The effect of chronic khat chewing on liver enzyme levels: a Yemenian study

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Background
Khat is a natural stimulant from the *Catha edulis* plant, which grows mainly in Yemen. The liver has been suspected to be vulnerable to the harmful effects of khat use.

Aim
The aim of the study was to investigate the effect of khat chewing on the liver function in healthy Yemeni individuals.

Methods
Liver function tests were performed on 30 chronic khat chewers (group I) and 20 individuals who did not chew khat (group II).

Results
Twenty percent of group I and only 5% of group II reported abnormally elevated alanine transaminase (ALT) levels, with no statistically significant difference between the mean ALT values ($P=0.208$); 13.3% of group I showed elevated aspartate aminotransferase levels ($P=0.058$). With regard to other liver function tests there was no statistically significant difference between the two groups. ALT levels increased with increasing duration of khat chewing.

Conclusion
Chronic khat chewing causes subclinical hepatocellular damage, whereas transient khat chewing has no effect on the liver function.

Keywords:
alanine transaminase, aspartate aminotransferase, chewing duration, khat, subclinical

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Introduction

Khat (*Catha edulis*) is a natural stimulant from the *C. edulis* plant (Fig. 1) found in the flowering evergreen tree or large shrub of the Celastracea family, which grows mainly in Yemen, Ethiopia, Somalia, Kenya, Saudi Arabia, and at high altitude areas in South Africa and Madagascar [1].

Early clinical observations suggested that khat had amphetamine-like properties [2]. Subsequent chemical analyses confirmed that the fresh leaves contain a number of compounds, including phenylalkylamine compounds (alkaloids) such as norpseudoephedrine (cathine) and α aminopropiophenone (cathinone), the latter being structurally related [3] and pharmacologically similar to amphetamine [4].

The liver has been suspected to be particularly vulnerable to the harmful effects of khat use [2,5], and a disturbance in liver function and architecture has been described in experimental animals both on short-term [6] and long-term [7] feeding with *C. edulis* leaves.

Khat administered chronically to animals causes an increase in liver transaminases, leading to signs of chronic hepatic inflammation. Recent studies in UK have revealed many cases of acute idiopathic severe liver damage in Somalian khat chewers who live there. Another study has shown a high prevalence of cryptogenic liver disease among Somalian khat chewers. Moreover, some of them who had autoimmune antibodies like SMA failed to respond to therapy with immunosuppressants and those who quit khat chewing recovered markedly and needed no more immunosuppressants [8].

This study was carried out to detect the effect of khat chewing on liver function in healthy Yemeni individuals.

Patients and methods

Study objectives

The aim of this study was to assess the liver function in healthy Yemeni chronic khat chewers and detect any significant difference in the liver function test results from those of healthy Yemeni individuals.

Method and study design

Fifty healthy Yemeni individuals of both sexes with a BMI less than 25 kg/m^2 were enrolled in our study from among the relatives of patients who were admitted to Al-Thawra University Hospital, Sana'a, Yemen. The 50 healthy individuals were categorized into two groups according to khat consumption: group I comprised 30 healthy khat chewers and group II comprised 20 healthy non-khat

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Figure 1

Morphology of the *Catha edulis* plant.

chewers. The mean duration of khat chewing in patients of group I was 10.32 ± 6.5 years; accordingly, patients in group I were further categorized into two groups: the first group comprised those who had been chewing khat for less than 10 years and the second group comprising those who had been chewing khat for at least 10 years. Patients with any chronic medical disease, diabetes mellitus, or with metabolic disorders, as well as those on regular medication, alcoholics, or those with positive HBV or HCV markers, were excluded from the study.

After signing a written informed consent, blood samples were collected and liver function tests were conducted. Also, HBsAg, HBc total Ab, and HCV Ab were tested using ELISA. Those who had abnormal liver enzyme levels were investigated for serum anti-smooth muscle antibody (ASMA), antinuclear antibody (ANA), and anti mitochondrial antibody (AMA) titers and were subjected to a conventional abdominal ultrasonographic examination.

Statistical methods

Patients' data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, Illinois, USA) for Windows 7. Quantitative variables were compared using the Student *t*-test and the Mann–Whitney test. Qualitative variables were comparedusing the χ^2 and Fisher exact tests when appropriate. *P*-value was considered significant if less than 0.05.

Results

The data of individuals included in the khat-chewer group and non-khat-chewer group are given in Table 1. Our study reported that the average quantity of khat chewed by each candidate in the khat-chewer group was 250 g/day. With regard to the liver function test, the values of total and direct bilirubin, prothrombin time (PT), prothrombin concentration (PC), and international normalized ratio (INR) of both groups were within the normal reference range. On analyzing the alanine transaminase (ALT) values in both groups it was reported that only one person (5%) among the non-khat chewers had a high ALT value, whereas six (20%) khat chewers had abnormally high ALT values; however, there was no statistically significant difference between the groups in terms of the mean ALT values ($P = 0.208$) (Table 2). With regard to the aspartate aminotransferase (AST) values in both groups it was reported that all non-khat chewers had values within the normal reference range, whereas four (13.4%) of the khat chewers had abnormally elevated AST values. On comparing the mean AST values between both groups it was reported that the mean AST values in the khat-chewer group was greater than that in the non-khat-chewer group with a *P*-value approaching significance (0.058) (Fig. 2). With regard to gamma glutamyl transferase (GGT) values there was one person (5%) among non-khat chewers and two (6.6%) among khat chewers with elevated GGT levels; however, on comparing the mean GGT values between the two groups, no statistically significant difference was detected ($P = 0.77$). The same results were obtained for phosphatase; no statistically significant difference was observed between the non-khat-chewer and khat-chewer groups.

With regard to total protein and albumin levels, only one person had a low level for both in each group; there was no statistically significant difference in their levels between the groups.

Table 1 Data and liver biochemical profile of both khat chewers (group I) and non-khat chewers (group II)

	Group I ($n=30$)		Group II ($n=20$)	
	Mean	Min–max	Mean	Min–max
Age	29.86	21–45	28.55	20–45
PT ($N\leq 16$ s)	12.5	1.22	12.6	1.49
PC (%)	93	0.099	93	0.12
INR ($N\leq 1.2$)	0.95	0.138	0.9	0.15
Total bilirubin ($N\leq 17$ mmol)	10.7	1.55	11.22	1.82
Direct bilirubin ($N\leq 3$ mmol)	2.18	0.36	2.33	0.45
Alkaline phosphatase ($N\leq 150$ mmol)	89.93	23.306	80.50	26.738
Total protein ($N\geq 60$ mg/dl)	67.57	3.901	67.6	4.88
Albumin ($N\geq 35$ mg/dl)	41.43	3.569	41.9	3.49
	Frequency	%	Frequency	%
Sex (male/female)	25/5	83.3/16.7	15/5	75/25
Cigarettes smoking (yes/no)	6/24	20/80	1/19	5/95
ALT (normal/abnormal)	24/6	80/20	19/1	95/5
AST (normal/abnormal)	26/4	86.6/13.4	20/0	100/0
GGT (normal/abnormal)	28/2	93.4/6.6	19/1	95/5
Total protein (normal/abnormal)	29/1	96.7/3.3	19/1	95/5
Albumin (normal/abnormal)	29/1	96.7/3.3	19/1	95/5

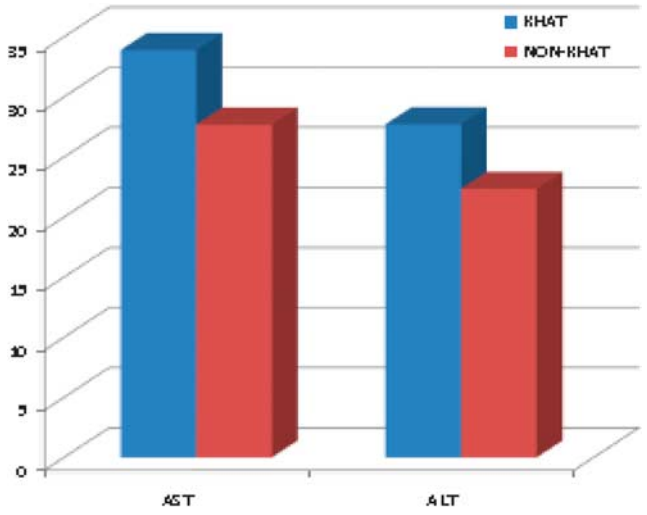
ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalized ratio; PC, prothrombin concentration; PT, prothrombin time.

Table 2 Comparison between the liver enzymes of khat chewers and non-khat chewers

	Group I		Group II		
	Mean	SD	Mean	SD	*P*-value
ALT ($N\leq 42$ mmol)	22.73	16.77	22.35	10.49	0.208
AST ($N\leq 42$ mmol)	33.90	13.306	27.70	6.317	0.058
GGT ($N\leq 50$ mmol)	23.83	13.144	22.60	16.63	0.771

ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.

Figure 2



Graph representing the aspartate aminotransferase (AST) and alanine transaminase (ALT) levels in both khat and non-khat chewers; there is no statistically significant difference between the two groups ($P=0.058$ and 0.208, respectively).

The khat chewers were divided into two groups according to the duration of khat chewing: the first group comprised those who had been chewing khat for less than 10 years and the second group comprised those who had been chewing khat for at least 10 years (Table 3). The results of our study showed that the duration of khat chewing had no effect on liver enzymes; in the khat-chewing group there was no association between the duration of khat chewing and level of ALT ($P=0.426$). The same result was observed for the levels of AST ($P=0.815$) and GGT ($P=0.232$).

Age did not have a significant effect on the level of liver enzymes in khat chewers; in group I there was no statistically significant difference in the mean age between individuals with normal ALT levels and those with elevated ALT levels ($P=0.934$); the same result was observed for AST ($P=0.714$) and GGT levels ($P=0.687$) (Table 4).

Blood samples were collected from eight individuals during khat chewing and from the remaining 22 after khat chewing. The results show that liver enzyme levels during khat chewing did not vary significantly from those collected after khat chewing. There was no association between ALT levels and sampling time ($P=0.536$); the same result was observed for AST ($P=0.195$) and GGT levels ($P=0.271$) (Table 3).

There was no association between smoking and abnormally elevated liver enzymes levels in the khat-chewing group, nor was there an association between smoking status and ALT ($P=0.819$) and AST levels ($P=0.107$) (Fig. 3).

Only one individual with abnormally elevated ALT levels in the khat-chewer group ($n=6$) showed positive ASMA and ANA, whereas the remaining were negative for ASMA, ANA, and AMA.

Only khat chewers ($n=8$) and non-khat chewers ($n=2$) with abnormally elevated serum liver enzymes were subjected to a conventional abdominal ultrasonographic examination. No abnormality was detected in any of them except for the case of two khat chewers: one of them with elevated serum ALT levels showed a bright liver with normal size and texture, and the second one with elevated serum ALT, AST, and GGT and decreased total

Table 3 Comparison of the liver enzyme levels according to the short-term and long-term effect of khat chewing, and the effect of cigarette smoking on the level of liver enzymes

	N (%)		
Khat Chewers group	<10 years ($n=9$)	≥10 years ($n=21$)	*P*-value
ALT (normal/abnormal)	8/1 (88.8/11.2)	16/5 (76.19/23.81)	0.426
AST (normal/abnormal)	8/1 (88.8/11.2)	18/3 (85.7/14.29)	0.815
GGT (normal/abnormal)	9/0 (100/0)	19/2 (90.5/9.5)	0.232
	N (%)		
	Chewing on sampling ($n=8$)	Not chewing on sampling ($n=22$)	
ALT (normal/abnormal)	7/1 (87.5/12.5)	17/5 (77.28/22.72)	0.536
AST (normal/abnormal)	8/0 (100/0)	18/4 (81.82/18.18)	0.195
GGT (normal/abnormal)	8/0 (100/0)	19/3 (86.37/13.63)	0.271
	N (%)		
	Smoker	Nonsmoker	
ALT (normal/abnormal)	5/1 (83.4/16.6)	19/5 (79.17/20.83)	0.819
AST (normal/abnormal)	4/2 (66.6/33.4)	22/2 (91.67/8.33)	0.107

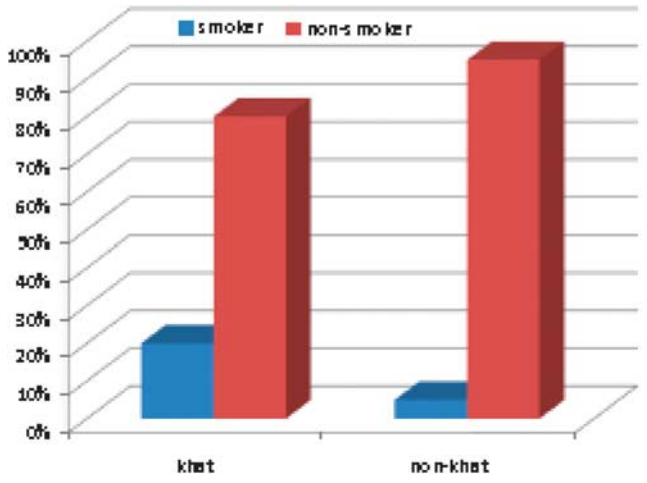
ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.

Table 4 The mean age in the khat-chewer group according to the liver enzyme level

	Normal enzyme level		Abnormal enzyme level		
Khat-chewer group age	Mean	SD	Mean	SD	
Age according to ALT levels	29.92	6.646	29.67	6.346	0.934
Age according to AST levels	29.69	6.577	31	6.583	0.714
Age according to GGT levels	29.7	6.45	31.33	8.02	0.687

ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.

Figure 3



The percentage of cigarette smokers among khat chewers and non-khat chewers.

protein and albumin levels, with an autoimmune profile showing positive ANA and ASMA titers (1/80 and 1/40, respectively), had a coarse liver texture with normal size and an enlarged spleen (14 cm), but with normal portal vein diameter.

Discussion

Our cross-sectional study reported that chronic khat chewing causes subclinical hepatocellular damage, which may be related to the duration of khat chewing or to the use of pesticides, whereas transient khat chewing has no effect on the liver function. Although there is no statistically significant difference in the abnormal increase observed in both ALT and AST levels among the khat chewers compared with the non-khat chewers, the increased ratios in the khat-chewer group may indicate possible khat-induced liver damage, which is commensurate with the results reported in other studies [9]. Human and animal studies demonstrate that regular intake of khat for long periods causes hepatocellular damage. Animal studies [7] demonstrated a significant increase in ALT and AST serum levels of rats fed khat for 6 months, whereas in other studies there was a nonsignificant increase [10]. A case report published in 2011 [11] supported the concept of khat chewing impairing the liver function.

With regard to the effect of khat chewing duration on the liver function, our study showed that ALT serum level was higher in those who had been chewing khat for 10 years or more, although the results were nonsignificantly different from those who had been chewing khat for less than 10 years (23.81 vs. 11.2%); however, this difference may indicate that the longer the duration of khat chewing, the more the hepatocellular damage. With regard to the AST and GGT levels, there was no statistically significant difference in their levels with the increase in chewing duration.

With regard to PT, PC, and INR, the values in both khat chewers and non-khat chewers were nearly equal and within the normal range, which was expected as the coagulation profile in liver disease is not affected during the early stages whatever the cause and our participants were normal healthy asymptomatic individuals. Moreover,

it is well known that the synthetic function of the liver changes in manifested or late-stage chronic liver disease. Similar results were also reported with regard to total bilirubin, direct bilirubin, alkaline phosphatase, and GGT; no statistically significant difference was observed in their levels between khat chewers and non-khat chewers, which is in agreement with that reported in animal studies conducted by Al-Zubairi *et al.* [10] and by Al-Meshal *et al.* [12]; however, these results are not in agreement with those reported by Al-Habori *et al.* [7] and Al-Mamary *et al.* [6], nor do they agree with the results of Tash *et al.* [13] in their studies on rats.

Total protein and serum albumin results showed no statistical difference between khat chewers and non-khat chewers. This may be explained by the fact that serum albumin reflects the synthetic function of the liver, which will decrease only in manifested or late-stage liver disease.

Age had no effect on liver function in the khat-chewing group, indicating that the difference in liver enzyme levels is mainly due to khat chewing and no other factor such as age, khat chewing duration, and sex has a role.

Khat chewing may be a risk factor for autoimmune hepatitis that responds well to treatment [14,15]; the results of our study showed that only one case of chronic khat chewing had a positive titer for ASMA and ANA. Whether these results are due to autoimmune hepatitis or are a hypersensitivity reaction to khat chewing can be determined only from larger randomized controlled studies including autoimmune profile and liver biopsies.

Moreover, we reported that cigarette smokers were more prevalent in the chronic khat-chewer group, similar to the results of Elmi [16], which may add a synergistic adverse effect in that group.

We should point out some limitations of the study. First, an antimicrosomal antibody was not tested in our studied groups, which could be attributed to the limited financial resources of our study, as Al-Thawra University Hospital is a nonprofit organization. Second, there exists a discrepancy between our study and other studies with regard to the results of both the abdominal ultrasonographic examination and the ALT levels, as the ultrasonographic examination is an operator-dependent imaging method (more than one person operated it in the current study); moreover, the relatively small sample size of our study may contribute to this discrepancy in the results.

Conclusion

We showed that chronic khat chewing causes subclinical hepatocellular damage, which may be related to the duration of khat chewing, and further randomized controlled studies with larger sample sizes are recommended.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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