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Increased Level of Hemoglobin A_{1C}, But Not Impaired Insulin Sensitivity, Found in Hypertensive and Normotensive Smokers

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Smoking is associated with an abnormal plasma lipoprotein pattern. Recently, both insulin resistance and normal insulin action have been reported in smokers. In a total of 191 hypertensive and normotensive subjects recruited from a health survey, serum lipoprotein lipids, glucose tolerance (by intravenous glucose tolerance test (IVGTT), insulin secretion, and insulin sensitivity (euglycemic insulin clamp) were compared in the 41 smokers and 150 nonsmokers. Subjects were examined in the morning during a fasting state and after abstinence from smoking for 10 to 12 hours. Smokers showed a higher level of hemoglobin A_{1c} (HbA_{1c}) as compared with nonsmokers, 4.9% versus 4.7% ($P < .05$). There were no significant differences in fasting glucose, insulin, or insulin-mediated glucose disposal. However, a number of indices of insulin sensitivity tended to show enhanced insulin action among smokers. Only lower glucose and insulin values during the late phase (40 to 90 minutes) of the IVGTT reached statistical significance. Compared with nonsmokers, smokers had an expected higher level of serum triglycerides (2.1 v 1.8 mmol/L, $P < .05$) and an increased low-density lipoprotein (LDL) to high-density lipoprotein (HDL) cholesterol ratio (4.5 v 3.9, $P < .05$). These differences between smokers and nonsmokers were similar in both hypertensives and normotensives. In conclusion, smokers examined in the abstinence phase showed no signs of impaired insulin action. Lipoprotein abnormalities and elevated HbA_{1c} may be caused in part by the insulin resistance induced during acute smoking and therefore may be quantitatively related to the time exposed to smoking. The effect on insulin sensitivity appears to be reversible over 10 to 12 hours.
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SMOKING IS ASSOCIATED with an increased incidence of cardiovascular disease in numerous epidemiologic studies.[1,2] The mechanisms underlying this association are only partly known but may involve a disturbed lipoprotein metabolism, as indicated by an increase in serum triglycerides and a decrease in serum high-density lipoprotein (HDL) cholesterol.[3,4]

Other potential atherogenic mechanisms induced by smoking include vasospasm, hyperfibrinogenemia, increased platelet aggregation, and impaired fibrinolysis.[5,6] Recently, smoking was found to be linked to insulin resistance, as determined by a modified somatostatin-infusion, insulin-suppression test.[7,8] However, this finding was challenged by a study using the modified minimal model for glucose uptake during an intravenous glucose tolerance test (IVGTT) in a large group of healthy, nonobese women,[9,10] in whom no differences between smokers and nonsmokers in terms of insulin sensitivity were found. These studies[7-10] demonstrated an increased level of serum triglycerides and a decreased level of HDL cholesterol.

The aim of the present study was to compare smokers and nonsmokers with respect to glucose metabolism, insulin secretion, and insulin sensitivity in a sample of hypertensive and normotensive subjects of both sexes.

SUBJECTS AND METHODS

Patients

Previously untreated hypertensive and normotensive subjects (n = 140 and 51, respectively) recruited from a health examination survey in Uppsala, Sweden, were investigated.[11] Their mean age was 57 years. Smokers (26 men, 15 women) and nonsmokers (93 men, 57 women) were identified in the total sample, based on a questionnaire about current smoking habits. The proportion of smokers among hypertensives was 28 of 112 (25%), and in normotensives, 13 of 38 (34%). No graded scale for smoking habits or tobacco consumption was used.

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Methods

All subjects were evaluated in the morning after a 10- to 12-hour fast when no smoking was allowed. A physical examination was performed with the measurement of height (meters), weight (kilograms), and waist and hip circumferences (centimeters). Body mass index (kg/m^2) and the waist to hip ratio were calculated. Blood pressure was measured in the supine position (mean of three readings after 10 minutes' rest, Korotkoff V) using a cuff of appropriate size.

Blood samples were drawn for quantification of cholesterol and triglyceride (TG) concentrations in serum, very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and HDL. Fasting plasma glucose and insulin concentrations (Phadeseph, Insulin RIA, Pharmacia, Uppsala, Sweden) and the mean fasting insulin of three values before an IVGTT, were determined. During the IVGTT (300 mg glucose/kg body weight), insulin and glucose values were determined at the peak (mean of values at 4, 6, and 8 minutes) and after 10 minutes at 10-minute intervals up to 90 minutes. The area under the curve, at peak, and for the rest of the curve (10 to 90 minutes) was calculated for glucose and insulin, respectively. The disappearance rate of glucose was expressed as a k value calculated from the formula $k = 100^e\log 2/T_{1/2}$, where $T_{1/2}$ is the time (minutes) required to halve the glucose concentration. Finally, a euglycemic insulin clamp[11] was performed, and the insulin-mediated glucose uptake (M) and the insulin sensitivity index (M/I), calculated as M divided by the mean plasma insulin concentration during the last 60 minutes of the procedure, were determined. In addition, the mean insulin concentration during the clamp was calculated. Metabolic clearance rate of glucose was calculated by dividing the amount of glucose metabolized (M value) by the plasma glucose concentration. Hemoglobin A_{1C} (HbA_{1C}) level was measured by high-performance liquid chromatography (normal range, 3.5% to 6.0%).[12] All methods are described elsewhere.[11]

Plasma free fatty acids (FFA) and blood hemoglobin levels and leukocyte count were determined and analyzed by routine laboratory methods. Blood hematocrit was calculated.

Statistics

All variables are shown as the mean ± SD. Student's t test was used for comparison of group means for continuous variables, and the chi-square test was used for analyzing any differences in sex distribution between groups. A multiple regression analysis was performed with M/I as the dependent variable and age, sex, smoking status, and diastolic blood pressure as independent variables. Due to the skewed distribution of insulin, we used both a Wilcoxon's rank-sum test and a t test (after log-transformation of insulin) for calculation of differences in insulin values during the IVGTT, with similar results. All significant differences between groups were also subject to analyses of covariance (taking age, sex, body mass index, and diastolic blood pressure into account). The level of significance used was P less than .05.

RESULTS

Smokers did not differ from nonsmokers in age, sex distribution, body mass index, waist to hip ratio, hemoglobin, hematocrit, or blood pressure (Table 1). A significantly higher level of HbA_{1C} was seen in smokers (4.86 ± 0.54) as compared with nonsmokers (4.67 ± 0.55) ($P < .05$), whereas no significant difference was found in fasting glucose (4.95 *v* 5.05 mmol/L) (Table 1). Fasting plasma insulin and mean fasting insulin before the IVGTT tended to be lower in smokers as compared with nonsmokers, whereas insulin values at 40 and 90 minutes were significantly lower ($P < .05$) in smokers as compared with nonsmokers (Fig 1A). No differences between the groups were seen for the

Table 1. Group Comparisons Between Nonsmokers and Smokers (mean ± SD)

Variable	Nonsmokers	Smokers	Difference (95% CI)	*P*
No.	150	41		
Sex (M/F)	93/57	26/15		
Age (yr)	57.1 ± 11.3	56.9 ± 11.5	0.2 (−3.80, 4.22)	.92
Body mass index (kg/m^2)	27.3 ± 4.8	26.6 ± 4.8	0.70 (−1.00, 2.39)	.41
Waist to hip ratio	0.89 ± 0.08	0.90 ± 0.09	−0.01 (−0.03, 0.02)	.67
Systolic blood pressure (mm Hg)	159.6 ± 25.4	153.1 ± 29.1	6.5 (−2.77, 15.76)	.16
Diastolic blood pressure (mm Hg)	96.4 ± 14.2	93.2 ± 15.5	3.2 (−1.90, 8.34)	.21
Hemoglobin (g/L)	142.3 ± 11.6	143.0 ± 14.1	−0.7 (−4.79, 3.62)	.75
Hematocrit (%)	42.2 ± 3.2	43.0 ± 3.6	−0.8 (−2.32, 0.60)	.24
HbA_{1C} (%)	4.67 ± 0.55	4.86 ± 0.54	−0.19 (−0.39, −0.0)	.048
Fasting glucose (mmol/L)	5.05 ± 0.73	4.95 ± 0.71	0.10 (−0.16, 0.36)	.43
Fasting insulin (mU/L)	8.96 ± 6.47	7.04 ± 5.58	1.91 (−0.31, 4.14)	.09
Mean fasting insulin (mU/L)	9.09 ± 6.56	7.09 ± 5.29	2.00 (−0.23, 4.23)	.07
Clamp				
M (mg glucose/kg BW/min)	6.50 ± 2.46	7.05 ± 2.02	−0.55 (−1.39, 0.28)	.19
M/I (mg glucose/kg BW/min/mU/L × 100)	7.37 ± 3.65	7.72 ± 3.36	−0.35 (−1.62, 0.92)	.58
MCR glucose (mg glucose/kg BW/min)	7.17 ± 0.24	7.80 ± 0.38	−0.63 (−1.62, 0.36)	.20
Mean clamp insulin (mU/L)	94.6 ± 1.8	97.3 ± 3.3	−2.7 (−10.37, 4.92)	.48
IVGTT				
Insulin peak (mU/L)	52.8 ± 31.9	58.7 ± 40.3	−5.9 (−19.7, 7.83)	.39
k value (%/min)	1.25 ± 0.42	1.29 ± 0.40	−0.04 (−0.19, 0.10)	.56
Glucose area, peak (mmol/L)	217.2 ± 2.9	207.0 ± 4.9	10.3 (−1.88, 22.4)	.09
Glucose area, 0 and 20-90 min (mmol/L)	1,423 ± 26	1,305 ± 40	118 (10.3, 225.4)	.03
Insulin area, peak (mU/L)	869.8 ± 41.7	947.1 ± 99.3	−77.4 (−266.5, 111.8)	.79
Insulin area, 0 and 20-90 min (mU/L)	4,070 ± 268	3,088 ± 361	982 (−98, 2,063)	.06

Abbreviations: 95% CI, 95% confidence interval; MCR, metabolic clearance rate; BW, body weight.

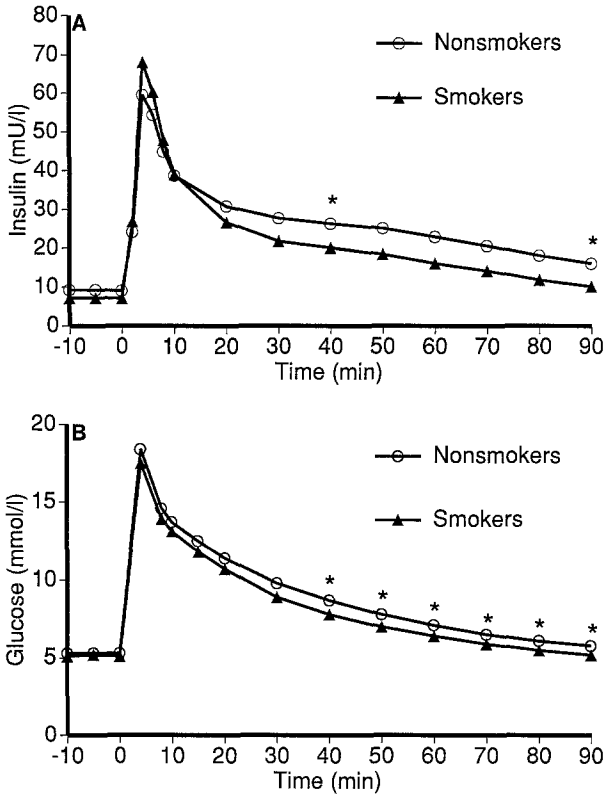

Fig 1. (A) Insulin and (B) glucose values during the IVGTT in smokers (n = 41) and nonsmokers (n = 150).

insulin peak or *k* value during the IVGTT. Neither M nor M/I differed between the groups (Table 1). Smoking was not independently related to M/I after allowance for sex, age, and diastolic blood pressure in a multiple regression analysis (data not shown). During the IVGTT, smokers showed lower glucose levels between 40 and 90 minutes (Fig 1B), resulting in a smaller area under the glucose curve ($P < .05$).

Due to a tendency for both higher total cholesterol and lower HDL cholesterol in smokers as compared with nonsmokers, the LDL:HDL ratio was significantly higher in smokers (4.45) than in nonsmokers (3.86). Serum TG (total TG, VLDL-TG, and LDL-TG) were significantly higher in smokers ($P < .05$). The blood leukocyte count was significantly higher in smokers ($P < .001$), but serum FFA did not differ between the groups (Table 2). All observed differences remained significant after analyses of covariance.

DISCUSSION

In this cross-sectional study cohort of both hypertensive patients and normotensive controls, a pattern emerged that can be described as follows: smokers had a slightly higher insulin sensitivity ($P = .19$), a slightly smaller insulin area (late insulin responses) at IVGTT ($P = .06$), a smaller glucose area at IVGTT ($P = .03$), and a lower mean fasting plasma insulin concentration ($P = .07$). These results fit with the suggestion that smokers, after refraining from smoking for 10 to 12 hours, indeed display a slightly enhanced insulin action as compared with nonsmokers. Similar results were obtained in pregnant smokers who exhibited a lower fasting blood glucose and an enhanced glucose removal during an IVGTT.[13]

In contrast, two previous studies have indicated that cigarette smoking is associated with insulin resistance,[7,8,14] although this was not confirmed recently in a study of 131 healthy, non-obese women.[9,10]

However, the significantly higher HbA_{1c} value found among smokers in this study does not fit into this pattern. Furthermore, this finding confirms previous observations in two large health surveys.[15,16]

There may be at least two alternative explanations for the observed increase in HbA_{1c} among smokers. One is that the formation and turnover of HbA_{1c} is influenced by factors other than blood glucose concentration. Smoking is known to generate free radicals in humans.[17] Recent studies suggest that the oxygen free radical activity may increase glycation of hemoglobin both in vivo and in vitro.[18,19]

Acute smoking has recently been shown to decrease insulin sensitivity both in healthy subjects and in non–insulin-dependent diabetic patients.[14,20] In individuals examined after an abstinence phase of 10 to 12 hours, the acute effects of smoking are likely to have waned, whereas the repetitive daily decreases in insulin sensitivity in smokers may have decreased peripheral glucose uptake to such an extent that

Table 2. Serum Lipoprotein Lipid Values, Blood Leukocyte Count, and Serum FFA in Nonsmokers and Smokers (mean ± SD)

Variable	Nonsmokers	Smokers	Difference (95% CI)	*P*
Cholesterol (mmol/L)				
Total	5.88 ± 1.12	6.25 ± 1.34	−0.37 (−0.79, 0.04)	.07
VLDL	0.48 ± 0.39	0.64 ± 0.52	−0.16 (−0.34, 0.02)	.08
LDL	4.24 ± 0.97	4.52 ± 1.19	−0.28 (−0.65, 0.08)	.12
HDL	1.15 ± 0.30	1.08 ± 0.23	0.08 (0.01, 0.16)	.08
LDL:HDL	3.86 ± 1.14	4.45 ± 1.70	−0.58 (−1.15, −0.01)	.048
TG (mmol/L)				
Total	1.75 ± 0.95	2.12 ± 1.10	−0.37 (−0.72, −0.03)	.033
VLDL	1.05 ± 0.82	1.35 ± 0.93	−0.30 (−0.60, 0.006)	.051
LDL	0.49 ± 0.17	0.58 ± 0.20	−0.09 (−0.15, −0.03)	.004
HDL	0.20 ± 0.07	0.20 ± 0.06	−0.00 (−0.03, 0.02)	.75
Leukocytes (10^6/L)	4.91 ± 1.40	6.18 ± 1.93	−1.27 (−1.29, −0.61)	.0003
FFA (mmol/L)	0.57 ± 0.20	0.53 ± 0.18	0.04 (−0.03, 0.11)	.24

blood glucose became elevated and the formation of HbA_{1c} was enhanced. This is also consistent with the epidemiologic findings of an increased risk for developing non–insulin-dependent diabetes in heavy smokers independently of body weight, both in males[21] and in females.[22]

The acute hemodynamic effects of smoking are elevated blood pressure and heart rate and increased peripheral vascular resistance.[23] The calculated increase in resistance is mainly derived from the acute elevation of blood pressure in conjunction with an increase in heart rate.[24] Skeletal muscle blood flow, in contrast, may be increased,[25,26] probably due to a β-adrenergic effect of circulating catecholamines, which are increased by smoking.[27] The vasoconstriction induced by smoking is mainly confined to skin and peripheral-limb vessels.[28] The circulatory effects of smoking are likely to be caused by catecholamines, since the outflow of sympathetic nerve impulses is decreased.[29] Consequently, the acute metabolic effects of smoking are less likely to depend on the effects of smoking on the circulation, but rather to be secondary to hormonal and metabolic changes. The elevated FFA,[30] catecholamines,[27] and growth hormone[14,31] may induce insulin resistance by different mechanisms during smoking.[32-34]

A number of observations indicate that in the fasting and smoke-free state, smokers in this cohort of hypertensive and normotensive subjects showed improved insulin action rather than the reverse. This observation and others, in contrast with the modest increase in insulin resistance reported by one group,[7,8] may be difficult to reconcile with the consistent finding in smokers (Table 2) of elevated serum TG and low HDL cholesterol.[35-37] This lipid profile commonly found in association with insulin resistance is thought to be an important contributing factor to the increased cardiovascular risk among smokers.[35,38] A decreased postprandial removal of TG,[39] as well as increased reesterification of FFA released by smoking,[30] are two mechanisms that may be responsible for the increase in serum TG.

A parallel phenomenon to the discrepancies between acute effects and findings in the abstinence phase is the frequent observation of a normal or low blood pressure in smokers independently of body weight,[40-43] a tendency also found in this study.

During acute smoking, a number of factors would act in a direction to increase insulin resistance, such as adrenaline and growth hormone release[34] and the increase in FFA.[30] Other factors may facilitate reversal, such as an increase in skeletal muscle blood flow,[25,26] lower body weight and caloric intake,[31] as well as an increased thermogenesis.[44] A delayed gastric emptying, resulting in a fiber-like effect on glucose absorption, may contribute to this process.[45]

Our data, like those of others, suggest that the acute increases in insulin resistance are rapidly reversible after 10 to 12 hours of abstinence. The metabolic derangements leading to increases in metabolic cardiovascular risk factors would thus be directly proportional to the time of exposure to smoking, ie, the daily number of cigarettes. Studies actually suggest that this dose-effect exists.[35] There may thus exist a difference in insulin resistance between lighter and heavier users of tobacco, which may also correlate with plasma lipoprotein and cholesterol. However, in this study, no graded scale of smoking habits or daily tobacco consumption was used, and therefore further investigations are needed.

Finally, lipoprotein disturbances in smokers were observed in this study similar to those previously shown,[3,4,35] eg, an increase of serum TG and an elevated LDL:HDL cholesterol ratio. The finding of an increased blood leukocyte count in smokers confirms previous studies[46] and might also be of importance, since a high leukocyte count is associated with an increased cardiovascular risk.[47]

In conclusion, smokers examined in the abstinence phase showed no signs of impaired insulin action. Lipoprotein abnormalities and elevated HbA_{1c} may be caused in part by the insulin resistance induced during acute smoking, and therefore may be quantitatively related to the time exposed to smoking. The effect on insulin sensitivity appears to be reversible over 10 to 12 hours.

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