The Relationship between Serum Levels of Vitamin C, Uric Acid and Antioxidant Condition with Coronary Artery Diseases: a Case-Control Study

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Abstract

Background Coronary hearth diseases are among the main causes of death in adults. Increase of oxidative stress and defects in antioxidant defense play a major role in endothelium performance and are an effective factor in progress of atherosclerosis. Some studies have also reported different malondialdehyde and total antioxidant capacity among the atherosclerosis patients.

Methods In this case-control study, 44 atherosclerosis patients referring to Shahid Madani treatment-education center were considered as the case group; while 44 healthy peoples were placed in the control group. Demographic data and anthropometric indices were measured. Food frequency questionnaire and international physical activity questionnaires were also completed. After 12 hours of fasting, 10 ml blood was sampled from the participants. Uric acid, vitamin C, TAC and MDA were also measured. The data were finally analyzed by SPSS Ver 22 software.

Results A significant difference was observed between the two groups in terms of uric acid ($P<0.001$) and vitamin C ($P<0.03$). However, mean MDA and TAC showed no significant difference between the two groups. The two groups' difference in terms of vitamin A, E and beta carotene, zinc and selenium intake was not significant. A significant difference was however detected between the two groups in terms of vitamin C ($P<0.047$). A significant relationship was also observed between the systolic pressure and CHD ($P<0.028$).

Conclusion Results of this study indicated that the uric acid and vitamin C levels of atherosclerosis patients had significant increase and decrease in comparison with the healthy subjects, respectively. Mean TAC and antioxidant levels of their diets (except for vitamin C) showed no significant difference. Systolic blood pressure of the patients was significantly higher than the controls.

Background

Coronary artery diseases (CAD) refer to a chronic disease which can remain symptom-less for years [1]. CAD is the first cause of death in today's societies. Moreover, this disease can head to high mortality and morbidity rates resulting in working and production disability of individuals. Furthermore, it accounts for the highest rank of health costs. Clinical spectrum of CADs includes silent ischemia (symptom-less), chronic stable angina, unstable angina, acute myocardial infarction, ischemic cardiomyopathy, sudden heart death, arrhythmias and cardiogenic shocks [2]. This disease accounts for 30% mortality cases all around the world [3]. In 2011, 375295 Americans lost their lives due to CADs. It is estimated that 635000 Americans experience new coronary attacks annually and 300000 individuals will have recurred attacks [4]. In Iran, this disease has the first rank among the death-causing

diseases with the mortality rate of 33-38% [5]. Various factors are involved in CAD development which can be divided into modifiable and non-modifiable factors. The latter includes high age, gender and family history of CAD; while the modifiable factors encompass smoking, high blood pressure (BP) and diabetes mellitus [6]. High serum level of uric acid (UA) is one of the risk factors in emergence of cardiovascular incidents. UA is an inflammation factor which can increase the cardio-related deaths in acute coronary syndrome patients by 450%. Blood UA is the final product of purine catabolism which has an antioxidant behavior and can stimulate the adhesion of granulocytes to the endothelial cells. In normal serum levels, UA acts like an antioxidant in the early stages of atherosclerosis and has been considered as one of the main factors of plasma antioxidant capacity. In abnormal levels (higher than 6 in women and higher than 6.5-7 in men) its antioxidant property will be reversed and it will serve as a pro-oxidant in late stages of atherosclerosis [2]. The relationship between serum levels of uric acid and progress of cardiovascular diseases has been reported for more than 50 years. Despite the significant correlation between the UA levels and coronary atherosclerosis suggested in previous studies and recognition of high UA as a risk factor for coronary artery damages, it is not clear whether UA is an independent cause of CAD or it depends on other cardiovascular risk factors [7]. A meta-analysis showed that hyperuricemia can increase the risk of CHD independent of other common risk factors [8]. It has been also suggested that increase of oxidative stress and antioxidant defense defects have a significant contribution in endothelium function disorders and can be classified as a contributing factor in progress of atherosclerosis [9].

Total antioxidant capacity (TAC) refers to a series of compounds which can protect the biological systems against the adverse impacts of oxygen and nitrogen reactive species. In fact, antioxidants play a crucial role in inhibition of these reactive species and preventing from their formation [10]. Epidemiologic studies have revealed that treatment with antioxidants such as vitamin C and antioxidant-containing foods can decline the inflammation markers and hence decrease the risk of CHDs [11]. Pharmacological doses of vitamin C stimulate the secretion of nitric oxide (NO) from endothelium and hence can

expand the vessels in coronary arteries. This in turn can decline the risk of cardiovascular diseases which is not definite. Numerous studies have revealed that high vitamin C levels have inverse relationship with serum UA level [12]. Regarding the pathogenic role of oxidative stress and its components in incidence of cardiovascular complications as well as the role of vitamin C and UA as the modifiable risk factors of cardiovascular diseases with high rate of prevalence, this study is aimed to measure the serum level of UA and vitamin C as well as the antioxidant status of CAD patients to evaluate their relationship and compare them with the healthy individual considered as the control group.

Methods

This case-control study was conducted on 44 coronary artery stenosis patients (27 men and 17 women with age range of 38-72 having the mean age of 58.5 8.1) who refered to angiography department of Shahid Madani hospital in Khorramabad. 44 healthy subjects (26 men and 18 women with age range of 35-70 and mean age of 56.2 8.5) were also considered as the control group. This research was approved by ethical committee of Isfahan University of Medical Sciences with the ethic code of IR.MUI.RESEARCH.REC.1397.357.

Simple sampling method was employed and all the patients had more than 50% stenosis in at least one of their major coronary arteries confirmed by a cardiologyst through use of coronary artery angiography. The control group were selected among the people with no coronary artery stenosis. Control group individuals were matched by the case group in terms of age, sex, BMI, geographical region and physical activity. Exclusion criteral included gout, Lesch-Nyhan syndrom, type II diabetes, malnutrition, pregnancy during the study, cardiomyopathy, previous myocardial infraction, unstable angina, history of congenital cardiac disorder, history of UA metablism disorder, history of oxalate renal stones, renal function disorder (GFR<30 ML/min), hepatic disorders, multiple sclorosis disease, any treatment for lowering serum UA, hypothyroidism, application of vitamin C supplement and antioxidant suppliments in last month. The interfering conditions and disorders were evaluated by examination and investigation of the medical files of the

patients and if they were positive, the paitent was excluded. The qualified individuals were entered into the study after explaining the goals of the study and attaining their written consent on participation in the study. Data collection was conducted by questionnaire, interviewing, blood sampling and investigation of the patients' files. The general information and demographic data were collected by a questionnaire as well as their oral responses. The participants' physical activity was measured by international physical activity questionnaire (IPAQ). Their antioxidant (beta carotens, vitamin C, E, selenium and zinc) intake was determined by food frequency questionnaire (FFQ). To obtain the normal food intake of the participants in the last year, the frquency of application of a specific type of food during a day, week, month or year was asked. By entering the values in an excel file, the consumption rate of each nurtient (in grams) was obtained and entered in a SPSS software. Using an excel file designed based on N4 software, the nurtitional substance of each participant was measured. The blood pressure of the particiapnts was also measured upon their enterance to the antiography department according to the method suggested by WHO. In this method, the patients were let rest for 15 min and their pressure was measured twice in a sitting position from their right hand; the mean of these two measuremtns was recorded as the blood pressure [13]. The fasting blood samples of the two groups were collected from 7:30 to 9:00 am and transferred to EDTA tubes. To prepare serum, the samples were centrifuged for 10 min at 3000 g. The obtained serum was transferred to three capped microtubes to evaluate serum levels of MDA, TAC and vitamin C. the samples were then kept at -80 until the analysis.

The uric acid tests had been previously conducted by an enzymatic method using commercial kits (Pars Azmoon, Tehran, Iran) and the data were available in the files. The measurements were conducted one day prior to angiography after 12 hours of fasting.

Vitamin C, MDA and TAC measurements were conducted using the kits of Kiazist Company (Hamedan, Iran) in the biochemistry lab of faculty of nutrition, Isfahan University of Medical Sciences.

The quantitative variables were reported as mean standard deviation (SD). To compare the data of the two groups, independent T test was employed. The data correlation was

assessed by Pearson correlation coefficient. The results were considered significant if p≤0.05. SPSS-22 software was used for data analysis.

Results

Table 1 provides a comparison between the two groups.

As this table suggests, the age range of case and control groups was 38-72 and 35-70, respectively. Their mean age (p=0.20), height (p=0.82), weight (p=0.9) and BMI (p=0.86) were not significantly different. The mean physical activity of the healthy subjects was significantly higher than the patients (p=0.027); while the mean systolic BP of the patients was higher than the healthy subjects (P=0.028). Moreover, their mean diastolic BP was not significantly different (p=0.39).

Table 1: Mean age, height, weight, BMI, physical activity and BP of the two groups

Variable	Patients group (case)		Healthy groups (control)		p
	Mean	SD	Mean	SD	
Age (year)	58.5	8.1	56.2	8.5	0.2
Height (cm)	167.3	8.6	167.7	10.2	0.82
Weight (kg)	74.9	13.5	75.3	11.1	0.9
BMI [1] (kg/m2)	26.9	5.1	26.7	3.03	0.86
Physical activity (MET.h/wk)	1017.3	181.3	1302	181.3	0.027
SBP [2] (mmHg)	12.5	1.4	11.8	1.5	0.028
DBP [3] (mmHg)	7.9	0.9	7.7	1.1	0.39

[1] Body mass index

[2] systolic blood pressure

[3] Diastolic blood pressure.

Table 2 lists the demographic data of the participants. Accordingly, the frequency distribution of the sex (p=0.83), job (p=0.83) and marital status (p=0.5) was not significantly different between the two groups. Based on Chi square test, the frequency distribution of background diseases was not significantly different between the two groups.

The residence area of the two groups was not significantly different (p=0.5). Furthermore, Mann-Whitney test showed no significant difference in the education level (p=0.26) and monthly income (p=0.64) of the two groups. The frequency of smoking and medication of the patients was significantly higher than the controls.

Table 2: Frequency of the qualitative variables of the two groups

Variable		Patients group (case)		Healthy group (control)		P
		frequency	%	frequency	%	
Sex	Men	27	61.4	26	59.1	0.83
	Women	17	38.6	18	40.9	
Marital status	Single	1	2.3	0	0	0.5
	Married	43	97.7	44	100	
Job	Clerk	9	20.5	9	20.5	0.24
	housewife	15	34.1	17	38.6	
	Worker	3	6.8	7	15.9	
	Farmer	10	22.7	4	9.1	
	Other	7	15.9	7	15.9	
Background diseases	No history	26	59.1	25	56.8	0.37
	hypertension	10	22.7	6	13.6	
	Hypertension and hyperlipidemia	5	11.4	9	20.5	
	Hyperlipidemia	2	4.5	4	9.1	
	Cardiac disorders	1	2.3	0	0	
Residence region	City	31	70.5	28	63.6	0.5
	Village	13	29.5	16	36.4	
Education level	Below diploma	33	75	29	65.9	0.26
	Diploma	9	20.4	9	20.4	
	Bachelor and higher	2	4.6	6	13.7	
Smoking		12	27.3	3	6.8	0.01
Medication		44	100	22	50	<0.001

Table 3 summarizes the nutritional intake of antioxidants in the two groups. As it can be seen, the mean vitamin C intake of the patients was significantly higher than the healthy subjects (p=0.047) the level of other micro nutrition intake was not significantly different between the two groups (p>0.05).

Table 3: Mean dietary antioxidant intake in the two groups

Nutrients	Patient group (case)		Healthy group (control)		P
	Mean	SD	Mean	SD	
Vitamin A (mg)	340.9	68.9	338.5	84.7	0.88
eta carotene (mg)	1492.9	367.1	1359.01	348.5	0.08
Vitamin C (mg)	69.1	22.5	61.4	11.7	0.047
Vitamin E (mg)	7.6	1.5	7.4	1	0.53
Zinc (mg)	7.3	1.2	7.8	1.1	0.14
Selenium (mg)	75.7	15.6	80.6	13.6	0.12

Serum levels of biochemical variables were compared with CAD in Table 4. The mean level of vitamin C was significantly higher in healthy subjects (p=0.03). Moreover, the UA of the patients was higher than the healthy controls (P<0.001). Therefore the serum level of vitamin C and UA showed a significant relationship with CAD. According to the results, although the mean TAC of the case group was higher than the controls, this difference was not significant (p=0.06). MDA was not significantly different between the two groups (p=0.25).

Table 4: mean biochemical variables of the two groups

Variable	Patients		Healthy subjects		P
	Mean	SD	Mean	SD	
Vitamin C (ug/ml)	59.8	19.1	71.8	18.6	0.03
Uric acid (mg/dl)	5.9	1.3	4.7	1.2	<0.001
TAC[1] (nmol/ml)	1155.5	190.1	1079.1	183.3	0.06
MDA[2] (nmol/ml)	0.2	0.04	0.21	0.06	0.25

[1]Total antioxidant capacity

[2] Malondialdehyde

Table 5: Pearson correlation coefficient between UA level and other variables

Variable	Uric acid	
	R	P
Vitamin C	-0.011	0.92
TAC	0.370	<0.001
MDA	-0.045	0.68
Vitamin A	-0.229	0.03
Beta carotene	0.06	0.58
Vitamin C	0.065	0.55
Vitamin E	-0.109	0.31
Zinc dietary intake	-0.311	0.003
Selenium dietary intake	-0.305	0.004

According to the Pearson correlation coefficient (r), the UA level has a direct relationship with the TAC (P<0.001) it however showed an inverse relationship with the vitamin A intake (0.03) and dietary Zinc intake (P=0.003). No other significant relationship was observed between the uric acid and other mentioned variables in Table 5 (p>0.05).

Discussion

This study evaluated the serum levels of vitamin C, UA and antioxidant condition in 44 angiographically-confirmed coronary artery stenosis patients and compared them with 44 controls. The findings revelaed that UA and vitamin C were significantly correlated to CAD while TAC and MDA showed no significant relationship with CAD.

Uric acid and CAD

Uric acid is the product of purine catabolism which can disturb the endothelial function of arteries and increase atherosclerosis by production of nitric oxide, proliferation of flat vascular muscles and increase of insulin resistance [14].

This study indicated that the mean uric acid level of the patients was higher than the healthy individuals ($p<0.001$) which is in line with the findings of Bagheri et al. [15]. According to Pearson correlation coefficient, the uric acid level had a direct relationship with the TAC ($P<0.001$). It however exhibited an inverse relationship with vitamin A ($P=0.03$) and zinc ($P=0.004$).

Although Framingham analysis and Aric study [16, 17] showed no relationship between the uric acid and CAD, numerous studies have reported a possible relationship between uric acid and emergence and severity of CAD [18-22].

Previous studies have reported the increased levels of uric acid in CAD patients.

Kim et al. investigated the relative risk of CAD with increase of blood UA in a meta-analysis on 26 cohort studies on about 400000 adults [23].

Ekici et al. (2015) showed that the serum level of UA is independently related to the severity and complexity of CAD [24].

In Iran, Goodarzinezhad et al. (2010) conducted an observational study in Tehran and showed the independent relationship of hyperuricemia with CAD only in men [25]. In some other studies, a significant relationship was observed in blood uric acid level and CAD just among women [26-28].

Despite these evidences and the complex relationship between uric acid and other known risk factors of CAD such as metabolic syndrome, obesity, diabetes and chronic renal disorders [29,30], it is not clear yet whether the elevated levels of uric acid is an independent risk factor or just a consequence or an index of CAD.

Vitamin C and CAD

Results of this study indicated that the mean serum level of vitamin C was significantly higher in healthy individuals compared to the patients. The vitamin intake of the patients was however higher than the healthy subjects while no significant difference was observed between the two groups in terms of vitamin E and A, beta-carotene, Zn and Se.

Better nutritional condition of the patients in this study could be due to higher dietary intake. As these people were aware of their disease, they might attempt to improve their condition by changing their diets.

Serdar et al. [31] and Delport et al. [32] showed the declined levels of plasma antioxidant (including vitamin A, C and E) in coronary artery stenosis patients.

Nojiri et al. studied the oxidative stress in coronary artery stenosis patients by evaluating the level of vitamin A, C and E as well as TAC in a case-control study. Their results indicated a decline in TAC and an increasein vitamin E [33].

Epidemiologic studies have revealed that treatment with antioxidants such as vitamin C and antioxidant-containing foods are related to decrease of inflammation markers and reduced risk of coronary hearth incidents [34, 35].

TAC and CAD

Increase of oxidative stress and defects in the antioxidant defense system plays a major role in endothelium function disorders and have been considered as the contributing factors in ateroscolisis progress [36].

Investigations on the relationship between the antioxidants and CAD are conflicting. In the present study, although the mean of TAC was higher in the patients group. This difference

was not significant; hence it can't be claimed that TAC is related to CAD. In a cross sectional study on 968 adults, no significant difference was observed in TAC and antioxidant enzymes activity of CAD group; uric acid and MDA were however increased in the CAD group [37].

In the work of Bagheri et al., CAD patients had higher UA and TAOC compared to the control group; their HDL chlestrol was however decreased. TAOC and its main factor (UA) were significantly associated with the prevalence and severity of CAD [15].

In a study by Gawron-Skarbek et al. [38], it was revealed that the CHD patients have higher levels of both TAC-FRAS and TAC-DPPH. In conterary, Khaki Khatibi et al. [39] showed that the TAC of the CAD patients is significantly lower than the healthy controls. One of the reasons for lack of significant relationship or increase of TAC in CAD patients could be due to the difference in the TAC measurment methods such as FRAP which is one of the causes of increase in UA level. Increase of UA level in CAD patients was reported in the previous studies.

MDA and CAD

MDA is the by-product of fatty acids oxidation with more than two double bonds. Enhanced lipid peroxidation and LDL oxidation are involved in CAD pathogenesis [40].

MDA was also measured. This study showed no significant difference in the plasma levels of MDA (as an index of lipid peroxidation) of the two groups. This is in line with the findings of Bagheri et al. [15]. Serdar et al. also reported enhanced levels of MDA in plasma and red blood cells in coronary artery stenosis patients [31].

Khaki Khatibi et al. [39] and Uppal et al. [41] also revealed the significant increase in MDA of the patients in comparison with the controls.

Lee et al. also indicated that MDA level of CAD patients was higher than the controls

Moreover, another study also reported an inceased level of plasma MDA among these patients [33,34].

The previous studies generally indicated a direct relationship between CAD and MDA.

Conclusions

Overall, the current study showed a significant relationship between the serum levels of UA and vitamin C with CAD. According to the findings, CAD patients possess higher UA and lower vitamin C levels in comparison with the healthy subjects. Concerning the association between CAD and TAC, although the TAC of the CAD patients was higher than the controls, this difference was not statistically significant. Results of this study showed that plasma MDA level, as an index of lipid peroxidation, exhibited no significant difference between the two groups.

Mean vitamin C intake of the patients was significantly higher than the healthy subjects. The mean of vitamin E and A, betacarotene, Se and Zn intake showed no significant difference between the two groups.

The other result was the direct association of UA and TAC. TAC relationship with vitamin A, Zn and Se was however inverse. There was no significant relationship between UA and vitamin C and MDA and vitamin C, E and betacarotene intake. Findings of this study were also indicative of a relationship between the physical activity and increase of systolic BP as well as no relationship between the education level, job, age, height, weight and BMI with CAD.

Abbreviations

CHD: Coronary hearth diseases, CAD: Coronary artery diseases, MDA: malondialdehyde,

TAC :total antioxidant capacity ,FFQ : Food frequency questionnaire, IPAQ : international physical activity questionnaires, UA : Uric acid, BMI : body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Isfahan University of Medical Sciences approved the protocol of this study.(Ethics ID: IR.MUI.RESEARCH.REC.1397.357)

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

The authors’ contributions are as follows: AMA conceived and developed the idea for the paper and revised the manuscript; AT contributed to data collection, Measurement of biochemical tests and interpretation of the data and wrote numerous drafts; AH, contributed to data analysis, MN Cardiac Advisor.

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