Effect of Habitual Khat Chewing on Glycemic Control, Body Mass Index, and Age at Diagnosis of Diabetes in Patients with Type 2 Diabetes Mellitus in Yemen

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ABSTRACT: Khat chewing is common in Yemen. We conducted this study to see if it affected diabetes control in patients with type 2 diabetes mellitus (DM). We studied 1540 patients with type 2 DM attending an endocrinology clinic in Sana'a, Yemen, of which 997 were khat chewers (KC) and 543 were non-khat chewers (NKC). The patients answered a questionnaire regarding khat chewing. Hemoglobin A1c (HbA1c) and body mass index (BMI) were measured. KC had a higher mean HbA1c of 9.8 (95% confidence interval (95% CI) 9.6–10) than the NKC, with a mean of 9.1 (95% CI 8.9–9.4) (adjusted odds ratios (AOR) 1.74, $P < 0.001$) after multivariate regression analysis. KC also had a lower mean BMI, 26.9 (95% CI 26.6–27.2), than the NKC, mean BMI 27.6 (95% CI 27.1–28) ($P < 0.01$). The mean age at diagnosis of DM among the KC group was 43.3 (10.1) and among the NKC group was 45.9 (11.8) (AOR 1.4 $P < 0.008$) after multivariate regression analysis. KC patients had a higher mean HbA1c, a lower BMI, and a younger age at diagnosis of type 2 DM when compared with NKC.

KEYWORDS: khat, type 2 DM, body mass index, HbA1c, obesity

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Introduction

Khat chewing is very common in Yemen. Khat (*Catha edulis*) leaves are commonly chewed by a large proportion of the population in Yemen and East Africa.[1] It has a mild stimulant effect. Users chew this stimulant habitually for its euphoric effects and as a recreational drug that also improves performance.[2] Many people chew it on a daily basis, mostly in the afternoon and evening periods. Chemical analysis confirms that the fresh leaves contain a number of compounds, including phenylalkylamine compounds (alkaloids) such as norpseudoephedrine (cathine) and alpha-aminopropiophenone (cathinone), the latter being structurally related and pharmacologically similar to amphetamine.[3] Khat chewing has been shown to be a risk factor for developing acute myocardial infarction and stroke.[4,5] Not much has been published on the effect of khat chewing on diabetes. It is believed by most people in Yemen that it has a beneficial effect on diabetes mellitus (DM) and that it lowers the blood glucose. We conducted this study to see if it actually had any benefit on diabetes control, since this was a common question asked by many patients.

Methods

A total of 1540 patients with type 2 DM attended a specialized endocrinology and diabetes clinic from May 2013 to April 2014. All the patients attending the clinic were asked to answer a questionnaire regarding khat chewing. (Patients were considered khat chewers (KC) if they had been chewing khat for more than 6 months and had started chewing khat before the diagnosis of diabetes. The ex-KC, who were few, were added to the non-khat chewers (NKC). Blood pressure (BP), weight, and height were measured, and body mass index (BMI) was calculated. The patients were also questioned about smoking as a habit and the frequency and duration of exercise. Hemoglobin A1c (HbA1c) was measured at the same visit or was included if done within less than three months prior to the clinic visit. HbA1c was measured using a Bio-Rad D-10 Hemoglobin A1c analyzer (Bio-Rad Laboratories). Type 2 diabetes was diagnosed according to the ADA/EASD 2012 criteria or noted in those patients who had been previously diagnosed with diabetes.[6,7] Hypertension was defined according to the 2013 ESH/ESC guidelines as a BP level of ≥140/90 mmHg or noted in patients with previously diagnosed hypertension.[8] Patients with type 1 DM (diagnosed on the basis of history or laboratory diagnosis) and those who were not of Yemeni origin were not included in the study. All patients gave their written, informed consent. Ethical approval of the research was obtained from the Ethical Committee at the Medical School, Sana'a University and the research was conducted in accordance with the Declaration of Helsinki.

Statistical analysis. Distribution of data was first illustrated by a scatter plot. Data were presented as mean with

standard deviation (SD) and 95% confidence interval (95% CI) of the mean and as median with 25% to 75% interquartile range (IQR). Coefficient of variation (CV) of the mean, defined as (SD/mean) × 100, which is simply the SD expressed as a percentage of the mean, was used for comparing the variability of two or more sets of variables with different units of measurement.

The data are presented in tables and graphs. Frequencies and percentages were used to describe qualitative data. The mean, SD, CV, and 95% CI were used to describe the quantitative data. Median 25% to 75% range (IQR) was computed to show the central tendency and its upper and lower quartiles, as this is a preferred measure to use with skewed distributions.

The Mann–Whitney *U* test was used as a non-parametric statistical test comparing the medians of non-normally distributed variables. Univariate analysis using chi-squared tests and Fisher's exact tests was used to show the significant associations among the elements of qualitative data, and independent samples *t*-test was used to show the significant differences between qualitative dichotomous data and quantitative data at 0.05 level of significance and 95% CI. The data processing was done using SPSS for Windows, version 18 (SPSS Inc.). A multiple logistic regression analysis was used to calculate adjusted odds ratios (AOR) and the corresponding 95% CI for outcomes in relation to exposures of interest.

Results

A total of 1540 Yemeni patients with type 2 DM aged 20 or older attended a specialized endocrinology clinic from May 2013 to April 2014. The mean duration of diabetes and median (IQR) were 5.6 years (95% CI 5.3–5.9) and 4 (range 0.9–8.0), respectively. The mean age of the population was 49.6 (95% CI 49.0–50.2). A total of 997/1540 patients (77.6%, 526/678 of the males, and 54.4%, 469/862 of the females) were KC and 543/1540 (22.4%, 152/678 of the males, and 45.6%, 393/862 of the females) were NKC. The characteristics of these patients can be seen in Table 1. The majority of the KC patients had been chewing khat for more than 10 years (83.5%, 832/997). The patients were subjected to a knowledge, attitude and practice (KAP) study regarding khat chewing. They were asked if they thought khat chewing was beneficial for diabetes. Of the 1540 patients, 865 (56.2%) thought that it was beneficial, only 189 (12.3%) thought that it was harmful, and 486 (31.5%) said that they did not know. Among the KC, 848/997 (85.05%) of them believed that khat chewing was beneficial for diabetes, only 32/997 (3.2%) thought that it was harmful, and 117/997 (11.73%) said that they did not know. Among the NKC, only 20/543 (3.68%) believed that it was good for diabetes, 157/543 (28.9%) believed that it was harmful, and 366/543 (67.4%) said that they did not know. The KC patients were also asked about the frequency of khat chewing: 64.8% (646/997) chewed khat on a daily basis, 21.6% (215/997) chewed khat two to six times per week, 4.5% (45/997) chewed khat weekly, 3.2% (32/997)

Table 1. Characteristics of the patients (age, age at onset of DM, duration of disease, height, weight, BMI, HbA1c, SBP, and DBP) for KC and NKC. The statistical test used is the Mann–Whitney *U* test.

PARAMETER	KHAT CHEWERS ($n = 997$)			NON-KHAT CHEWERS ($n = 543$)			*P*-VALUE
	MEAN (SD) CV	95% CI	MEDIAN (25,75 IQR)	MEAN (SD) CV	95% CI	MEDIAN (25,75 IQR)	
Age of patients (years)	48.20 (10.96) 22.6%	47.52–48.88	49.00 (40.00–55.00)	52.15 (12.36) 23.7%	51.11–53.20	50.00 (45.00–60.00)	<0.001
Age at onset of DM (years)	43.14 (10.16) 23.55%	42.51–43.77	43.00 (35.00–50.00)	45.90 (11.78) 25.66%	44.90–46.89	45.00 (38.00–53.00)	<0.001
Duration of disease (years)	5.14 (5.54) 107.8%	4.80–5.49	4.00 (0.8–8.0)	6.33 (6.57) 103%	5.78–6.89	5.00 (1.00–10.00)	0.004
Height (m)	1.59 (0.09) 5.66%	1.587–1.6	1.59 (1.52–1.66)	1.56 (0.08) 5.1%	1.549–1.563	1.55 (1.50–1.61)	<0.001
Weight (kg)	67.89 (12.07) 17.77%	67.14–68.64	66.15 (60.30–74.70)	66.53 (13.28) 19.9%	65.41–67.65	65.25 (57.15–74.25)	0.023
BMI (kg/m^2)	26.88 (4.84) 18.0%	26.58–27.18	26.45 (23.68–29.60)	27.55 (4.94) 17.93%	27.13–27.96	27.26 (24.03–30.59)	0.006
HbA1c	9.81 (2.71) 27.62%	9.64–9.98	9.4 (7.6–11.90)	9.09 (2.45) 26.95%	8.86–9.30	8.50 (7.23–10.60)	<0.001
SBP (mmHg)	128.40 (18.17) 14.15%	127.27–129.52	130.00 (110.00–140.00)	127.46 (18.14) 14.23%	125.93–129.0	130.00 (110.00–140.00)	0.295
DBP (mmHg)	74.22 (9.94) 13.3%	73.61–74.84	80.00 (70.00–80.00)	73.06 (9.28) 12.7%	72.27–73.84	70.00 (70.00–80.00)	0.024

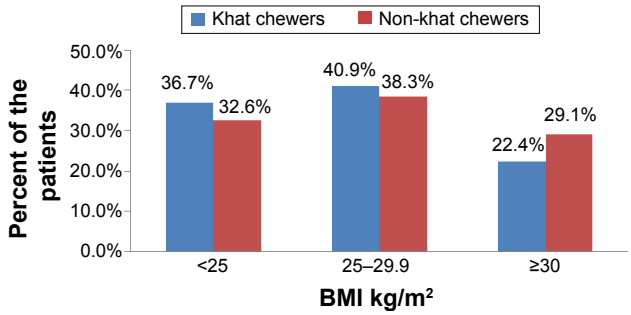

Figure 1. BMI and khat chewing. There was a higher prevalence of normal BMI among the KC group (36.7%, 366/997) than among the NKC group (32.6%, 177/543). Those who were overweight comprised 40.9% of the KC group (408/997) and 38.3% of the NKC group (208/543). Those with obesity constituted a higher percentage of the NKC group, 29.1% (158/543), than the KC group, 22.4% (223/997) ($P = 0.013$).

chewed khat one to three times per month, and 5.9% (59/997) chewed khat less than once monthly.

Khat chewing and the BMI. The mean BMI of the KC group was 26.9 kg/m^2 (95% CI 26.6–27.2) and of the NKC group was 27.6 kg/m^2 (95% CI 27.1–28), $P < 0.01$. Among patients with a normal BMI (<25 kg/m^2), the frequency of KC was higher than NKC. By contrast, among patients with BMI classified as obese (≥30 kg/m^2), the frequency of NKC was higher than KC ($P = 0.013$) (Fig. 1). In a subgroup of patients who were diabetic for less than a year, a higher percentage of patients in the KC group (32.3%) had a normal BMI compared with those in the NKC group (25.4%).

Khat chewing and HbA1c. The mean HbA1c of the KC group was 9.8% (95% CI 9.6–10), whereas that of the NKC group was 9.1% (95% CI 8.9–9.4) ($P < 0.01$). The distribution of the patients is illustrated in Figure 2. It shows a higher rate of patients who were NKC among the lower HbA1c groups and a higher prevalence among patients who were KC in those

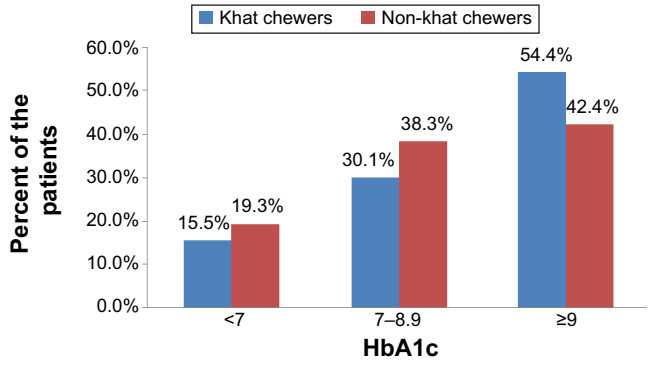

Figure 2. HbA1c classification and khat chewing. In patients who were KC, there was a higher prevalence in the groups with a higher HbA1c, ≥9% (75 mmol/mol). Among those who did not chew khat, there was a higher prevalence in the lower HbA1c groups, <7% (53 mmol/mol) and 7–8.9% (53–74 mmol/mol) ($P < 0.001$).

with a higher HbA1c. Also, in a subgroup of patients who were not on medications, there was a significant difference in the mean HbA1c, 10.7% (2.9) in the KC group compared with 9.6% (2.8) in the NKC group ($P = 0.006$). Patients were also questioned about hypoglycemia during or after khat chewing, and 97.5% (958/997) reported no hypoglycemia related to khat chewing.

Univariate analysis and relative risk (RR) of different variables associated with poor glycemic control (HbA1c ≥ 9%) in the study are presented in Table 2. Out of eight variables tested, significant association was observed with male gender (RR = 1.12; 95% CI 1.02–1.24), age at diagnosis <40 years (RR = 1.13; 95% CI 1.02–1.25), duration of diabetes ≥10 years (RR = 1.28; 95% CI 1.15–1.42), habitual khat chewing (RR = 1.28; 95% CI 1.15–1.44), BMI < 25 kg/m^2 (RR = 1.24; 95% CI 1.12–1.37), use of insulin (RR = 1.24; 95% CI 1.08–1.42), and low level of exercise (RR = 1.32; 95% CI 1.15–1.5).

On multivariate stepwise logistic regression analysis, out of the seven significant variables in univariate analysis, three variables retained their significant independent association with poor glycemic control as shown in Table 3. These variables were duration of diabetes ≥10 years (AOR = 2.06; 95% CI 1.56–2.73), habitual khat chewing (AOR = 1.74; 95% CI 1.33–2.28), and BMI < 25 kg/m^2 (AOR = 1.37; 95% CI 1.063–1.773).

We also checked HbA1c between KC and NKC in patients using different medications for diabetes. The largest group was of patients not on medications ($n = 374$), of which 254 were KC and 120 NKC. In this group, the mean HbA1c among the KC was 10.7% (SD 2.9) and among the NKC was 9.6% (SD 2.8); P value was 0.006. The second group of patients was those on sulfonylureas ($n = 182$), of whom 132 were KC and 50 were NKC. In this group of patients, the mean HbA1c of the KC was 10.7% (SD 2.7) and of the NKC was 9.7% (SD 1.9); P value was 0.003. The third group of patients was those on metformin ($n = 173$), of whom 104 were KC and 69 were NKC. In these patients, the mean HbA1c was 8.2% (SD 2.2) for the KC and 7.7% (SD 2.0) for the NKC; P value was 0.464. The fourth group of patients was of those being treated with insulin ($n = 172$), comprising 95 KC and 77 NKC. In these patients, the mean HbA1c was 9.9% (SD 2.5) for the KC and 9.3% (SD 2.2) for the NKC; the P value was 0.567.

Khat chewing and age of diagnosis of type 2 DM. The mean age of diagnosis of type 2 DM among the khat chewing group was 43.3 (10.1), whereas that among the non-chewing group was 45.9 (11.8) ($P < 0.001$). Among subgroups of patients who had a normal or overweight BMI, we also found a significant difference in the age of diagnosis. Among KC with a BMI < 30 kg/m^2, the mean age of diagnosis of diabetes was 43.6 (10.8), and among NKC with the same BMI range, the mean age of diagnosis of diabetes was 47.4 (13.5); $P = 0.021$. Among patients who were obese (BMI ≥ 30 kg/m^2), there was no significant difference in the mean age of diagnosis

Table 2. Univariate analysis of variables associated with poor glycemic control, defined as HbA1c ≥9.0% (75 mmol/mol), as a dependent variable and male gender, age of diagnosis <40 years, duration of disease >10 years, BMI <25 kg/m², insulin therapy, and decreased exercise as independent variables.

VARIABLE	HbA1c ≥ 9.0% (*n* = 772)	HbA1c < 9.0% (*n* = 768)	RR* (95% CI)***	χ^{2**}	*P*-VALUE
1. Gender			1.12	4.93	0.026
Male	362	316	(1.02–1.24)		
Female	410	452			
2. Age at diagnosis			1.13	5.2	0.02
<40	290	245	(1.02–1.25)		
≥40 years	482	523			
3. Duration of disease			1.28	17.9	<0.001
≥10	207	136	(1.15–1.42)		
<10 years	565	632			
4. Smoking			1.1	2.8	0.09
Yes	170	142	(0.99–1.25)		
No	601	626			
5. Daily khat chewing			1.27	22.2	<0.001
Yes	370	276	(1.15–1.41)		
No	402	492			
6. BMI			1.24	16.69	<0.001
<25	311	232	(1.12–1.37)		
≥25	461	536			
7. Medication			1.24	8.0	0.005
Insulin	125	101	(1.08–1.42)		
Oral agents	419	521			
8. Exercise/week			1.32	14.6	0.0001
≤1 time/week	156	141	(1.15–1.5)		
2–6 times/week	616	627			

Notes: *RR: relative risk, **χ^2: Yates corrected, and ***95% CI: 95% confidence interval.

of diabetes among KC (44.0 (9.6)) compared with NKC (45.3 (11.1)) ($P = 0.541$). A univariate analysis of the risk factors associated with an earlier age at diagnosis is shown in Table 4. Out of five variables tested, significant association was observed only with male gender (RR = 1.25; 95% CI 1.09–1.43) and habitual khat chewing (RR = 1.31; 95% CI 1.12–1.53). On multivariate stepwise logistic regression analysis, the same two variables retained their significant independent association with an earlier age at diagnosis, as shown in Table 5. These variables are male gender (AOR = 1.34; 95% CI 1.06–1.68) and habitual khat chewing (AOR = 1.39; 95% CI 1.09–1.77).

Table 3. Multivariable logistic regression analysis of variables independently related to poor glycemic control defined as HbA1c > 9.0%.

INDEPENDENT VARIABLES	S.E.	WALD	*P*-VALUE	AOR	95% CI FOR AOR	
					LOWER	UPPER
Duration of disease (≥10 year)	0.14	25.44	<0.001	2.06	1.56	2.73
Daily khat chewing (yes)	0.13	14.45	<0.001	1.64	1.27	2.12
BMI (<25 kg/m²)	0.13	5.9	0.015	1.373	1.063	1.773

Khat chewing and the age of patients with type 2 DM. The age distribution of the patients with type 2 DM can be seen in Figure 3. There was a higher frequency of KC in those aged ≤44 years, whereas there was a higher frequency of patients in the NKC group in those aged ≥55 years ($P < 0.001$).

Khat chewing and smoking. Among the khat chewing patients, smoking was quite common; 30.19% ($n = 301$) of the KC were smokers and only 2.02% ($n = 11$) of the NKC were smokers. Among the males, 27.7% were smokers, and among the females, 14.4% were smokers. The most common forms of smoking among the males were cigarettes, 95.2%; mada'a (water pipe), 3.2%; and shisha, 1.6%. Among the females, the most common forms of smoking were mada'a (water pipe), 74.2%; shisha, 18.5%; and cigarettes, 7.3%.

Table 4. Univariate analysis of variables associated with early age at diagnosis of diabetes (defined as age <40 years) as the dependent variable and male gender, smoking, habitual khat chewing, BMI ≥ 25, and decreased exercise as independent variables.

VARIABLES	AGE AT ONSET (<40 YEARS) *n* = 535	AGE AT ONSET (≥40 YEARS) *n* = 1005	RR* (95% CI)***	χ^{2}**	*P*-VALUE
1. Gender			1.25	9.75	0.002
Male	265	413	(1.09–1.43)		
Female	270	592			
2. Smoking			1.15	2.57	0.1
Yes	121	191	(0.98–1.35)		
No	414	813			
3. Habitual khat chewing			1.31	12.2	0.0004
Yes	378	619	(1.12–1.53)		
No	157	386			
4. BMI			0.94	0.6	0.4
≥25	339	658	(0.82–1.09)		
<25	196	347			
5. Exercise/week			0.87	2.1	0.14
≤1 time/week	92	205	(0.72–1.05)		
2–6 times/week	443	800			

Notes: *RR: relative risk, **χ^{2}: Yates corrected, and ***95% CI: 95% confidence interval.

Discussion

We have shown in our study that habitual khat chewing, long duration of diabetes, and BMI < 25 kg/m^2 were independently associated with poor glycemic control defined as HbA1c ≥ 9.0% (75 mmol/mol). We also have proved in this study that habitual khat chewing and male gender were independent risk factors for earlier age at diagnosis of type 2 diabetes in this large sample of Yemeni patients.

Khat chewing is a common tradition in Yemen. The majority of the adult population chews khat on a regular basis. Most of the khat chewing takes place in the afternoon and may continue to the evening according to the purpose, whether studying, working, or at leisure.[9,10] In our study on 1540 patients with type 2 DM, 77.6% of the males and 54.4% of the females were KC. Out of these patients, 64.8% chewed khat on a daily basis, with 83.5% having chewed khat for more than 10 years. A recent study has mentioned that up to 67.8% of women in Sana'a, Yemen, reported that they have chewed khat sometime during their lifetime.[11]

Table 5. Multivariable logistic regression analysis of variables independently related to age at diagnosis of diabetes <40 years.

VARIABLE	S.E.	WALD	*P*-VALUE	AOR	95% CI FOR AOR	
					LOWER	UPPER
Gender (male)	0.12	9.32	0.002	1.42	1.13	1.79
Khat chewing (yes)	0.12	7.02	0.008	1.39	1.09	1.77

Studies in other countries where khat chewing is common, as in Ethiopia, have also shown khat chewing to be common among younger ages in university students,[12] and a study done in Aden, Yemen, also found khat chewing to be common among medical students.[13]

Khat chewing was associated with a lower BMI in the diabetic patients. The mean BMI was 26.9 kg/m^2 in the KC group compared with 27.6 kg/m^2 in the NKC group. A study done on Wistar Ottawa Karlsburg W (WOKW) female rats also showed a reduction in body weight when fed khat.[14] Another factor may be that anorexia frequently follows khat chewing. This may be because of a delay in gastric emptying,[15] a slower whole gut transit time,[16] or the anorexigenic effect of khat may be secondary to central mechanisms mediated via cathinone.[17] We had previously shown that obesity is much more common among female Yemeni diabetic patients in comparison with male patients.[18] Since khat chewing is more common among males, this may be a factor in causing less obesity among males with type 2 DM.

In our patients, khat chewing was associated with a higher HbA1c. About 57.6% of the NKC patients and 45.6% of the KC patients had an HbA1c less than 9% (75 mmol/mol), which is counter to the general belief among patients that khat chewing is good for diabetes. Also, in a subgroup of 393 patients not on medications, HbA1c was significantly higher in KC, 10.7% (86 mmol/mol), than in NKC, 9.6% (81 mmol/mol). It is possible that these patients present when they become more symptomatic because the economic burden

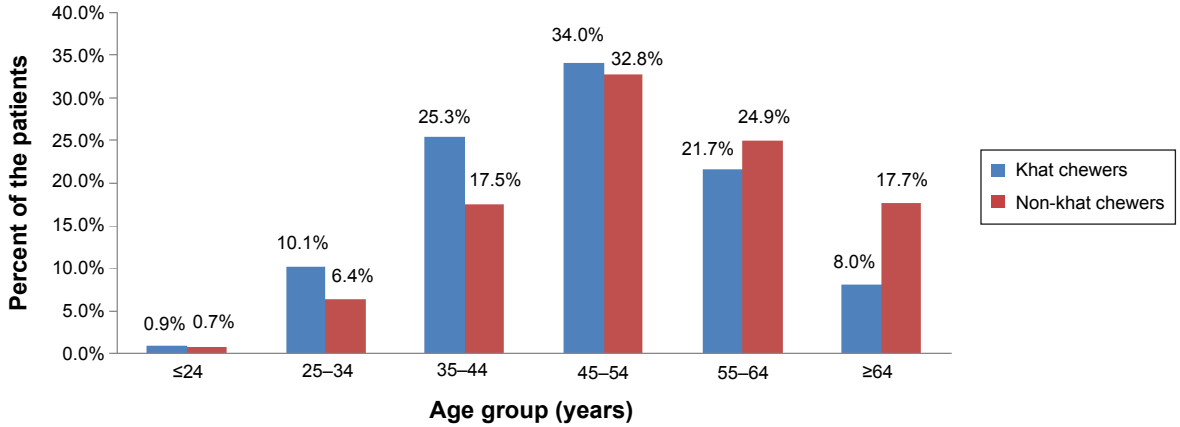

Figure 3. The age of patients with type 2 diabetes in relation to khat chewing. There was a higher frequency of KC among the younger age groups and a higher frequency of NKC among those aged ≥55 years ($P < 0.001$).

of khat chewing causes the patient to delay seeking medical assistance. For patients who chew khat on a regular basis, the habit can be quite costly.[11] A previous study done on a small number of Somali patients did not show any direct effect of khat chewing on blood sugar levels in nondiabetic subjects.[19] Another study showed an increase in glucose and C-peptide levels during khat chewing in diabetic individuals, especially in those with high sugars, but no effect on serum glucose and C-peptide levels in healthy individuals.[20] However, the limitation of this study was separate statistical analysis of C-peptide and blood glucose. It is well known that both variables should be tested together to be meaningful. Therefore, when we tried to calculate the increment (Δ) of mean C-peptide/glucose ratio at two and three hours after khat chewing in this study, we found that in diabetic patients, there was either a decrease or a very small increment (−0.02 to 0.04), indicating that there was no significant effect on insulin secretion in response to khat.

The age of diagnosis of diabetes was found to be significantly lower among KC than NKC, even among those who had a normal or overweight BMI. This may be a direct effect of khat chewing or because of the pesticides used on the khat plant. A study by El-Hadrani and Al Hoot showed diabetes to be more common among KC and attributed it to the use of pesticides.[21]

The age distribution of the patients with type 2 DM showed a higher prevalence of the KC in the younger age groups, but as the age increased, there were fewer KC, especially among those over the age of 65 (8.0% KC, 17.7% NKC). It has been shown in other studies that KC increased the risk of hypertension, myocardial infarctions, strokes, and mortality,[4,5,22–24] which might explain the lower number of older patients with type 2 diabetes who chew khat. In our patients, we did not see any significant difference in BP, measured during the clinic visit, between the KC and NKC. It has been shown that BP increases in KC after starting khat chewing, reaching a peak three hours after starting chewing and declining one hour after spitting the leaves.[24] The majority of our patients came in the morning or early afternoon before they started chewing khat. Also, many of the patients who had a history of hypertension (29.1% of the patients in our study) were already on medications (87.1%). This can explain why we did not find any significant difference in BP between the KC and NKC in our study.

Conclusion

It seems that khat chewing by patients with type 2 diabetes in Yemen is likely associated with poor glycemic control, lower BMI, and probably an earlier age at diagnosis of diabetes. Male patients were found to be more frequent KC and more prone to earlier onset of the disease. Poor glycemic control was independently related to long duration of diabetes, habitual khat chewing, and lower BMI. We recommend further studies on the effect of khat on beta-cell function in patients at risk of type 2 diabetes.

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Author Contributions

Conceived and designed the study: BAA. Analyzed the data: BAA and AAG. Wrote the first draft of the manuscript: BAA. Contributed to the writing of the manuscript: BAA and AAG. Agreed with manuscript results and conclusions: BAA and AAG. Jointly developed the structure and arguments for the paper: BAA and AAG. Made critical appraisal and approved the final version: AAG and BAA. All authors reviewed and approved the final manuscript.

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