Acute Effects of Nicotine on Serum Glucose, Insulin, Growth Hormone, and Cortisol in Healthy Smokers

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Cigarette smoking impairs glucose tolerance and alters serum levels of hormones involved in glucose metabolism, but the role of nicotine in such hormonal alterations is not well understood. In order to isolate the effects of transdermal nicotine on serum glucose, insulin, growth hormone, and cortisol in smokers, we conducted a randomized double-blind placebo-controlled cross-over study involving 34 healthy volunteer smokers between 18 and 55 years of age. Administration of a 14-mg transdermal nicotine patch resulted in nonsignificantly lowered fasting quantitative insulin-sensitivity index ($P = .11$) and a nonsignificant 9.3-mg/dL mean increase in serum glucose levels during a 75-g oral glucose tolerance test (OGTT) at time 60 minutes ($P = .12$). There were no substantial differences between groups in the areas under the curve (AUCs) for glucose ($P = .33$) or insulin ($P = .79$) during the OGTT. Levels of insulin and cortisol also were not significantly altered by nicotine. A secondary finding observed in the overall study group (primarily in females) was that nicotine caused a 29% median decrease in serum growth hormone ($P = .02$). We conclude that nicotine patches may lead to mild hyperglycemia and lowered insulin sensitivity. Further research is needed to determine the clinical implications of the unexpected finding that nicotine decreased growth hormone levels in female smokers.

CIGARETTE SMOKING is a risk factor for type II diabetes mellitus, but the mechanisms underlying the association are not clear.[1,2] Previous investigations have indicated that cigarette smoking may induce insulin resistance,[3-6] impair glucose tolerance,[7] and increase levels of glucose counter-regulatory hormones such as growth hormone and cortisol.[8-12] Long-term use of nicotine gum may be associated with hyperinsulinemia,[4] but in general it is not clear which component of tobacco smoke accounts for these hormonal changes. Nicotine has been investigated as a candidate in human studies,[9,12-14] but its role has not been established.

In the research described here, nicotine patches were used to isolate the effects of nicotine on serum glucose, insulin, cortisol, and growth hormone in healthy smokers. Because the pharmacokinetics of transdermal nicotine have been well described,[15] this system provides an objective method to deliver nicotine exposure that has not been employed in previous studies of nicotine's effects on glucose metabolism. Our hypothesis was that during an oral glucose tolerance test (OGTT), acute nicotine exposure would lower insulin sensitivity, increase glucose and insulin levels, and result in counter-regulatory changes in cortisol and human growth hormone levels.

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MATERIALS AND METHODS

This was a double-blind, placebo-controlled, cross-over study. Each subject completed 2 OGTTs, once with a placebo patch in place, and once with a nicotine patch. The nicotine patches were Nicoderm CQ 14 mg (GlaxoSmithKline, Research Triangle Park, NC); the placebo patches were fashioned locally from chrome silver with adhesive to be virtually identical to the nicotine patch. There was a wash-out period (minimum 3 days) between the 2 testing sessions. Since the elimination half-life of nicotine is approximately 3.2 hours,[16] this interval was judged long enough to separate the effects of the 2 treatment periods. The sequence of patch assignment was determined by a computerized random number generator. Both subjects and investigators were blinded to the identity of the patches until the data analysis phase of the study. Each subject gave informed consent; the study was approved by the Committee for the Protection of Human Subjects at Dartmouth-Hitchcock Medical Center.

We recruited 34 healthy smokers aged 18 TO 55 years using local hospital newsletter advertisements and fliers. Subjects were ineligible if they had a diagnosis of diabetes or hypertension, had previous adverse reactions to nicotine or latex, smoked less than 10 cigarettes per week, took medications that could potentially alter glucose levels, or could not provide informed consent. A brief medical history questionnaire and physical examination was performed at a recruitment visit to confirm eligibility. All participants were paid $50 upon completion of both study sessions.

Subjects were instructed to refrain from smoking, eating, or drinking anything except water, or using any nicotine products after 10 PM on the night before the study. Nicotine and placebo patches were assigned at the recruitment visit in a double-blind fashion. After overnight fasting and abstinence from nicotine, each smoker applied either a 14 mg nicotine patch or a placebo patch at approximately 5:30 AM. The 14-mg dose was to promote tolerability and protect against adverse reactions to nicotine. At predicted time of peak nicotine levels, approximately 3 hours later,[17] a 2-hour 75-g OGTT was administered . Glucose levels (time 0, 60, 90, and 120 minutes) and insulin levels (time 0 and 60 minutes) were then measured during the OGTT.

To confirm the effectiveness of the nicotine patch, and as a rough measure of subject compliance with time of patching and abstinence from cigarettes and coffee, we measured nicotine, cotinine, and caffeine levels on all subjects at the baseline OGTT blood draw. At 8:30 AM an initial 30-mL aliquot was drawn for baseline (time 0) nicotine, cotinine, caffeine, glucose, insulin, cortisol, and growth hormone levels. A caffeine dose of 4.45 mg/kg, corresponding to 2 cups of drip-filtered ground roasted coffee, leads to mean caffeine concentrations of

Table 1. Baseline Characteristics of Subjects (N = 33)

Subject Characteristic	Minimum	Maximum	Mean	SD
Mean body weight (kg)	45.8	113.4	72.4	16.0
Mean height (m)	1.4	1.9	1.7	.1
Mean body mass index (BMI)	18.7	37.2	25.1	4.7
Mean age (yr)	18.0	55.0	25.4	10.6
Mean no. of cigarettes/d	10.0	40.0	12.4	7.8
Mean no. of years of tobacco use	<1.0	43.0	8.0	11.0

approximately 28 mmol/L (5,432 ng/mL).[18] Assuming an elimination half-life of approximately 3 to 6 hours,[19] we expected levels no greater than the upper limit of the expected residual concentration range 7 to 11 mmol/L (1,358 to 2,134 ng/mL) if subjects complied with caffeine abstinence for at least 9 hours after drinking 2 cups of coffee or more. Cortisol and growth hormone levels were assayed at baseline; glucose was assayed at baseline, and at 60, 90, and 120 minutes; and insulin was measured at baseline and 1 hour.

All blood specimens were packed in ice while awaiting processing and stored at −70°C pending analysis. Growth hormone, insulin, and cortisol were measured on the Immulite analyzer (Diagnostics Products Corp, Los Angeles, CA). Growth hormone and insulin tests were solid-phase 2-site chemiluminescent immunometric assays, and the cortisol method was solid-phase competitive chemiluminescent immunoassay. Plasma nicotine, cotinine and caffeine concentrations were measured by gas chromatography with nitrogen phosphorus detection, modified for analysis using a capillary GC column (Clinical Pharmacology Laboratories, UCSF-San Francisco General Hospital, San Francisco, CA).[20] One subject was removed from the analysis after he acknowledged that he had eaten food prior to one of his/her test sessions, leaving a total of 33 subjects.

Calculation of Insulin Sensitivity Index and Area Under Glucose/Insulin Curves

The quantitative insulin-sensitivity check index (QUICKI) used to estimate insulin sensitivity at baseline, and was calculated as: QUICKI = 1/(log [fasting insulin] + log [fasting glucose]).[21] The areas under the curve (AUC) for glucose and insulin during the 2-hour OGTT were calculated by standard methods. Because of its lower correlation with steady-state plasma glucose, AUC should be regarded as secondary to QUICKI as a surrogate measure of insulin resistance.[22] For glucose (at time 0, 60, 90, 120 minutes): $AUC_{glu} = 60 \times 0.5 \times ([glucose]_{T0} + [glucose]_{T60}) + 30 \times 0.5 \times ([glucose]_{T60} + [glucose]_{T90}) + 30 \times 0.5 \times ([glucose]_{T90} + [glucose]_{T120})$. For insulin (at time 0 and 60 minutes): $AUC_{ins} = 60 \times 0.5 \times ([insulin]_{T0} + [insulin]_{T60})$.

Statistical Methods

We computed paired *t* tests to compare within-subject differences in glucose and insulin levels between placebo and nicotine visits. In the case of growth hormone and cortisol levels, which were not normally distributed, we used the Wilcoxon signed-ranks test, a nonparametric alternative to the paired *t* test.[23] For comparison of difference variables for growth hormone and cortisol levels between males and females, we used the Mann-Whitney *U* test, a nonparametric alternative to the unpaired *t* test. We explored relationships between key variables by computing Pearson correlation coefficients for bivariate comparisons of body mass index, nicotine levels, glucose, and insulin. Correlations involving nicotine levels as a variable were performed only during nicotine administration, and only at baseline (time 0) when nicotine levels were measured. We designed the study to have approximately 85% power to detect a difference in glucose levels of 15 mg/dL with at least 30 subjects. All statistical analyses were done using SPSS 10.1 (SPSS, Inc, Chicago, IL).

RESULTS

The baseline characteristics of the subjects are summarized in Table 1. Mean age was 25.4 ± 10.6 years (mean ± SD). Females accounted for 19 of 34 (55.9%) of subjects. Subjects did not report withdrawal effects during placebo patch administration, nor did they report nicotine effects from nicotine patches. The subjects smoked a mean (±SD) of 12.4 ± 7.8 cigarettes per day, had been smoking for an average of 8.0 ± 11.0 years, and had a mean body mass index of 25.1 ± 4.7. The mean baseline nicotine levels (ng/mL) and standard deviations were 10.4 ± 5.5 (nicotine patch) and 3.3 ± 3.9 (placebo patch). Mean cotinine levels (ng/mL) were 151.9 ± 89.2 (nicotine patch) and 116.4 ± 83.7 (placebo patch). The mean morning caffeine levels (ng/mL) were 286.0 ± 346.8 (nicotine patch) and 257.0 ± 405.3 (placebo patch). The highest caffeine level observed was 1,720 ng/mL (ie, within the range for compliance with fasting).[18] Laboratory data were complete in 31 of 34 subjects; missing data were due to difficulties with specimen processing.

Body mass index was correlated with higher baseline serum levels of glucose ($r = 0.46$, $P = .01$) and insulin ($r = 0.57$, $P = .002$) during placebo administration, and inversely with insulin action as measured by QUICKI ($r = -0.58$, $P = .001$).

During nicotine administration, there were no significant correlations between baseline serum nicotine and fasting glucose ($r = -0.07$; $P = .70$) or insulin levels ($r = -0.08$; $P = .66$).

Table 2. Paired *t*-Tests for Within-Subject Differences, Nicotine Versus Placebo (N = 33)

Difference (nicotine-placebo)	Mean Nicotine	Mean Placebo	Mean Difference (95% CI)	*P* Value
Time 0 min glucose (mg/dL)	90.90	90.75	0.15 (−2.4, 2.7)	.91
Time 60 min glucose (mg/dL)	140.69	131.44	9.25 (−2.3, 20.8)	.12
Time 90 min glucose (mg/dL)	113.76	110.91	2.85 (−10.0, 15.7)	.66
Time 120 min glucose (mg/dL)	96.42	98.00	−1.58 (−13.8, 10.6)	.80
Total glucose AUC (mg/dL/2 h)	13,950.00	13,502.81	447.19 (−466.1, 1360.5)	.33
Time 0 min insulin (uIU/mL)	7.96	6.87	1.09 (−1.5 3.7)	.41
Time 60 min insulin (uIU/mL)	39.56	39.34	0.22 (−8.6, 9.1)	.96
Time 0 min QUICKI	0.36	0.37	−0.01 (−0.03, 0.003)	.11
Total insulin AUC (μIU/mL/2 h)	1,425.55	1,386.27	39.27 (−253.9, 332.5)	.79

Abbreviation: CI, confidence interval.

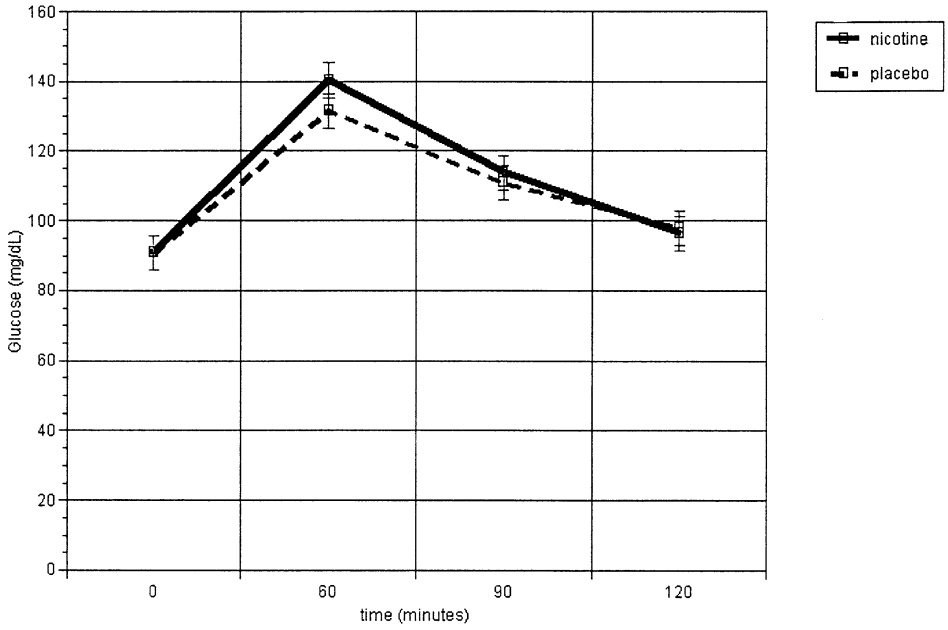

Fig 1. Mean glucose levels during a 2-hour OGTT.

The glucose levels during the OGTTs are summarized in Table 2 and Fig 1. During placebo administration, subjects' mean baseline glucose levels rose from approximately 90 mg/dL to 131 mg/dL by time 60 minutes, returning essentially to baseline by 120 minutes. The pattern in the nicotine arm was similar, except that mean peak glucose at time 60 was modestly higher (by 9.3 mg/dL, $P = .11$) than during placebo administration. Compared with placebo, nicotine resulted in a borderline significantly lowered QUICKI ($P = 0.11$). However, there was no significant difference ($P = .33$) in the AUC for glucose during the OGTT (Table 2).

Baseline cortisol was not significantly altered by nicotine ($P = .37$, Wilcoxon signed-ranks test). However, nicotine caused a 29% median decrease in serum growth hormone ($P = .02$), a finding that was observed primarily in females. There was a statistically significant 45.7% median decrease in growth hormone levels when females (N = 19) were analyzed separately ($P = .03$), whereas the median decrease among males was zero (N = 14; $P = .55$ by Wilcoxon signed-ranks test).

DISCUSSION

In this double-blind, cross-over, randomized study, we isolated the effects of nicotine on glucose metabolism in smokers. The administration of a 14-mg nicotine patch resulted in a borderline significant elevation in glucose levels during a 2-hour OGTT, and a nonsignificant lowering of baseline insulin sensitivity as assessed by the QUICKI index. Nicotine administration also resulted in a decrease in growth hormone levels.

It has been observed, as early as 1934, that smoking is associated with hyperglycemia.[24] More recent experimental studies, typically involving healthy smokers under age 65, have shown that cigarette smoking can acutely induce insulin resistance[1,3,5,6,15,25] and impair glucose tolerance.[4,7] Moreover, in retrospective studies comparing smokers to matched nonsmoking controls, smokers are relatively glucose-intolerant,[26] and have slightly higher mean hemoglobin A_{1c} levels.[27] In addition, large-scale prospective epidemiological studies have indicated that smoking increases the risk of type 2 diabetes.[2,28,29] Long-term use of nicotine gum has been associated with hyperinsulinemia and insulin resistance, implicating nicotine as a possible causative agent in the relationship between smoking and insulin resistance.[4] However, intravenous administration of low doses of nicotine did not alter insulin or glucose levels in a study involving healthy, normal weight males.[30]

In contrast to our findings, several previous studies of the effects of intense smoking exposure on glucose metabolism have shown more pronounced increases in glucose levels.[3,14] This may be because the slow, steady delivery of nicotine from a transdermal patch functions as a less potent stimulus of hyperglycemia than cigarette smoking. This may also explain the lack of increase in insulin and cortisol in response to transdermal nicotine. Our findings in humans are consistent with those of Swislocki et al, who found no significant effect of smokeless nicotine on glucose tolerance or insulin sensitivity in rats.[31,32] Another consideration is that other components of tobacco smoke may potentiate nicotine-induced impairment of glucose tolerance.

In contrast to our suggestive findings in the nicotine versus placebo analysis, we found no significant correlation between nicotine levels and glucose, insulin, and insulin sensitivity during nicotine administration, associations our study was not powered to detect. Aside from insufficient statistical power, another possible explanation for the lack of correlation between nicotine levels and insulin sensitivity is the trend towards lower nicotine levels in subjects with higher body mass index. It has been observed previously that subjects with higher body mass index achieve lower maximum nicotine concentrations during patch administration,[33] and thus body mass index may mask nicotine's relationship with insulin sensitivity measures.

Many previous studies of other hormonal effects of smoking

have also investigated intense tobacco smoke exposures with relatively high doses of nicotine.[9,12-14] For example, an increase in serum human growth hormone levels was observed after subjects smoked 3 cigarettes within 30 minutes.[34] The fact that another study investigating the effects of low-dose nicotine in cigarettes showed no significant increase in growth hormone[5,10] suggests that the effects of nicotine on this hormone may be dose-dependent.

An intriguing secondary finding in our study was the substantial decrease in growth hormone during nicotine as compared to placebo administration. Although the lowering of growth hormone was statistically significant in the entire study group, the effect was actually confined to females. Most studies of male smokers have shown an increase or no change in growth hormone in response to smoking.[8-12,14] However, we are aware of only one previous study of nicotine or cigarette smoking and growth hormone that included female smokers.[35] In this study, there was no significant change in growth hormone levels within 60 minutes of smoking 2 nonfiltered cigarettes within 8 minutes. Other prior investigations specifically excluded women, one because of the relatively high variation in growth hormone levels noted during a pilot phase of the study.[12] Despite the fact that we also observed substantial variation in growth hormone levels, the within-subject difference in growth hormone levels was large enough to achieve statistical significance in women. We view this finding as noteworthy and suggestive, but not conclusive, given that it was a secondary analysis and that our study involved multiple statistical comparisons.

Our study was not designed to measure insulin-like growth factor-1 (IGF-1) levels in serum, a time-integrated marker of growth hormone exposure. Data regarding the association between IGF-1 and cigarette smoking are not entirely consistent. Several investigations have reported an inverse association between smoking and IGF-1,[36-38] although others have not found such a relationship.[34,39,40]

Sexual dimorphism in growth hormone secretion has been repeatedly observed.[41-47] Premenopausal healthy women secrete 1.5 to 3.1 times more growth hormone than men,[45] and studies of serum basal and ambulatory growth hormone levels, and pituitary responsiveness to growth hormone–releasing hormone (GHRH) have all shown higher levels among women.[41-44,46] However, the clinical implications, if any, of lowered growth hormone in females exposed to nicotine are unclear.

We found that one subject was noncompliant with dietary restrictions imposed prior to the test, and this subject was removed from the analysis. The possibility that other noncompliance went undetected cannot be discounted. However, mean caffeine levels measured 286.0 $\pm$ 346.8 ng/mL (nicotine patch) and 257.0 $\pm$ 405.3 ng/mL (placebo patch) revealing compliance with abstinence from caffeinated beverages. In addition, all subjects were specifically asked when they last ate or smoked and they responded that they had complied with dietary and nicotine restrictions. Eliasson et al used nicotine levels of greater than 8 ng/mL as their cutoff level for noncompliance with smoking abstinence.[48] The mean baseline nicotine level in the Eliasson study following "verified abstention from smoking during the night before" was 2.8 ng/mL, which is comparable to the level observed in the placebo group in our data (3.3 ng/mL). Similar basal levels of nicotine were observed in other investigations.[13] Using a basal nicotine cutoff of $>$8ng/mL as possible evidence of noncompliance, a total of 3 subjects in the present study had questionable compliance with smoking restrictions, although all 3 subjects affirmed that they had abstained as directed. Many subjects indicated that they smoked right up until 10 PM, and nonzero nicotine levels may have reflected heavy smoking the night before the test. Reanalysis of our data excluding these 3 individuals did not substantially change any of our overall results, and did not alter our conclusions. The levels of glucose observed at baseline and during the OGTTs did not lead us to suspect any additional noncompliance beyond the one subject who admitted it. Nonetheless, it is possible that noncompliance could have adversely affected our power to detect a significant effect of nicotine on glucose tolerance.

Our findings regarding growth hormone need to be confirmed in additional studies of female smokers, and measurement of markers of overall growth hormone secretion such as IGF-1 and IGF binding protein-3 (IGFBP-3) should be performed. Growth hormone deficiency in adults is associated with insulin resistance, increased low-density lipoprotein and cholesterol, and possibly higher rates of mortality due to cardiovascular disease.[49]

In summary, at the dose used in this study, nicotine patches led to mild hyperglycemia and lowered insulin sensitivity, but neither result was statistically significant. Further research is needed to determine the clinical implications of the unexpected finding that nicotine decreased growth hormone levels in female smokers.

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