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Impact of Khat (*Catha edulis*) Chewing on Inflammatory Markers and Advanced Glycation End Products among Yemeni Women

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ABSTRACT
Khat chewing has spread widely among women in Yemeni society. This modifiable lifestyle may increase the level of inflammatory markers and advanced glycation end productions (AGE, s). **L**imited data are available. There is limited data on the impact of khat chewing on inflammatory markers and AGE, s. Therefore, this project aimed to study the effect of khat chewing on inflammatory markers and AGE, s in Yemeni females. One hundred and eighty Yemeni females signed the consent form and donated blood 60 of them were non-khat chewers (control group), and 120 were daily khat chewers. The levels of high-sensitivity C-Reactive Protein (hs-CRP) and interleukin were higher in khat chewers than in non-Khat chewers. There were no differences in total white blood cells, neutrophils, and lymphocytes between khat chewer and non-Khat chewer females. The levels of (AGEs) were similar between khat chewers and non-khat chewers females (P=0.612). Analysis of covariantcet (ANCOVA) showed that khat chewing increased hs-CRP and interleukin-6 levels among khat chewers ($p < 0.005$; $p < 0.034$) compared to non-khat chewer. In conclusion, khat chewing increased hs-CRP, a cardiovascular risk prediction factor, and interleukin-6, which is associated with obesity, insulin resistance, and type 2 diabetes mellitus (T2DM). Therefore, women with continuous khat chewing are at a high risk of developing cardiovascular diseases and T2DM.

CONTENTS

1. Introduction:

The habit of khat chewing has prevailed for centuries among populations in the Horn of Africa and Arabian Peninsula, including Yemen. Although khat chewing is known to cause health issues in some individuals, it is estimated that 20 million people worldwide regularly chew khat[1]. Khat has been a part of Yemeni culture for a long time and is chewed on virtually every social occasion. Nearly 90% of adult males and more than 50% of females chewed on khat for 3 to 4 h. daily[2]. The daily chewing Khat lead to produce Reacctive oxygen species (ROS) and oxidative toxicity [3], which is always associated with high inflammation.

Inflammatory status and AGEs are associated with chronic diseases such as diabetes and cardiovascular diseases. There is growing evidence that inflammation may play a crucial intermediary role in the pathogenesis of diabetes

and cardiovascular diseases[4,5]. The AGEs are generated from endogenous or exogenous sources are the most important mediators of metabolic disorders and exhibiting a critical cardiometabolic impact in both nondiabetic and diabetic populations[6,7].

Khat chewing has spread widely among women in Yemeni society. This modifiable lifestyle may play a role in inflammatory status and AGEs, which may increase the risk of diabetes and cardiovascular diseases among khat chewers. A recent study reported that khat had a modulating effect on inflammation[8]. There are no published data on the effect of khat on advanced glycation end-products. Therefore, this study aimed to invistigate the effect of khat on inflammatory markers and advanced glycation end-products among Yemeni women.

2. Materials And Methods

The current study is an analytical cross-sectional study aimed at evaluating the effect of chronic khat chewing on some inflammation parameters and advanced glycated end products. The sample size was calculated using WinPepi software. Brochures including all the informations about the study were distributed in women's clubs located in the city of Sana'a , Yemen. In addition, in the social media advertising to collect volunteer was continued until the required sample size was reached . Sixty women were non-khat chewers (control group), and 120 were daily khat chewers. Before enrolling in the study, the participants attended a screening session to assess their suitability for the study and their accessibility to participate in this research. The screening session included a brief medical history interview assessment of current and past khat habits and use of other substances. The participants were free from high Blood pressure, Diabetes, Liver, Kidney, Heart diseases, Fever, or a recent history of infection and were not taking any medications. The Institutional Review Board (IRB) of the Faculty of Sciences, Sana'a University, approved this study, which performed in accordance with Helsinki Declaration.

After explaining the purpose and nature of the study a signed consent from was obtained from each participant. Then, 5 ml venous blood from the overnight fasting subject was collected into Ethylenediaminetetraacetic Acid (EDTA) and gel tubes. The EDTA tube was immediately processed to measuring the total white blood cells (WBCs) and differential counts. The gel tube was centrifuged at 3500 rpm for 10 min. within half an hour of sample collection, and serum was aliquoted into two Eppendorf tubes and frozen at -20ºC for inflammatory markers and AGEs measurement.

Anthropometric parameters

Anthropometric parameters, including age, weight, and height, were measured on the same day blood samples were collected. Weighting was measured by using a standard weighing scale electronic scale model balance (BOSCH FD 8905, Vietnam). Height without shoes was measured using freestanding stadiometers (Leicester, China). Body Mass Index (BMI) was calculated as the weight in kilograms divided by the height in meters squared.

Inflammatory marker and advanced glycation end products analysis

Complete blood count (CBC) was analyzed using an automated hematology analyzer (Mindray 5500 Mindray, China). Total white blood cells, neutrophils, and lymphocytes counts were reported to indicate non-specific inflammation in each participant. High-sensitivity C-reactive protein (hs-CRP) level were measured using a particle-enhanced turbidimetric assay commercial kit from Roche Diagnostics (Reference number 04628918190, Roche Diagnostic GmbH, Germany) in a fully automated chemistry analyzer (COBAS INTEGRA, Germany). Low and high hs-CRP control sera were run first, and if the results were within the specified range, the samples were analyzed.

Interleukin-6 was measured using commercial kits from Roche Diagnostics, REF 05109442190

(Roche Diagnostics GmbH, Germany) in a fully automated quantitative immunoassay analyzer Cobas e 411 (Roche diagnostic, Germany). Low and high Interleukin-6 control sera were run first, and if the results were within the given range, the samples proceeded for analysis.

AGEs were measured by competitive ELISA kit catalog number STA-817 (Cell Biolabs, Inc., US). The principle of AGEs measurement is as follows:, first, an advanced glycation end products (AGEs) conjugate is coated on an ELISA plate. Unknown AGE protein samples or AGE-BSA standards we are then added to the AGEs conjugate preabsorbed ELISA plate. After a brief incubation, an anti-AGEs polyclonal antibody was added, followed by an HRP-conjugated secondary antibody. The content of AGEs protein adducts in an unknown sample was determined by comparison with a predetermined- AGEs-BSA standard curve.

Statistical analysis

The statistical analyses were performed on Social Package of Social Sciences (SPSS) version 11.5 (SPSS Inc., Chicago, IL, USA). Inflammatory markers (total WBCs, neutrophils, lymphocytes, hcCRP, and IL6) and AGEs were not normally distributed and were thus log-transformed. The log-transformed parameters means and 95% confidence intervals were transformed back and reported as geometric means. The mean differences in the inflammatory markers and AGEs between groups of study (non-khat chewers and daily khat chewers) were evaluated using an independent t-test. If there was a significant difference in these parameter means between the groups, a linear regression model (enter) was used to configure the confounding factors for each difference in Inflammatory markers and AGEs under study. Subsequcntly, a general linear model with univariate analysis (ANCOVA) was applied to determine whether this difference was due to the khat chewing effect per se or associated with cofounders rather than the khat chewing effect. The accepted level of significance was set below 0.05 ($p < 0.05$).

3. Results

One hundred and eighty subjects signed a consent form and donated their blood. Sixty subjects were non-khat chewing (control group), and 120 were khat-chewing females. The anthropometric characteristics of the subjects are shown in (Table 1). The weight of khat chewer was higher that those of non-khat chewers (P=0.036), while there were no differences in age, height, and body mass index between the Khat and non-khat chewers.

Table 1: Anthropometric parameters among non-khat chewers and khat chweres women

Group	Non-Khat chewer (n=60)	Khat chewers (n=120)	*p*-value
Age	39.36 (38.0-40.7)	39.41 (38.07-40.8)	0.958
Weight (kg)	64 (61.6-66.5)	67.7 (65.2-70.4)	0.036
Height (m^2)	1.55(1.54-1.56)	1.56 (1.55-1.57)	0.102
BMI	26.7 (25.8-27.6)	27.8 (26.9-28.8)	0.095

BMI; body mass index

Table 2 shows that serum hs-CRP and interleukin-6 levels were higher in khat chewers than non-khat chewers (P=0.0004; 0.009). In contrast, there were no differences in total white blood cells (P= 0.067), neutrophils (P= 0.71) 0.950), and lymphocytes (P= 0.953) between female khat chewers and females. Advanced glycation end products (AGEs) levels were similar in khat chewers (P= 0.612) and control females.

Table 2: Effect of khat chewing on inflammatory markers and advanced glycation end products

Group	Non-Khat chewer (n=60)	Khat chewers (n=120)	*P*-value
Inflammatory Markers			
hsCRP	3.0 (2.38-3.78)	4.47 (3.67-5.45)	**0.0004**
IL6	4.15 (3.7-4.66)	5.03 (4.54-5.56)	**0.009**
WBC	5.0 (4.6-5.4)	5.4 (5-5.9)	0.067
% Neutrophiles	48 (45-51.4)	47 (44.6-50.4)	0.71

% Lymphocytes	39 (36.2-42.3)	40 (37.8-43.2)	0.953
Advanced Glycation End Products			
AGEs (ug/ml)	6.12 (4.76-7.87)	6.10 (4.93-7.56)	0.612

hs-CRP; high-sensitivty C-reactive protein, WBC; total white blood cells, AGEs; advanced glycation end-products,

Analysis of covariance (ANCOVA) was used to analyze whether if khat chewing was the effector of the inflammatory markers, hs-CRP, and interleukin-6. Therefore, these markers were first screened for covariances by linear regression for inclusion in the ANCOVA. Linear regression showed that interleukin-6 and BMI were covariant factors for hs-CRP, and BMI, hs-CRP, lymphocytes, neutrophils, and age were covariant factors for interleukin 6. ANCOVA adjusted for BMI and interleukin 6 showed that hs-CRP was significantly higher among khat chewers (P= 0.005) than in the control group (Table 4). When interleukin-6 was Analyzed by ANCOVA adjusted for BMI, hs-CRP, lymphocytes, neutrophils, and age, interleukin-6 levels remained significantly higher among khat chewers than among non-khat chewers females (P= 0.034) (Table 4).

Table 3: Linear regression analysis of hs-CRP, interleukin-6 with body mass index, total and diferntial white blood cells. age and advanced glycation end products

Covariant Factor	hsCRP	Interleukin 6
BMI	**0.174 (0.001)**	**0.063(0.048)**
IL6	**0.339 (0.003)**	-
hsCRP	-	**0.115(0.003)**
Total WBCs	0.043 (0.845)	0.119(0.354)
Lymphocytes	0.002 (0.985)	**-0.161 (0.011)**
Neutrophiles	0.039 (0.710)	**-0.142 (0.021)**
Age	-0.039 (0.291)	**0.060 (0.005)**
AGEs	-0.030 (0.479)	0.023 (0.348)

BMI; body mass index, hs-CRP; high-sensitivty C-reactive protein, WBC; total white blood cells, AGEs; advanced glycation end-products,

Table 4: Covariant analysis of khat chewing effect on inflammatory markers

High-sensitive C-reactive Protein (hsCRP)			
Covariant Factor	**Non-Khat chewer**	**Khat chewers**	**P value**
Independent t Test			
hsCRP	3.0 (2.38-3.78)	4.47 (3.67-5.45)	**0.0004**
ANCOVA Adjusted for (BMI and interleukin- 6)			
hsCRP	3.16 (2.72-3.66)	4.26 (3.68-4.95)	**0.005**
Independent t Test			
IL6	4.15 (3.7-4.66)	5.03 (4.54-5.56)	**0.009**
ANCOVA (adjusted for BMI, hsCRP, lymphocytes, neutrophiles and age)			
IL- 6	4.23 (3.91-4.57)	4.78 (4.41-5.16)	**0.034**

hs-CRP; high-sensitivty C-reactive protein, ANCOVA; nalysis of covariant, BMI; body mass index

4. Discussion

This study aimed to investigate tudy the effect of khat chewing on inflammatory markers and advanced glycation end-products in Yemeni females. To the best of our knowledge, there are no published data on the effects of the khat chweing on hs-CRP, interleukin-6, and AGEs. The current study found that khat chewing is associated with high levels of serum hs-CRP and interleukin-6. Analysis of the covariants showed that khat chewing increased hs-CRP and interleukin-6 levels. Previous study has reported that khat extracts increase IL-6 gene expression in human ovarian adenocarcinoma cell lines [9]. Interleukin-6 and TNFα expression significantly increased in the cathinone and cathinone-treated mice group[9].

A recent study found that khat extract increased levels of the pro-inflammatory cytokine TNF-alpha, IL-6, and WBC (lymphocytes, monocytes, neutrophils, and eosinophil) were elevated in a mouse model[10,11]. In contrast, a previous study reported that secretion of inflammatory cytokines (TNFα and IL-6) was inhibited in khat-treated peripheral blood mononuclear cells,

whereas khat increased anti-inflammatory cytokine IL-10 and IL-2[12].

Khat chewing is a risk factor for the development of type 2 DM[13-15]. A chronic, low-grade inflammatory state is closely associated with IR[16]. The Inflammatory biomarkers IL-6 and hs-CRP are associated with prediabetes and T2DM[17]. Chronic inflammation, such as increased production of IL-6 and high-sensitivity C-reactive protein, causes insulin resistance in adipose tissue, skeletal muscle, and the liver by interfering with insulin signaling pathways[18]. In addition, the main constituent of khat is cathinone, which is involved in the persistent increase in catecholamines in the blood during khat sessions. This increased catecholamine level raises the levels of triglycerides and free fatty acids[19]. High levels of triglycerides and free fatty acids are associated with the deposition of triglycerides in the liver, muscle, and adipose tissues, resulting in impaired sensitivity to insulin in these tissues. Interleukin-6 induces insulin resistance by decreasing the expression of insulin receptor substrate (IRS-1) and glucose transporter (GLUT4) in adipocytes and muscles[20,21]. hs-CRP binds to leptin, which blocks leptin signaling, modulates its central action and hypothalamic signaling, and interferes with glucose homeostasis, insulin sensitivity, and energy homeostasis[22,23].

Khat chewing has been reported to increase the risk of acute myocardial infarction (AMI)[24-27], which may be explained by the coronary vasospasm effect of khat chewing and thrombus formation due to catecholamine-mediated platelet aggregation[26,28]. In addition, khat chewing increases blood pressure[29-31] and heart rate[25,32]. The khat component, cathinone has been reported to have positive chronotropic and inotropic effeacts on isolated atria [26,30]. Inflammation plays a role in the initiation and progression of atherosclerotic disease[33]. Interleukin-6 and hs-CRP have been reported to be risk factors for coronary heart diseases[35,36]. Interleukin-6 is an inflammatory cytokine that mediates the propagation of the inflammatory response and the initiation and progression of the atherosclerotic process[37], as well as induces hs-CRP production[38].

5. Study Limitations

The current study limitations include the following: first, the subjects were women, and the findings may not apply to the overall population. Second, the subjects recruited in this study were from Yemen, so the results cannot be generalized to other ethnicities. Third, the small sample size limits its statistical power. Fourth, the study was funded by authors and thus could not include many inflammatory markers to figure out the complete inflammation scenario of the Khat effect.

6. Conclusion

Khat chewing increased hsCRP level , which is a cardiovascular risk factor. Furthermore, khat chewing is associated with high levels of interleukin-6, which is considered a low-grade inflammatory factor that may increase the risk of developing diabetes in khat chewers.

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