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RAPID COMMUNICATION

Smoking is not associated with nonalcoholic fatty liver disease

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Abstract

AIM: To analyze the relationship between smoking and nonalcoholic fatty liver disease (NAFLD).

METHODS: This is a cross-sectional study of a healthy population, carried out in a check-up unit of a university hospital in Mexico City. We enrolled 933 subjects, 368 current smokers (cases) and 565 persons who had never smoked (controls). Demographic, metabolic and biochemical variables were measured in the two groups. NAFLD was determined by ultrasound and metabolic syndrome according to ATPIII.

RESULTS: A total of 548 men (205 cases and 343 controls) and 337 women (114 cases and 223 controls) were included in the analysis. Statistical differences between cases and controls were observed only in high blood pressure prevalence (6.6% *vs* 11.3%, $P < 0.05$; cases and controls respectively), high-density lipoproteins (1.00 ± 0.26 *vs* 1.06 ± 0.28 mmol/L, $P < 0.005$), triglycerides (2.18 ± 1.49 *vs* 1.84 ± 1.1 mmol/L, $P < 0.001$), and erythrocyte sedimentation rate (11.3 ± 9.3 *vs* 13.5 ± 11.9 mm/h, $P < 0.001$). No differences were observed in the prevalence of NAFLD (22.27% *vs* 29.68%, P = NS) and metabolic syndrome (41.69% *vs* 36.74%, P = NS). Univariate analysis showed that smoking was not a risk factor for NAFLD (OR = 0.89, 95% CI 0.65-1.21).

CONCLUSION: No differences in NAFLD prevalence were observed between current smokers and nonsmokers, and furthermore, no differences were observed in heavy smokers (more than 20 packs/year), indicating that there is no relationship between smoking and NAFLD.

Key words: Smoking; Nonalcoholic fatty liver disease; Metabolic syndrome

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is an increasingly recognized condition that may progress to end-stage liver disease[1]. The clinical implications of NAFLD are derived mainly from its common occurrence among the general population (from 2.8% to 25%) and its potential to progress to fibrosis, cirrhosis and liver failure[2].

Obesity or a high body mass index (BMI) is a major risk factor for development of liver disease, and the prevalence of NAFLD is elevated 4.6-fold among obese people. In obese subjects, metabolic syndrome that links type 2 diabetes mellitus, dyslipidemia and hypertension to a visceral or male pattern of adipose tissue distribution is a more important risk factor for most comorbidities of obesity than obesity *per se*[3]. Other risk factors associated with NAFLD are waist circumference (> 102 cm for males and > 88 cm for females)[4], hyperinsulinemia, hypertriglyceridemia and impaired glucose tolerance or type 2 diabetes[5,6]. In fact, hepatic steatosis (HS) is now considered to be the hepatic manifestation of insulin resistance (IR)[7].

Smoking is a well-studied risk factor for many malignant neoplasms, cardiovascular diseases, chronic obstructive pulmonary diseases and other important diseases[8]. However, it was recently shown that smoking is associated with many of the risk factors for NAFLD, particularly obesity[9], IR, diabetes and dyslipidemia[10].

Basic and clinical research demonstrates that smoking alters enzymatic and inflammatory pathways in liver physiology[11,12], and is considered to be a risk factor for liver neoplasm, and affects the prognosis of chronic liver diseases[13,14].

Currently, there is no information available about the epidemiologic importance of smoking in NAFLD. The aim of this study was thus to investigate the relationship between smoking and NAFLD.

MATERIALS AND METHODS

Study population

We conducted a cross-sectional study in the Check-up

Unit of the Diagnostic Clinic at the Medica Sur Clinic and Foundation (a university hospital with subspecialty care) in Mexico City, Mexico. This hospital provides private care for mainly middle- and high-income individuals from Mexico City and the surrounding metropolitan areas. Our sample population was formed from a series of consecutive asymptomatic subjects who were referred to the Check-up Unit by their companies as an annual requirement. The study was approved by the Human Subjects Committee of The Medica Sur Clinic and Foundation as conforming to the ethical guidelines of the 1975 Declaration of Helsinki, and written informed consent was obtained from all participants before entry. After informed consent was obtained, all patients were asked to complete a questionnaire that included demographic and medical variables. Cases were defined as current tobacco smokers (and were classified according to the number of packets smoked per year), while controls were defined as patients who had never smoked.

Questionnaire

Subjects were asked to complete a questionnaire that asked for information on demographic data, age, gender, alcohol consumption, smoking habits, diabetes mellitus, hypertension, chronic liver disease, hyperlipidemia, and the use of drugs that predispose to NAFLD.

Physical examination

Body weight was measured, in light clothing and without shoes, to the nearest 0.10 kg. Height was measured to the nearest 0.5 cm. BMI was calculated as weight (kg) divided by height (m) squared. Waist circumference (to the nearest 0.1 cm) was measured at the midpoint between the lower border of the rib cage and the iliac crest, and hip circumference was similarly obtained at the widest point between hip and buttock.

Three blood pressure readings were obtained at 1 min intervals, and the second and third systolic and diastolic pressure readings were averaged and used in the analyses.

Smoking exposure

In a detailed questionnaire, all participants were asked about smoking frequency, duration and type of cigarette. Secondhand smoking was not evaluated. Subjects exposed to chemical or industrial gases were excluded, as were those regularly exposed to other environmental smoke (i.e., open fires using firewood and crop residues as fuel). Based on the number of cigarettes and years of smoking, we calculated pack/year (each pack was considered consisting of 200 cigarettes).

Metabolic syndrome

Participants having three or more of the following criteria were defined as having the metabolic syndrome. The criteria were defined according to the Executive Summary of the Third Report of the National Cholesterol Education Program[15]. (1) Abdominal obesity: Waist circumference > 102 cm in men and > 88 cm in women; (2) Hypertriglyceridemia: Triglycerides $\geqslant$ 1500 mg/L (1.69 mmol/L); (3) Low high-density lipoprotein (HDL) cholesterol: HDL < 400 mg/L (1.04 mmol/L) in men and < 500 mg/L (1.29 mmol/L) in women; (4) High blood pressure: $\geqslant$ 130/85 mmHg (17.33/11.33 kPa); (5) High fasting glucose: $\geqslant$ 1100 mg/L ($\geqslant$ 6.1 mmol/L).

Hepatic steatosis

The diagnosis of NAFLD was first suspected in those subjects with a record of at least six months of abnormal serum aminotransferase levels that were not related to other causes of liver disease, including hepatitis B and C virus infections, autoimmune disorders, alcohol consumption or hemochromatosis, and who had ultrasonographic findings compatible with HS. Real-time ultrasonographic studies were performed while the subjects were fasting. A 3.5 MHz transducer (Elegra; Siemens Medical Systems, Mountain Grove, CA, USA) was used to obtain the following images: sagittal view of the right lobe of the liver and right kidney; transverse view of the left lateral segment of the liver and spleen; transverse view of the liver and pancreas, and any focal areas of altered echotexture. The protocol used to evaluate the pattern of HS by ultrasound was graded according to the method of Saadeh *et al*[16]. In the second evaluation, all studies for each subject were viewed side-by-side in a masked fashion ($\varkappa$ = 0.92).

Analytical procedures

Plasma glucose of subjects in the fasting state was measured in duplicate using an automated analyzer. The coefficient of variation for a single determination was 1.5%. Cholesterol, HDL-cholesterol and triglyceride concentrations were measured by enzymatic colorimetric methods, using CHOL, HDL-C plus (second generation) and triglyceride assays (Roche Diagnostics Co., Indianapolis, IN, USA), respectively. Low-density lipoprotein (LDL) cholesterol concentrations were calculated using the Friedewald formula[17].

Statistical analyses

Means and standard deviations were used to describe the distributions of continuous variables in comparisons between smokers and controls. The nonparametric Mann-Whitney *U* test was applied because of the nonnormal distribution of some of these variables. By means of cross-tabulations, the risks associated with the probability of having HS were estimated. Odds ratios (ORs) were calculated with the independent variables coded in a binary form. Statistical significance was determined by Fisher' s exact test (two-tailed) and 95% confidence intervals. To derive adjusted OR (by confounders) associated with the probability of HS, multivariate unconditional logistic regression analyses were conducted. Multicollinearity in the adjusted models was tested by deriving the covariance matrix. All statistical analyses were conducted using the statistics program SPSS/PC version 12.0 (Chicago, IL, USA).

RESULTS

We enrolled 885 consecutive subjects: 319 current smokers

Table 1 Comparative characteristics between smokers and nonsmokers

Variable	Smokers (n = 319) (mean ± SD)	Non-smokers (n = 566) (mean ± SD)	P
Age (yr)	46.9 ± 11.19	46.8 ± 12.05	NS
Weight (kg)	75.5 ± 15.99	73.84 ± 14.14	NS
Gender n (%)			
Male	205 (64.26)	343 (60.60)	NS
Female	114 (35.74)	223 (38.40)	
Height (m)	1.68 ± 0.09	1.66 ± 0.09	NS
BMI (kg/m^2)	26.8 ± 4.49	26.6 ± 4.02	NS
Overweight and obesity n (%)			
BMI ⩾ 25 kg/m^2	205 (64.26)	369 (65.19)	NS
BMI ⩾ 30 kg/m^2	54 (16.93)	105 (18.55)	NS
Waist circumference (cm)	84.3 (11.2)	83.4(11.5)	NS
Glucose (mmol/L)	5.42 ± 1.53	5.42 ± 1.52	NS
Type 2 diabetes mellitus n (%)	12 (3.7)	13 (2.3)	NS
High blood pressure (> 17.33/11.33 kPa) n (%)	21 (6.6)	64 (11.3)	< 0.05
Cholesterol (mmol/L)	5.4 ± 1.14	5.33 ± 0.95	NS
C-LDL (mmol/L)	3.48 ± 0.97	3.46 ± 0.85	NS
C-HDL (mmol/L)	1.0 ± 0.26	1.06 ± 0.28	< 0.005
Triglycerides (mmol/L)	2.18 ± 1.49	1.84 ± 1.10	< 0.001
C-reactive protein (mg/L)	3.5 ± 6.03	3.4 ± 5.10	NS
Erythrocyte sedimentation rate (mm/h)	11.3 ± 9.38	13.5 ± 11.90	< 0.001
Albumin (g/L)	4.0 ± 0.28	4.0 ± 0.31	NS
Total bilirubin (mg/L)	0.9 ± 0.39	1.27 ± 8.31	NS
ALT (UI/L)	31.4 ± 20.33	33.3 ± 26.8	NS
AST (UI/L)	26.9 ± 10.25	28.9 ± 16.28	< 0.05
Metabolic syndrome n (%)	133 (41.69)	208 (36.74)	NS
ALT 2 times upper normal limit value n (%)	4 (1.25)	8 (1.41)	NS
Hepatic steatosis n (%)	87 (27.27)	168 (29.68)	NS

(205 men and 114 women) and 566 controls (343 men and 223 women). The general characteristics between groups are described in Table 1. We observed that both groups were very similar, although there were significantly more hypertensive subjects in the nonsmoker group (11.3% *vs* 6.6%, $P < 0.05$). In the current smokers group, serum levels of triglycerides were higher (2.18 ± 1.49 *vs* 1.84 ± 1.1 mmol/L, $P < 0.005$); While in contrast, they showed lower levels of HDL cholesterol (10.0 ± 206 *vs* 10.6 ± 2.8 mg/L, $P < 0.001$). Other differences between the groups were observed in erythrocyte sedimentation rate and AST values. We did not observe any differences in the prevalence of metabolic syndrome and HS. When only subjects with HS were analyzed according to smoking status, only differences in globulin values were significant (Table 2).

Univariate unconditional logistic regression analysis revealed no increased risk for HS in smoking subjects. Several models were tested, with smokers divided into subgroups depending on their smoking amount: > 10 packs/year but ⩽ 20 packs/year, and > 20 packs/year, and then compared with all other subjects and with nonsmoking subjects only (Table 3). Although there appeared to be a dose-dependent effect, this could not be confirmed. Similar analyses were made using ALT values (twice the upper normal limit value) comparing smoking and smoking intensity, which found no statistical associations (Table 4).

Table 2 Comparative characteristics in liver function tests between smokers and nonsmokers (including only subjects with hepatic steatosis)

Variable	Smokers (n = 87) (mean ± SD)	Non-smokers (n = 168) (mean ± SD)	P
Albumin (g/L)	4.07 ± 0.23	4.10 ± (0.37)	NS
Total bilirubin (mg/L)	0.94 ± 0.31	0.93 ± 0.37	NS
ALT (UI/L)	43.7 ± 24.6	49.07 ± 40.7	NS
AST (UI/L)	32.3 ± 13.0	35.2 ± 22.9	NS
Alkaline phosphatase (UI/L)	71.2 ± 18.0	74.7 ± 24.0	NS
Lactate dehydrogenase (UI/L)	154.9 ± 24	160.6 ± 30	NS
ALT 2 times upper normal limit value n (%)	2 (2.4)	8 (4.8)	NS

Table 3 Univariate model for increased risk of hepatic steatosis

Variable	OR (95% CI)
Smoking (n = 319)	0.89 (0.65-1.21)
Smoking > 10 pack/yr (n = 152)[1]	1.30 (0.88-1.92)
Smoking > 10 pack/yr (n = 137)[2]	1.16 (0.76-1.64)
Smoking > 20 pack/yr (n = 77)[1]	1.42 (0.84-2.43)
Smoking > 20 pack/yr (n = 64)[2]	1.54 (0.94-2.52)

[1] *vs* smokers less than 10 packs/yr and nonsmokers; [2] *vs* nonsmokers only.

Table 4 Univariate model for increased risk of ALT twice the upper normal limit value

Variable	OR (95% CI)
Smoking (n = 319)	0.88 (0.26-2.96)
Smoking > 10 pack/yr (n = 152)[1]	Not calculated[3]
Smoking > 10 pack/yr (n = 137)[2]	0.43 (0.05-3.39)
Smoking > 20 pack/yr (n = 77)[1]	Not calculated[3]
Smoking > 20 pack/yr (n = 64)[2]	Not calculated[3]

[1] *vs* smokers less than 10 packs/yr and non-smokers; [2] *vs* nonsmokers only; [3] Could not be calculated as there were no subjects with an ALT level twice the upper normal limit value in the specified group.

DISCUSSION

The liver is a complex organ that has numerous enzymatic pathways involved in its physiology; Many drugs can alter these delicate processes. In particular, substances derived from smoking could impair antioxidant mechanisms[11], induce cytochrome P450[18], other enzymatic pathways[19,20] and inflammatory cytokines[12]. Although the clinical importance of smoking in hepatology has been described, specifically in hepatocellular carcinoma[13], chronic infection due to hepatitis C virus[13,21] and alcoholic cirrhosis[22], less is known about NAFLD. In the present study, we found that smoking was not associated with NAFLD or elevated liver enzymes in subjects without

chronic liver disease. Recently, a prospective study by Suzuki *et al*[23] demonstrated the importance of smoking in increased levels of ALT (only in subjects who started smoking in the study); This finding supported a putative relationship between NAFLD and smoking, although in our study, the effect of chronic smoking did not appear to be significant. Indeed, such an association is implicated by data other than an epidemiological study. Currently, smoking is known to be associated with several metabolic disturbances that are considered risk factors for NAFLD. In large study cohorts, smoking increases the prevalence of diabetes mellitus, and subjects who smoke have greater IR[24], which are considered to be the hallmarks of NAFLD[2,25].

In this study, we did not find associations between smoking and smoking intensity (number of packs/year), and the prevalence of HS and ALT at twice the upper normal limit value. As the data showed both samples were very similar. It suggests that smoking does not affect directly the prevalence of NAFLD, despite our inability to evaluate insulin values and the IR index.

Another important risk factor for NAFLD is obesity, and especially the distribution of adipose tissue. The study of den Tonkelaar *et al*[9] clearly showed that smoking could influence the distribution of adipose tissue, with an increased waist/hip ratio that is considered metabolically important[26], in other nonrelated liver diseases[27-29] and NAFLD[30]. In this study, we did not observe statistical differences related to obesity, fasting serum glucose levels or prevalence of metabolic syndrome; We found minimal (but significant) differences between current smokers and nonsmokers in levels of serum triglycerides and HDLs. This indicates that the samples are very similar, and the primary variable of the study (smoking) does not influence the prevalence of NAFLD. We observed that smoking subjects had a lower prevalence of high blood pressure, where this unexpected result did not change the results in the multivariate analysis (data not shown). Similar findings are reported in samples that analyze metabolic syndrome in non-diabetic subjects[31,32]. This phenomena could be due to a long term exposure to nicotine that alters stress response resulting in a reduction in the number or affinity of receptors mediating effects of nicotine in different central nervous system structures that integrate the neuroendocrine stress response and may also lead to lower responses of other stress hormones (ACTH, prolactin, growth hormone) to a variety of stimuli[33].

However, limitations of the study should be mentioned, which could explain the lack of association between smoking and NAFLD. First, we did not evaluate IR; the information derived from this variable could partially explain our results and clarify whether smoking impairs insulin sensitivity in our population (particularly considering a potential bias because our sample includes only a selected group of subjects). The other factor that helps to explain this result is that we did not evaluate physical activity, which is another factor related to IR and possibly affected by smoking[34]; Ultrasound is non-invasive but highly unspecific in the diagnosis of NAFLD, but in large populations it does not confer ethical conflicts. Finally the low number of subjects with ALT values twice the upper normal limit value, could underpower statistical models.

In conclusion, this is the first study that has analyzed specifically the importance of smoking in NAFLD. Although some evidence suggests a role in this disease, we could not observe differences between current smokers and nonsmokers; Furthermore, no differences are found in heavy smokers (> 20 packs/year), indicating that there is no relationship between smoking and NAFLD.

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