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Chimo, a smokeless tobacco preparation, is associated with a higher frequency of type 2 diabetes.

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Keywords: tobacco; diabetes mellitus; body mass index; Venezuela.

Abstract. The relationship between smokeless tobacco (ST) use and type-2 diabetes (T2D) has only been reported in Swedish men, though with contradictory results. In Venezuela, chimó is the most common ST preparation. The relationship between chimó and T2D in Venezuela is unknown. The objective of the study was to evaluate the relationship between chimó use and T2D in a population with high prevalence of ST use in the Andes region of Venezuela. An observational, cross-sectional, correlational study was designed. During 2013-2014, 759 consecutive subjects aged 20 years or older were evaluated in a medical center. Anthropometric measurements and responses to a standard questionnaire were obtained. Blood glucose and lipid concentrations were measured. The mean age was 53.1 years, 58% were female, and 24.1% reported ST use. ST use was more frequent in men than women (32.9% vs. 17.7%; $p < 0.001$). ST users showed lower body mass index (BMI), body fat and total cholesterol, but a higher frequency of T2D, than non-ST users. Logistic regression analysis, adjusted by age, family history of T2D, and hypertriglyceridemia, demonstrated that ST use was associated with an increased odd for T2D by 77% (OR 1.77; 95% CI 1.15 - 2.72) among ST-users. In conclusion, chimó, a ST form frequently used in the Andes region of Venezuela, is associated with a higher frequency of T2D and lower fat mass. Implications of these findings are discussed.

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Chimó, una preparación de tabaco sin humo, está asociada con una elevada frecuencia de diabetes mellitus tipo 2.

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Palabras clave: tabaco; diabetes mellitus tipo 2; indice de masa corporal; Venezuela.

Resumen. La relación entre el uso de tabaco no inhalado (TBNI) y la diabetes mellitus tipo 2 (DM2) ha sido únicamente reportada en hombres de Suecia, con resultados contradictorios. En Venezuela, el chimó es la preparación más común de TBNI. La relación entre el chimó y la DM2 en Venezuela es desconocida. El objetivo de este estudio fue evaluar la relación entre el uso de chimó y la DM2 en una población con elevada prevalencia de uso de TBNI en la región de los Andes de Venezuela. Se diseñó un estudio observacional, transversal, tipo correlacional. Durante 2013-2014, 759 sujetos de 20 o más años fueron evaluados de forma consecutiva en un centro médico. La edad promedio fue 53,1 años, 58% fueron mujeres y 24,1% reportó uso de TBNI. El uso de TBNI fue más frecuente en hombres que en mujeres (32,9% vs. 17,7%; p < 0,001). Los consumidores de TBNI mostraron menor índice de masa corporal (IMC), grasa corporal y colesterol total, pero mayor frecuencia de DM2 que los no consumidores de TBNI. El análisis de regresión logística ajustado por edad, historia familiar de DM2 e hipertrigliceridemia, demostró que el uso de TBNI se asoció con un incremento de 77% de probabilidad de presentar DM2 (OR 1,77; 95% CI 1,15 – 2,72). En conclusión, el chimó, una forma de TBNI frecuentemente usada en la región de los Andes de Venezuela, está asociada con una mayor frecuencia de DM2 y con una menor masa grasa. Se discuten las implicaciones de este hallazgo.

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INTRODUCTION

Active and passive smoking have been associated with increased risk of type-2 diabetes (T2D)(1). However, the relationship between smokeless tobacco (ST) use and T2D has only been reported in Scandinavian men (using "snus", a moist tobacco product also containing salt and related to dry snuff), though with contradictory results. In 2000, Persson *et al.*(2), in a population-based cross-sectional study, including 3,128 men, aged 35 to 56 years, indicated that heavy use (3 or more boxes per week) of moist snuff was associated with a higher prevalence of T2D (Odds ratio [OR] 2.7, 95% confidence intervals[CI] 1.3 - 5.5). In 2004, Eliasson *et al.*, reported the Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) study (3), a population-based cross-sectional and prospective study including 3,384 men, aged 25 to 74 years. In the cross-sectional analysis (OR 1.18, 95% CI [0.48–2.90]) and during the follow up (no cases of T2D in this category), snus users did not show an increased risk of developing T2D. In 2012, Östenson *et al.*(4), in a prospective population-based study on 2,383 men with 10-year follow-up, observed that the risk for incident T2D was significantly increased in those with heavy use(5 or more boxes per week) compared with non-use of ST

(OR 3.3, 95% CI [1.4-8.1]). In 2017, Rasouli *et al.*(5), analyzed a case-control data with 724 T2D subjects and 200 latent autoimmune diabetes of adulthood (LADA) as cases, matched with 699 population-based controls from Sweden. A non increased OR with heavy use (>10 boxes) of snus for T2D (OR 1.00, 95% CI [0.47 - 2.11]) and for LADA (OR 1.01, 95% CI [0.45 - 2.29]) was found. These results were similar than cross-sectional data reported in the Norwegian HUNT study (OR 0.92, 95% CI[0.46 - 1.83]) with 21,473 subjects and 829 prevalent cases of T2D. In the same year, Carlsson *et al.* (6), analyzed data from five Swedish cohort studies conducted between 1991and 2013 (54,531 never-smoking men and 2,441 incident cases of T2D). The Hazard Ratios (HR) for current users of snus was 1.15 (95% CI1.00–1.32) and increased with every box added per week (HR 1.08[95% CI: 1.01–1.16]).

The prevalence of ST use ranges from 2% to 40% according to the region of the world(7), and the use of ST has been associated with increased risk for coronary heart disease(8), stroke(9), and oropharyngeal cancer(10). In Venezuela, chimó is the most common ST preparation, composed of tobacco leaf, sodium bicarbonate, brown sugar, ashes from the mamón tree (*Meliccocca bijuga*) and vanilla and anisette flavorings. The ingredients vary according to the region of Venezuela considered. A small amount of chimó is placed between the lip or cheek and the gum and leaves are left there for some time, usually 30 minutes. The mixture of chimó and saliva is spitout (11). In the Andes region of Venezuela a high prevalence of ST use (38%) was found (12). This prevalence was higher in men than women (58% vs. 18% respectively, $p < 0.0001$) and increased with age.(12)

The prevalence of diabetes reported in Venezuela, weighting data of published studies (7.7%) (13) is similar to the worldwide prevalence (8.8%)(14). Given the dimensions of the diabetes epidemic on a global scale, particularly, the rising prevalence of T2D in Venezuela (13-15), it is critical that various drivers for T2D, especially those that have been un- or under-recognized, are better understood to fashion successful preventive measures. Considering that the relationship between chimó use and T2D has not been previously reported, the objective of this study was to determine this relationship in Venezuela.

PATIENTS AND METHODS

Design and Subjects

An observational, cross-sectional, correlational study was designed. From 2013 to 2014, 759 subjects aged 20 years or older, consecutively attended in a medical center located in Timotes were included. Timotes is a primarily agricultural population of the Andean region of Venezuela (Mérida State), with 18,179 inhabitants and located at an altitude of 2,025 meters with an average annual temperature of 16 °C. All the study patients were assessed by a physician specialist in Internal Medicine. All participants completed a questionnaire, including information about age, gender, family and personal history of diabetes and tobacco use. Chimó use was interrogated as given in Table I. Anthropometric measurements were obtained following standardized procedures. Weight was measured with the fewest clothes possible, without shoes, using a calibrated scale (OMRON® HBF-510LA; Omron Healthcare, Inc., 2011, Illinois, USA), which also calculates body fat using bioelectrical impedance measurements. Height was measured using a metric tape on the wall. Waist circumference was measured using a metric tape, at a level just above the iliac crest. Hip circumference was measured at the femoral greater trochanters. Body mass index (BMI; kg/m^2) and waist/hip index (waist circumference/hip circumference) were calculated. A fasting

TABLE I
QUESTIONNAIRE OF SMOKELESS TOBACCO USE

Questions	Answers
Had you ever used smokeless tobacco as chimó, chewing tobacco or snus?	Yes, I currently use
	Yes, but not in the last 12 months
	No, I never used
Number of years of use	_____ years
Frequency of use	Daily
	Weekly
	Less than weekly

blood sample was obtained for biochemical data (fasting glucose and lipid profile) and was processed in two different private laboratories. Pregnant women were excluded. All subjects signed an informed consent for participation.

Variables definitions

ST use was defined as daily or weekly consumption of chimó for the last twelve months. No others forms of ST use were reported. T2D was established by self-report or if the fasting plasma glucose was ≥ 126 mg/dL (16).Individuals were classified according to BMI as normal weight (BMI < 25 kg/m^2), overweight (BMI ≥ 25 kg/m^2 and < 30 kg/m^2) or obese (BMI ≥ 30 kg/m^2) (17).

Statistical analysis

All calculations were performed using the SPSS 20 software (IBM corp, released 2011, Armonk, NY, USA). A test of normality (Kolmogorov-Smirnov and Q-Q plots) was initially performed for each variable. Data for continuous variables were presented as mean ± standard error of the mean (SEM), except blood glucose, which was not normally distributed and was presented as median and interquartile range (IR). Differences between mean values were assessed by Student's t-test or ANOVA. Difference between glucose median values was assessed by Mann-Whitney U test or Kruskal-Wallis test. Frequencies were presented as percentage and 95% CI. The Chi-square test was applied to compare different frequencies. Logistic regression was used to determine multivariate risk factors associated with T2D.The statistical significance was considered with alpha level of $p < 0.05$.

RESULTS

Subject characteristics

Overall, 759 subjects completed the data, with a mean age of 53.1 years, of whom 58% were female and 24.1% reported current ST use. ST use was higher in men than women (32.9% versus 17.7%, respectively; $p < 0.001$) (Table II). Current ST-users had lower BMI, body fat percent and total cholesterol, than non-ST users and former users, but similar indices of central obesity (waist circumference and waist/hip index). Almost one third (28.6%) of the sample

TABLE II
SUBJECT CHARACTERISTICS ACCORDING TOBACCO USE

Characteristics	Smokeless Tobacco Use		
	Never	Former	Current
Total: n (%)	411 (54.2)	165 (21.7)	183 (24.1)
Male (%)/Female (%)*	129(40.5)/282(64.1)	85(26.6)/80(18.2)	105(32.9)/78(17.7)
Age (years)*	51,2 ± 0.81	56.6 ± 1.33	54.3 ± 1.10
Body Mass Index (kg/m^2)†	28.7 ± 0.24	29.1 ± 0.41	27.4 ± 0.37
Waist Circumference (cm)	95.3 ± 1.02	95.0 ± 2.01	94.7 ± 1.40
Waist/Hip Index	0.9 ± 0.02	1.0 ± 0.01	0.9 ± 0.00
Body Fat (%)*	34.6 ± 0.67	32.0 ± 1.08	28.9 ± 1.05
Blood Glucose (mg/dL)†	96.0 ± 29.9	103.0 ± 61.2	99.0 ± 59.0
Total Cholesterol (mg/dL)†	176.2 ± 4.60	171.3 ± 5.53	156.0 ± 5.38
Triglycerides (mg/dL)†	162.0 ± 5.22	195.5 ± 13.51	170. 3 ± 9.84
Family History of Diabetes	53.5 (48.2 – 57.9)	58.8 (51.2 – 66.3)	51.4 (44.1 – 58.6)
Type-2 Diabetes†	23.8(19.6 – 27.9)	32.7 (25.5 – 39.8)	35.5 (28.5 – 42.4)
Obesity	34.5 (29.9 – 39.1)	37.6 (30.2 – 44.9)	28.4 (21.8 – 34.9)
Overweight	45.5 (40.6 – 50.3)	39.4 (31.9 – 46.8)	45.9 (38.6 – 53.1)
Normal weight	20.0 (16.1 – 23.8)	23.0 (16.5 – 29.4)	25.7 (19.3 – 32.0)

Continue variables are presented as means ± SEM, except blood glucose is presented as median (interquartile range). Differences were assessed by ANOVA for all variables except blood glucose by Kruskal-Wallis test. Data of frequencies are presented as percent (95% CI). *$p < 0.001$;†$p < 0.05$. Obesity: BMI ≥ 30 kg/m^2; Overweight: BMI 25 - 29.9 kg/m^2; Normal weight: BMI < 25 kg/m^2.

had T2D. Although similar in weight and body composition, subjects with diabetes were older and with higher level of blood glucose, total cholesterol and triglycerides than non-diabetic subjects (Table III).

Tobacco use and T2D

The frequency of T2D was higher in ST users (35.5% in ST users, 95% CI [28.6 - 42.4] vs. 26.4% in non-ST users, 95% CI [22.8 - 30.0]; $p < 0.006$) (Table II). Daily use of chimó was observed in 76% of ST users. When frequency of T2D was categorized in daily vs. non-daily users, no difference was observed(34.7% vs. 29.5%, $p= 0.222$; respectively). However, when subjects were categorized according to the presence of obesity, the relationship between ST and T2D only remain significant in non-obese subjects(Table IV). Logistic regression was applied with the variables that remained significant in the model, such as age, family history of T2D, and hypertriglyceridemia. Chimó use increased the odds for T2D by 77% among ST-users (OR 1.77, 95% CI[1.2 - 2.7]) (Table V). Not surprisingly, age, hypertriglyceridemia and family history of T2D, were also associated with

TABLE III
SUBJECTS CHARACTERISTICS ACCORDING TO TYPE-2 DIABETES PRESENCE

Characteristics	Type-2 Diabetes	
	Present	Absent
Total: n (%)	217 (28.6)	542 (71.4)
Male (%)/Female (%)	97(30.4)/120(27.3)	222(69.6)/320(72.7)
Age (years)*	61.2± 0.90	49.9±0.70
Body Mass Index (kg/m^2)	28.3 ± 0.34	28.5 ± 0.22
Waist Circumference (cm)	94.2 ± 1.77	95.5 ± 0.83
Waist/Hip Index	1.01 ± 0.00	0.98 ± 0.01
Body Fat (%)	31.9 ± 1.01	32.9 ± 0.58
Blood Glucose (mg/dL)*	191.0 ± 138.0	92.0 ± 16.2
Total Cholesterol (mg/dL)	160.9 ± 5.82	174.0 ± 3.59
Triglycerides (mg/dL)†	193.3 ± 11.7	162.5 ± 4.62
Family History of Diabetes(%)*	67.7(67.4 – 73.9)	48.7 (44.4 – 52.9)
Smokeless Tobacco (Chimó)(%)†	30.0 (23.9 – 36.1)	21.8 (18.3 – 25.2)
Obesity (%)	34.1 (27.9 – 40.4)	33.6 (29.6 – 37.5)
Overweight (%)	42.4 (35.8 – 48.9)	45.0 (40.8 – 49.1)
Normal weight (%)	23.5 (17.8 – 29.1)	21.4 (17.9 – 24.8)

Continue variables are presented as means ± SEM, except blood glucose is presented as median (interquartile range). Differences were assessed by Student-t test for all variables except blood glucose by Mann-Whitney U test. *$p < 0.001$;†$p < 0.05$.Obesity: BMI ≥ 30 kg/m^2; Overweight: BMI 25 - 29.9 kg/m^2; Normal weight: BMI < 25 kg/m^2.

TABLE IV
RELATIONSHIP BETWEEN TYPE-2 DIABETES PRESENCE AND SMOKELESS TOBACCO USE ADJUSTED BY OBESITY

Obesity	Smokeless Tobacco			
		T2D	non-T2D	OR (95% CI)
Present	ST users	14.9 (10.1 – 19.6)	22.5 (18.9 – 26.0)	0.60 (0.29 - 1.24)
	ST non-users	85.1 (80.3 – 89.8)	77.5 (23.9 – 81.0)	
Absent*	ST users	37.8 (31.3 – 44.2)	21.4 (17.9 – 24.8)	2.23 (1.46 - 3.39)
	ST non-users	62.2 (55.7 – 68.6)	78.6 (75.1 – 82.0)	

Data are expressed as percentage (95% CI). CI: Confidence Intervals: OR: Odds ratio; ST: Smokeless Tobacco; T2D: Type-2 diabetes. *$p < 0.001$.

TABLE V
RISK FACTORS ASSOCIATED WITH TYPE-2 DIABETES

	OR	95% CI
Age	1.06	1.04 - 1.07
Smokeless tobacco (chimó)	1.77	1.15 - 2.72
Hypertriglyceridemia	2.76	1.82 - 4.17
Family History of Diabetes	3.37	2.22 - 5.11

Logistic Regression Analysis. OR: Odds ratio; CI: Confidence Interval.
Hypertriglyceridemia: triglycerides ≥ 150 mg/dL.

increased odds for T2D. In this sample, nutritional state or obesity was not related to T2D risk (p= 0.754), and therefore, it was not included in the analysis.

DISCUSSION

Chimó, a ST preparation frequently consumed in the Andes region of Venezuela, was associated with a higher frequency of T2D, despite being related with lower BMI and body fat. The findings of this study add evidence supporting the possible association between ST use and T2D observed in Swedish men heavy users of snus.

The link between tobacco use and T2D could be related to β-cell dysfunction due to nicotine exposure. Using the glucose-clamp method, an acute infusion of nicotine impaired insulin action in patients with diabetes but not in healthy volunteers (18). Some studies have found neuronal nicotinic acetylcholine receptors (nAChRs) expressed on many different non-neuronal cell types including pancreatic islet cells (19, 20). Presence of neuronal nicotinic receptors sensitive to nicotine in pancreatic cells, may modulate cholinergic-dependent pancreatic islet cell function and mediate tobacco toxicity (21). Nicotine exposure via nAChRs can also cause β-cell dysfunction, increasing β-cell apoptosis, mitochondrial dysfunction, oxidative stress, inflammation, and eventually loss of β-cell mass (22). Brown sugar, a component of chimó preparation, could be a potential factor that increases the risk for T2D. Sugar consumption, especially as sugar-sweetened beverages, has been associated with a greater incidence of T2D (23). However, more research is needed to establish this potential link (24).

In smokers, nicotine acutely increases energy expenditure and reduces appetite, leading to lower body weight than in non-smokers and inversely, smoking cessation is frequently followed by a weight gain (21). In this study, similar to smokers, ST users have lower BMI and body fat than non-ST users. The effect on weight and insulin resistance could explain why the relationship between ST use and T2D was only significant in non-obese subjects. Therefore, even though weight gain leads to insulin resistance, glucose intolerance and T2D, in this study the association of T2D and lower BMI is not paradoxical. In the same way, a higher proportion of ST users - with lower weight - in the group with diabetes, could explain that no differences in body composition were found between the groups with or without diabetes.

Some limitations of the present study deserve to be mentioned. In Venezuela, chimó is generally produced using traditional methods,

with many different presentations for sales and no fixed doses used. As a result, exact amounts of chimó use cannot be measured like other tobacco products that are sold in standard formats (e.g., packs or cartons). Moreover, the components found in the tobacco leaf in chimó preparation are unknown. In the present study, blood concentrations of nicotine or cotinine (nicotine metabolite) were not measured. The transversal model of the study does not allow to determine causal relationship between the chimó and T2D, but highlight the need for future prospective studies, to determine if these findings are generalizable.

This is the first report relating chimó use and T2D. Chimó use increased the odds of T2D in an Andean Venezuelan population by 77%, despite being associated with lower fat mass, which after further consideration of the effects of nicotine on energetics and appetite is not inconsistent. Almost six of every10 men and two of every 10 women report chimó use in the Andes region of Venezuela, increasing the prevalence of T2D in the exposed population and representing a significant public health problem. Further studies will be necessary to evaluate the precise epidemiological impact and mechanisms of pathogenesis with ST use in Venezuela, other areas of Latin American, and most importantly, other areas around the world.

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