

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

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Abstract

Background: Coronary Heart Disease (CHD) is 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. The aim of this study is to measure the serum level of UA and vitamin C as well as the antioxidant status of CHD patients to evaluate their relationship and compare them with the healthy individual.

Materials and methods: The present case-control study was performed on 44 cases and 44 controls. Demographic data and anthropometric indices were measured. Food frequency questionnaire (FFQ) and international physical activity questionnaire were also completed. After 12 hours of fasting, 10 ml blood was sampled from the participants. Uric acid (UA), 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 intake ($P < 0.047$). A significant relationship was also observed between the systolic blood pressure and CHD ($P < 0.028$).

Conclusion: Our results suggest that increasing of serum uric acid and a decrease in serum vitamin C level can be considered as risk factors for CHD patients. Due to the lack of significant correlation between TAC and CHD in this study, it seems that different results will be obtained with increasing sample size.

Background

Coronary Artery Disease (CAD) refers 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 lead 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, cardiac arrhythmia and cardiogenic shocks [2]. This disease accounts for 30% mortality cases all over the world [3]. In Iran, this disease has the first rank among the death-causing diseases with the mortality rate of 33-38% [4]. Various factors are involved in CAD development which can be divided into modifiable and non-modifiable factors. The non-modifiable factors include high age, gender and family history of CAD; while the modifiable factors encompass smoking, high blood pressure (HBP) and diabetes mellitus [5]. 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 4.5 times [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 [6]. A meta-analysis showed that hyperuricemia can increase the risk of CHD independent of other common risk factors [7]. Total antioxidant capacity 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 [8]. 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 [9]. 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 [10]. Regarding the pathogenic role of oxidative stress and its components in incidence of cardiovascular complications, as well as talking about the role of vitamin C and UA, on the other hand 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 in the angiography Department of Shahid Madani Hospital in Khorramabad, Iran. The case and control group underwent coronary angiography and based on the results of angiography, 44 patients with coronary artery disease (27 men and 17 women with age range of 38-72 having the mean age of 58.5 \pm 8.1) were selected as case group and 44 healthy individuals (26 men and 18 women with age range of 35-70 and mean age of 56.2 \pm 8.5) were selected as 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 cardiologist using coronary artery angiography. Based on the number of involved vessels, 16 patients had single-vessel disease and 28 patients had multi-vessel disease. 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 criteria included gout, Lesch-Nyhan syndrom, type II diabetes, malnutrition, pregnancy during the study, cardiomyopathy, previous myocardial infarction, unstable angina, history of congenital cardiac disorder, history of UA metabolism disorder, history of oxalate renal stones, renal function disorder (GFR<30 ML/min), liver diseases, multiple sclerosis disease, any treatment for lowering serum UA, hypothyroidism, consumption of vitamin C supplement and antioxidant supplements in last month. The confusing conditions and diseases were evaluated by examination and investigation of the medical files of the patients and if they were positive, the patient was excluded. The qualified individuals were entered into the study after explaining the goals of the study and written informed consent was signed by every patient or her/his legally authorized

representative prior to study participation. Data collection was conducted by questionnaires, 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 carotene, 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 frequency of consumption 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 nutrient (in grams) was obtained and entered in a SPSS software. Using an excel file designed based on N4 software, the nutrient amounts of each participant was measured. The blood pressure of the participants was also measured initially their entrance to the angiography 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 measurements was recorded as the blood pressure [11]. 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's correlation coefficient. The results were considered significant if $p \leq 0.05$. SPSS-22 software was used for data analysis.

Results

As table 1 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 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 ($p=0.37$). The frequency distribution of residence region 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 ($p=0.01$) and medication ($p<0.001$) of the patients was significantly higher than the controls.

Table 3 summarizes the dietary antioxidant intake 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 micronutrients intake was not significantly different between the two groups ($p>0.05$).

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 mean level of UA the patients was higher than the healthy controls ($P<0.001$). Therefore the serum levels 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 ($p=0.25$).

According to the Pearson correlation coefficient (r), the UA level has a direct relationship with the TAC; it however showed an inverse relationship with the vitamin A, Zinc and Selenium dietary intake. 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 status in 44 angiographically-confirmed CHD patients and compared them with 44 controls. The findings revealed 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 [12]. 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. [13]. 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 ($P=0.03$), Zinc ($P=0.003$) and Selenium ($P=0.004$).

Although Framingham analysis and Aric study [14, 15] showed no relationship between the uric acid and CAD, numerous studies have reported a possible relationship between uric acid and incidence and severity of CAD [16-20]. 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 [21]. Ekici et al. showed that the serum level of UA is independently related to the severity and complexity of CAD [22]. In Iran, Goodarzinejad et al. conducted an observational study in Tehran and showed the independent relationship of hyperuricemia with CAD only

in men [23]. In some other studies, a significant relationship was observed in blood uric acid level and CAD just among women [24-26].

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 disease [27,28], it is not clear yet whether the elevated levels of uric acid is an independent risk factor or just a consequence or only 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 C 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. [29] and Delport et al. [30] showed the declined levels of plasma antioxidant (including vitamin A, C and E) in CHD patients. Nojiri et al. studied the oxidative stress in CHD 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 increase in vitamin E [31]. 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 heart incidents [32, 33].

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 atherosclerosis progress [34]. 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 [35]. In the work of Bagheri et al., CAD patients had higher UA and TAC compared to the control group; their HDL cholesterol was however decreased. TAC and its main factor (UA) were significantly associated with the prevalence and severity of CAD [13]. In a study by Gawron-Skarbek et al. [36], it was revealed that the CHD patients have higher levels of both TAC-FRAS and TAC-DPPH. In contrary, Khaki Khatibi et al. [37] showed that the TAC of the CHD 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 increased UA level, is one of the causes of increase this variable. 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 [38]. 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. [13]. Serdar et al. also reported enhanced levels of MDA in plasma and red blood cells in CHD patients [29]. Khaki Khatibi et al. [37] and Uppal et al. [39] also revealed the significant increase in MDA of the patients in comparison with the controls. Lee et al. [40] also indicated that MDA level of CAD patients was higher than the controls. Moreover, another studies also reported an increased level of plasma MDA among these patients [31,41]. The previous studies generally indicated a direct relationship between CAD and MDA.

Study limitations

Several limitations of our study have also to be addressed. The first limitation is the small sample size. Second, although most potential confounders were carefully controlled, since some of the study subjects may had several chronic disease, we could not eliminate the possible effect of underlying diseases and medications used for these diseases on the present findings.

More perspective studies with large sample sizes and using other markers of oxidative stress are essential to confirm these findings.

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 results was the direct association of UA and TAC. But relationship with vitamin A, Zn and Se intake 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.

Declarations

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Authors' contributions

The authors' contributions are as follows: All authors have participated in the work and have reviewed and agree with the content of the article. All authors have read and approved the manuscript. AMA conceived and developed the idea for the paper, helped to draft and revised the manuscript and approved the final manuscript. AT contributed to data collection, measurement of biochemical tests and interpretation of the data and wrote numerous drafts; revised the manuscript, and approved the final manuscript. AH contributed to data analysis, MN Cardiac Advisor.

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Availability of data and materials

The datasets used and/or analyzed during the current study are only available to the corresponding author upon reasonable request.

Ethics approval and consent to participate

written informed consent was signed by every patient or her/his legally authorized representative prior to study participation. 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

Competing interests

The authors declare that they have no competing interests.

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Abbreviations

CHD: Coronary Heart 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

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Tables

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	8.4	167.7	10.2	0.82
Weight (kg)	74.9	13.5	75.3	11.1	0.9
BMI (kg/m ²)	26.9	5.1	26.7	3.03	0.86
Physical activity (MET.h/wk)	1017.3	181.3	1302	181.3	0.027
systolic BP (mmHg)	12.5	1.4	11.8	1.5	0.028
Diastolic BP (mmHg)	7.9	0.9	7.7	1.1	0.39

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: Mean dietary antioxidant intake in the two groups

Nutrients	Patient group (case)		Healthy group (control)		P
	Mean	SD	Mean	SD	
Vitamin A (µg)	340.9	68.9	338.5	84.7	0.88
Beta carotene (µg)	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 (µg)	75.7	15.6	80.6	13.6	0.12

Table 4: The comparison of the Mean \pm SD of biochemical markers in the case and control groups

Variable	Patient group (case)		Healthy group (control)		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
Total antioxidant capacity (nmol/ml)	1155.5	190.1	1079.1	183.3	0.06
Malondialdehyde (nmol/ml)	0.2	0.04	0.21	0.06	0.25

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

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