

Khat chewing and cardiovascular risk profile in a cohort of Yemeni patients with angiographically documented coronary artery disease

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ABSTRACT

Objective We sought to explore the prevalence of khat chewing and cardiovascular risk profile in a cohort of Yemeni patients with angiographically documented coronary artery disease (CAD).

Methods We enrolled 100 consecutive Yemeni patients who underwent elective coronary catheterisation. Patients were considered eligible for enrolment if they had angiographically documented significant CAD (>50% obstruction). History of khat chewing was obtained and recorded at the time of presentation. Coronary angiography was performed using the standard technique. Reference vessel diameter and the per cent diameter stenosis were measured using quantitative coronary analysis. Patients were classified according to the number of sizable coronary arteries affected by significant stenosis into three groups: single-vessel disease, two-vessel disease and multi-vessel disease groups.

Results The mean age was 54.7±11.8 years (16% females); 86% were khat users, 46% had single-vessel disease, 36% had two-vessel disease and 18% had multi-vessel disease. Fifty-four per cent were smokers, 11% were diabetic and 15% were hypertensive. The mean body mass index was 24.7±3.6, the mean serum low-density lipoprotein cholesterol was 129±41 mg/dl, whereas the mean serum triglyceride level was 187±90 mg/dl; the mean serum high-density lipoprotein cholesterol was 38±11 mg/dl. No correlation was found between the extent of CAD and any of the clinical, echocardiographic or laboratory data.

Conclusions In Yemeni patients undergoing elective coronary angiography, khat use was highly prevalent, whereas several classic risk factors were relatively infrequent. None of the risk factors or khat use differed substantially with the extent of CAD.

INTRODUCTION

Chewing the fresh leaves of *Catha edulis* (khat) is a deeply rooted habit in Yemen, and to a lesser extent in a number of countries in the Horn of Africa and the Arabian Peninsula. Nearly 20 million people are regularly using khat worldwide, according to a recent report.¹ Nevertheless, the problem of khat use does also exist in the Western world, despite its difficult cultivation and distribution, and the limitations on its illegal use. In one previous announcement, 7 metric tons of khat traverse the Heathrow airport in London every week, coming from Yemen, Kenya and Ethiopia.² In the USA, Yemeni and East African drug dealers are distributing khat, according to a statement from the National Drug Intelligence Center.³ Since it has a

short shelf-life, khat has to be distributed swiftly. In order to maintain its efficacy for a longer period, synthetic forms were developed, including hagigat, mephedrone and graba. Hagigat capsules (cathinone, 200 mg) are labelled as a natural stimulant in Israel.⁴

The main active substances in fresh khat leaves are cathinone, cathine and norephedrine.⁵ Cathinone, the chief active ingredient of khat, bears high structural and functional similarity to amphetamine.⁶ Acting as an indirect sympathomimetic, it induces catecholamine release in central dopaminergic and serotonergic synapses, as well as from peripheral noradrenaline storage nerve endings.^{7–9} Centrally, cathinone causes hyperactivity, excitability, euphoria and restlessness.⁸ Peripheral (cardiovascular) effects include an increase in heart rate and blood pressure—in human volunteers—and a positive inotropic and chronotropic effect in isolated atria.^{10–11} Moreover, khat use was claimed as an independent risk factor for acute myocardial infarction (MI).¹² Interestingly, the diurnal pattern of MI in khat users was unusual: it was shifted to the late afternoon and evening, which corresponds with the time of a khat session.¹³ In a recently published study, khat users who presented with acute coronary syndrome had worse short-term and long-term outcome versus non-users.¹⁴ In a prospective study, we sought to explore the prevalence of khat chewing and cardiovascular risk profile in a cohort of Yemeni patients with angiographically documented coronary artery disease (CAD).

PATIENTS AND METHODS

Cohort selection

The current study enrolled 100 consecutive Yemeni patients who underwent elective coronary catheterisation in the cath labs of Sanaa University during the period from November 2010 to May 2011. Patients underwent elective coronary catheterisation either for suspected CAD, or recurrent symptoms despite adequate prior anti-ischemic therapy. Patients were considered eligible for enrolment if they had angiographically documented significant CAD, defined as 50% or more luminal obstruction of at least one sizable epicardial coronary artery (measuring 2.5 mm or more in diameter), seen in two different projections, or at least 50% luminal obstruction of the left main coronary artery. History of khat chewing was obtained and recorded at the time of presentation. We excluded patients with acute coronary syndrome, those with an estimated creatinine clearance <60 ml/min, and those with contrast hypersensitivity. Before enrolment, an informed written consent was obtained from each

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patient, and the protocol was reviewed and approved by our local Institutional Human Research Committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2002.

Definition of risk factors

Diabetes mellitus was defined according to the diagnostic criteria described by the American Diabetes Association as a fasting plasma glucose ≥ 126 mg/dl, and/or a 2-h postload glucose ≥ 200 mg/dl, or specific antidiabetic drug therapy.¹⁵ Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mm Hg, previously recorded by repeated non-invasive office measurements, which leads to lifestyle modification or antihypertensive drug therapy.

Coronary angiography

Femoral artery access was adopted, and coronary angiography was performed using the standard technique. If indicated, ad hoc percutaneous coronary intervention was carried out in the same session. Reference vessel diameter and the per cent diameter stenosis were measured using quantitative coronary analysis (Inturis Allura, Phillips Medical Systems, The Netherlands). The outer diameter of a contrast-filled catheter was used for calibration. Lesions were analysed in multiple projections and stenosis severity measured from the most severe angiographic view. The reference vessel diameter was measured adjacent to the stenosis at the most healthy appearing segment. Patients were classified according to the number of sizable coronary arteries affected by significant stenosis ($\geq 50\%$ luminal obstruction) into three groups: single-vessel disease (SVD), two-vessel disease (TVD) and multi-vessel disease (MVD) groups. Significant stenosis of the left main coronary artery was assigned as TVD. MVD was defined as either significant stenosis of more than two sizable coronary arteries, or significant stenosis affecting the left main and the right coronary arteries.

Echocardiographic evaluation

Assessment of regional and global left ventricular systolic function was performed in all patients by transthoracic echocardiography. Doppler echocardiography was performed using a General Electric Vivid 3 Pro cardiac ultrasound machine (General Electric, Horten, Norway) equipped with harmonic

imaging capabilities. A 2.5 MHz phased array probe was used to obtain standard 2-D, M-mode and Doppler images. Global left ventricular systolic function was assessed in apical 2-chamber and 4-chamber views using the biplane modified Simpson's method. Left ventricular hypertrophy was assessed using the standard method. Regional wall motion was assessed according to the standard 16-segment model recommended by the American Society of Echocardiography.¹⁶

Statistical analysis

Continuous variables were presented as mean \pm SD, if they were normally distributed. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between the three individual groups were performed using the unpaired t-test for continuous, and Pearson's χ^2 test for categorical variables. Pearson correlation coefficient test was performed to study the correlation between the extent of CAD and any of the clinical, echocardiographic or laboratory parameters. All tests were two-sided and a probability value of $p < 0.05$ was considered statistically significant. Analyses were performed with SPSS V.12.0 statistical package (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Baseline characteristics

A total of 100 Yemeni patients scheduled for elective coronary angiography were enrolled in the current study. In this group of Yemeni patients, 86% were khat users, 46% had SVD, 36% had TVD and 18% had MVD. Baseline clinical characteristics and echocardiographic data are summarised in table 1. The mean age of the whole cohort was 54.7 ± 11.8 years (16% females). Left ventricular ejection fraction progressively decreased as the extent of CAD increased ($p = 0.03$), whereas female gender showed a trend to be less frequent with more extensive CAD ($p = 0.059$). Yet, the other clinical as well as echocardiographic parameters were statistically matched among the three groups ($p > 0.05$ for all).

Laboratory data

Laboratory data are summarised in table 2. The mean serum low-density lipoprotein cholesterol was 129 ± 41 mg/dl, whereas

Table 1 Baseline clinical and echocardiographic data of the whole series as well as the three study groups

	Whole series No=100	SVD No=46	TVD No=36	MVD No=18	p Value
Age (years)	54.7 ± 11.8	54.8 ± 11.9	54.5 ± 11.5	54.4 ± 10.9	0.922
Female gender	16 (16)	11 (23.9)	2 (5.6)	3 (16.7)	0.059
Smoking	54 (54)	27 (58.7)	21 (58.3)	6 (33.3)	0.149
Hypertension	15 (15)	7 (15.2)	5 (13.9)	3 (16.7)	0.54
Diabetes mellitus	11 (11)	5 (10.9)	4 (11.1)	2 (11.1)	0.88
Khat use	86 (86)	40 (86.9)	31 (86.1)	15 (83.3)	0.934
Body mass index	24.7 ± 3.6	24.8 ± 4.0	24.7 ± 3.6	24.3 ± 2.2	0.87
Heart rate (beat/min)	82 ± 13	82 ± 12	82 ± 15	80 ± 12	0.83
SBP (mm Hg)	134 ± 27	136 ± 26	133 ± 29	131 ± 28	0.81
DBP (mm Hg)	83 ± 16	84 ± 16	81 ± 16	84 ± 15	0.67
Ejection fraction (%)	53 ± 11	56 ± 10	51 ± 11	49 ± 13	0.03
LVH	44 (44)	19 (41.3)	19 (52.8)	6 (33.3)	0.349
SWMA	94 (94)	43 (93.5)	35 (97.2)	16 (94.1)	0.714

Continuous variables are presented as mean \pm SD, whereas categorical variables are presented as frequency (percentage).

DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; MVD, multi-vessel disease; SBP, systolic blood pressure; SVD, single-vessel disease; SWMA, segmental wall motion abnormality; TVD, two-vessel disease.

Table 2 Laboratory data of the whole series as well as the three study groups

	Whole series No=100	SVD No=46	TVD No=36	MVD No=18	p Value
Haemoglobin (gm/dl)	13.9±1.7	13.9±1.9	13.9±1.5	13.9±1.9	0.98
Serum creatinine (mg/dl)	1.0±0.3	1.0±0.3	1.1±0.4	1.1±0.3	0.60
Fasting plasma glucose (mg/dl)	128±46	125±48	125±40	140±52	0.44
Total cholesterol (mg/dl)	202±51	203±48	199±49	203±63	0.93
Triglycerides (mg/dl)	187±90	188±98	181±72	196±102	0.83
LDL (mg/dl)	129±41	132±43	123±41	133±35	0.54
HDL (mg/dl)	38±11	39±9	39±12	35±11	0.41

All variables are presented as mean±SD.

HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MVD, multi-vessel disease; SVD, single-vessel disease; TVD, two-vessel disease.

the mean serum triglyceride level was 187±90 mg/dl; the mean serum high-density lipoprotein cholesterol was 38±11 mg/dl. All laboratory data were statistically matched among the three groups ($p>0.05$ for all). No correlation was found between the extent of CAD and any of the clinical characteristics, echocardiographic or laboratory data.

DISCUSSION

Main findings

The current pilot cross-sectional study demonstrated that in Yemeni patients with stable angina pectoris undergoing elective coronary angiography, khat use was highly prevalent (86%), whereas the classic cardiovascular risk factors were relatively infrequent; diabetes mellitus 11% and hypertension 15%. Nearly half the patients had SVD, a little more than one third had TVD; the rest had MVD. Apart from a trend for female gender to be less prevalent in those with more extensive CAD, none of the classic cardiovascular risk factors or khat use differed substantially among the three groups categorised according to the number of sizable coronary arteries affected by significant stenosis.

Khat use as a risk factor for coronary atherosclerosis

Among the detrimental effects of cathinone, premature atherosclerosis might potentially occur. Being analogous to amphetamine, cathinone induces catecholamine release from the peripheral storage sites. In a case series of acute coronary syndrome associated with crystal methamphetamine use, five out of six patients who presented with amphetamine-induced MI had obstructive CAD.¹⁷ Quite similar findings were observed in patients who presented with acute chest pain after methamphetamine use.¹⁸ Another recent report demonstrated that over 80% of khat users who underwent coronary angiography had evidence of significant coronary stenosis.¹⁴ It was assumed that long-standing exposure to high levels of plasma catecholamines 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. Nevertheless, the current study in Yemeni patients with stable angina pectoris did not show any substantial difference in khat use among the three groups classified by the extent of CAD. It might be that cathinone acts primarily by mechanisms that enhance plaque vulnerability and susceptibility to rupture with consequent thrombotic events rather than by substantially increasing the total atherosclerotic burden.

Khat use and classic cardiovascular risk factors

The remarkably high prevalence of khat use (86%) in the current cohort of Yemeni patients can be seen in view of the

local culture in Yemen wherein the use of khat is a legal and socially acceptable behaviour, and is concurrent with the figures (79%) recently reported in literature.^{13 19} With the exception of smoking, the classic cardiovascular risk factors tended to be less frequent in our cohort. Interestingly, cigarette smoking was restricted to khat users: 62.8% versus 0% in non-users (data not shown). This can be attributed to the increased desire to smoke cigarettes during the khat session; khat chewing behaviour favours passive smoking as well, since khat users prefer closed and warm places.²⁰ Furthermore, the mean body mass index was in the normal range, whether in the whole cohort, or in the three groups classified by CAD extent. This can be viewed in the context of the anorexigenic effect of cathinone which contributes to depressed appetite and low body weight in khat users.²¹ Likewise, the mean fasting plasma glucose was rather high in our cohort (128±46 mg/dl), although the prevalence of diagnosed diabetes mellitus was low (11%). This might denote underdiagnosis of diabetes mellitus in our cohort, and warrants further investigation to determine the real-life prevalence of cardiovascular risk factors in Yemeni patients with established CAD. Although fasting plasma glucose was numerically higher in patients with MVD as compared with those with SVD and TVD, the difference did not meet statistical significance; a fact that might be due to the small sample size. In contrast, the mean serum triglycerides and low-density lipoprotein cholesterol were high, and the mean high-density lipoprotein cholesterol was low in the whole series, as well as in the three groups (table 2). The relatively low prevalence of several classic cardiovascular risk factors in the current series of patients, despite a rather extensive coronary affection by significant stenosis (54% had more than one vessel affection), would probably highlight the influence of khat use (added to the effect of smoking) in promoting coronary atherosclerosis. Similarly, khat chewing was associated with higher rates of mortality and complications in patients presenting with acute coronary syndrome, despite a lower prevalence of cardiovascular risk factors.¹⁴ Additionally, although the prevalence of hypertension and diabetes mellitus was low in the current series, left ventricular hypertrophy was diagnosed in 44% of patients (table 1). Again, this could be, at least in part, attributed to the chronic exposure to high plasma catecholamines, which might act through the activation of certain signal transduction pathways that eventually increase the expression of growth factor genes in the cardiac muscle.

Conclusion

In Yemeni patients with stable angina pectoris undergoing elective coronary angiography, khat use was highly prevalent, whereas several classic cardiovascular risk factors were relatively infrequent. None of the classic cardiovascular risk factors or

khat use differed substantially among the three groups classified according to the number of sizable coronary arteries affected by significant stenosis.

Limitations of the study

Our findings are based on a single centre study with a relatively small sample size of the cohort. Multicentre studies using the same protocol and examining a larger number of patients are needed. Moreover, the study population was based on a group of Yemeni patients with a predominance of khat use. Whether our results can be extrapolated to other ethnicities, or to groups with lower frequency of khat use, remains to be determined. Additionally, since we enrolled patients with essentially stable CAD, our observations might not be safely applicable to patients presenting with acute coronary syndrome. Finally, the effect of khat on the periprocedural complications of elective coronary angiography was not studied; however, such information was clearly out of scope of the current study.

Contributors Both authors have contributed to the basic concept and design of the study, acquisition of data, analysis and interpretation. WN has drafted the manuscript, AKS has reviewed it, and both have approved the submission of the manuscript for publication.

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