Journal of Internal Medicine 1991; 230: 17–22 ADONIS 0954682091001138

Cardiovascular risk factors in young snuff-users and cigarette smokers

M. ELIASSON, D. LUNDBLAD & E. HÄGG*

*From the Department of Internal Medicine Luleå-Boden, Central Hospital, Luleå, and the *Department of Internal Medicine, University Hospital, Umeå, Sweden*

Abstract. Eliasson M, Lundblad D, Hägg E (Department of Internal Medicine Luleå-Boden, Central Hospital, Luleå, and Department of Internal Medicine, University Hospital, Umeå, Sweden). Cardiovascular risk factors in young snuff-users and cigarette smokers. *Journal of Internal Medicine* 1991; 230: 17–22.

We studied cardiovascular risk factors in 21 young men who were habitual snuff-users, and compared them with the same risk factors in 18 non-tobacco-users and 19 cigarette smokers of the same age and body mass index. Both snuff-users and smokers showed increased levels of alcohol and coffee consumption and a decreased level of physical exercise compared to non-users. Both groups of tobacco-users showed increased serum insulin levels compared to the control group at similar blood glucose concentrations. In contrast to the smokers, snuff-users showed no significant elevation of diastolic blood pressure, haemoglobin concentrations, white cell count, serum cholesterol or triglyceride levels. Snuff users had higher plasma fibrinogen levels than non-users ($P = 0.07$). The use of snuff by young men appears to have less impact than smoking on cardiovascular risk factors, with the possible exception of elevated serum insulin and plasma fibrinogen levels.

Keywords: blood pressure, fibrinogen, insulin, lipids, smoking, snuff.

Introduction

Cigarette smoking is a well-established risk factor for the development of cardiovascular disease. It increases the risk of myocardial infarction, sudden death [1] and stroke [2], particularly in the presence of other risk factors. In the USA and Sweden cigarette smoking is decreasing among men, but the use of smokeless tobacco in the form of moist oral snuff (snuff-dipping) is increasing, mainly among young men [3, 4]. In 1985, a consensus conference of the United States National Institute of Health on smokeless tobacco concluded that no data were available on the potential effects of snuff on the cardiovascular system [3]. Such studies were considered to be urgently required.

In order to determine the potential effects of snuff use on the cardiovascular system and on cardiovascular risk factors, we conducted a study in young, healthy male snuff-users, and compared them with smokers and non-tobacco-users.

Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, LDL = low-density lipoprotein, Lp(a) = lipoprotein (a), PAI = plasminogen activator inhibitor, tPA = tissue plasminogen activator.

Materials and methods

Study samples

Male volunteers, who were snuff-users, smokers or non-tobacco-users, were recruited from populations of university students and teachers. However, because of the low prevalence of smoking among students, we had to advertise in the local newspaper in order to find enough smokers. Therefore 35% of the group of smokers were blue-collar workers. The inclusion criteria were as follows: a history of never having used tobacco (non-users), use of at least one can (50 g) of moist snuff per week (snuff-users) for 2 years, or a history of smoking at least 10 cigarettes per day (smokers) for 2 years.

The three groups of volunteers were of similar age and body mass index (BMI). Subjects with a BMI > 28 kg m^{-2}, or who were aged > 31 years of age were excluded from the study. Non-tobacco-users

consisted of 18 subjects who had never used tobacco. Snuff-users consisted of 21 subjects who used snuff daily, five of whom were ex-smokers and had stopped smoking 2–8 years before the study. Smokers consisted of 19 subjects who smoked cigarettes daily, one of whom had used snuff until 6 years prior to the study.

None of the subjects was suffering from any chronic or acute illness or was taking any medication. One snuff-user had undergone a splenectomy because of trauma and was excluded from the haematological analysis. All subjects gave their informed consent to participate in the study, which had been approved by the Ethics Research Committee of Umeå University.

All subjects underwent a physical examination and completed a questionnaire regarding life-style habits. Present and lifetime cumulative tobacco consumption was calculated (one cigarette is equivalent to 1 g of tobacco, one can of moist snuff is equivalent to 50 g of tobacco). Alcohol consumption was calculated as g of absolute alcohol consumed per month. Height and weight were measured with the subjects wearing indoor clothing, without shoes, and BMI was calculated as weight (kg)/height $(m)^2$. Examination took place at 08.00 hours, after an overnight fast and abstention from tobacco, and after abstention from alcohol for 24 h.

Blood pressure was recorded twice, in the supine position after resting for 5 min, using a random-zero sphygmomanometer (Hawksley Gelman Ltd, Lancing, East Sussex, UK) with a standard 12×35 cm cuff, unless the upper arm circumference was greater than 32 cm, in which case a 15×43 cm cuff was used. The mean value of the two readings was used in subsequent analyses.

Blood samples were drawn with minimal venous occlusion after supine rest for 30 min. Samples were kept at -70 °C until analysis. Haemoglobin, white cell and platelet counts, blood glucose and plasma fibrinogen levels were analysed on the day of sampling. Fibrinolytic variables were analysed in 11 of the 18 non-users (61.1%), 14 of the 21 snuff-users (66.7%) and 13 of the 19 smokers (68.4%). Insulin samples were not available for two non-tobacco-users, two snuff-users and one smoker.

Assay methods

Haemoglobin concentration, white blood cell and platelet counts were determined on a Coulter-S analyser (Coutler Electronics, Hialeah, Florida, USA). Blood glucose was measured by a glucose oxidase method (Glucinet, Sclavo Diagnostics, Sienna, Italy). Serum insulin was determined by a competitive radioimmunoassay (Phadeseph, Pharmacia Diagnostics AB, Uppsala, Sweden). The RIA was calibrated against WHO standard 66/304. Serum cholesterol, high density lipoprotein (HDL) cholesterol and serum triglyceride levels were determined by enzymatic methods (Boehringer Mannheim GmBH, Mannheim, Germany). Serum low density lipoprotein (LDL) cholesterol was estimated according to the formula of Friedewald, as follows:

$$\text{LDL cholesterol} = \text{serum total cholesterol} - \text{HDl cholesterol} - [0.45 \times \text{triglycerides}]$$

Serum lipoprotein (a) [Lp(a)] was determined with an enzyme immunoassay (TintElize Lp(a), Biopool AB, Umeå, Sweden).

Plasma fibrinogen was measured by a thrombin reaction-rate method (BioMe'rieux, Marcy-l'Etoile, France). Plasma tissue plasminogen activator (tPA) antigen concentrations were determined in citrated plasma by an enzyme-linked immunosorbent assay (Imulyse, Biopool AB, Umeå, Sweden) [5]. Plasma plasminogen activator inhibitor (PAI) activity was measured in citrated plasma with a chromogen substrate assay (Spectrolyse/pL, Biopool AB, Umeå, Sweden) [6].

Plasma nicotine and cotinine (the primary metabolite of nicotine) were determined by a single-step liquid-liquid extraction followed by capillary gas chromatography. Nicotine and cotinine were detected by means of a nitrogen-sensitive detector [7].

Statistical analyses

The results are expressed as mean values $\pm$ SD. Because of an asymmetrical distribution of many variables, the Mann-Whitney *U*-test for non-parametric data was used to test differences between groups. *P*-values of < 0.05 were regarded as statistically significant.

Results

Tobacco use was similar in duration and amount in the two groups of tobacco users (Table 1), but life-style habits differed between the groups. Total coffee consumption was almost fivefold higher among smokers than among subjects who did not use

Table 1. Mean values for studied variables in Group A (non-tobacco-users), Group B (snuff-users) and group C (smokers)

Variable	A ($n = 18$)	B ($n = 21$)	C ($n = 19$)	*P*-value
Age (years)	24.4 (2.6)	24.1 (3.4)	25.3 (3.8)	
BMI (kg m^{-2})	22.2 (1.6)	22.0 (1.7)	23.0 (3.3)	
Duration of tobacco use (years)	0	7.0 (3.8)	9.1 (3.8)	
Present tobacco consumption: (g $week^{-1}$)	0	146 (60)	134 (29)	
Cumulative tobacco consumption (kg)	0	52.2 (35.1)	65.9 (35.4)	
Coffee intake (cups d^{-1})	1.3 (1.3)	3.0 (1.7)	5.9 (2.6)	A–B < 0.01 A–C < 0.001 B–C < 0.001
Alcohol consumption (g $month^{-1}$)	147 (182)	284 (200)	442 (315)	A–B < 0.01 A–C < 0.001
Physical activity (times $week^{-1}$)	2.3 (1.6)	1.3 (1.6)	0.7 (1.1)	A–B < 0.05 A–C < 0.01
P-nicotine (ng ml^{-1})	0.9 (0.5)	3.2 (1.3)	3.3 (2.7)	A–B < 0.001 A–C < 0.001
P-cotinine (ng ml^{-1})	2.0 (2)	326 (113)	237 (102)	A–B < 0.001 A–C < 0.001 B–C < 0.05
Haemoglobin (g l^{-1})	144 (8.3)	144 (8.5)	155 (8.4)	A–C < 0.01 B–C < 0.01
White cell count ($\times 10^9$ l^{-1})	4.7 (1.3)	5.4 (1.5)	7.2 (1.9)	A–C < 0.001 B–C < 0.01
Platelet count ($\times 10^9$ l^{-1})	246 (43)	266 (50)	264 (77)	
Fibrinogen (g l^{-1})	1.78 (0.3)	2.00 (0.4)	2.12 (0.8)	A–C < 0.05
Blood glucose (mmol l^{-1})	4.4 (0.3)	4.3 (0.4)	4.4 (0.4)	
Serum insulin (mU l^{-1})*	3.6 (1.0)	5.5 (3.3)	8.6 (13.8)	A–B < 0.01 A–C < 0.01
Serum cholesterol (mmol l^{-1})	4.39 (0.61)	4.45 (0.60)	5.28 (1.14)	A–C < 0.01 B–C < 0.01
Serum HDL-cholesterol (mmol l^{-1})	1.08 (0.18)	1.13 (0.28)	1.13 (0.31)	
Serum LDL-cholesterol (mmol l^{-1})†	3.00 (0.59)	2.97 (0.77)	3.34 (0.93)	
LDL/HDL ratio	2.86 (0.74)	2.87 (1.26)	3.16 (1.17)	
Serum triglycerides (mmol l^{-1})	0.68 (0.33)	0.75 (0.24)	1.83 (1.12)	A–C < 0.001 B–C < 0.001
Serum Lp(a) (mg l^{-1})	212 (203)	139 (185)	133 (179)	

* Serum insulin values are not available for two non-tobacco users, two snuff-users and one smoker.
† LDL cholesterol calculated according to Friedewald's formula (see text).
Standard deviations are shown in parentheses.

tobacco. The same significant difference was observed for boiled coffee consumption (data not shown). Alcohol consumption was closely correlated with tobacco consumption habits, with smokers having the highest intake. Smokers exercised less than non-tobacco-users. Snuff-users were found to be intermediate between smokers and non-tobacco-users with regard to alcohol and coffee consumption, as well as physical activity.

Plasma nicotine levels were low or undetectable in non-tobacco-users, and the highest value (2.4 ng ml^{-1}) was well below the mean values for tobacco-users. One smoker had a plasma nicotine level of 13.0 ng ml^{-1}; otherwise all values for tobacco-users

were < 10 ng ml^{-1}. Snuff-users showed significantly higher levels of plasma cotinine than smokers, and cotinine concentrations in non-tobacco-users were either undetectable or < 8 ng ml^{-1}.

No group differences in pulse rate or systolic blood pressure were found (data not shown). The mean diastolic blood pressure was 72.8 mmHg for non-tobacco-users, 71.9 mmHg for snuff-users and 77.5 mmHg for smokers ($P < 0.05$ for difference between non-tobacco-users and smokers). If the above-mentioned smoker with the higher plasma nicotine concentration was excluded from the analysis, the difference was no longer significant.

Smokers had higher mean haemoglobin levels and erythrocyte volume fractions (data not shown), as well as higher white cell counts and plasma fibrinogen levels than control subjects. All differences were statistically significant. Both tobacco groups showed a tendency toward higher platelet counts. Plasma fibrinogen levels were higher among snuff-users than in controls, but the difference was not statistically significant ($P = 0.07$). No differences in tPA levels or PAI activity were observed between the groups (data not shown).

Mean blood glucose levels did not differ between the groups. Both groups of tobacco-users had higher serum insulin levels than non-tobacco-users. Total serum cholesterol and triglyceride levels were elevated in the cigarette-smokers. No change in lipid profiles were found among snuff-users.

Discussion

The use of smokeless tobacco in the form of moist oral snuff is becoming increasingly popular among young men in North America and Scandinavia. Three million American teenage boys use snuff [3], and in Sweden 31% of men aged 16–24 years use snuff daily [4]. In northern Sweden 22% of men aged 25–64 years are snuff-users [8], and there are indications that snuff use may eventually lead to cigarette smoking among young men [4]. The aim of the present study was to determine whether the use of snuff has any negative effects on cardiovascular risk factors among young men.

Considerable differences in life style were observed in the three groups of subjects, with lower levels of physical activity, and higher levels of alcohol and coffee consumption among tobacco-users. These findings should be borne in mind when evaluating group differences.

The low plasma nicotine levels were generally consistent with the fact that subjects had abstained from smoking and taking snuff [9]. However, one smoker had a plasma nicotine concentration that indicated that he had smoked prior to the examination. The finding of significantly higher plasma cotinine levels in the morning among snuff-users compared to smokers may reflect a higher steady-state concentration during the previous day [10], supporting the suggestion of Benowitz *et al.* that snuff-users show a higher rate of nicotine absorption than smokers [9]. Alternatively, snuff-users may swallow nicotine which, on absorption from the gut, is converted to cotinine, thus avoiding entry to the systemic circulation as nicotine [11].

Cross-sectional epidemiological studies have demonstrated lower blood pressure among smokers than among matched non-smokers [12], a finding that is at least partly explained by the lower BMI among smokers. Malignant hypertension appears to be more common among smokers [13].

Nicotine administered as cigarettes, snuff or chewing tobacco produces an acute increase in both heart rate and blood pressure, with equal peak responses [9]. In a study of young men, a significantly higher diastolic blood pressure was noted among users of smokeless tobacco (the type of which was not stated) [14]. In this study snuff use before or during blood pressure measurement was not taken into account. The haemodynamic effects of snuff persist for at least 90 min after removal [9], while the blood pressure elevation in smokers recovers more rapidly. It is important to take this into consideration when assessing the results.

We found no effect of tobacco use on systolic blood pressure, but smokers had a higher diastolic pressure than non-users, which may be explained by lower levels of physical activity and a slightly higher BMI. Snuff-users showed no change in diastolic blood pressure. Smokers and snuff-users have been found to have increased rates of urinary excretion of catecholamines [11]. The higher blood pressure levels observed in these subjects during exposure to tobacco may be due to sympathetic stimulation. The finding of raised levels of plasma noradrenaline during acute exposure to snuff supports this view (authors' unpublished data). It is still unclear whether snuff use leads to chronic hypertension.

Carbon monoxide exposure from cigarette smoke leads to hypoxaemia, which causes polycythaemia in chronic smokers [15]. On stopping smoking the

haemoglobin levels return to normal concentrations [16]. The unchanged haemoglobin levels in our snuff-users were thus expected. White cell [17] and platelet counts [18] are known to be elevated in chronic smokers, and our results confirmed these findings. No leukocytosis was found among snuff-users, but these individuals showed a similar trend toward higher platelet counts as the smokers.

Three studies have reported that elevated plasma fibrinogen levels are an independent risk factor for myocardial infarction and stroke [18–20]. A strong correlation with smoking was found but, even after correction for this, fibrinogen remained an important risk factor. Giving up smoking causes fibrinogen levels to decline [16], with a reduction in the risk of coronary heart disease [21]. The Northwick Park Heart Study concluded that 'a very substantial part of the relation between smoking and ischaemic heart disease is probably mediated through the fibrinogen level' [21].

Elevated plasma fibrinogen levels, together with polycythaemia, leukocytosis and thrombocytosis contribute to higher blood and plasma viscosity [16] and hypercoagulability, with enhanced risk of occlusive thrombus formation in smokers [18]. Increased uptake of fibrinogen in the vascular endothelium, which leads to the binding of low-density lipoproteins, may be an early mechanism of atherosclerosis [18, 19].

We found a difference of about 0.3 g l^{-1} in plasma fibrinogen levels between smokers and non-tobacco-users, which is equal to the mean difference that has been observed in prospective studies between subjects with or without myocardial infarction [19, 20]. Snuff-users had slightly lower plasma fibrinogen levels than smokers, but the difference compared to non-tobacco-users was not statistically significant ($P = 0.07$).

Impaired fibrinolysis has been observed among young patients with myocardial infarction [22], and this was a predictor of reinfarction [23]. In two small studies, healthy male chronic smokers were found to have elevated levels of the fibrinolytic inhibitor (PAI) [24, 25]. We found no consistent differences in plasma levels of tPA and PAI between tobacco-users and control subjects.

Prospective studies have indicated that hyperinsulinaemia may be an independent risk factor for coronary heart disease [26]. Fasting blood glucose and serum insulin levels have not been found to differ between smokers and non-smokers of the same body weight [26, 27]. One study found a lower glucose disposal rate during intravenous glucose-tolerance testing in smokers than in non-smokers [27].

Although smoking may release insulin-antagonistic hormones, no insulin resistance has been observed in insulin-clamp studies among type 1 diabetic patients who smoke [28]. Therefore our finding of elevated fasting serum insulin levels among both smokers and snuff-users was unexpected. Lower levels of physical activity among tobacco-users, and a slightly higher BMI in smokers may be contributory factors [26]. Ethanol acutely induces insulin resistance [29], but studies on its long-term effects are lacking. As tobacco-users showed a two- to threefold higher level of alcohol consumption than non-tobacco-users, this may have contributed to their higher serum insulin levels.

A recent review of the effect of cigarette smoking on serum lipids reported significantly higher levels of atherogenic lipids, and lower HDL cholesterol levels, among smokers [30]. These changes may account for as much as 9% of the excess coronary risk in smokers. Smoking does not appear to affect Lp(a) levels [31]. The serum lipid levels in the smokers in our study were consistent with these findings, except that we observed no lowering of HDL-cholesterol levels. Nicotine chewing gum has not been shown to affect plasma lipoproteins [7], and we were unable to detect any effect of snuff use on lipid levels. This suggests that smokers' hyperlipidaemia is not due to nicotine consumption.

We conclude that the use of smokeless tobacco in the form of moist oral snuff does not appear to have any significant impact on cardiovascular risk factors in healthy young men, with the possible exception of elevated serum insulin levels. The finding of higher fibrinogen levels among snuff-users, although of borderline significance, is notable. We confirm previous reports that smokers have more corpuscular elements in the blood, raised plasma fibrinogen levels and hyperlipidaemia.

Acknowledgements

The determination of plasma nicotine and cotinine was performed at the Analytical Department, Pharmacia LEO Therapeutics AB, Helsingborg, Sweden. This study was supported by Norrbottens's Local Authority Research Fund.

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Received 16 July 1990, accepted 18 December 1990.

Correspondence: Dr Mats Eliasson, Medical Department, Luleå Hospital, S-951 28 Luleå, Sweden.