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The Effect of qat chewing on the level of total homocysteine in patients with and without coronary artery disease

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Abstract

The main objective of this study was to investigate the effects of qat chewing on the level of plasma total homocysteine concentration in patients with and with- out coronary artery disease(CAD) .Men scheduled for coronary angiography were selected. Venous samples were taken from the patients in fasting before angiography. Data about age, risk factors (e.g. hypertension diabetes, smoking, hyperlipidemia, obesity)were obtained from prepared questionnaires.Total plasma homocysteine concentration were measured by Alchitect homocysteine assay. According to the result of angiography the study groups were divided into three groups: 30 patients with coronary artery disease (CAD) and qat chewing, 30 patients without significant (CAD) and qat chewing, and 30 patients without significant (CAD) and non qat chewing. The mean ± SD of total plasma homocysleine concentration was significantly raised in patients with and with- out (CAD) chewing qat (17.2± 2.49,15.2± 1.676µmol/L) respectively to patients without (CAD) and non-chewing qat (11.2±0.96µmol/L) (P<0.001).These result, high level of homocysteine among patients chewing qat can be attributed to the qat's contents (tannin) which lower the absorption of vitamins (B6,B12 and folic acid) which are important in metabolism of homocysteine.

Key words: Coronary artery disease, homocysteine, qat

INTRODUCTION:

Homocysteine is an intermediate sulphur-containing amino acid in one-carbon metabolism, which comprises the folate cycle and methionine pathway, regulates the transfer of carbon groups and related to essential physiological process. These include formation of purines and thymidine for DNA and RNA synthesis, methylation of DNA, RNA, lipids and proteins, and regulation of oxidative stress. Homocysteine is formed in cells from the essential amino acid methionine via methyl transfer reactions, and can be removed from the cell via remethylation to methionine, irreversible trans-sulphuration to cysteine or release of excess intracellular homocysteine into plasma 40.

The intracellular concentration of homocysteine is regulated via these processes that require the action of several enzymes and cofactors. Approximately 70% of plasma homocysteine is disulphide bound to proteins. The remaining 30% is bound to cysteine or homocysteine to form homocysteine-cysteine or homocysteine – homocysteine (or homocysteine).Mixed disulfides, only a very small portion present as unbound free homocysteine.

The term total homocysteine (tHcy) refers to the sum of all homocysteine species (uelandetal). Until recently, it was believed that the normal range for homocysteine was 5-15µmol/L. It is now widely accepted that the normal range of (tHcy) may be 10 to 12 µmol/L for middle aged adult and values exceeding this range considered to be a risk factor for cardiovascular disease (Jacobsen, 1998; Christenetal, 2000).

In 1969, it was thought that there is a connection between homocysteine and cardiovascular disease, when it was observed in people with a rare hereditary condition, called homocystinuria (the deficiency of one of the three main enzymes in homocysteine metabolism, causes homocysteine to accumulate in the blood and to be

excreted in urine) that is able to develop severe cardiovascular disease in their early ages. Also, abnormal homocysteine elevation occurs among people whose diet contains inadequate amounts of folic acid, vitamin B6, or vitamin B12(Verhoef et al ,1997; Malinow et al,1999)...

Evidence also suggests that the increased homocysteine levels are a risk factor for premature coronary artery disease (CAD) and myocardial infarction (MI) in young patients. Moreover, higher levels of homocysteine are associated with the increase thrombogenicity and oxidative stress status, over the activation of redox-sensitive inflammatory pathways, impaired endothelial function and atherogenesis while mild hyper homocysteinemia is associated with decreased fibrinolytic activity (Schwartz etal, 1997; Sadeghianetal,2006).

Studies that were done in the 1980s and 1990s linked elevated blood levels of homocysteine to increased risk of premature coronary artery disease, stroke, and venous blood clots, even among people with normal cholesterol levels ((Loralie et al, 2000; Tanne et al 2003).

Qat or Catha Edullis is a natural stimulant that is grown in Ethiopia, Kenya, Somalia, Yemen and many other parts of the world. People chew qat leaves as a social custom and to attain state of stimulation ((Kalix ,1992).

Qat is believed to be much less than amphetamine, a drug with similar structure and more potency. There are three main alkaloids that are present in qat leaves; cathinone, cathine, and ephedrine (kalix, 1988 and kalix, 1992). Cathinone, is the main active ingredient in qat leaves, which causes the release of endogenous catecholamines from peripheral and central neurons. The major metabolites of Cathinone are norSpseudo ephedrine and ephedrine, these two substances have weak sympathomimetic activities and central stimulant properties. Moreover, Ephedrine, is responsible for the central nervous system effects, while nor pseudoephedrine is responsible for its peripheral effects (kalix, 1988).

Cathinone and its major metabolite (Ephedrine and norpseudoephedrine) causes dose-related vasoconstriction of blood vessels (Al-Motarreb etal, 2003).

In addition, all, cathinone, norpseudoephedrine and noradrenaline contribute to the mechanism of elevated blood pressure observed in subjects during and after the qat-chewing sessions. It also explains the clinical observations of cold extremities of chewers at the end of qat sessions 41.

Since, there are no studies on the linked between the habit of qat chewing and the levels of homocysteine in patients with and without CAD, therefore, the aim of the present study, is to assess this relation among Yemeni qatchewers patients.

Subjects and methods:

The Study population consists of

The consecutive male patients admitted to the department of angiography of different centers in Sana'a city from October, 2011 to July, 2012. According to angiography results, the patients were divided into three groups, matched in age, 40 ± 5 years old.:

Group 1 (N=30): adult male qat chewers with a significant CAD (≥50% luminal obstruction), in at least one of their major coronary arteries (i, e. the left main coronary artery or the left anterior descending coronary artery with its major diagonal branches, the right coronary artery or the circumflex coronary artery with its major marginal branch).

Group 2 (N=30): adult male qat chewers with un-significant CAD (<50% luminal obstruction).

Group 3 (N=30): adult male non-qat chewers and un-significant CAD (<50% luminal obstruction) as a control group.

The patients with diabetes, hypertension, thyroid dysfunction, hyperlipidemia, renal failure, obesity and other CAD risk factors were excluded from the study.

Informed consent was obtained from each patient according to the guidelines of our ethics committee.

Biochemical measurements

After an overnight fasting, I0 cc venous blood was drawn just before the coronary angiography, plasma was immediately separated and stored at -20oC, until measurements of total homocysteine. Homocysteine was measured with Architect homocysteine assay.

Statistical analysis

Results were presented as means and standard deviations. Data were analyzed with SPSS version 16. Plasma homocysteine was taken as a continuous variable to allow for risk analysis. Differences between groups were evaluated using student t-test.Pvalues < 0.05 were considered statistically significant.

Result:

Total plasma homocysteine were measured in all study groups. The mean ±SD of total homocysteine in qat chewers with significant CAD, qat chewers with non-significant CAD and non-qat chewers with non-significant CAD were 17.2± 2.49, 15.2 ± 1.676 and 11.2 ± 0.969 µmol/L respectively, as shown in table 1. There wasa highly significant difference in homocysteine levelsbetween the control group and the other two groups of the study, P<0.001.Also, there was a highly significant difference between the adult male qat chewers with significant CAD and adult male qat chewers with non-significant CAD,P<0.001 . The prevalence of stable angina was significantly higher in adult male non-qat chewers and with non-significant CAD 23(76.7%) than the adult male qat chewers with CAD 7(23.3%) and adult male qat chewers with non-significant CAD 14(46.7%) P<0.001. In the other hand, the prevalence of unstable angina is a highly significant in adult male qat chewers with CAD 20(66.7%) than that of adult male qat chewers with non- significant CAD and adult male non qat chewers with non-significant CAD P<0.001.

Table(1): The levels of total homocysteine and clinical characteristic ofthe study groups.

Risk factors	Qat chewers with CAD (N=30)	Qat chewers with non – significant CAD (N=30)	Non-qat chewers with non-significant CAD (N=30)	P value
tHcy (µmol/L) (mean± SD)	17.2±2.49	15.2 ±1.676	11.2±0.969	<0.001
Myocardical infraction %	4 (13.3%)	0(0)	0(0)	<0.001
Stable angina %	6 (20%)	14(46.7%)	23(76.7%)	<0.001
Unstable angina%	20(66.7%)	16(53.3%)	7(23%)	<0.001

Discussion

In spite of multiple studies, the role of hyperhomocysteinimia as a risk factor of coronary artery disease (CAD) is still disputed.Gupta etal. (2005) ;Chwasko and Jakubowski, 2005, have estimated that a 5µmol/L homocysteine increases CAD risk as much as a 20µg/dlcholesterol increases. On the other hand, a prolonged decreases of homocysteine by3-4µmol/L was associated with 30-40% reduction in risk of CAD.

Nygard etal(1995).found a strong association between elevated tHcy concentration and overall mortality in CAD patients.

Although almost all retrospective and most of prospective studies have confirmed the role of homocysteine as an independent risk factor of CAD, but some studies suggested that hyperhomocysteinimia may be secondary to preclinical vascular disease(Wlickenetal, 1997; Brattstrom, 1997).

Additionally, several studies demonstrated that hyperhomocysteinimia is a casual risk factor for CAD (Graham etal, 1997; Donner etal, 1998).

In other words, elevated of homocysteine interacts with other convention risk factors and in combination with these factors increase the risk of atherothrombotic vascular disease.

The involvement of homocysteine in vascular disease may, at least in part, be due to its metabolic conversion to tHcys, there may be modifying protein lysine residues and causing protein and

cell damage (Mercie etal,2000; Chawsko and Jakubowski,2005).

Also, homosystiene may undergo autooxidation and oxidation by other thiols, resulting reactive oxygen species, that generate oxidative stress and caused endothelial cell damage, increased platelets aggregation, oxidation of LDL and proliferation of vascular smooth muscle cells. Such process may promote atherosclerosis (Jacobsen, 2000; Jakubowskietal, 2000)

Whatever the indications from the above studies, on the level of the homocyctiene and its association with the coronary heart disease, our results showed that there are association between levels of homocycteineandqat chewing among patient with and without CAD. Though, in our result, homocyctiene level increases with the habit of qat chewing,among patients and this could be attributed to many factors:

First, the effects of tannins in qat contents whichis believed to delay intestinal absorption of vitamin B6, folate and B12 (Halbach, 1972), which homocysteine is converted to cysteine by B6-dependent cysthothionine B synthase and the remethylation of homocysteine back to methionine which is carried out by vitamin B12 dependent methionine synthase and bataine-homocysteine methyl transferase (BHMT). The folate cycle generates 5-methylylene tetrahydrofolate for remethylation of homocysteine back to methionine (Muddetal, 1995) So, low level of B6, folic acid and B12 are known to be associated with increased level of tHcys as reported by Rasmussen etal, 1996 and Haoetal, 2007.

Second, Tash et al.(2001) reported that the habit of chewing qat causesanincrease in the level of malondialdehyde and decrease of antioxidant enzyme, which may be attributed to mutation in methylene tetrahydrofolate reductase (MTHFR). This enzyme isrequired for conversion of homocysteine to methionine, polymorphism of MTHFR in individual with TT genotype leads to reduce enzyme activity and increase homocysteine concentration (Bailey and Gregory, 1999)

Conclusion:

In qat user patient with and without coronary artery disease(CAD) the level of plasma tHcyis highly significant increase if compared to patient without(CAD) and non qat chewer.

Limitation of the study:

The limitation of the present investigation include not assessed several factors that might be associated to elevated tHcy, such as folate ,vitamin B6 and B12 concentration and our findings with a relatively small size of the cohort.

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