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Original article

The Severity and Extent of Coronary Artery Disease in Khat User Yemeni Patients

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Abstract

Background: Khat is the leaves of the Catha Edulis plant, contains cathinone, ephedrine, epinephrine, and other substances. Khat chewing is one of the major social habits in Yemen and some studies reported that the khat chewing is associated with worse outcome in patients with acute coronary syndrome compared with non-khat users but there are limited data about the effect of khat and the severity of coronary artery disease. ***Objectives:*** This study was performed to determine the extent and severity of coronary artery disease in khat chewer patients in Yemen. ***Patients and Method:*** Patients who underwent coronary angiography as a planned procedure at the cardiac center of Al-Thawra Modern General Hospital over six months duration were included in this cross-sectional prospective study. A well-designed questionnaire was filled which including complete personal and clinical history for each patient, the presence of CHD risk factors, echocardiography, and coronary angiography findings. The data after that were analyzed using the SPSS program and different correlations were statistically established among variables. ***Results:*** The total number of patients admitted with a diagnosis of ischemic heart disease and planned for coronary angiography were 365 patients in which khat chewer patients group were 306 (84%) compared with 59 (16%) of non-khat chewers. The mean ages were (55+ -10 vs. 57+ -9, P=0.396). History of smoking was (83% vs. 17%, P<0.001) in khat chewers and non-khat chewers respectively. The prevalence of DM & HTN were (44% vs. 36%, P=0.243) & (30% VS. 39%, P=0.I194) in comparing both groups respectively. The history of the acute coronary syndrome was more prevalent among the khat chewer patients group (54% vs. 24%, P<0.001). Impaired LV systolic function was more prevalent among khat chewer patients group associated with a significant statistical difference & EF<50% was(39% vs. 23%, P=0.024) in both groups respectively. The significant coronary stenosis was more frequent in the khat chewer patients group (66% vs. 45%, P=0.O42). The khat chewer patients group also had more atherosclerotic coronary arteries (64% vs. 50%, P=0.056), more prevalence of multi-vessel disease (27% vs. 22%, P=0.090), and more frequent of type C coronary artery lesions complexity (20% vs. 12%, P=0.011). On the other hand, the history of recurrent stable angina was more prevalent among the non-khat chewer patients group (76% vs. 45%, P<0.001) & the normal coronary arteries were more frequent among the non-khat chewer patients group (46% vs. 29%, P<0.001). ***Conclusion:*** Khat chewer patients had more atherosclerotic coronary arteries, more lesion complexity, a severe form of coronary artery disease, and more prevalence of the multi-vessel disease. Finally, we concluded that khat chewing is one of the risk factors of coronary artery disease in Yemen.

Keywords: ***Coronary Artery Disease, ACS, Coronary Angiography, Khat chewers, Yemeni Patients, Cross-sectional prospective study.***

Introduction

Chewing the leaves of khat or qat (Catha edulis Forsk) is a social habit in Yemen and East African countries [1,2]. A recent report suggests that nearly 20 million people worldwide are regularly using khat [3]. People chewing fresh khat leaves daily on a regular basis mainly in the afternoon, although some people start to chew khat in the morning [1,2]. At the present time, easy transportation of khat and easing of importation restrictions has helped this habit spread to countries such as the USA and Western Europe where Yemeni, Somali, and other East African countries are living[1,2]. People chew khat for its central nervous system stimulant effects such as euphoria, energy, alertness and for the social purpose [4,5].

The pharmacological effect of khat chewing is mainly due to the cathinone, cathine, and norephedrine present in the fresh leaves [4,5,6,7]. Cathinone, the chief active ingredient of khat, bears high structural and functional similarity to amphetamine [4]. It operates through the same mechanism as amphetamine which

explains the observed central nervous system stimulant effects in the khat chewer [4]. Cathinone acting as indirect sympathomimetic, it induces catecholamine release in central dopaminergic and serotonergic synapses, as well as from peripheral noradrenaline storage neuron endings [8-12]. Cathinone increases blood pressure and heart rate through noradrenaline (norepinephrine) release from peripheral neurons similar to amphetamine [4]. Cardiovascular effects of khat chewing in humans include elevated blood pressure and increases in heart rate [7,11,13], (has positive inotropic and chronotropic actions in isolated atria) [12,14]. Increases in blood pressure and heart rate have been observed in human volunteers after chewing khat which coincides with raised plasma cathinone concentrations [15]. Khat chewing, however, has been reported to have adverse effects on various human body systems [23].

In addition to its effects on blood pressure, khat has also been associated with the increased incidence of acute coronary vasospasm and myocardial infarction (MI) [16]. As one of the constituents of khat, cathinone is reported to be associated with severe coronary vasoconstriction and a severe negative inotropic effect on the cardiac muscle, suggesting that coronary spasm contributes to the development of acute myocardial infarction [17,18]. Cardiovascular complications from cathinone abuse may, therefore, be similar to those of amphetamine [4].

Khat chewing changes the circadian rhythm of acute myocardial infarction presentation [19], and it was an independent dose-related risk factor for acute myocardial infarction (AMI) [20].

Al-Motarreb et al. reported that about 59% of khat chewers had onset of symptoms of acute myocardial infarction during the khat-effective period compared with only 36.4% of non-khat chewers had a new onset of AMI [19]. Also, Alkadi et al. reported that the vast majority of MI events (70%) occurred either during or immediately after completion of a khat chewing session and they considered khat chewing a risk factor for AMI [21]. Khat chewers also had a high risk of death, recurrent myocardial ischemia, cardiogenic shock, and ventricular arrhythmia [22].

Patients and Method

A Patients who underwent coronary angiography as a planned procedure to role out coronary artery disease at the cardiac center of Al-Thawra Modern General Hospital over six months duration for April 2011 to September 2011 were included in this cross-sectional prospective study. A well-designed questionnaire was filled which including complete personal and clinical history for each patient, the presence of CHD risk factors, echocardiography, and coronary angiography findings. The severity of stenosis, atherosclerosis, the extent of lesions, and types of lesions of the coronary arteries were estimated visually in most of the cases, and the results were determined after discussion and agreement between the doctors in cath. Lab., after that the digital films of CAG were revised by other interventional cardiologists to confirm the data of the previous results of the CAG and decrease the intra-observer and inter-observer faults. Definitions: Ejection fraction (EF) was an indicator for left ventricular systolic function and divided into two groups [1,2], preserved left ventricular systolic function; if EF was >= 50% and impaired systolic left ventricular function; if EF was <50%. The data after that were analyzed using the SPSS program and different correlations were statistically established among variables. Normal CAG referred to the patients with no CAD or those with near-normal or had mild CAD (0%-<50% stenotic lesions), non-significant lesions CAD referred to stenosis >=30% & <50% of left main coronary or the patients with moderate CAD (>=50% & <70% stenotic lesions) of a major epicedial or branch vessel. Another hand, the significant CAD defined as stenosis of 50% or more of the diameter of the left main coronary artery or stenosis of 70% or more of the diameter of a major epicardial or branch vessel, as well as the total occlusion, referred to complete obstruction of entire diameter of coronary vessels [3]. The complexity of lesions was divided into three types (A, B & C) according to criteria established by a joint ACC/AHA Task Force suggested [4]. In type, A coronary lesion either: discrete lesion (<10mm length), concentric, readily accessible, non-angulated segment <45 degrees, smooth contour, little calcium, less than totally occlusive, not ostial in location or absence of thrombus. Type B coronary artery lesions; tubular (10-20 mm), eccentric, moderate tortuosity of the proximal segment, moderately angulated segment > 45 degrees < 90 degrees, irregular contour, moderate calcification, some thrombus present, ostial in location or bifurcation lesion. In the type C coronary artery lesion, the diffuse lesion (>20mm), excessive tortuosity of the proximal segment, extremely angulated segment (90 degrees), and total occlusion The extent of the coronary arteries lesions was either single-vessel disease, two-vessel disease, or three-vessel disease of major coronary artery branches (LAD artery, LCX artery, and RCA) or left main coronary artery disease [4].

Result

The total number of patients involved in this study was 365 patients admitted to the cardiac center of Al Thawra Modern General hospital, Sana'a, Yemen to undergo clinically indicated and elective coronary angiography in which, khat chewer patients group was 306 (84%) compared with 69 (16%) of non-khat chewer patients group and in comparative analysis between khat chewer patients and non-khat chewer patients; mean ages of patients were approximately equal in both groups (55+- 10 vs. 57+- 9) and there was no significant difference (P-value =0.396) (Table 1). Khat chewing was more prevalent among males than females (males: 84%. 257 & females: 16%.49) vs. (males: 24%.14 & females: 76%.45) in both groups respectively and P-values<0.001 (Table 1). Regarding history of risk factors among khat chewer and non-khat chewer patients, the smoking history were in 83% (255) vs.17% (10) of khat chewer and non-khat chewer patients respectively and P-value was<0.001 and the history of DM were in 44% (134) vs. 36% (21) of khat chewer and non-khat chewer patients respectively and these results showed slightly higher prevalence of DM among khat chewer patients but no significant statistical significances between both groups and the P-value was o.243 (Table 1). Previous clinical history of HTN were in 30% (93) vs. 39% (23) of khat chewer and non-khat chewer patients respectively and there was no significant statistical differences between both groups and the P-value was 0.194 (Table 1). The history of acute coronary syndrome (STEMI, NSTEMI or unstable angina) were more prevalent among khat chewer patients group, 54% (165) vs.24% (14), and the P-value was <0.001 in comparing both groups respectively but in other hand, the history of recurrent stable angina was more prevalent among non-khat chewer patient group, 76% (45) vs. 45% (139) and the P-value <0.001 in comparing with khat chewer patient group respectively (Table 1). Symptoms of HF were in 13% (40) vs. 15% (9) of khat chewer and non-khat chewer patients respectively and were approximately similar between both groups of patients and this result showed no significant statistical differences between both groups and the P-value was o.653 (Table 1). Impaired LV systolic function was more prevalent among khat chewer patients group and EF <50% was 39% (120) vs. 23% (14), and the P-value was P=O.O24 in both groups respectively and it

observed that, the presence of this important clinical difference between both groups, it is also associated with a statistical significant differences (P-value=0.o24) (Table 1). The results of comparative analysis of coronary angiography between khat chewer patients group and non-khat chewer patients group showed that, khat chewer patients group had more atherosclerosis in their coronary arteries (64%, 196 vs. 50%, 30) (P-value=o.o56) (Table 1), more prevalence of three vessels disease (27%, 38 vs. 22%, 13) (P-value=0.090) (Figure 1) and more frequent of type C coronary artery lesions (20%, 62 vs. 12%, 7) (P-value < 0.011) (Figure 2). Total occlusions of coronary arteries were slightly more prevalent among khat chewer patients group but without statistical significant (11%, 34 vs. 6.8%, 4) (P-value=0.042), as well as the significant coronary artery stenosis (>=50% in left main coronary artery and >=70% in other major coronary branches) were more frequent in khat chewer patients group (55%, 168 vs.47%, 28) in comparison with non-khat chewer patients group (Figure 3). In other hands, the non-Khat chewer patients group had less atherosclerotic coronary arteries, more prevalence of normal coronary arteries (46%,27 vs. 29%, 90) (Figure 3).

Table (1) comparative analysis between khat chewers and non-khat chewers patients

Variables		Khat Users (n=306)	Non Khat Users (n=59)	P-value
Age(mean s± SD)		55±10	57±9	0.396NS
Smoking(n,%)		(255)83%	(10)17%	<0.001
History of DM(n,%)		(134)44%	(21)36%	0.243NS
History of HTN(n,%)		(93)30%	(23)39%	0.194NS
Symptoms of HF(n,%)		(40)13%	(9)15%	0.653NS
(n,%)History of ACS	MI&UA	(165)54%	(14)24%	<0.001
	Stable angina	(139)45%	(45)76%	<0.001
EF(n,%)	<50%	(120)39%	(14)23%	0.024
Stable angina		(196)64%	(30)50%	0.056

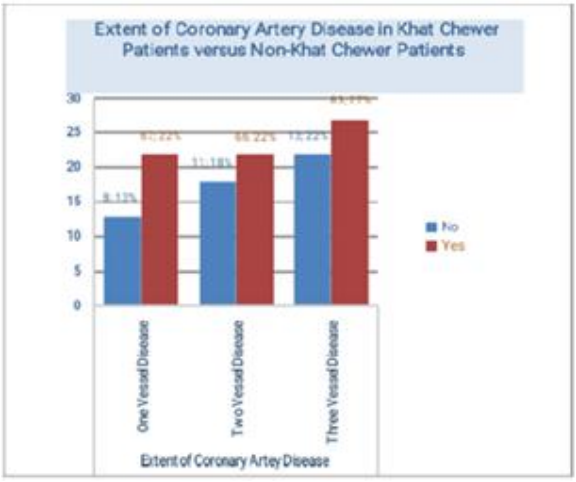

Figure 1

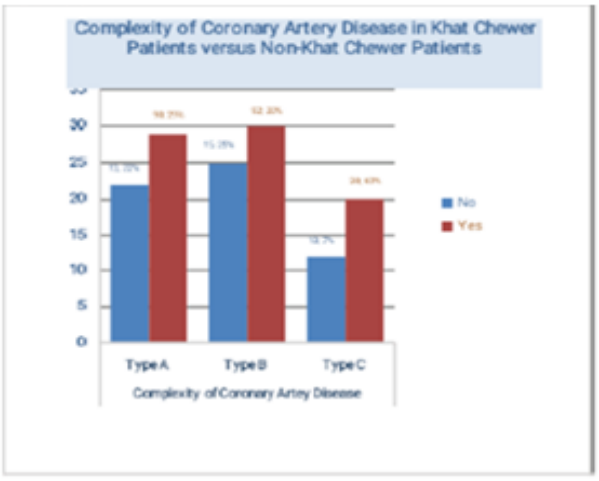

Figure 2

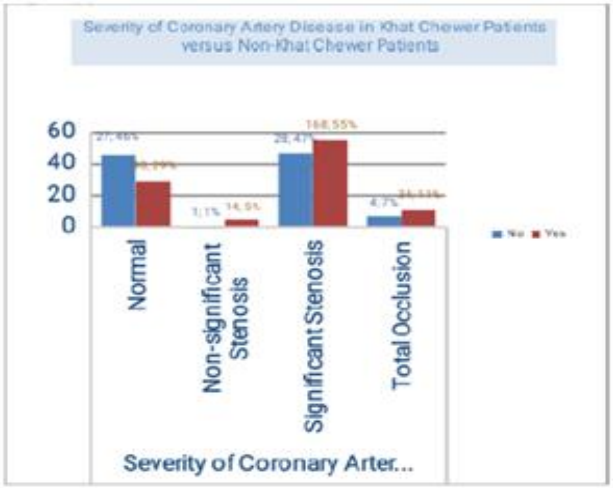

Figure 3

Discussions

In his cross-sectional prospective study, khat chewers were 84% of the study population (365 patients with ischemic heart disease (IHD) and this is because khat chewing is legal and it is socially accepted habit and widely spread throughout Yemen [13]. This percentage is nearly similar to the figures reported in many studies from the same area [17-23][28-,31]. Khat chewers were younger in age compared to non-khat chewers and chewing khat was more prevalent among males (about 70.4% (257 of 365 patients)). This data goes with what reported in many studies from Yemen[17-23][28-,31]. In the review of the prevalence of the major cardiovascular risk

factors, we found that the prevalence of diabetes mallets (DM) was slightly higher among khat chewers but there was no significant statistical difference between both groups. On the opposite side, the prevalence of hypertension(HTN) was slightly higher among the non-khat chewers, but also there was no significant statistical difference between both groups.

Even with consideration of the effect of these cardiovascular risk factors (with the exception of smoking) on coronary arteries, we found that the prevalence of coronary artery atherosclerosis and coronary artery stenosis were more prevalent among khat chewers with highly significant statistical difference than non-khat chewers, and this indicates that khat has a role in the pathogenesis of coronary artery atherosclerosis and coronary artery stenosis and the development of acute coronary syndrome (ACS) and other forms of IHD even in patients with low cardiovascular risk factors. Smoking habits were highly prevalent among khat chewers (83%) in our study. Khat chewing accompanied with smoking is a common habit among Yemeni people and this percentage in our study is nearly similar to the figures reported in many studies from Yemen [18-22],[29-31],[33]. Traditionally, smoking is one of the major risk factors for the development of acute myocardial infarction, particularly in young patients with normal coronary arteries [32]. Widespread use of khat, especially its concurrent use with tobacco, remains a public health challenge in many countries including Asia, Europe, Australia, and the United States [3]. Al-Motarreb et al reported that khat chewing increases the desire to smoke more cigarettes during the session [20]. In addition to the increased desired to smoke cigarettes during the khat session, khat also leads to passive smoking as chewers like to be in close and warm rooms [28]. al'Absi et al studied the effects of concurrent tobacco and khat use and suggested that the adverse effects of khat use may lie in its association with tobacco use [33]. Al-Motarreb et al found that cigarette smoking was an important risk factor for AMI with a linear increase of risk with doses (number of cigarettes per day) in khat chewers. Furthermore, they reported that the risk of khat chewing and smoking was significant and independent from each other (OR=7.02 and 5.8 respectively) [20]. The increased prevalence of smoking, diabetes, and hypertension plays a vital role in the development of heart failure and makes it difficult to determine the effect of khat [22,34].

Analysis of coronary angiographies of both groups showed that khat chewers patients had more prevalence of atherosclerotic coronary arteries, more lesion complexity, more severe forms of coronary artery disease, and more prevalence of the multi-vessel disease, while non-khat chewers had more prevalence of normal coronary arteries and less atherosclerotic changes. Moreover, khat chewer patients had a history of more prevalence of acute coronary syndrome whereas the history of recurrent stable angina was more prevalent among non-khat chewer patients.

These would highlight the influence of chewing khat (in addition to smoking) in promoting coronary atherosclerosis and the development of ACS and other forms of IHD, and these findings go with what was reported in many studies [21,22,30]. The pharmacological effect of khat chewing is mainly due to the cathinone, cathine, and nor-ephedrine present in the fresh leaves [4-7]. Among the detrimental effects of cathinone, premature atherosclerosis might potentially occur. It was assumed that long-standing exposure to high levels of plasma catecholamine may trigger signal transduction pathways that augment the expression of inflammatory cytokine genes in vascular walls, thereby contributing to the induction and/ or acceleration of atherosclerosis in khat users [22].

Wijetunga et al found that 5 of 6 patients with amphetamine-associated MI had obstructed coronary artery disease [35]. Similar observations as reported by Tunipsead et al [36]. Both normal and advanced coronary atherosclerosis was reported with cocaine-induced AMI [37,38]. Waleed M Ali e al reported ha 81.7% of khat chewer patients who underwent coronary angiography had evidence of significant coronary artery stenosis although they were less likely to have a history of DM, hyperlipidemia, HTN, obesity, or renal impairment and they suggested that long-term exposure to hyper catecholamine might induce or exacerbate atherosclerosis in khat chewers [22]. Similarly, Shujaa AK and Nammas W. reported that in 100 Yemeni patients with stable angina pectoris who underwent coronary angiography, khat chewers were 86% and they found an extensive coronary affection by significant stenosis (54% had more than one vessel affection), despite a relatively infrequent prevalence of the classical cardiovascular risk factors and they suggested that, this would probably highlight the influence of khat use (added to the effect of smoking) in promoting coronary atherosclerosis [29]. Al-Shami and Al-Motarreb evaluated the effect of khat chewing on the coronary arteries in patients with a history of heart failure. They found that a history of chewing khat was an independent risk factor for coronary heart disease (CHD), and they found that anatomical significant coronary artery lesions (>=50%) were more prevalent in khat chewers (74% Vs. 26%) and physiologically significant lesions (>=70%) were also more prevalent in khat chewer 55% Vs. 22%) compared with non-khat chewers. They reported that the previous observations remained significant even after restriction of the traditional risk factors for CAD-like DM, HTN, smoking, family history of CAD, and obesity [30]. Al-Motarrreb et al in their study suggested that the recent increase of AMI in Yemen is related to khat chewing behavior, in addition to the adoption of the way of life as in industrialized countries and the atherosclerotic etiology [20]. Many studies reported that both the intensity (quantity) and the duration of chewing khat could contribute to the development of MI [20,21,39]. Al-Moarreb et al in their study demonstrated that khat chewing is a potential risk factor for AMI, further highlighted by the high proportion of khat chewers with AMI under 45 years of age [19] and W.M. Ali et al and Gulf RACE-1, reported that khat chewers have significantly higher rates of death, cardiogenic shock and strokes complications compared with non-khat chewers despite the fact that they had lower cardiovascular risk profiles, including the low prevalence of diabetes and prior cardiovascular diseases [31]. Although we found that, the symptoms of heart failure (HF) were approximately similar between khat chewers and non-khat chewers (13% Vs. 15%), the incidence of impaired left ventricular (LV) systolic function was more prevalent among khat chewer patients and EF < 50% was found in 39% of khat chewers compared with 23% of non-khat chewers and this goes with what was reported in many studies [22,29,30]. There were several case reports from different parts of the world showing that khat chewing was commonly associated with severe ischemic cardiomyopathy and stroke [40,41,42]. Al-Shami and Al-Motarreb in their study found that LV contractility (LVEF%) was lower in khat chewers compared with non-khat chewers [30]. Also, Shujaa AK and Nammas W. found that LVEF progressively decreased as the extent of CAD increased in khat chewer patients [29].

Waleed M.Ali et al reported that khat chewing was found to be an independent risk factor for death and for recurrent cardiac ischemia, heart failure, and stroke. They hypothesized that long-term exposure to the catecholamine-like effects of khat increased the risk of ischemic cardiomyopathy once the patient develops ACS [22].

Conclusion

The khat chewer patients had more extent of CAD than non-khat chewer patients and the occurrence of three vessels disease were more in khat chewer patients and they also had severe forms and more lesion complexity of CAD. We concluded that, the khat chewing is one of the risk factors of coronary artery disease in Yemen.

Ethical Considerations

All patients gave verbal informed consent prior to taking part in the study after the discussion with them about the objective and importance of the research and they were assured that all the data gathered would be handled with full confidentiality and would be used solely for research purposes. No formal hospital or local ethical committee operates at Al-Thawra general hospital, Sana'a.

Declaration of Interest

The authors declare that they have no conflict of interest. The authors alone are responsible of the content and writing of the article.

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Author Contributions

Al-Zendani AS and Al-Dobhani BA conceived and designed the study, supervised the data collection and drafting the article. Then all authors contributed to data analysis, give final of version to be published, and agree to be accountable for all aspects of the work.

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