 17.6
LDL	144.2 $\pm$ 32.9	115.2 $\pm$ 17.1
Serum triglyceride (mg/dl)	110.5 $\pm$ 40.5	68.4 $\pm$ 22.0

Abbreviations: SD = standard deviation, BMI = body mass index, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

TABLE II Changes from baseline of anthropometric and metabolic parameters during smoking cessation ($\Delta\%$ mean $\pm$ SD)

	Nicotine replacement (6 weeks)	No nicotine replacement (8 weeks)
Body weight	+2.5 $\pm$ 2.4%	+4.5 $\pm$ 3.4
Waist-hip ratio	—	+3.3 $\pm$ 5.6
Fasting glucose	-1.5 $\pm$ 20	+2.1 $\pm$ 17.5
Fasting insulin	+11 $\pm$ 34	+7 $\pm$ 38
Insulin sensitivity index ($10^{-4} \times \text{min}^{-1}/(\mu\text{U}/\text{ml})$)	-14 $\pm$ 26 ^a	+2 $\pm$ 51 ^a
Serum cholesterol		
Total	-2 $\pm$ 12	-9 $\pm$ 15.5 ^b
HDL	+16 $\pm$ 14 ^c	+13 $\pm$ 19.2 ^d
LDL	-5 $\pm$ 14	-4 $\pm$ 14
Serum triglyceride	+1 $\pm$ 35	+3 $\pm$ 31

^a*p* = 0.047.

^b*p* = 0.06.

^c*p* = 0.004.

^d*p* = 0.08.

Abbreviations as in Table I.

Changes in the anthropometric variables and biochemical analyses during the study are shown in Table II. Subjects began to gain weight during nicotine replacement (0.3 ± 0.2 kg/week for 6 weeks) and continued to do so after nicotine replacement was stopped (0.2 ± 0.2 kg/week for 8 weeks) ($p = 0.3$). The fasting insulin levels increased during phase 2 (nicotine replacement therapy) but decreased during phase 3 (no smoking, no nicotine replacement). The mean SI decreased by 14% during phase 2 in correlation with the 2.5% increase in body weight (Table II, Fig. 1), but increased by 16% during phase 3 (in comparison with phase 2) [$p = 0.047$; 95% confidence interval (CI): 0.05, 5.73], although weight gain continued at a rate not different from phase 2 (repeated measures analysis of variance $p = 0.63$; 95% CI: $-2.81, +1.79$). The Pearson correlation coefficients between the changes in SI and percentage weight gain were -0.79 ($p = 0.005$) for period 2 and -0.05 ($p = 0.70$) for period 3 (Fig. 1). Serum lipid and lipoprotein concentrations showed smaller changes during both periods (2 and 3): low-density lipoproteins (LDL) decreased by 5% during phase 2, but increased by 1% in phase 3, and total cholesterol decreased by 2 and 7%, respectively. High-density lipoprotein concentration increased by 16% ($p = 0.004$) in phase 2 compared with baseline and decreased by 3% in phase 3 compared with phase 2.

Discussion

We have demonstrated that smoking cessation is associated with a steady weight gain (0.2 kg/week for 14 weeks and more), which is not prevented by transdermal nicotine replacement. As expected,¹⁸ this weight gain was associated with a decrease in insulin sensitivity during the nicotine replacement period, although a similar weight gain after nicotine withdrawal was associated with an increase in insulin sensitivity.

It has been known for years that smoking cessation results in weight gain (mean 2.8 ± 4.4 kg in men and 3.5–5.0 kg in women);^{8,9,19} indeed, the increase in the prevalence of overweight in the United States has been attributed in part to smoking cessation.⁹ Although the exact mechanism for this effect is not known, several contributory factors have been proposed, such as increased food intake,²⁰ alteration in physical activity,²¹ and change in metabolic rate.^{9,22} Some authors have implicated nicotine, one of the myriad chemicals present in inhaled tobacco smoke, for this weight gain,²³ but others have failed to prevent this weight gain with the use of nicotine replacement during smoking cessation.^{24,25} Our results are in agreement with those of Hajek *et al.*²⁴ and Sutherland *et al.*²⁵ which suggest that ingredients in inhaled tobacco smoke other than nicotine play an important role in weight gain. Thus, alternative approaches are needed to minimize weight gain after smoking cessation.

Insulin resistance is associated with weight gain.^{18,26} Insulin-mediated glucose disposal declines by 30 to 40% when an individual is 40% over ideal body weight.²⁷ This increase in insulin resistance seems to result from alterations in both the number of insulin receptors and postreceptor activity.²⁶ What-

FIG. 1 Percent changes from baseline in weight and insulin sensitivity during smoking cessation and nicotine replacement (mean $\pm$ standard error of the mean). NRT = nicotine replacement therapy. $\square$ = Weight, $\blacksquare$ = insulin sensitivity.

ever the reason for the weight gain observed during smoking cessation, it was associated with an increase in insulin resistance in our subjects during nicotine replacement therapy and is consistent with previous reports.¹⁸ In contrast, the increase in insulin resistance stopped and even improved during continuous weight gain observed after nicotine replacement was stopped. Therefore, it is conceivable that nicotine rather than weight gain is responsible for the initial increase in insulin resistance observed in the present study.

Cigarette smoking is associated with decreased insulin sensitivity.^{7,8} It is known that smoking acutely impairs insulin action and leads to insulin resistance.^{4–10} These reports support a causative relationship between nicotine and insulin action and confirm the observation of Eliasson *et al.*¹⁰ that nicotine is one of the major mediators of insulin resistance in smokers. Nicotine is known to enhance the activity of the sympathetic nervous system, to raise the circulating levels of catecholamines, growth hormone, adrenocorticotrophic hormone, cortisol, prolactin, and beta-endorphin, and to decrease estrogen levels,²³ all powerful antagonists of insulin action. The conflicting observations of Bolli *et al.*²⁸ that nicotine-based chewing gum did not alter glucose uptake during a 6-h clamp in type II diabetic patients and those in the present work could be due to differences in lifestyle, diet, the presence of non-insulin dependent diabetes mellitus (NIDDM), and degree of physical activity.

Our study has several limitations. First, we confirmed smoking cessation by self-reports and not by laboratory analysis. Second, serum nicotine and cotinine levels were not measured, and therefore we cannot compare the nicotine exposure during active smoking in the study cohort with that during nicotine patch replacement. Third, we failed to prevent weight gain by a weight control program when our preliminary objective was to isolate the effect of nicotine replacement on insulin sensitivity from that of expected weight gain. Nevertheless, our use of a prospective approach, compared with earlier cross-sectional studies, increases the importance

of our observations. In addition, our longitudinal design was better suited to test the role of nicotine while keeping diet and physical activity constant.

Conclusion

Nicotine is the main ingredient in cigarette smoke causing insulin resistance, as observed in smokers and ex-smokers receiving nicotine replacement therapy. However, it is the withdrawal of ingredients other than nicotine in cigarette smoke that is responsible for the weight gain associated with cessation of smoking.

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