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Short Communication

Impact of Chronic Khat Chewing on Carotid Doppler Flow Velocities and Indices in Yemeni Volunteers

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ABSTRACT

Chewing Khat is considered as a major deep-rooted sociocultural habit in Yemen. This custom has been causing various health problems. Using Doppler ultrasonography, this study assessed the changes that occurred in bilateral carotid arteries' flow velocities and Doppler indices in Yemenis who regularly chewed Khat for years. Convenient sampling was conducted from August 2017 to August 2018 for 384 participants of whom 179 were excluded and the sample size became 205 participants including 108 (52.7%) Khat chewers and 97 (47.3%) non-Khat chewers. The mean age of the sample was 28.29 ± 7.0 years. In all cases, the carotid Doppler ultrasound scanning protocol, based on the standards of American Institute of Ultrasound in Medicine, was performed to measure carotid Doppler velocities and indices, in addition to internal carotid flow volume. The Khat chewing information of participants was obtained by a standardized questionnaire, and SPSS was used for result analysis. There were differences in systolic velocities between Khat chewers and non-chewers with lower values for the chewers, and they were significant in the right common carotid artery and in the internal carotid artery. The carotid Doppler indices, except the right internal carotid artery, were significantly decreased, and the Right internal carotid artery blood flow volume was significantly increased among Khat chewers compared to that of non-chewers. Moreover among Khat chewers, Doppler indices and most of the peak systolic velocities had a significantly negative correlation with the Khat chewing period. Therefore, this study may provide

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an interpretation of the high prevalence of hemorrhagic stroke among Yemeni population in their middle age, and suggest the mechanism that may cause this type of stroke. More studies are recommended to confirm this finding using the transcranial Doppler technique.

Keywords: Carotid, chronic Khat chewing, Doppler index, Doppler velocity, Yemen

INTRODUCTION

In Yemen, Khat (qat, kat) chewing is considered as a major deep-rooted sociocultural phenomenon. Khat is an evergreen shrub belonging to the Celastraceae family that was named by a botanist, Peter Forsskal who uttered "Catha" (referred to the Catha edulis tree) from the Arabic name "Khat" (Numan, 2012).

Earlier, the clinical observation concluded that Khat had amphetamine-like properties. Then in subsequent chemical analysis, it was suggested that the fresh Khat leaves contained a number of compounds, including phenylalkylamine compounds (alkaloids) such as norpseudoephedrine (cathine) and alpha aminopropiophenone (cathinone) (Hassan et al., 2007). The latter is the main active ingredient in fresh Khat leaves (Kalix, 1990) which is pharmacologically similar and structurally related to amphetamine (Hassan et al., 2007).

Chewing Khat evidently leads to a significant rise of arterial systolic and diastolic blood pressure and pulse rate (Hassan et al., 2005; Hassan et al., 2007; Yehia, 2015), and it is an established risk factor for cardiovascular disease with cigarette smoking (Tesfaye et al., 2008).

Because the regular Khat chewing is associated with the increased diastolic blood pressure resulting from the effect of Cathinone as a peripheral vasoconstrictor, the sustained effect on the cardiovascular system may occur that can contribute to the elevation of blood pressure at the population level (Geta et al., 2019; Mega & Dabe 2017; Getahun et al., 2010; Andualem et al., 2002). Furthermore, the regular intake of Khat is associated with an increased risk of acute myocardial infarction (Al-Motarreb et al., 2005).

The flow velocities were increased and the Doppler indices were decreased when assessing the immediate effect of Khat chewing on Doppler hemodynamics of common carotid arteries (Ibrahim et al., 2017). Doppler ultrasonography scan is non-invasive and appropriate for the bedside examination. With the measuring of flow volumes in the carotid arteries (CAs), this technique has been used to detect extracerebral blood flow among healthy populations. Doppler's indices; resistive index (RI) and pulsatility index (PI) are common parameters for characterizing the waveform to translate the vascular resistance (Ibrahim et al., 2017).

Originally, Pourcelot (1976) introduced RI to assess peripheral vascular diseases. The RI and PI have become important parameters in studying the effect of many diseases on vascularity in different organs, then, according to Ibrahim et al. (2017), they are used to assess the effects of Khat chewing on CAs hemodynamics.

To our knowledge, no study has been investigated the accumulative effects of chronic Khat chewing on CAs hemodynamics. Therefore, the study aimed to determine the effect of chronic Khat chewing on the Doppler flow velocities and indices of CAs in order to estimate its effect on the vascular system and cerebral perfusion.

MATERIALS AND METHODS

For this prospective study, Two radiologists approved the procedures, and a qualified sonographer, who had a Master degree in medical diagnostic ultrasound and seven years field experience, performed imaging of bilateral CAs using Doppler ultrasonography to measure the peak systolic velocity (PSV), end diastolic velocity (EDV), resistivity index (RI), and pulsatility index (PI) among 384 Yemeni participants conveniently selected according to the Table of Krejcie and Morgan (1970). After applying the inclusion and exclusion criteria, the sample size became 205 participants divided into two groups; Khat chewers (n = 108) and non-Khat chewers (n = 97). Then, flow volume was calculated in the bilateral internal carotid arteries (ICAs).

The demographic data were obtained from participants including age, governorate, occupation, and body mass index. Then the information of their chewing Khat habit were collected including the daily duration of chewing in hours and the period of chewing in years using a standardized questionnaire and data collection sheet.

Participants were scanned in the Radiology Department of University of Science and Technology Hospital (USTH), Sana'a, Yemen, from August 2017 to August 2018, using a high-resolution ultrasound system (model: TUS-Aplio 400 / Toshiba-MEC-US) equipped with a linear high frequency probe (Figure 1).

CAs were scanned to determine Doppler parameters in the supine position with supported knees. The operator seated on the right of the patient. The neck scanning was enhanced by tilting and rotating the head away from the side being examined, with possible appropriate adjustment for the head and neck position. Transducer several positions were used to investigate the CAs in the longitudinal and the short-axis (transverse) views that obtained from different anterior and lateral or posterolateral approaches for getting the best view of vessels. Then sweeping of probe was performed to determine the values of Doppler carotid parameters using the manual and automatic calculation software, with beam angle of Doppler was maintained ≤ 60 degrees at all times. All measurements in spectral Doppler were obtained with a small sample volume (≤ 2 mm) and in the center stream of the flow at the area of the greatest velocity shift (Figure 2 and 3).

Figure 1. High-resolution ultrasound system (model: TUS-Aplio 400 / Toshiba-MEC-US)

The blood volume of ICAs was calculated, in 98 participants, by measuring the average peak flow velocity times the cross-sectional area of this circular vessel (Blanco, 2015).

ETHICAL CONSIDERATIONS

Formal approval was obtained from the Research Ethics Committee, Faculty of Medicine and Health Sciences at University of Science and Technology Yemen (USTY) (MECA No.: EAC/UST133), and a written agreement was received from the Radiology Department of the USTH. Then the scanning procedures were explained to the participants before taking written informed consents from them.

By applying the inclusion criteria, the study sample includes Yemeni adults (Khat and non-Khat chewers) on condition that they are non-smokers, non-hypertensive, non-diabetic, and without cardiopulmonary disorders, history of severe dyslipidemia and known kidney diseases so as to avoid significant effect in the extracranial blood flow velocities.

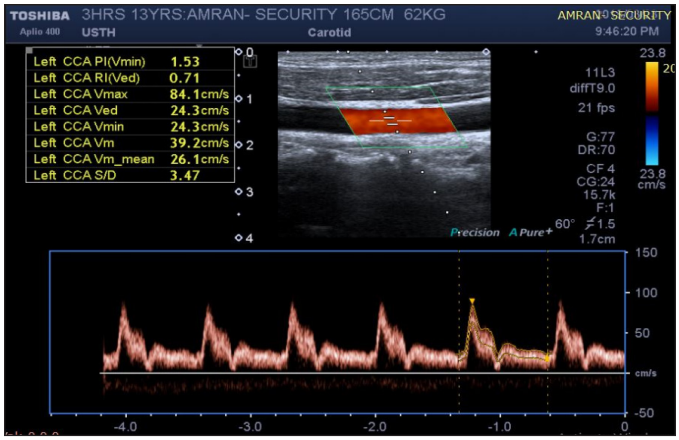

Figure 2. Doppler interrogation of Lt CCA hemodynamics for a Khat chewer participant has a 13 year period of chewing

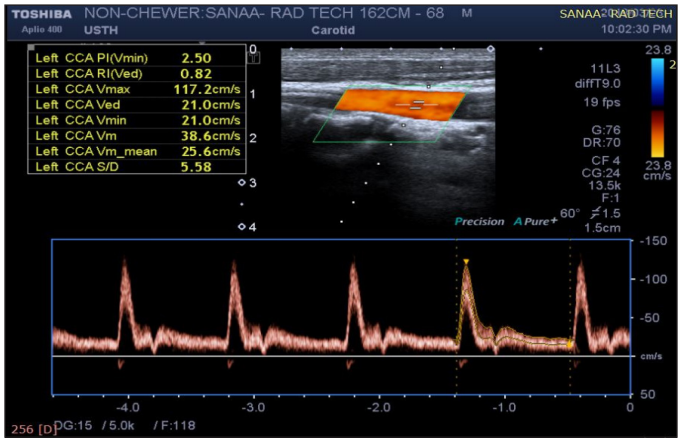

Figure 3. Doppler interrogation of Lt CCA hemodynamics for non-Khat chewer participant

STATISTICAL ANALYSIS

All statistical analyses were achieved by SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). The variables were expressed as mean ± standard deviation. The normality of data was examined using the Kolmogorov-Smirnov test. An Independent sample t-test was used to compare between the variables with respect to the two groups (Khat and non-Khat chewers). Pearson's correlation was also used to analyze the associations among the variables and to determine their significance. After the analysis, the data were presented using figures and tables. A p-value < 0.05 was considered as statistically significant.

RESULTS

The 205 Yemeni participants; 21 (10.2%) females and 185 (89.8%) males were investigated using Doppler ultrasound. The mean age was 28.3 ranging from 16 to 45 years.

This study showed the differences between Khat and non-Khat chewers regarding Doppler parameters, particularly Doppler indices. These differences were significant in PSV of right common carotid artery (RT CCA), internal carotid artery (ICA), and EDV of both external carotid arteries (ECAs), in addition to RI and PI of bilateral CCAs, and ECAs. Moreover, in the chewers' group, the results showed significant correlations between the period of chewing and the carotid Doppler parameters as follows:

A decreased PSV was observed in all bilateral CAs of the Khat chewers' group compared to those of the non-Khat chewers, and was statistically significant only in the RT CCA ($p < 0.001$) and RT ICA ($p = 0.042$).

In the Khat chewers group, the PSV had a significantly negative correlation with the period of chewing only in the RT CCA ($p = 0.01$), left CCA (LT CCA) ($p < 0.001$) and ECA ($p = 0.005$).

A significant increased EDV ($p < 0.001$) was observed only in the bilateral ECAs of Khat chewers' group compared to that of the non-Khat chewers. Furthermore, the EDV in the bilateral ECAs had a significantly positive correlation with the period of chewing in the RT ECA ($p = 0.046$) and LT ECA ($p <0.001$).

There was no significant difference in Doppler parameters between genders in the Khat Chewers group. Moreover, higher carotid flow velocities in males compared to females were observed in the control group. But this trend did not reach statistical significance except that of RT CCA PSV ($p < 0.001$).

The ultrasound Doppler machine automatically calculated the Doppler indices of bilateral CAs. The comparison of RI and PI values between the two groups is demonstrated in Table 1 in which a significant difference was noticed with decreased RI and PI in bilateral CAs of Khat chewers, except in LT ICA.

In the Khat chewers' group, Doppler indices had a significantly negative correlation with the period of chewing in the bilateral CAs, except in the RT ICA RI and LT CCA PI (Table 2, Figures 4 and 5).

Table 1
Comparison of carotids Doppler indices between Khat and non-Khat chewers

Doppler index	**Chewing Status**	**Mean**	**Std. Deviation**	**t-test Sig. (2-tailed)**	**Doppler index**	**Chewing Status**	**Mean**	**Std. Deviation**	t-test Sig. (2-tailed)
RT CCA RI	chewer	0.7739	0.04767	0.026	**RT CCA PI**	chewer	1.9072	0.45763	**0.000**
	non-chewer	0.7884	0.04401			non-chewer	2.2053	0.49456	
RT ICA RI	chewer	0.6143	0.08511	0.012	**RT ICA PI**	chewer	1.0879	0.36626	**0.000**
	non-chewer	0.6457	0.09150			non-chewer	1.3101	0.45799	
RT ECA RI	chewer	0.8190	0.07414	0.000	**RT ECA PI**	chewer	2.3366	0.81658	**0.000**
	non-chewer	0.8625	0.08737			non-chewer	2.8952	1.05374	
LT CCA RI	chewer	0.7584	0.04853	0.000	**LT CCA PI**	chewer	1.8256	0.46958	**0.000**
	non-chewer	0.7861	0.05281			non-chewer	2.1576	0.54098	
LT ICA RI	chewer	0.6079	0.08068	0.701	**LT ICA PI**	chewer	1.1028	0.34266	**0.178**
	non-chewer	0.6124	0.08661			non-chewer	1.1657	0.32052	
LT ECA RI	chewer	0.8143	0.07303	0.001	**LT ECA PI**	chewer	2.1790	0.69968	**0.000**
	non-chewer	0.8528	0.08805			non-chewer	2.8276	0.86916	

Table 2
Correlation between Doppler indices of CAs and period of Khat chewing

Dependent variable		RI						PI					
		RT CCA	**RT ICA**	**RT ECA**	**LT CCA**	**LT ICA**	**LT ECA**	**RT CCA**	**RT ICA**	**RT ECA**	**LT CCA**	**LT ICA**	LT ECA
Period of Khat chewing (yrs.)	**Pearson Correlation**	-0.369**	-0.152	-0.319**	-0.319**	-0.193*	-0.395**	-0.264**	-0.190*	-0.318**	-0.185	-0.285**	**-0.322****
	Sig. (2-tailed)	0.000	0.117	0.001	0.001	0.045	0.000	0.006	0.049	0.001	0.055	0.003	**0.001**
	N	108	108	108	108	108	108	108	108	108	108	108	**108**

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

In the control group, bilateral CCAs Doppler indices were significantly different between the genders (p =0.01, and 0.008 of RI), and (p =0.001, and 0.002 of PI) for Right and Left respectively.

Table 3
Comparison of internal carotids flow volume between Khat and non-Khat chewers

Doppler Parameter	Chewing Status	N	Mean	Std. Deviation	Sig. (2-tailed)
RT ICA flow	**chewer**	49	433.0524	135.56262	**0.044**
volume (ml/min)	**non chewer**	49	378.3753	129.33580	
LT ICA flow	**chewer**	49	491.1616	145.26714	**0.060**
volume (ml/min)	**non chewer**	49	438.6129	127.82918	

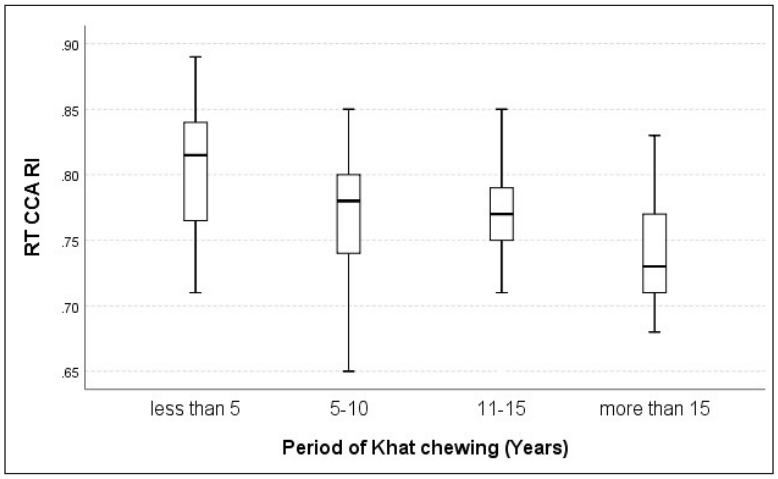

Figure 4. Correlation of right CCA RI with period of Khat chewing

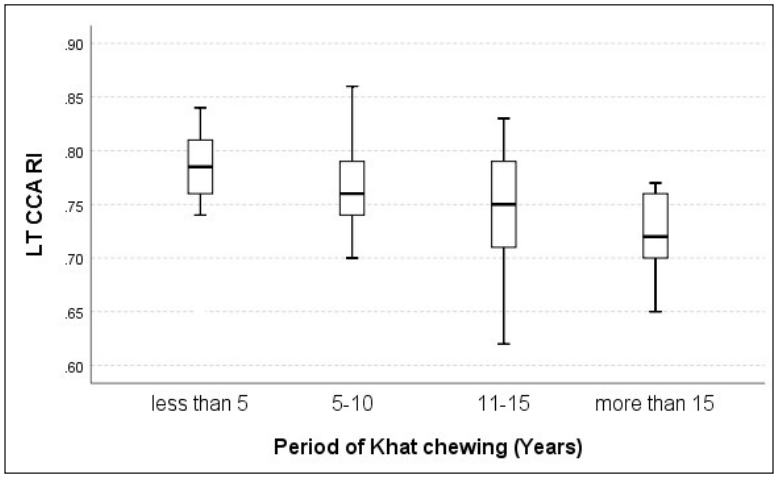

Figure 5. Correlation of left CCA RI with period of Khat chewing

DISCUSSION

This study revealed that the chronic Khat chewing significantly altered the carotids blood hemodynamics by decreasing the PSVs and Doppler indices, in addition to increasing the flow volume as discussed in details below.

In the control group, CAs flow velocities in males were higher compared to females, which supports the previous findings in a healthy adults (Yazici et al., 2005). Also there was no statistical significantly difference in Doppler parameters between genders in the Khat Chewers.

Khat chewing causes increased blood pressure and heart rate (Hassan et al., 2007; Yehia, 2015; Ibrahim et al., 2017), therefore, it is considered a risk factor for cardiovascular complications (Balint et al., 2009; Al-Motarreb et al., 2010; Al Suwaidi et al., 2013).

The decreased PSVs in CAs of Khat chewers compared to those of non-Khat chewers in the current study is consistent with the proven inverse relationship between the velocity and pressure according to physics laws controlling hemodynamics such as Bernoulli principle (Kirsch et al., 2013). This result agrees also with that of Homma et al. (2009) who noticed that the PSV is lower in the hypertensive patient compared to healthy individuals.

These decreased PSVs in the CAs of Khat chewers compared to those of non-Khat chewers were statistically significant in the RT CCA and RT ICA, while the decreased PSVs in addition to the Doppler indices in CAs of Khat chewers was not statistically significant in the LT ICA. This may be attributed, according to Homma et al. (2009), to the probability of slower velocity in the ICA or the effect of anatomical variation in cerebral vessels on ICA, which are anatomically closer in distance to ICA than CCA.

Since Agunloye and Owolabi (2014) reported that the decreased PSVs were associated with stroke, the lower PSVs among Khat chewers in the current study may consolidate that Khat can be a cause of cerebral complications beside causing cardiovascular events (Vanwalleghem et al., 2006; Kulkarni et al., 2012; Balint et al., 2009; Al-Motarreb et al., 2010; Al Suwaidi et al., 2013). Moreover, Ibrahim et al. (2017) indicated that the EDVs in CAs of Khat chewers were mostly increased, which is in line with the current study finding.

To confirm the aforementioned findings, the decrease in RI and PI is mathematically consistent with the decrease in PSVs and the increase in EDVs (Chow et al., 2013). Moreover, the decrease in RI and PI in CAs i.e. leading to low blood resistance in extracranial blood vessels agrees with an increased blood flow volume in bilateral ICAs, that statistically significant in the Right one, of the Khat chewers group compared to non-chewers (Table 3).

Moreover, these findings agree with the results of Ibrahim et al. (2017) who revealed that cerebral perfusion may be affected and increased by Khat chewing.

Since the active gradient in Khat (Cathinone) is pharmacologically similar and structurally related to amphetamine (Wabe, 2011), the decrease in Doppler indices and

increased cerebral perfusion are also noticed as amphetamine impact on cerebral capillary (Russo et al., 1991; Hassan et al., 2007), which may interpret the correlation of amphetamine abuse to hemorrhagic stroke (Westover et al., 2007).

Consequently, a decreased Doppler indices and increased cerebral perfusion may interpret the desirable and acutely psychostimulant effects of Khat chewing including mental alertness, increased energy, wakeful, optimism feelings, increased flow of ideas during activity of studying and enhanced concentration (Balint et al., 2009; Al'Absi, Khalil et al. 2013, Dachew et al., 2015), and also interprets its side effects including intracranial swelling, edema and hemorrhage (Abdul-Mughni et al., 2018).

The correlation between Khat and strokes was proven due to the effect of cathinone on the Central Nervous System (CNS), which finally led to platelets aggregation (Vanwalleghem et al., 2006, Kulkarni et al., 2012). Although this mechanism relates to the ischemic stroke, the mechanism related to the hemorrhagic one correlates with chronic Khat Chewing (Attafi, 2018; Ali et al., 2011; Benois et al., 2009), to the best of our knowledge, has not been established and no study has discussed the cause of increased hemorrhagic strokes among Khat chewers. Nevertheless, it is recommended for further studies (Sallam et al., 2009; Makwana et al., 2017).

Additionally, a study conducted in Sana'a city, Yemen revealed that hemorrhagic strokes happened mostly (51.7%) among patients aged between 15-44 years, and 43.4% of the entire sample were Khat chewers (Sallam et al., 2009). However, another study conducted on Mukalla city, Yemen revealed that the mean age of stroke among the study sample was similar to that noticed in other Middle East countries (Bamekhlah et al., 2014), which was within the 6^{th} and 7^{th} decade with predominance of the ischemic over hemorrhagic type (El-Hajj et al., 2016). This controversial argument resulting from one country can be due to regional and cultural reasons. In Yemeni Northern mountainous areas, Khat is grown and cultivated from hundreds of years (World Bank, 2007; Numan 2012), while it is not cultivated in Southern coastal areas (World Bank, 2007).

Therefore, Khat chewing could be one of the main causes of hemorrhagic stroke in Yemen, and it may become like untreated hypertension (Woo et al., 2004).

Accordingly, this is the first study that reveals and discusses the mechanism of hemorrhagic stroke based on the significantly decreased resistance of extracranial and cranial blood flow among Khat chewers.

When evaluating the Doppler parameters in CAs among the Khat chewers' group itself, it was revealed that the RI, PI and most of the PSVs had a negatively significant correlation with the period of chewing indicating that these Doppler parameters decrease with the increasing period of chewing (Table 2, Figures 4 and 5), which confirmed and supported the previous findings in the comparison between Khat and non-Khat chewers' groups.

These results with the results of Balint et al. (2009), Al-Motarreb et al. (2010) and Al Suwaidi et al. (2013), who reported that chronic Khat chewing has obvious effects on cardiovascular system may strengthen the previous suggested conclusion that Khat could be a risk factor of hemorrhagic stroke. They may also reinforce the interpretation of why the hemorrhagic stroke mostly occurs among younger population in Yemen while it mostly occurs among the elderly in the other Middle East countries (Vanwalleghem et al., 2006; Sallam et al., 2009; Kulkarni et al., 2012; El-Hajj et al., 2016).

Therefore, this study is important and can be a clinical guideline for physicians in preventing or at least decreasing the complications associated with cerebrovascular perfusion resulting from chronic Khat chewing, particularly among those with known cardiovascular disorders.

Further studies are recommended to address the B-mode sonography of carotid arteries and to use transcranial Doppler ultrasound technique which can provide measurements of cerebral blood flow with higher temporal resolution (Markus, 2004).

CONCLUSION

Chronic Khat chewing has mostly significant alterations in the blood flow velocities and Doppler indices of CAs (i.e., decreasing the PSVs, RI, PI, and increasing the EDVs), in addition to increasing Flow Volume of ICAs, which proved the relationship between the regular Khat chewing and stroke. Moreover, the negative correlation between carotid Doppler indices and the period of Khat chewing could help in the illustration of the mechanism through which Khat chewing could be a risk factor of hemorrhagic stroke.

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