The Insulin Resistance Syndrome in Smokers Is Related to Smoking Habits

Björn Eliasson, Stig Attvall, Marja-Riitta Taskinen, Ulf Smith

Abstract The relationship between smoking habits, insulin resistance, and related risk factors for cardiovascular disease was examined in 57 middle-aged male smokers whose degree of insulin resistance was quantified by using the euglycemic clamp technique. Smoking habits correlated with degree of insulin resistance and consequently with various manifestations of the insulin resistance syndrome including levels of insulin, high-density lipoprotein cholesterol, triglycerides, and plasminogen activator inhibitor-1 (PAI-1) activity. Smoking habits, independent of degree of insulin resistance, were also related to levels of total cholesterol and low-density lipoprotein cholesterol as well as triglycerides. Stepwise regression analyses considering the effects of age, lean body mass, body fat, body mass index, waist/hip ratio, and alcohol consumption showed that only smoking habits and percent body fat were independently related to degree of insulin resistance. This study shows that insulin resistance and the insulin resistance syndrome are important but not unique contributors to the strong risk profile for cardiovascular disease in middle-aged men who smoke. (Arterioscler Thromb. 1994;14:1946-1950.)

Key Words • insulin resistance • insulin resistance syndrome • blood lipids • plasminogen activator inhibitor-1 • cigarette smoking

Smoking is a major risk factor for cardiovascular morbidity and mortality. However, it is unclear how smoking elicits its harmful effects, although many pharmacological actions are recognized. In addition, smoking is associated with differences in lifestyle, such as diet and degree of physical activity, which could contribute to the increased risk of cardiovascular disease (CVD). Smokers exhibit a number of characteristics that are established risk factors for CVD. These include a larger waist-hip ratio (WHR), which is an indicator both of fat distribution and risk for CVD, and elevated fibrinogen and triglyceride as well as lower high-density lipoprotein cholesterol (HDL-C) levels. An acute effect of cigarette smoking is to increase the activity of the sympathetic nervous system and the levels of circulating catecholamines. Since catecholamines are powerful antagonists to insulin action, smoking may be linked to insulin resistance. Smoking can, in fact, acutely impair insulin action. In a transsectional study, Facchini et al report that chronic smokers exhibit traits of impaired insulin action, including higher triglyceride and lower HDL-C levels, than a matched group of nonsmoking individuals. Consequently, cigarette smoking has been recognized as an independent risk factor for non–insulin-dependent diabetes mellitus (NIDDM) in both men and women.

In the present study we examined insulin sensitivity with the euglycemic hyperinsulinemic clamp technique and the relation of insulin sensitivity to cardiovascular risk factors within a large number of smokers. The results clearly show a correlation between smoking habits and degree of insulin resistance as well as various manifestations of the insulin resistance syndrome (IRS), including lower HDL-C and higher insulin and triglyceride levels and plasminogen activator inhibitor-1 (PAI-1) activity. Our findings show that IRS is an important, albeit not the only, reason for the increased risk for CVD in smokers.

Methods

Fifty-seven nonobese male smokers, 40 to 60 years of age, were recruited via a newspaper advertisement. They had smoked more than 10 cigarettes per day for at least 10 years. They were all healthy, normotensive (blood pressure less than 140/90 mm Hg), and took no chronic medication. The clinical characteristics of the subjects are shown in Table 1. All subjects gave their informed consent to participation in the study. The study was approved by the Ethics Committee of Göteborg University.

The subjects were screened before they were admitted to the study. At screening, the subjects were interviewed and underwent a physical examination, and routine biochemical tests for hematologic, renal, and hepatic function were performed. Blood pressure was measured by using a sphygmomanometer after the subjects had rested in the supine position for at least 10 minutes. The average weekly consumption of alcohol, number of cigarettes smoked per day, and cigarette brand used were reported. The manufacturers supplied information on the nicotine content of the cigarettes. The subjects were also asked about heredity for diabetes and/or hypertension; this was positive in 13 of 57 individuals.

Body weight was recorded to the nearest 0.1 kg with the subjects wearing only underwear and socks. Length was measured and body mass index (BMI) calculated. Waist and hip circumferences were measured by using a nonelastic tape with the subjects standing. The waist circumference was measured in the midaxillary line midway between the lowest rib margin and the iliac crest and the hip circumference at the widest diameter around the buttocks according to World Health Organization criteria. The WHR was calculated from these measurements. Naturally occurring 40K was measured in a whole-body counter, and lean body mass (LBM) was calculated from the assumption that one kilogram equals 68.1 mmol potassium as reported by Forbes et al. Body fat was calcu-

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Results

The results of the biochemical analyses are shown in Table 2. All individuals had normal fasting glucose levels (<6.7 mmol/L). However, 6 subjects had elevated triglyceride levels (>2.2 mmol/L), and 9 had total cholesterol >6.5 mmol/L. The mean glucose level at steady state during the clamp, i.e., during the last 30 minutes of the clamp, was 4.92 (±0.02) (SEM) mmol/L. Steady-state plasma insulin was 60.1 (±1.6) mU/L, and the GIR was 8.66 (±0.25) mg • kg • LBM⁻¹ • min⁻¹. There was no difference in GIR for the groups with heredity for diabetes and/or hypertension compared with the other subjects (8.68 and 8.74 mg • kg • LBM⁻¹ • min⁻¹, respectively).

Table 3 shows the correlations between the biochemical and anthropometric parameters with smoking habits, expressed as nicotine consumed per day, as well as insulin sensitivity, expressed as GIR during the clamp.

Smoking habits were negatively correlated with both LBMB and GIR (Fig 1), while positive correlations were seen with several biochemical risk factors for CVD. Although these were generally correlated with GIR, notable exceptions were found. In particular, total cholesterol and low-density lipoprotein cholesterol (LDL-C) were positively related to smoking, but they did not correlate with GIR (Table 3). In contrast, percent body fat as well as the biochemical markers of insulin resistance were related to GIR (Fig 1). Interestingly, FFA levels both in the fasting state and during the hyperinsulinemic clamp were closely related to GIR.

To separately analyze the relation of these biochemical risk factors for CVD to smoking habits and insulin sensitivity, multiple linear regression analyses were performed. As shown in Table 4, GIR was related to the FFA levels in the fasting state and during the euglycemic clamp as well as to fasting insulin, C-peptide, HDL-C, and apoA-II. The correlations with apoA-I and PAI-1 activity were of borderline significance (P<0.1).

Smoking habits were related to FFA levels during the clamp as well as triglyceride, total cholesterol, LDL-C, and apoB. Thus, GIR was generally related to various markers of IRS, and smoking habits were related to cholesterol and triglyceride levels. The relations between these variables and smoking habits are shown in Fig 2.

Table 1: Anthropometric and Clinical Characteristics of the 57 Study Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.9</td>
<td>6.3</td>
<td>40-60</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.4</td>
<td>7.7</td>
<td>57.2-92.7</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>59.7</td>
<td>5.6</td>
<td>47.6-73.4</td>
</tr>
<tr>
<td>Body fat, kg</td>
<td>17.6</td>
<td>5.9</td>
<td>6.8-29.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.7</td>
<td>2.0</td>
<td>18.1-26.4</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.92</td>
<td>0.04</td>
<td>0.79-1.0</td>
</tr>
<tr>
<td>No. of cigarettes/d</td>
<td>22.3</td>
<td>8.1</td>
<td>10-45</td>
</tr>
<tr>
<td>Nicotine, mg/d</td>
<td>23.3</td>
<td>10.9</td>
<td>3.6-54.0</td>
</tr>
<tr>
<td>Smoking, y</td>
<td>30.5</td>
<td>7.1</td>
<td>15-45</td>
</tr>
</tbody>
</table>

Table 2: Fasting Metabolic and Hemostatic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mmol/L</td>
<td>5.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td>6.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Free fatty acids (fasting), mmol/L</td>
<td>0.52</td>
<td>0.02</td>
</tr>
<tr>
<td>Free fatty acids (during clamp), mmol/L</td>
<td>0.042</td>
<td>0.003</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.4</td>
<td>0.1</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.1</td>
<td>0.04</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.8</td>
<td>0.1</td>
</tr>
<tr>
<td>LDL/HDL cholesterol</td>
<td>3.9</td>
<td>0.3</td>
</tr>
<tr>
<td>PAI-1 activity, U/mL</td>
<td>13.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and PAI-1, plasminogen activator inhibitor-1.
and alcohol consumption. After five regression steps the sole remaining independent variables in this model were smoking habits (amount of nicotine consumed per day) and percent body fat (data not shown).

### Discussion

This study showed for the first time that in a large group of healthy male smokers the amount of nicotine smoked per day is related to degree of insulin resistance. Thus, the established effect of smoking on various risk factors for CVD such as elevated triglyceride and lower HDL-C levels and higher PAI-1 activity can to a large extent be attributed to a concomitant insulin resistance in smokers. This conclusion is further substantiated by the finding that the incidence of NIDDM is also higher in smokers. Several prospective studies have shown that the degree of insulin resistance is a major predictor of future risk for NIDDM.

Apart from smoking habits, the only significant independent contribution to insulin sensitivity, measured as GIR during the euglycemic clamp, was percent body fat. It should be emphasized that the present study included only healthy middle-aged and nonobese men. In the normal population several other factors influence insulin sensitivity.

It is also clear that smoking habits, independent of GIR, were related to levels of total cholesterol and LDL-C. Several studies have also shown that smokers have higher cholesterol levels than nonsmokers (for review, see Reference 13). In addition, smoking habits per se, at least in part independent of degree of insulin resistance, seem to contribute to the higher levels of triglycerides in smokers.

There are several possible mechanisms whereby smoking can elicit insulin resistance. Multiple cardiovascular, endocrine, and neurohumoral effects of cigarette smoking are well known. An additional possibility is the smoking-related differences in lifestyle, including diet and degree of physical activity. Although the individu-
tivity, this possibility is less likely to account for the insulin resistance.

We have shown that smoking six cigarettes at a rate of two per hour acutely impairs insulin action in healthy individuals, probably due to the release of catecholamines and other counterregulatory hormones. Furthermore, Hellerstein et al report that smoking leads to acute increases in plasma glucose and FFA levels, probably due to an enhanced fat cell lipolysis. These findings, together with the present results and the transactional study by Facchini et al, strongly suggest that smoking elicits IRS, the extent of which is a function of smoking habits.

In a separate study we found that chronic smokers, even after 48 hours of tobacco abstinence, have higher levels of circulating noradrenaline than a matched group of nonsmokers (Axelsen et al). These results further emphasize the potential role of the counterregulatory hormones in eliciting insulin resistance in smokers.

Using the euglycemic hyperinsulinemic clamp technique, we have also confirmed the findings by Facchini et al that smokers, when compared with a carefully matched group of nonsmoking control subjects, are insulin resistant and exhibit the various traits of IRS (B. Eliasson, N Mero-Matikainen, M-R Taskinen, U. Smith, unpublished data, 1994).

At the cellular level catecholamines, in part through elevated cAMP concentrations, impair both the insulin signaling/transduction pathways and the intrinsic activity and synthesis of the glucose transport proteins (for review, see Reference 31). In addition, increased lipolysis and elevated FFA levels are important for the insulin resistance induced by the catecholamines.

In the present study, we found a negative correlation between FFA levels and insulin sensitivity, supporting a role by the fatty acids in modulating insulin action. However, fasting FFA levels were not correlated with smoking habits (Table 3). The reason for this is unclear, but it may be related to the 8 hours of smoking abstinence or to an increased elimination rate of FFAs during the euglycemic clamp was underestimated in the present study by expressing the data per kilogram LBM. This is an important issue to address, since smoking leads to a peripheral vasoconstriction that can impair tissue uptake/release.

Smokers have been reported to have a higher WHR than nonsmokers. Although insulin resistance is related to a high WHR in obese individuals, no such correlation could be found in the present group of nonobese smokers. Percent body fat, rather than BMI or WHR, was an independent contributor to degree of insulin resistance. It should also be emphasized that the effect of smoking on insulin-stimulated glucose uptake during the euglycemic clamp was underestimated in the present study by expressing the data per kilogram LBM.

A negative correlation was found between smoking habits and total LBM (Table 3) (mean LBMs were 61.2±1.5 and 58.2±1.2 kg for subjects with low and high levels of nicotine consumption, respectively). Since LBM is the major compartment for glucose disposal during a euglycemic clamp, this difference in body composition further underscores the degree of insulin resistance in high nicotine consumers.
The correlation between insulin sensitivity and nicotine consumption per day does not necessarily implicate nicotine as the causal factor. In fact, we saw no clear evidence of insulin resistance in individuals who used snuff to reach the same steady-state nicotine levels as those seen in smokers. Smokers, however, became less sensitive to insulin. Thus, it may well be that factors other than nicotine in cigarette smoke play a pathophysiological role for the development of insulin resistance. This is an important point to clarify, since smokers use nicotine-containing chewing gum or dermal patches to help them quit smoking.

In conclusion, the present study shows for the first time that there is a relationship between degree of insulin resistance and smoking habits. This impairment in insulin sensitivity is likely to account for the risk factors for CVD related to IRS in smokers. However, smoking is also associated with higher total cholesterol and LDL-C levels, and this association is unrelated to a concomitant insulin resistance. The present data also emphasize the role of environmental factors in modulating insulin action and precipitating risk factors for CVD.

Acknowledgments

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