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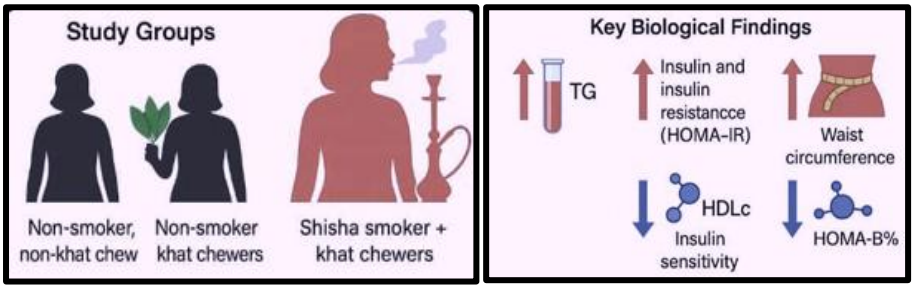
Association of Khat chewing and shisha smoking with metabolic syndrome and diabetes factors among Yemeni women

Dheya Abdull **Hameed**[1], Maher Ali **Almaqtari**[1+], Mona Abdullah **Al-Tahami**[1], Riyadh **Saif-Ali**[2], Saad **Al-Arnoot**[1]

Abstract

Khat chewing and shisha smoking have spread among women in Yemeni society; thereby, these modifiable lifestyles may contribute to the development of metabolic syndrome. Therefore, this study aimed to investigate the association of Khat chewing and combined shisha smoking and Khat chewing with metabolic syndrome factors among Yemeni females. An analytical cross-sectional study was conducted. One hundred and eighty Yemeni females signed the consent form and donated blood; 60 of them were non-smoking non-Khat chewers (control group), 60 were non-smoking Khat chewers, and 60 were shisha-smoking Khat chewers. Analysis of covariance (ANCOVA) showed that Khat chewing was associated with higher triglycerides (TG) (p = 0.001) and waist circumference (p = 0.001) in non-smoking Khat chewers compared with non-smoking non-Khat chewer women. In addition, ANCOVA showed that TG is an important covariate associated with insulin resistance among khat-chewing women. In conclusion, Khat chewing is associated with a higher risk of metabolic syndrome and type 2 diabetes mellitus in Yemeni females.



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Highlights

- Khat chewing associated with higher TG and waist circumference in Yemeni women.
- Khat chewing is associated with low levels of HDLc and insulin sensitivity.
- Khat chewing is a risk factor for metabolic syndrome and diabetes.

[1]Sana'a University, Faculty of Sciences, Sana'a, Yemen. [2]Sana'a University, Faculty of Medicine, Sana'a, Yemen. **+Corresponding author:** Maher Ali Almaqtari, **Phone:** +00967773262252, **Email address:** m.almaqtari@su.edu.ye

1. Introduction

The habit of Khat chewing has prevailed for centuries among populations in the Horn of Africa and the Arabian Peninsula, including Yemen. Although Khat chewing is known to cause health issues, it is estimated that 20 million people worldwide have regular chewing of Khat (Corkery *et al.*, 2010). Khat has been a part of Yemeni culture for a long time and is used on virtually every social occasion. Nearly 90% of adult males and more than 50% of females chew Khat for 3 to 4 h daily (Al-Mugahed, 2008). The Khat (*Catha edulis* Forsk) belongs to the family *Celastraceae*, and it is highly abused for its stimulant property (Widler *et al.*, 1994).

Khat leaves contain variable concentrations of amines such as cathinone, cathine, norephedrine (Geisshüsler and Brenneisen, 1987), ephedrine, and pseudoephedrine. Cathinone is the major component responsible for the Khat effects (Caveney *et al.*, 2015), which is structurally and functionally like amphetamines causing psychostimulatory effects. After the first few hours of Khat chewing, Khat chewers experience euphoria, improve capacity to relate ideas, enhance self-esteem, increase alertness, and increase imaginative ability. Toward the end of the Khat session, most Khat chewers experience hyperthermia, mydriasis, anorexia, irritability and insomnia (Al-Motarreb *et al.*, 2002).

In 2020, World Health Organization (WHO) estimated that 1.07 billion males and 231 million females aged 15 years and over consumed a tobacco product (WHO, 2021), and over 8.7 million people died from a tobacco-related disease in 2019 (GBD, 2020). In Yemen, 3.8 million males and 770,000 females aged ≥15 years consumed a tobacco product (WHO, 2021). Shisha is a method of smoking tobacco through water. Shisha smoking involves burning flavored tobacco (molasses), using coal. The smoke contains components from both tobacco and coal. These include polycyclic aromatic hydrocarbons, volatile aldehydes, carbon monoxide, nitric oxide and furan (Cobb *et al.*, 2012).

The presence of volatile aldehydes has also been reported in shisha smoke, including formaldehyde, acetaldehyde, acrolein, propionaldehyde and methacrolein. These chemicals have been correlated with various respiratory disorders, respiratory tract irritation, chronic obstructive pulmonary disease and lung cancer. Specifically, formaldehyde and acrolein are both potent carcinogens that may promote the development of leukemia (Kang *et al.*, 2021). In addition, carbon monoxide levels have been observed to significantly increase after shisha smoke, resulting in increasing carboxyhemoglobin concentrations, headaches and shortness of breath (La Fauci *et al.*, 2012). Increasing nicotine levels after smoking shisha for 5 min have been shown to induce increases in heart rate and may contribute to various cardiovascular diseases (Kadhum *et al.*, 2014). Metabolic syndrome (MtS) is associated with chronic diseases such as diabetes and cardiovascular diseases. Metabolic disorders, hyperglycemia, abdominal obesity, hypertension, and dyslipidemia are risk factors for diabetes and cardiovascular diseases. There are conflicting results on the association of Khat with metabolic syndrome factors, glucose (Alshagga *et al.*, 2016), obesity (Alshagga *et al.*, 2016), and blood pressure (Mega and Dabe, 2017). There is limited data on the combined association of Khat chewing and smoking with metabolic syndrome and diabetic factors, particularly among women. However, a few studies have begun exploring this area—for instance, one study investigated the impact of Khat chewing on inflammatory markers and advanced glycation end products among Yemeni women, highlighting its potential role in metabolic and inflammatory pathways (Al-Maqtari *et al.*, 2024).

Khat chewing accompanied by shisha smoking has been widely spread among women in Yemeni society. This modifiable lifestyle may play a role in metabolic syndrome and diabetic factors, which may increase the risk of cardiovascular diseases and diabetes among smoker Khat chewers Yemeni females. Therefore, this study aimed to study the association of Khat chewing as well as the combined association of Khat chewing and shisha smoking with metabolic syndrome and diabetic factors among Yemeni women.

2. Experimental

2.1. Study design and participants

This study is analytical cross-sectional, which was conducted to evaluate the association of chronic Khat chewing as well as combining khat chewing and shisha smoking with metabolic syndrome and diabetic factors. This study was reviewed and approved by Research Ethics Committee of the Institutional Review Board (IRB), Faculty of Sciences, Sana'a University (Reference number: IRBSSU/3-2019) on January 7th, 2019. All participants provided written informed consent to participate in the study. The recruiting of subjects for this current study was by distribution of study brochures at women's gathering clubs in Sana'a city and social media advertising. Women's gathering clubs in Yemen are private villas with coffee shop and gym facilities for fitness and weight loss, as well as halls with special local furniture to facilitate women gathering for shisha smoking and or Khat chewing. Altruism and free medical checkups for metabolic syndrome [systolic and diastolic pressure, triglycerides (TG) and high-density lipoprotein cholesterol (HDLc)] and diabetic factors [fasting blood glucose (FBG), insulin, insulin resistance (HOMA-IR), insulin sensitivity (HOMA-IS) and β-cell function (HOMA-B%)] motivated subjects to participate in this study.

The sample size was calculated by the winPepi program. The sample size, 180 subjects to detect significant difference in means between the target and control groups at 95% significance level and 80% power of the study. Sixty women, non-Khat chewers non-smokers (control group), 60 women were daily Khat chewer non-smoker, and 60 women were daily Khat chewer accompanied with shisha smoking. Before enrolling subjects in this study, participants attended a screening session to assess their suitability for the study accessibility to participate in this research. The screening session included a brief medical history interview and assessment of current and past Khat and smoking habits, as well as the use of other substances.

2.1.1. Inclusion criteria

Participants who met the following inclusion criteria were selected for this study: non-pregnant Yemeni women aged 30-60 years, without history of diabetes, cardiovascular, kidney, liver diseases, and not taking any medications. Furthermore, the control group women without a history of past smoking and Khat chewing habits and who were not passive smokers. In addition, the Khat chewer non-smoker group chew approximately 100-150 grams of fresh Khat daily for 5-6 h for more than a year without history of past smoking habit and were not passive smokers. Moreover, Khat chewer shisha smoker group chew approximately 100-150 grams of fresh Khat daily for 5-6 h for more than year, accompanied by smoking shisha during Khat session for more than a year.

2.1.2. Exclusion criteria

The following exclusion criteria were applied: pregnant women or women aged <30 and >60 years, history of diabetes, cardiovascular, kidney or liver disease or taking medications. Additionally, the control participants with history of past smoking, Khat chewer or passive smoke were excluded. Furthermore, the Khat chewer non-smoker group not daily chewing Khat or chewed Khat for less than year, consuming less than 100 or more than 150 grams of fresh Khat, or participating in Khat session of less than five or more than 6 h per day, or having history of past smoking habit or passive smoker. Moreover, Khat chewing group, the exclusion criteria are same as Khat chewing group and the participants were excluded if Khat session with smoking shisha were not combined.

2.2. Anthropometric and physiological parameters

Physiological parameters of systolic and diastolic blood pressure as well as anthropometric parameters of weight, height, and waist circumference were measured on the same day of blood collection. Subject weight with light clothes was measured using a standard body weighing scale (BOSCH FD 8905, Germany). Height without shoes was measured using a freestanding stadiometer (Leicester, China). Waist circumference was measured in a standing midway between the superior iliac spine and lower rib margin. The formula, weight in kilograms divided by height in square meters was used to calculate the body mass index (BMI). Blood pressure (BP) measurements were taken from each participant's left arm in the seated position using an automatic blood pressure monitor (Omron IntelliSense, Vietnam). Two to three successive BP readings were obtained at 5 min intervals and averaged.

2.3. Blood and biochemical analysis

Venous blood, 3-mL of overnight fasting subject was collected into a gel tube by nursing staff at Sehatak Specialized Laboratory and centrifuged at 3500 r.p.m for 10 min within half an hour of sample collection, and serum was aliquoted into two Eppendorf tubes and frozen at –20 ^{0}C for biochemical analysis. The following biochemical tests were analyzed by medical laboratory specialists in Sehatak Specialized Laboratory. Glucose (REF 3L82-2030-4129/R5), TG (REF 7D74-2030-3140/R3) and HDLc (REF 3K33-20.30-4129/R5) from Abbott Laboratories were measured by fully automated chemistry analyzer (Ci4100, Abbott, USA). Insulin (REF 12017547122) from Roche Diagnostic GmbH, Germany, was measured in a fully automated quantitative immunoassay analyzer (Cobas e 411, Roche Diagnostics GmbH, Germany). Low and high glucose, TG, HDLc, and insulin control sera were run to validate the accuracy and precision of the analytical instruments before processing samples. HOMA-IR, HOMA-IS and HOMA-B% were calculated using the Homeostasis Model Assessment (HOMA2) calculator v2.2, which is available from the Oxford Centre for Diabetes, Endocrinology, and Metabolism.

2.4. Statistical analysis

Social Package Social Sciences (SPSS) version 11.5 (SPSS Inc., Chicago, IL, USA) was applied for statistical analyses in this project. Metabolic syndrome and diabetic factors were not normally distributed, so they were log-transformed to proceed with the statistical analysis. Then, the log-transformed means and 95% confidence intervals were back-transformed and reported as geometric means. Analysis of variance (ANOVA) was performed to determine if there were significant differences between the means of the three groups. IF the ANOVA indicated a significant difference, a Tukey's Honestly Significant Difference (HSD) test was used as a post-hoc test to identify which specific group means differ from each other. Linear regression model (enter) was used to configure the confounding factors for each outcome variable. A general linear model with univariate analysis (ANCOVA) was applied to control cofounders to analyze the association of Khat chewing, and shisha smoking per se. The accepted level of significance was set below 0.05 ($p < 0.05$)

3. Results

The age and anthropometric characterizations of the subjects are shown in **Table 1**. There was no difference in age, weight, height, and body mass index between Khat chewer shisha smoker and Khat chewers non-smoker compared to non-Khat chewer non-smoker group.

Table 1. Age and anthropometric parameters of study groups.

Group	Non-Khat chewer non-smoker control group (n=60)	Khat chewer non-smoker (n=60)	Khat chewer smoker (n=60)	*ANOVA p*-value	Khat chewer non-smoker × control group	Khat chewer smoker × control group
Age (year)	39.4 (37.4 – 41.4)	40.2 (38.2 – 42.3)	38.7 (36.9 – 40.5)	0.553	0.830	0.868
Height (meter)	1.55 (1.53 – 1.56)	1.56 (1.54 – 1.57)	1.56 (1.55 – 1.58)	0.315	0.694	0.282
Weight (Kg)	64.0 (60.3 – 67.9)	67.0 (63.9 – 70.3)	68.5 (65.2 – 72.1)	0.177	0.439	0.161
BMI	26.7 (25.3 – 28.2)	27.7 (26.5 – 28.8)	28.0 (26.7 – 29.4)	0.346	0.561	0.336

Note: BMI = body mass index. Results are presented as geometrical mean and confidence interval.
Source: Elaborated by the authors.

3.1. Association of Khat chewing and smoking with metabolic syndrome factors

The Khat chewer smoker and Khat chewer non-smoker females have higher serum levels of TG ($p = 0.007$; $p = 1.0x10^{-5}$) and lower HDLc ($p = 0.036$; $p = 0.015$) compared to non-smoker non-Khat chewing females, respectively (**Table 2**). There was no significant difference in the systolic and diastolic blood pressure among Khat chewer non-smoker females ($p = 0.291$; $p = 0.516$) and smoker Khat chewing females ($p = 0.175$; $p = 0.963$) compared to the control group, respectively. Although waist circumference was significantly higher in non-smoker Khat chewers ($p = 0.004$) and smoker Khat chewers ($p = 0.036$) compared with non-smoker non-Khat chewing females, there were no differences in weight and BMI between groups.

Table 2. Association of Khat chewing and smoking with metabolic syndrome.

Group	Non-Khat chewer non-smoker control group (n=60)	Khat chewers non-smoker (n=60)	Khat chewers smoker (n=60)	*ANOVA* *p*-value	Khat chewer non-smoker × control group	Khat chewer smoker × control group
Systolic blood pressure (mmHg)	112 (108 – 116)	108 (104 – 112)	107 (104 – 111)	0.16	0.291	0.175
Diastolic blood pressure (mmHg)	76 (74 – 79)	75 (72 – 77)	77 (75 – 79)	0.354	0.516	0.963
Waist circumference (cm)	84.0 (81.1 – 86.9)	92.9 (89.3 – 96.5)	89.6 (86.3 – 93.1)	**0.001**	**0.004**	**0.036**
Triglycerides (mmol/l)	1.0 (0.9 – 1.1)	1.4 (1.3 – 1.6)	1.3 (1.1 – 1.4)	**$2x10^{-5}$**	**$1x10^{-5}$**	**0.007**
HDLc (mmol/l)	1.5 (1.4 – 1.5)	1.3 (1.2 – 1.4)	1.3 (1.3 – 1.4)	**0.01**	**0.015**	**0.036**
Triglycerides/ HDLc ratio	0.75 (0.66 – 0.85)	1.22 (1.04 – 1.39)	1.04 (0.91 – 1.17)	**0.00002**	**0.00001**	**0.01**
Triglycerid index	5.36 (5.30 – 5.42)	5.54 (5.47 – 5.62)	5.49 (5.42 – 5.56)	**0.0005**	**0.0004**	**0.017**

Note: HDLc = high-density lipoprotein cholesterol. Results are presented as geometrical mean and confidence interval.
Source: Elaborated by the authors.

Table 3 illustrates that abdominal obesity (waist circumference ≥ 80 cm) was significantly more prevalent among khat-chewing women, both non-smokers (87%, $p = 0.000001$) and smokers (77%, $p = 0.0004$), compared to the non-khat chewer, non-smoker women (43%). Similarly, the prevalence of hypertriglyceridemia (TG ≥ 1.7 mmol/L) was higher among khat-chewing non-smoker women (33%, $p = 0.0002$) and smoker khat chewers (25%, $p = 0.005$), in contrast to only 7% in the control group. Abnormally low HDL cholesterol was also more common among non-smoker khat chewers (53%, $p = 0.021$) compared to the control group (33%). However, there were no statistically significant differences between groups in the distribution of elevated blood pressure or FBG. Metabolic syndrome, defined as the presence of at least three out of five metabolic factors, was non-significantly more prevalent among non-smoker khat chewers (33%, $p = 0.074$) and smoker khat chewers (27%, $p = 0.19$) compared to the control group (20%). Likewise, elevated BMI was observed more frequently among both khat-chewer groups (75%) than in non-khat chewers (62%), though this difference was also not statistically significant ($p = 0.085$).

Analysis of covariance (ANCOVA) was used to analyze if Khat chewing per se was the main associated factor with metabolic syndrome factors (TG, waist circumference, and HDLc), and these parameters were screened for covariances by linear regression to be included in the ANCOVA (**Table 4**).

Table 3. Distribution of metabolic syndrome factors among the study group according to the harmonized criteria for metabolic syndrome.

Group	Non-Khat chewer non-smoker (control group) (n=60)	Khat chewers non-smoker (n=60)	Khat chewers smoker (n=60)
1- Blood pressure Systolic (≥ 130 mmHg) OR Diastolic (≥ 85 mmHg)	15 (25%)	8 (13%) *p = 0.08*	10 (17%) *p* = 0.18
2- Abdominal obesity (waist circumference ≥ 80 cm)	26 (43%)	52 (87%) **p = 0.000001**	46 (77%) **p = 0.0004**
3- Triglycerides (≥ 1.7 mmol/l)	4 (7%)	20 (33%) **p = 0.0002**	15 (25%) **p = 0.005**
4- High-density lipoprotein cholesterol (≤1.3 mmol/l)	20 (33%)	32 (53%) **p = 0.021**	24 (40%) *p* = 0.29
5- Glucose (≥ 5.56 mg/dl)	25 (42%)	21 (35%) *p* = 0.29	19 (32%) *p* = 0.17
Metabolic syndrome (three abnormal finding out of 5)	12 (20%)	20 (33%) *p = 0.074*	16 (27%) *p* =0.19
Body mass index ≥ 25	37 (62%)	45 (75%) *p = 0.085*	45 (75%) *p = 0.085*

Source: Elaborated by the authors based on Alberti *et al.*, (2009).

Table 4. Linear regression correlation of waist circumference, triglycerides and HDLc with age and metabolic syndrome factors.

Covariate factor	Waist circumference Beta (95% IC) *p*-value	Triglyceride Beta (95% IC) *p*-value	HDLc Beta (95% IC) *p*-value
Age	−0.01 (−0.74 – 0.24) 0.879	0.27 (0.01 – 0.03) **0.001**	0.06 (−0.004 – 0.01) 0.482
Fasting blood glucose	−0.03 (−1.78 – 1.01) 0.653	0.08 (0.023 – 0.14) 0.111	0.19 (0.01 – 0.07) **0.011**
Insulin	0.16 (0.01 – 0.11) *0.056*	0.31 (0.002 – 0.01) **0.001**	−0.13 (−0.002 – 0.00) 0.134
Systolic blood pressure	0.09 (−0.034 – 0.212) 0.228	−0.09 (−0.01 – 0.002) 0.211	−0.10 (−0.01 – 0.001) 0.181
HDLc	−0.22 (−17.94 – −4.49) **0.004**	−0.15 (−0.612 – −0.033) **0.029**	–
Triglycerides	0.165 (0.05 – 7.05) 0.045	–	−0.18 (−0.16 – −0.01) **0.029**
waist circumference	–	0.141 (0.000 – 0.013) **0.045**	−0.22 (−0.01 – −0.002) **0.004**

Note: HDLc = high-density lipoprotein cholesterol.
Source: Elaborated by the authors.

3.1.1. Association of Khat chewing and shisha smoking with waist circumference

Linear regression analysis identified that insulin, TG, and HDLc were cofounders for waist circumference. As a result, the association of Khat chewing and shisha smoking with waist circumference was analyzed by ANCOVA adjusted for HDLc, insulin, and TG, as shown in Table 5. The abscission of Khat chewing with increasing waist circumference remains significant even after adjustment for insulin, TG, and HDLc (p = 0.001), where smoking did not add further association with waist circumference (p = 0.043).

Table 5. Association of Khat chewing and shisha smoking with metabolic syndrome adjusted for covariate factors.

Group	Non-Khat chewer non-Smoker (control group)	Khat chewer non-smoker	Khat chewer smoker	p-value	Khat chewer non-smoker × control group	Khat chewer smoker × control group
ANOVA						
Waist circumference	84.0 (81.1 – 86.9)	92.9 (89.3 – 96.5)	89.6 (86.3 – 93.1)	0.001	0.004	0.036
ANCOVA adjusted for triglycerides, HDLc, insulin						
Waist circumference	86.5 (83.4 – 89.5)	91.2 (87.9 – 94.4)	88.7 (85.7 – 91.8)	0.004	0.001	0.043
ANOVA						
Triglycerides	1.0 (0.9 – 1.1)	1.4 (1.3 – 1.6)	1.3 (1.1 – 1.4)	$2.0x10^{-5}$	$1.0x10^{-5}$	0.007
ANCOVA adjusted for insulin, HDLc, waist circumference and age						
Triglycerides	1.01 (0.99 – 1.2)	1.37 (1.23 – 1.48)	1.25 (1.13 – 1.37)	0.003	0.001	0.036
ANOVA						
HDLc	1.5 (1.4 – 1.5)	1.3 (1.2 – 1.4)	1.3 (1.3 – 1.4)	0.01	0.015	0.036
ANCOVA (adjusted for waist circumference, triglycerides, FBG)						
HDLc	1.39 (1.33 – 1.47)	1.36 (1.29 – 1.43)	1.34 (1.28 – 1.40)	0.455	0.452	0.211
ANCOVA (adjusted for waist circumference)						
HDLc	1.42 (1.35 – 1.49)	1.34 (1.28 – 1.40)	1.33 (1.27 – 1.39)	0.150	0.103	0.079
ANCOVA (adjusted for triglycerides)						
HDLc	1.43 (1.36 – 1.50)	1.33 (1.27 – 1.40)	1.33 (1.27 – 1.40)	0.127	0.083	0.069
ANCOVA (adjusted for FBG)						
HDLc	1.46 (1.38 – 1.52)	1.31 (1.25 – 1.38)	1.33 (1.26 – 1.39)	0.010	0.006	0.013

Note: HDLc = high-density lipoprotein cholesterol; FBG = fasting blood glucose.
Source: Elaborated by the authors.

3.1.2. Association of Khat chewing and shisha smoking with triglycerides

Linear regression showed that age, insulin, waist circumference, and HDLc are covariate factors for triglycerides levels, and thus association of Khat chewing and smoking with TG was analyzed by ANCOVA adjusted for insulin, HDLc, waist circumference, and age (Table 5). This ANCOVA model showed that TG remains significantly higher among non-smoker Khat chewers (p = 0.005) and smoker Khat chewers (p = 0.036) compared to non-smoker non-Khat chewing females.

3.1.3. Association of Khat chewing and shisha smoking with HDLc

Triglycerides, waist circumference, and FBG are covariate factors for HDLc, so the effect of Khat chewing and shisha smoking on HDLc was analyzed by ANCOVA adjusted for TG, waist circumference, and FBG. The significant low HDLc among smokers and non-smoker Khat chewers compared to control group (p = 0.036; p = 0.015) was gone after a multivariate analysis (ANCOVA) adjusted for TG, waist circumference and FBG (p = 0.452; p = 0.211) (Table 5). To figure out the covariate responsible for lowering HDLc among smokers and non-smoker Khat chewers, ANCOVA analysis of HDLc adjusted for FBG significantly lower among smoker and non-smoker Khat chewers compared to control group (p = 0.013; p = 0.006). In contrast, ANCOVA analysis of HDLc adjusted for FBG, waist circumference or TG showed that significantly lower levels of HDLc disappeared in both smokers (p = 0.079; p = 0.103) and non-smokers (p = 0.069; p = 0.083) Khat chewers compared to control group.

3.2. Association of Khat chewing and smoking with diabetic factors

Furthermore, the results showed that serum levels of insulin were significantly increased in both smoker Khat chewing and non-smoker Khat chewing groups (p = 0.005; p = 0.001) without changes in the levels of FBG (p = 0.985; p = 0.971), respectively, when compared to the control group (Table 6). Moreover, insulin sensitivity was significantly low among smoker Khat chewing and non-smoker Khat chewing females (p = 0.007; p = 0.003), respectively, resulting in increased insulin resistance (p = 0.006; p = 0.004), and increased beta-cell secretion (p = 0.016; p = 0.002).

Analysis of covariance, ANCOVA) was used to analyze if Khat chewing per se was the main associated factor with diabetic factors (insulin, HOMA-IR, HOMA_IS, and HOMA_B%). Therefore, these parameters were screened for covariances by linear regression (Table 7).

Table 6. Association of Khat chewing and smoking with diabetic parameters.

Group	Non-Khat chewer non-smoker, control group (n=60)	Khat chewers non-smokers (n=60)	Khat chewer and smoker (n=60)	*ANOVA* *p*-value	Khat chewer non-smoker × control group	Khat chewer smoker × Control group
			Diabetic factors			
FBG	5.41 (5.25 – 5.57)	5.37 (5.11 – 5.64)	5.44 (5.15 – 5.74)	0.924	0.971	0.985
Insulin	56.6 (50.9 – 63.0)	76.67 (68.2 – 86.3)	74.0 (64.9 – 84.4)	0.001	0.001	0.005
HOMA_IR	1.29 (1.15 – 1.43)	1.73 (1.53 – 1.95)	1.71 (1.47 – 1.97)	0.002	0.004	0.006
HOMA_B%	94 (86 – 101.6)	117 (106 – 130)	113 (102.3 – 123.8)	0.002	0.002	0.016
HOMA_IS	81 (72.5 – 89.7)	60 (53.2 – 67.7)	62 (53.6 – 71)	0.001	0.003	0.007

Note: FBG = fasting blood glucose; HOMA_IR = insulin resistance; HOMA_B% = β-cell function; HOMA_IS = insulin sensitivity.
Source: Elaborated by the authors.

Table 7. Linear regression correlation of insulin, insulin resistance and insulin sensitivity and β-cell function with age and metabolic syndrome.

Covariate factor	Insulin Beta (*p*-value) 95% IC	HOMA-IR Beta (*p*-value) 95% IC	HOMA-IS Beta (*p*-value) 95% IC	HOMA-B% Beta (*p*-value) 95% IC
Age	−0.08 (-1.3 – 0.21) 0.293	−0.14 (−0.04 – 0.001) *0.072*	0.11 (−0.143 – 1.12) 0.129	−0.06 (−1.1 – 0.55) 0.423
HDLc	−0.11 (-32.7 – 9.2) 0.134	−0.02 (−0.68 – 0.44) 0.831	0.04 (−10.1 – 25.3) 0.608	−0.21 (−59 – −13.2) 0.007
Systolic blood pressure	−0.08 (−0.47 – 0.3) 0.258	0.02 (−0.01 – 0.011) 0.804	0.06 (−0.21 – 0.43) 0.433	−0.18 (−0.9 – −0.08) 0.018
Triglycerides	0.31 (17.8 – 37.64) 0.001	0.41 (0.48 – 1.01) 0.001	−0.38 (−30.6 – −13.9) 0.001	0.14 (−0.84 – 21.1) *0.064*
Waist circumference	0.14 (0.061 – 0.97) *0.056*	0.12 (−0.01 – 0.02) *0.092*	−0.13 (−0.80 – −0.03) *0.082*	0.13 (−0.06 – 0.95) *0.084*

Note: HOMA-IR = insulin resistance; HOMA-IS = insulin sensitivity; HOMA-B% = β-cell function; HDLc = high-density lipoprotein cholesterol.
Source: Elaborated by the authors.

3.2.1. Association of Khat chewing and shisha smoking with insulin

Triglycerides, FBG, and waist circumference were detected as insulin covariate factors by linear regression analysis. **Table 8** shows that the association of Khat chewing and smoking with significant higher insulin levels was reduced after multivariate analysis (ANCOVA) adjusted for TG, FBG, and waist circumference but still at a borderline higher among smoker and non-smoker Khat chewers females compared to non-smoker chewers subjects ($p = 0.056$; $p = 0.087$) and similar finding when adjusted only for TG ($p = 0.037$; $p = 0.073$). In addition, the significant higher insulin levels among smoker and non-smoker Khat chewers females did not disappear when ANCOVA analysis adjusted for FBG and waist circumference without adjustment for TG ($p = 0.009$; $p = 0.004$), indicating that the TG is cofactor of higher insulin levels in smoker and non-smoker Khat chewers females as compared to control.

3.2.2. Association of Khat chewing and shisha smoking with insulin resistance

Linear regression analysis showed that age, waist circumference, and TG are covariates that may affect insulin resistance. The significantly higher insulin resistance among smoker and non-smoker Khat chewers subjects concerning the control group disappeared when ANCOVA analysis adjusted for age, waist circumference, and TG ($p = 0.148$; $p = 0.428$), indicating that Khat chewing and smoking had no direct association with insulin resistance (**Table 8**). Moreover, ANCOVA analysis adjusted for only age and waist circumference showed that TG was the main covariate factor that had an impact on insulin resistance among smokers and non-smoker Khat chewers ($p = 0.014$; $p = 0.023$) as compared to non-smoker non-Khat chewers subjects.

3.2.3. Association of Khat chewing and shisha smoking with insulin sensitivity

Insulin sensitivity covariate factors were TG and waist circumference as identified by Linear regression analysis. The significant low insulin resistance among smoker and Khat chewers subjects ($p = 0.007$; $p = 0.003$) compared to control females disappeared when ANCOVA analysis adjusted for TG and waist circumference ($p = 0.103$; $p = 0.303$) as shown in **Table 8**. Furthermore, ANCOVA analysis adjusted for waist circumference without including TG showed that TG was the main covariate factor for decreasing insulin sensitivity among smokers and non-smoker Khat chewers ($p = 0.014$; $p = 0.017$) as compared to non-smoker non-Khat chewers subjects.

3.2.4. Association of Khat chewing and shisha smoking with beta cell secretion

Systolic blood pressure, HDLc, waist circumference, and TG were HOMA-B% covariate factors. ANCOVA analysis adjusted for systolic blood pressure, HDLc, waist circumference, and TG was depicted in (**Table 8**). The significantly higher HOMA-B% among smokers and Khat chewers ($p = 0.016$; $p = 0.002$) compared to non-smoker non-Khat chewing females disappeared when ANCOVA analysis adjusted for systolic blood pressure, HDLc, waist circumference and TG ($p = 0.187$; $p = 0.10$).

Table 8. Association of Khat chewing and shisha smoking with diabetic parameters adjusted for covariate factors.

Group	Non-Khat chewer non-smoker (control group)	Khat chewer non-smoker	Khat chewers smoker	*p*-value	Khat chewer non-smoker versus control group	Khat chewer smoker versus control group
ANOVA						
Insulin	56.6 (50.9–63.0)	76.67 (68.2–86.3)	74.0 (64.9–84.4)	**0.001**	**0.001**	**0.005**
ANCOVA (adjusted for triglycerides, FBG, and Waist circumference)						
Insulin	62.2 (55.7–69.3)	71.6 (64.1–79.8)	72.3 (65.0–80.2)	0.117	0.087	0.056
ANCOVA (adjusted for FBG and waist circumference)						
Insulin	59.0 (52.9–66.1)	74.8 (67.0–83.6)	72.8 (65.3–81.1)	**0.007**	**0.004**	**0.009**
ANCOVA (adjusted for triglycerides)						
Insulin	61.7 (55.1–69.0)	71.4 (64.0–80.0)	72.9 (65.3–81.3)	0.083	0.073	**0.037**
ANOVA						
HOMA_IR	1.29 (1.15–1.43)	1.73 (1.53–1.95)	1.71 (1.47–1.97)	**0.002**	**0.004**	**0.006**
ANCOVA (adjusted for triglycerides, waist circumference and age)						
HOMA_IR	1.47 (1.29–1.66)	1.58 (1.39–1.77)	1.66 (1.48–1.85)	0.349	0.428	0.148
ANCOVA (adjusted for waist circumference and age)						
HOMA_IR	1.36 (1.18–1.54)	1.67 (1.48–1.88)	1.69 (1.49–1.89)	**0.025**	**0.023**	**0.014**
ANOVA						
HOMA_IS	80.6 (72.5–89.7)	60 (53.2–67.7)	61.7 (53.6–71)	**0.001**	**0.003**	**0.007**
ANCOVA (adjusted for triglycerides and waist circumference)						
HOMA_IS	72.0 (64.1–80.7)	65.9 (58.7–73.8)	63.0 (56.4–70.4)	0.261	0.303	0.103
ANCOVA (adjusted for waist circumference)						
HOMA_IS	77.1 (68.2–87.1)	62.2 (55.2–70.3)	62.2 (55.2–70.0)	**0.021**	**0.017**	**0.014**
ANOVA						
HOMA_B%	93.5 (86–102)	117 (106–130)	113 (102–124)	**0.002**	**0.002**	**0.016**
ANCOVA (adjusted for waist circumference, Systolic blood pressure, HDLc, triglycerides)						
HOMA_B%	107 (95.7–118)	121 (110–132)	117 (107–127)	0.205	0.10	0.187

Note: HOMA-IR = Insulin resistance; HOMA-IS = insulin sensitivity; HOMA-B% = β-cell function; HDLc = high-density lipoprotein cholesterol; FBG = fasting blood glucose.
Source: Elaborated by the authors.

4. Discussion

Our finding that Khat chewing is significantly associated with increased waist circumference without affecting BMI and weight which is in agreement with Al Khader, Geta and Al-Duais studies (Al-Duais and Al-Awthan, 2019; Al Khader and Darwish, 2009; Geta *et al.*, 2019). However, Al-Dubai and Girma studies (Al-Dubai *et al.*, 2014; Girma *et al.*, 2015) reported that Khat chewing association with BMI

This disagreement may be due to the differences in the participant BMI between our study compared to Al-Dubai study in Yemeni adult male (Al-Dubai *et al.*, 2014) and Girma study on Ethiopian adults (Girma *et al.*, 2015). In in Al-Dubai study was 21.7 in control group versus 20.4 in the Khat chewer group (Al-Dubai *et al.*, 2014), and in Girma study, the BMI of the control group was 19.7 versus 22.3 in Khat chewer (Girma *et al.*, 2015) and whereases in our study BMI of control group was 26.7 vs 27.7 in Khat chewers. In this current study, Khat chewing associated with increased waist circumference in Khat chewer females because Khat chewers are usually physically inactive, which might be associated with an increased waist circumference.

The current study found no association of Khat chewing with blood pressure, which agreed with a Al Khader's study in Yemen (Al Khader and Darwish, 2009), however, in Hassan's studies found that Khat chewing associated with high blood pressure during Khat session (Hassan *et al.*, 2000) whereases in this current study the association of Khat chewing in next morning of Khat sessions was assessed. On the other hand, Berhane and Getahun studies on Ehiopian found a modest association with diastolic blood pressure (Berhane *et al.*, 2006; Getahun *et al.*, 2010) while another study in Ethiopian reported both diastolic and systolic blood pressure were higher among Khat chewers compared to non-Khat chewers (Geta *et al.*, 2019). Asfaw study among Ethiopian Khat chewers showed that Khat associated with increased blood pressure when comparing blood pressure before and after a Khat-chewing session (Asfaw, 2023), which is an acute association of Khat chewing but the next day, blood pressure among Khat chewers was conflicted data.

Meta-analysis found that Khat chewing associated with increased diastolic and systolic blood pressure by 5 and 8 mmHg, respectively, (Mega and Dabe, 2017), the subjects from Ethiopia much more than from Yemen. This contrast in the results may be due to Khat origin, which it is known that Ethiopian Khat has a higher concentration of cathinone 0.34 mg per gram of fresh Khat compared to 0.07 in Yemeni Khat (Geisshüsler and Brenneisen, 1987). The cathinone is the principal active constituents of Khat that act as a vasoconstrictor activity, which may explain increasing blood pressure (Brenneisen *et al.*, 1990). Khat chewing induces small and transient rises in blood pressure (Al-Motarreb *et al.*, 2002; Hassan *et al.*, 2000; Hassan *et al.*, 2005), and cathinone has similar effects concurring with the presence of cathinone in blood plasma (Brenneisen *et al.*, 1990; Kalix, 1990). A certain degree of blood pressure tolerance seems to develop in daily Khat chewers (Kalix *et al.*, 1990).

Furthermore, in this current study, increased serum levels of TG were associated with Khat chewing, which is in agreement

with Tekle study on Ethiopian (Tekle *et al.*, 2022), while Al-Duais reported Khat chewing lowering TG levels (Al-Duais and Al-Awthan, 2019), and Al-Zubairi *et al.* (2003) found no association of Khat chewing with TG levels. Cathinone is the main constituent of Khat, which involves the inhibition of monoamine transporters such as dopamine transporter and noradrenaline transporter re-uptake in peripheral and CNS (Majchrzak *et al.*, 2018), resulting in a persistently increased catecholamine in blood during Khat session (4 h). This persistent increase of catecholamine in the blood may raise TG (Good *et al.*, 2020) and free fatty acid levels (Jocken and Blaak, 2008; Minatoguchi *et al.*, 1997).

Moreover, our study found that Khat chewing is associated with low levels of serum HDLc, which agreed with Al-Akwa and Alam studies(Al-Akwa, 2009; Alam *et al.*, 2014), while Al-Duais, Tekle, and Al-Zubairi studies reported non-significant low levels of HDLc among Khat chewers (Al-Duais and Al-Awthan, 2019; Al-Zubairi *et al.*, 2003; Tekle *et al.*, 2022). Multivariate analysis of this current study showed that Khat chewing did not associate with decreased serum HDLc levels among Khat chewer females. However, Khat chewing may indirectly lower serum levels of HDLc via increasing serum levels of TG. High levels of TG increase its transporter, very low-density lipoprotein (VLDL), which is associated with a higher amount of cholesteryl ester transfer protein (CETP). The CETP mediates the transfer of cholesterol esters from HDL to VLDL in exchange for TG, resulting in small dense HDLc rich with TG, which is catabolized more rapidly, leading to low levels of HDLc (Brinton *et al.*, 1994; Swenson, 1991).

In addition, this present study showed that Khat chewing did not affect FBG levels in normal subjects, which agreed with Alsalahi and Saif-Ali studies (Alsalahi *et al.*, 2016; Saif-Ali *et al.*, 2003). This present study found that Khat chewing is associated with significantly high insulin levels and insulin resistance, low insulin sensitivity, and compensated beta-cell secretion. There is limited data on the association of Khat with insulin levels, which reported that c-peptide levels were higher in Khat chewers than non-Khat chewers (Saif-Ali *et al.*, 2003).

This presented study found that Khat chewing non-significantly associated with higher serum insulin levels among Khat chewer females, but Khat indirectly associated with insulin levels through higher levels of TG, which is the main covariate that had an impact on insulin levels as shown by ANCOVA analysis. Triglycerides were not only the main covariate that accompanied higher insulin levels but also the main covariate that associated with insulin sensitivity and resistance. Triglycerides are associated with low insulin sensitivity and insulin resistance and thus beta-cell compensated by increasing insulin secretion, which normalizes blood sugar.

In this present study, the combined association of smoking and Khat chewing was addressed, which showed that smoking has no additional association with waist circumference, TG, or HDLc. Few studies addressed the combined association of Khat chewing and smoking with BMI, waist circumference, blood pressure, or lipid profiles. Al-Zubairi study on Yemeni males showed no association of smoking and Khat chewing with the levels of HDLc and TG (Al-Zubairi *et al.*, 2003) and Khat chewing or daily smoking slightly increased diastolic blood pressure in Ethiopians without affecting systolic blood pressure (Berhane *et al.*, 2006; Tesfaye *et al.*, 2008). The combination of the Khat and smoking was not shown in Berhane study on the same time, it reported adverse effects were significantly higher among those who co-used tobacco, coffee, or tea with Khat (Berhane *et al.*, 2006).

The main constituent of Khat is cathinone, which is involved in the persistent increase of catecholamine in blood during Khat sessions, resulting in increased levels of TG (Good *et al.*, 2020) and free fatty acids (Jocken and Blaak, 2008). High levels of blood TG and free fatty acids are associated with the deposition of TG in the liver, muscle, and adipose tissue, which decreases insulin sensitivity in these tissues. The beta cells secrete more insulin to overcome this impaired insulin sensitivity, resulting in insulin resistance (metabolic syndrome), which is known as a prediabetic state. Recently, Khat chewing has been reported as a risk factor for developing type 2 diabetes mellitus (Al-Sharafi and Gunaid, 2015; Badedi *et al.*, 2020).

The presented study limitations include the following: first, all subjects recruited in this study are women, so the results cannot be generalized to overall population. Second, the observed associations Khat chewing, metabolic and diabetic factors in the study do not imply causal relations of cardiovascular and diabetes. Third, the small sample size limits its statistical power. Fourth, the association of active and passive smoking with metabolic syndrome among the Khat chewer needs further study. Fifth, levels of total cholesterol and LDL cholesterol have not been measured, which are essential for studying the metabolic profile of subjects and assessing the associated cardiovascular risk.

5. Conclusions

Khat chewing was associated with higher waist circumference and TG and lower HDLc, which are cardiovascular and diabetes risk factors. Moreover, Khat chewing is associated with decreased insulin sensitivity and increased insulin resistance indirectly through increased waist circumference and blood TG levels. As a result, beta cells significantly compensated for this insulin resistance by increasing insulin secretion, which was indicated by higher serum insulin without differences in FBG levels between Khat chewer females and non-smoker non-Khat chewer subjects. When Khat chewing is associated with dyslipidemia and insulin resistance continues for a long time, beta-cell exhaustion may be developed, and beta cells might fail to secrete enough insulin, which may ultimately develop type 2 diabetes.

Authors' contribution

Conceptualization: Mona Abdullah AL-Tahami; **Data curation:** Mona Abdullah AL-Tahami; **Formal Analysis**: Riyadh Saif-Ali; **Funding acquisition:** Mona Abdullah AL-Tahami; **Investigation**: Mona Abdullah AL-Tahami; **Methodology:** Mona Abdullah AL-Tahami; **Project administration:** Not applied; **Resources:** Riyadh Saif-Ali; **Supervision:** Maher Ali Almaqtari; **Software:** Riyadh Saif-Ali; **Validation:** Maher Ali Almaqtari; Dheya Abdull Hameed; **Visualizing**: Riyadh Saif-Ali; **Writing-Original draft:** Mona Abdullah AL-Tahami; **Writing review & editing:** Maher Ali Almaqtari; Riyadh Saif-Ali; Saad Al-Arnoot.

Conflict of interest

The authors declare that there is no conflict of interest involving this manuscript.

Data availability statement

All data sets were generated or analyzed in the current study.

Artificial Intelligence usage statement

The authors declare that they did not use Artificial Intelligence tools at any stage of the preparation, correction, or evaluation of this work, including Graphical Abstract preparation.

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