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Cigarette smoking, oral moist snuff use and glucose intolerance

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Abstract. Persson P-G, Carlsson S, Svanström L, Östenson C-G, Efendic S, Grill V (Karolinska Hospital and Karolinska Institutet, Stockholm, Sweden). Cigarette smoking, oral moist snuff use and glucose intolerance. *J Intern Med* 2000; **248:** 103–110.

Objective. To investigate the association between cigarette smoking and use of oral moist snuff and impaired glucose tolerance and type 2 diabetes.

Design. We performed a population-based cross-sectional study of glucose intolerance and tobacco use in Stockholm during 1992–94. The sample consisted of 3128 men, aged 35–56 years, of whom 52% had a family history of diabetes. In an oral glucose tolerance test, we detected 55 men with type 2 diabetes and 172 with impaired glucose tolerance. Information on cigarette smoking and oral moist snuff use was collected by a questionnaire.

Results. The odds ratio of type 2 diabetes was increased for smokers of 25+ cigarettes day^{-1} (odds ratio = 2.6, 95% confidence interval = 1.1–5.9) as well as for moist snuff dippers of 3+ boxes week^{-1} (odds ratio = 2.7, 95% confidence interval = 1.3–5.5). The odds ratio of relatively high (highest tertile) fasting insulin levels in subjects with impaired glucose tolerance associated with cigarette smoking of 25+ cigarettes day^{-1} was 1.5 (95% confidence interval = 0.7–3.6). The corresponding estimate of a relatively low (lowest tertile) 2 h insulin response was 2.5 (95% confidence interval = 0.9–7.1).

Conclusions. These results indicate that heavy users of cigarettes or moist snuff have an increased risk of type 2 diabetes. The results could suggest that tobacco use is associated with a low insulin response.

Keywords: cigarettes, epidemiological study, glucose intolerance, tobacco use, type 2 diabetes.

Introduction

An increased risk of type 2 diabetes amongst smokers has been found in some prospective studies [1–5] but not in all [6, 7]. However, no evidence exists as to whether the use of oral moist snuff, which is another nicotine-containing smoke-free tobacco product used by many young and middle-aged people in Sweden, increases the risk of type 2 diabetes. A previous Swedish study [8] found that snuff use increased the mortality of cardiovascular diseases. Since the risk of cardiovascular disease is associated with a risk of type 2 diabetes, it is not unlikely, but unproven, that snuff use as well as smoking is associated with type 2 diabetes.

The mechanisms that could explain an association between smoking and diabetes are not known. Experimental findings suggest that smoking causes insulin resistance [9–11]. This effect could be due to a stimulation of the sympathetic nervous system by nicotine. Indeed, long-term use of nicotine-containing chewing gum was associated with insulin resistance [12]. Also, other studies indicate that acute administration of nicotine induces insulin resistance [13, 14]. As to effects on insulin secretion, an acute episode of smoking was not found to affect insulin secretion [10, 13], whereas an influence on insulin secretion by long-term nicotine and/or other constituents of cigarette smoking has not been investigated.

Furthermore, it is possible that other constituents of cigarette smoking than nicotine could be implicated in effects on glucose intolerance. Comparing the influence of cigarette smoking and moist snuff

could yield further insight into the importance of various constituents.

The aim of this study was to investigate the association between cigarette smoking and moist snuff use, on the one hand, and type 2 diabetes and impaired glucose tolerance, on the other. Furthermore, we wished to assess the possible impact of smoking and snuff use on insulin sensitivity and secretion.

Materials and methods

Study population

The design of this population-based cross-sectional study has previously been presented elsewhere [15]. In brief, the study was performed in men born during 1938–57 (aged 35–56 years) who were living in four suburban municipalities of Stockholm: Sigtuna, Upplands-Bro, Tyresö and Värmdö. The sample was selected from the population register of Stockholm County Council. The study was designed to focus on family history of diabetes. Accordingly, we employed a selection procedure by which we obtained a sample where 50% of the participants had a strong family history of diabetes. To obtain this enriched study population, subjects were collected in two steps. First, we sent a short postal questionnaire to all men and collected information on country of birth, presence of diabetes in the subject and amongst relatives. Subjects who did not respond were asked a second time. Of 12 952 men, 10 236 (79%) responded to the questionnaire. Based on the responses, we identified 2106 (20.6%) subjects with a strong family history of diabetes, defined as at least one first-degree relative (mother, father, sister or brother) or two second-degree relatives (grandparent, uncle or aunt) with diabetes. We identified 3329 (32.5%) subjects without diabetes in the family, i.e. respondents who had neither first- nor second-degree relatives, or cousins with known diabetes. We excluded 1531 (15%) men who did not fit the criteria of either of these two groups, 2800 (27.4%) men who were unable to provide complete answers on the presence of diabetes in relatives, 212 (2.1%) men who were born outside Sweden and 258 (2.5%) men who had diabetes known to themselves.

As a second sampling step, we selected all 2106 men with a family history of diabetes as well as an age-stratified (within 5-year age groups) random sample of 2424 men amongst those who did not have a family history of diabetes. The number of men in this latter group was chosen so that the age distribution was similar to that of the men with a family history of diabetes. The subjects were contacted by telephone and invited to participate in a health examination. In total, 3162 (70%) men agreed to participate.

Health examination

The health examination was carried out at the local health care centres in the four participating municipalities. The subjects arrived at the health care centre in the morning (07.00–08.30 h) after an overnight fast (from 22.00 h). The men were instructed to refrain from vigorous physical activity on the evening before and on the morning of the examination. Smokers were encouraged not to smoke on the morning of the day of the examination. Upon arrival, all men were asked to confirm the information regarding the presence of diabetes amongst relatives given in the initial questionnaire. Failure to confirm the questionnaire information resulted in exclusion of 33 men who did not fit either the family history with diabetes group or the group without such a history. One person did not complete the oral glucose tolerance test (OGTT), leaving 3128 (70%) men who successfully completed the study.

The health examination included a standardized 75 g OGTT according to WHO 1985 [16]. Venous blood sampling was performed in the fasted state and 2 h after glucose ingestion. Plasma samples were obtained after centrifugation and stored at −20°C for later analysis of glucose and insulin. During the OGTT, the subjects filled out a detailed questionnaire on tobacco use, dietary habits, physical activity and psychosocial conditions. The health examination also included measurements of the subject's weight, height and waist/hip ratios when wearing light indoor clothes without shoes. Blood pressure was recorded by a nurse with the subject in the supine position.

Classification of disease

The classification of impaired glucose tolerance and

diabetes followed WHO 1985 criteria, i.e. 2 h plasma glucose levels between 7.8 and 11.0 mmol L^{-1} for impaired glucose tolerance (n = 172) and 11.1 mmol L^{-1} or higher for diabetes (n = 55). Insulin resistance was based on homeostasis model assessment (HOMA) [17], using concomitantly recorded fasting insulin and glucose levels. The HOMA algorithm was slightly modified as suggested by Lithell *et al.* [18] and was computed as insulin × glucose (equivalent to the original algorithm, removing the constant 22.5). Because chronic hyperglycemia *per se* severely affects insulin sensitivity and secretion, we restricted the analyses of insulin resistance and insulin secretion to subjects with impaired glucose tolerance. Amongst these, we defined as insulin-resistant those men who belonged to the highest tertile on HOMA (insulin resistance algorithm). We defined low insulin response amongst men with impaired glucose tolerance as the tertile with the lowest increment in insulin levels between 0 and 2 h after glucose ingestion.

Classification of exposure

Tobacco use. Information on tobacco use was obtained by questionnaire. The subjects were asked if they had ever smoked cigarettes daily. Those who had smoked were asked if they currently smoked. Based on the answers, we classified respondents into never, former and current smokers. Information on the number of cigarettes smoked per day was collected, and in the analyses former and current smokers were combined. We also asked the subjects if they had used oral moist snuff daily. All men who had ever used snuff were asked if they currently used snuff. Accordingly, subjects were classified into never, former or current users. We also asked for the weekly number of boxes (50 g each) of snuff consumed.

Physical activity. Data on physical activity were collected by detailed questionnaire. We asked the subjects how physically active during leisure time they had been during the last year. The subjects were provided with four response options, ranging from sedentary leisure time to regular exercise. The respondents' physical activity was classified as low or moderate if it included activities primarily without sweating, such as bicycling or walking, and as high if it included activities of higher intensity, such as running, tennis, swimming at least 30 min, these activities being pursued once a week or more often.

Alcohol consumption. Information on alcohol consumption was obtained from the questionnaire. Subjects were asked about consumption of beer, wine, dessert wine and liquor. For each item, frequency and amount consumed on each occasion were registered. To calculate total alcohol consumption, we transformed each item into 100% alcohol and combined them. The estimated contents of 100% alcohol mL^{-1} were 0.05 mL for beer, 0.12 mL for wine, 0.19 mL for dessert wine and 0.4 mL for liquor. For the analyses, total 100% alcohol consumption per week was divided into three groups: low (< 72.1 mL), medium (72.1–158.8 mL) and high (> 158.8 mL). The subjects' body mass index (BMI) was computed as body weight in kilograms divided by the square of height in metres (kg m^{-2}). A total of 116 subjects had missing data on alcohol consumption; these men were not included in the analyses.

Data analysis

To calculate the association between tobacco use and glucose intolerance, we estimated odds ratios together with 95% confidence interval with the use of multiple logistic regression analysis. Subjects with normal glucose tolerance constituted the comparison group in all analyses. Adjustment for confounding was done by including variables in the logistic regression model (see footnotes to Tables 1 and 2). The analyses were performed with the SAS/STAT statistical package [19].

Results

Type 2 diabetes

The odds ratio of type 2 diabetes was 30% increased in former as well as current cigarette smokers compared with never-smokers. The prevalence of diabetes increased with number of cigarettes consumed per day but not clearly with duration of smoking (Table 1). Adjustment for the use of moist snuff did not change these results (results not

Table 1 Odds ratios of impaired glucose tolerance and type 2 diabetes associated with tobacco use

Tobacco use	Normal glucose tolerance (n^a)	Impaired glucose tolerance			Type 2 diabetes		
		n^a	OR[b]	95% CI	n^a	OR[b]	95% CI
Cigarettes							
Never	1072	62	1.0		14	1.0	
Former	995	61	0.9	0.6–1.3	21	1.3	0.7–2.7
Current	714	43	1.0	0.7–1.6	17	1.3	0.6–2.7
No. of cigarettes day^{-1}							
Never	1072	62	1.0		14	1.0	
1–24	1494	81	0.9	0.6–1.3	25	1.1	0.5–2.1
25+	204	22	1.3	0.7–2.2	13	2.6	1.1–5.8
Duration of smoking							
Never	1072	62	1.0		14	1.0	
≤ 19 years	678	39	0.9	0.6–1.4	11	1.3	0.6–2.9
20+ years	1026	65	1.0	0.7–1.4	27	1.3	0.7–2.6
Moist snuff							
Never	1915	121	1.0		34	1.0	
Former	376	19	0.7	0.4–1.2	5	0.8	0.3–2.0
Current	492	26	0.8	0.5–1.3	13	1.5	0.8–3.0
No. of boxes of snuff $week^{-1}$ in current snuffers							
Never	1915	121	1.0		34	1.0	
≤ 2	235	10	0.7	0.4–1.4	1	0.2	0.0–2.0
3+	256	15	0.8	0.4–1.4	12	2.7	1.3–5.5
Current consumption of cigarettes or snuff							
Never	895	55	1.0		9	1.0	
Moist snuff only	121	6	0.9	0.4–2.1	4	3.9	1.1–14.3
Cigarettes only	517	31	1.0	0.6–1.6	14	1.8	0.7–4.5

[a]The numbers differ as a result of missing data.
[b]Multiple logistic regression estimated odds ratios, adjusted for age (35–40, 41–46, 47–51 and 52–56 years), body mass index (≤ 24.9, 25.0–27.9, 28.0–29.9 and 30.0+ $kg\ m^{-2}$), family history of diabetes (yes/no), physical activity (high/low) and alcohol consumption (low, medium and high).

shown). Current users of moist snuff had a 1.5 times higher prevalence of diabetes compared with non-snuffers, whereas no increased prevalence was seen in former snuff users. The odds ratio was as high as 2.7 in current snuffers with the highest snuff consumption (≥ 3 boxes $week^{-1}$). These results were not affected by adjustment for smoking in the analyses (results not shown).

We also estimated odds ratios of diabetes and impaired glucose tolerance separately in current smokers without previous snuff use and in current snuffers without previous smoking (Table 1). Compared with never-users of tobacco, these 'clear-cut' smokers and snuffers had 1.8 times and almost 4 times increased prevalence of diabetes, respectively, although the confidence intervals were wide.

Cigarette smoking was also examined in combination with family history of diabetes. As previously described [20], family history of diabetes *per se* was associated with an odds ratio of 4.1 (95% CI = 2.1–8.3) for diabetes and 1.6 (95% CI = 1.2–2.3) for impaired glucose tolerance. Cigarette smokers having a family history of diabetes had nearly a six times increased odds ratio, but the confidence interval was wide (OR = 5.9, 95% CI = 1.4–25.3). No corresponding increased risk was observed for snuff use (data not shown).

Impaired glucose tolerance

No increased prevalence of impaired glucose tolerance was found in cigarette smokers or in users of oral moist snuff (Table 1).

Insulin resistance and secretion in subjects with impaired glucose tolerance

The odds ratio of insulin resistance (HOMA) in men

Table 2 Odds ratios of HOMA (insulin resistance) and of 2 h insulin response in men with impaired glucose tolerance associated with tobacco use

Tobacco use	tolerance (n[a])	HOMA (resistance) highest third (≥ 161.1)		2 h insulin response lowest third (≤ 71.9 mU L^{-1})	
		n[a]	Normal glucose OR[b] (95% CI)	n[a]	OR[b] (95% CI)
Cigarettes					
Never	1072	21	1.0	11	1.0
Former	995	19	0.8 (0.4–1.5)	20	1.8 (0.8–3.8)
Current	714	9	0.6 (0.3–1.4)	17	2.4 (1.1–5.2)
No. of cigarettes day^{-1}					
Never	1072	21	1.0	11	1.0
1–24	1494	18	0.6 (0.3–1.1)	30	2.0 (1.0–4.0)
25+	204	10	1.5 (0.7–3.6)	6	2.5 (0.9–7.1)
Duration of smoking					
Never	1072	21	1.0	11	1.0
≤ 19 years	678	10	0.7 (0.3–1.6)	11	1.6 (0.7–3.7)
20+ years	1026	18	0.8 (0.4–1.5)	26	2.3 (1.1–4.9)
Moist snuff					
Never	1915	37	1.0	28	1.0
Former	376	3	0.4 (0.1–1.3)	12	2.2 (1.1–4.4)
Current	492	9	0.9 (0.4–2.0)	8	1.2 (0.5–2.8)
No. of boxes of snuff $week^{-1}$					
Never	1915	37	1.0	28	1.0
≤ 2	471	4	0.5 (0.2–1.6)	13	2.1 (1.1–4.1)
3+	388	7	0.7 (0.3–1.7)	7	1.2 (0.5–2.9)

[a]The numbers differ as a result of missing data.
[b]Multiple logistic regression estimated odds ratios, adjusted for age (35–40, 41–46, 47–51 and 52–56 years), body mass index (≤ 24.9, 25.0–27.9, 28.0–29.9 and 30.0+ kg m^{-2}), family history of diabetes (yes/no), physical activity (high/low) and alcohol consumption (low, medium and high).

with impaired glucose tolerance was not consistently increased or decreased for users of cigarettes or moist snuff (Table 2), although there was a tendency in most categories for a reduced occurrence of insulin resistance compared with never-smokers or -snuffers. The odds ratio of a low 2 h insulin response in men with impaired glucose tolerance was 1.8 for former smokers and 2.4 for current smokers (Table 2). The odds ratio of low 2 h insulin response associated with former or current cigarette smoking increased both with daily consumption and with the duration of smoking. Former snuffers but not current snuffers had an increased risk of a low 2 h insulin response, but no corresponding increase was seen with regard to insulin resistance as assessed by HOMA. Snuff users with moderate (less than 3 boxes $week^{-1}$) consumption had an increased risk of low insulin response (Table 2). Corresponding analyses in subjects with normal glucose tolerance did not yield any significant associations between tobacco use and insulin resistance or low insulin response (results not shown).

Discussion

Previous cohort studies have found that heavy smokers experience up to a threefold increased incidence of type 2 diabetes as compared with never-smokers [1–5]. The findings in this study confirm these observations. The reasons that some previous studies did not find an increased risk of diabetes in smokers [6, 7] could be that these studies did not contain information on the number of cigarettes smoked per day [5], or did not adequately

control for confounders such as obesity, family history with diabetes, physical activity and alcohol intake [4].

Previous observations on smoking and impaired glucose tolerance are few [21, 22] and do not indicate an increase in risk. In our study, the association between smoking and impaired glucose tolerance was weak. A risk dilution would be expected in this milder form of glucose intolerance considering the fact that only a minority of subjects with impaired glucose tolerance eventually develop diabetes.

We found in the present study, to our knowledge for the first time, an association between heavy use of oral moist snuff and type 2 diabetes. Since plasma nicotine levels have been found to be similar during smoking and snuffing [9], these results could indicate that nicotine is responsible for the major diabetogenic effect of snuffing and smoking. With regard to cardiovascular disease, most studies have indicated a lower impact of snuff than of smoking [23–26], implying that other constituents of tobacco rather than nicotine are additive risk factors. If future cohort studies confirm the association between snuffing and diabetes, there will be a need for preventive action against snuffing as well as smoking in order to reduce the incidence of diabetes.

Previous studies based on the euglycaemic hyperinsulinaemic clamp technique found that smoking is associated with insulin resistance [10, 27]. Also, fasting insulin levels – a surrogate measure of insulin resistance [28] – were somewhat elevated in non-diabetic smokers [29]. In the present study, the impact of smoking on insulin resistance and insulin secretion was analysed in subjects with impaired glucose tolerance, i.e. a state in which a possible influence of diabetes-associated metabolic abnormalities was minimized. The analyses indicated that low insulin secretion rather than insulin resistance was associated with smoking or the use of snuff. These results are surprising and controversial since several studies have demonstrated that acute smoking or administration of nicotine gives rise to insulin resistance in non-diabetic subjects with no change in insulin secretion [10, 13]. Furthermore, a small clinical study in type 2 diabetic subjects indicated that patients who smoked were more insulin-resistant than were those who did not [30]. The fact that insulin resistance was not associated with smoking in our study could perhaps be due to the fact that smoking was negatively associated with obesity, i.e. the major insulin resistance factor in diabetes. Although the results were adjusted for this factor, the possibility of some residual confounding is hard to exclude. Another possible explanation is that we assessed long-term rather than short-term use of tobacco in our study. However, as outlined in the introduction, a long-term negative influence of tobacco on insulin secretion is, at least in theoretical terms, compatible with influences of nicotine or other constituents of tobacco use.

As to the type of diabetes discovered in this study, it was mild and without symptoms. Subjects with presently detected diabetes had mild diabetes at least during the first year following diagnosis (data not shown). Hence, risk factors may differ from those in people with more severe forms of diabetes. It should also be mentioned that the lower age limit of 35 years was aimed at minimizing the probability of type 1 diabetes. Advantageously, men with impaired glucose tolerance and diabetes reported about their smoking and snuffing habits under similar circumstances as those with normal glucose tolerance who constituted the reference group, implying that differential misclassification was less likely.

In this study, it was not possible to determine tobacco habits prior to the onset of the glucose intolerance. As a consequence, it was not possible to distinguish former tobacco users from current users at the time of onset of disease, meaning that some of the men classified as current smokers or snuffers may have started using tobacco after the onset of glucose intolerance and some of those classified as former tobacco users may have been current smokers or snuffers at the time of onset of glucose intolerance. Hypothetically, if smokers have increased risk of glucose intolerance, given that such a risk is more pronounced for current than for previous smokers, then it is likely that the estimates presented in this study have been biased towards unity for current smokers and exaggerated for former smokers. This may explain the small difference in odds ratios associated with former and current smoking and why the odds ratio of a low insulin response in men with impaired glucose tolerance associated with former snuff use was stronger than with current snuff use.

In summary, the present study has for the first time demonstrated an association between use of

moist snuff and type 2 diabetes. Furthermore, we provide evidence that smoking and snuff use negatively affect insulin secretion.

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