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Original Article

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

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ABSTRACT

Coronary artery disease (CAD) 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 affecting factors in the progress of atherosclerosis. The aim of this study was to measure serum levels of uric acid (UA) and vitamin C as well as the antioxidant status in patients with CAD, and compared them with those in healthy individuals. The present case-control study was performed on 44 cases and 44 controls. Demographic data and anthropometric indices were measured. The Food Frequency Questionnaire (FFQ) and International Physical Activity Questionnaire (IPAQ) were completed. After 12 hours of fasting,10 mL blood was sampled from the participants. Serum levels of UA, vitamin C, Total Antioxidant Capacity (TAC) and Malondialdehyde (MDA) were also measured. The data were finally analyzed by SPSS v22. A significant difference was observed between the groups in terms of UA and vitamin C. However, mean levels of MDA and TAC were not significantly different between groups. The differences between groups in terms of vitamin A, vitamin E, beta-carotene, zinc and selenium intakes were not significant either. A significant difference was detected between the groups in terms of vitamin C intake. Our results suggest that increase in UA and decrease in vitamin C in serum levels can be considered as risk factors for CAD patients. Due to a lack of any significant correlation between TAC and CAD risk in this study, further study with bigger sample size is needed.

Keywords: Ascorbic acid; Uric acid; Atherosclerosis; Coronary artery disease

INTRODUCTION

Coronary artery disease (CAD) refers to a chronic disease which can remain without any symptoms for years [1]. CAD is the first cause of death in Contemporary Iranian Society in 2012 [2]. Moreover, this disease can lead to high mortality rates, or may result in debilitating the individual and it is the first cause of a person's health expenses [2]. The clinical spectrum of CAD includes silent ischemia (symptomless), chronic stable angina, unstable angina,

acute myocardial infarction, ischemic cardiomyopathy, sudden death, cardiac arrhythmia and cardiogenic shocks [2]. This disease accounts for 30% of the mortality cases all over the world [3]. In Iran, it ranks first among the lethal diseases with a mortality rate of 33%–38% [4]. Various factors are involved in CAD development; these can be divided into modifiable and non-modifiable factors. The non-modifiable factors include old age and a family history of CAD; the modifiable factors encompass smoking, high blood pressure (HBP) and diabetes mellitus [5]. A high serum uric acid (UA) level is one of the risk factors in the emergence of cardiovascular incidents. UA is an inflammation factor which can increase cardio-related deaths in acute coronary syndrome patients by 4.5 times. Blood UA is a final product of purine catabolism that has antioxidant properties and also stimulates the adhesion of granulocytes to endothelial cells at normal serum levels, UA acts similarly to antioxidants in the early stages of atherosclerosis and is a potent factor in plasma antioxidant capacity. However, at abnormal and above normal levels (above 6 in women and above 6.5–7 in men), its antioxidant properties are reversed and it acts as a pro-oxidant in the late stages of atherosclerosis. [2]. The relationship between serum levels of UA and the progress of cardiovascular diseases (CVDs) has been reported for more than 50 years. Despite the significant correlation between UA levels and coronary atherosclerosis suggested in previous studies and the recognition of high UA as a risk factor in coronary artery damage, it is not clear whether UA is an independent cause of CAD or depends on other cardiovascular risk factors [6]. A meta-analysis has showed that hyperuricemia can increase the risk of coronary heart disease (CHD) independent of other common risk factors [7].

It has also been suggested that increased oxidative stress and antioxidant defense impairment play a significant role in endothelial dysfunction and play a role in the development of atherosclerosis. Total antioxidant capacity refers to a series of compounds which can protect biological systems against the adverse impacts of reactive kinds of oxygen and nitrogen. In fact, antioxidants play a crucial role in the inhibition of both synthesis and activity of reactive oxygen species/reactive nitrogen species in the body [8]. Epidemiologic studies have revealed that treatment with antioxidants such as vitamin C and antioxidant containing foods can decrease the inflammation and hence, reduce the risk of CHD [9]. Pharmacological doses of vitamin C stimulate the secretion of nitric oxide (NO) from the endothelium and can therefore, expand the coronary arteries. This, in turn, may possibly lessen the risk of CVDs.

Numerous studies have revealed that high vitamin C levels have an inverse relationship with UA serum levels. Pharmacological doses of vitamin C in the body by stimulating the secretion of NO from the endothelium cause vasodilation, especially in the coronary arteries, and consequently reduces the risk of CVD, which is not certain [10]. Considering the pathogenic role of oxidative stress and its components in the incidence of cardiovascular complications, and the role of vitamin C and UA on the one hand, and the high rate of prevalence in the modifiable risk factors of CVDs on the other, this study is aimed at measuring serum levels of UA and vitamin C as well as determining the antioxidant status of CAD patients to evaluate possible correlations and to compare these patients with healthy individuals.

MATERIALS AND METHODS

This case-control study was conducted in the angiography Department of Shahid Madani Hospital in Khorramabad, Iran. The case and control groups underwent coronary angiography and based on its results, 44 patients with CAD (27 men and 17 women between

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38-72 years of age with a mean age of 58.5 ± 8.1 years) were selected as the case group and 44 healthy individuals (26 men and 18 women between 35–70 years of age with a mean age of 56.2 ± 8.5 years) that are hospital based controls, were selected as the control group. The research was approved by the Ethical Committee of Isfahan University of Medical Sciences (Ethics code: IR.MUI.RESEARCH.REC.1397.357). The simple sampling method was employed; all the patients had more than 50% stenosis in at least one of their major coronary arteries confirmed by a cardiologist based on coronary artery angiography. Based on the number of the involved vessels, 16 patients had a single-vessel, and 28 patients a multi-vessel condition. The control group constituted individuals with no coronary artery stenosis. The control group was matched with the case group in terms of age, sex, body mass index (BMI), geographical region and physical activity. Exclusion criteria included gout, Lesch-Nyhan syndrom, type II diabetes, malnutrition, pregnancy, cardiomyopathy, previous myocardial infarction, unstable angina, history of congenital cardiac disorder, history of UA metablism disorder, history of oxalate renal stones, renal function disorder (glomerular filtration rate < 30 mL/min), liver diseases, multiple sclerosis, any treatment for lowering serum UA levels, hypothyroidism, and consumption of vitamin C and antioxidant supplements in the month prior to the start of the study. Conditions and diseases which could have undermined the study were evaluated by examining the medical files of the patients and if they turned out to be hindrances, the patient was excluded. The qualified individuals entered the study after being informed of the study goals; a written informed consent was signed by every patient or her/his legally authorized representative prior to participation in the study. Data collection was conducted by questionnaires, interviews, blood sampling and investigation of patient medical files. General information and demographic data were collected by a questionnaire as well as interviews. The participants' physical activity was measured using the International Physical Activity Questionnaire (IPAQ). Their antioxidants (beta-carotene, vitamin C, E, selenium and zinc) intake was determined using the Food Frequency Questionnaire (FFQ). Using an excel file designed with N4 software, the nutrient amounts related to each participant were measured.To obtain the normal dietary pattern of the participants during the previous year, the consumption frequency of specific types of food during each day, week, month or throughout the entire year was asked. Then, by entering these numbers in the Excel file, the gram of consumption of each food item was obtained and these values were entered into SPSS software version 22 (IBM Corp., Chicago, IL, USA). Using an excel file designed with N4 software, the nutrients amounts related to each participant were measured. The blood pressure of the particiapnts was also measured prior to their enterance to the angiography department in accordance with the method suggested by World Health Organization. In this method, the patients are allowed to rest for 15 minutes subsequent to which their blood pressure is measured twice in sitting position from the right hand; the mean of the 2 measuremens is recorded as the patient's blood pressure [11]. The fasting blood samples of the two groups were collected from 7:30 to 9:00 AM and transferred to ethylenediaminetetraacetic acid tubes. To prepare the serum, the samples were centrifuged for 10 minutes at 3000 g. The obtained serum was transferred to three capped microtubes to evaluate malondialdehyde (MDA), total antioxidant capacity (TAC) and vitamin C serum levels. The samples were then kept at −80°C until the analysis. UA tests had been conducted by an enzymatic method using commercial kits (Pars Azmoon, Tehran, Iran) and the data were available in the medical records. The measurements were conducted one day prior to angiography after 12 hours of fasting. Vitamin C, MDA and TAC measurements were conducted using commercial kits (Kiazist, Hamadan, Iran) in the biochemistry lab of the Faculty of Nutrition, Isfahan University of Medical Sciences.

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The quantitative variables were reported as mean ± standard deviation (SD). To compare the data of the 2 groups, the 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 v22 software was used for data analysis.

RESULTS

As **Table 1** suggests, the age range of the case and control groups was 38–72 and 35–70 years, respectively. The mean age ($p = 0.20$), height ($p = 0.82$), weight ($p = 0.9$) and BMI ($p = 0.86$) were not significantly different between the two groups. The mean physical activity level of the controls was significantly higher than that of the patients ($p = 0.027$). The mean systolic BP of the patients was higher than that of the controls ($p = 0.028$). On the other hand, the mean diastolic BP was not significantly different between the groups ($p = 0.39$).

Table 2 lists the demographic data of the participants. Accordingly, the frequency distribution of sex ($p = 0.83$), occupation ($p = 0.24$), and marital status ($p = 0.50$) was not significantly different between the two groups. Based on the χ^2 test, the frequency distribution of underlying diseases and residence region was not significantly different between the groups ($p = 0.37$ and $p = 0.50$, respectively). Furthermore, the Mann-Whitney test showed no significant difference in education level ($p = 0.26$) and monthly income ($p = 0.64$) between groups. The frequency of smoking ($p = 0.01$) and medication ($p < 0.001$) in the patients was significantly higher as compared to the controls.

Table 3 summarizes the dietary antioxidant intake in groups. The mean value of vitamin C intake in the patients was significantly higher than that in the healthy subjects ($p = 0.047$). The intake levels of other micronutrients were not significantly different between groups ($p > 0.05$).

The serum levels of the biochemical variables of both groups are presented in **Table 4**. Serum level of vitamin C in the case group was 59.8 ± 19.1 μg/mL and that in the control group was 71.8 ± 18.6 μg/mL, respectively. The mean level of vitamin C is significantly higher in the controls ($p = 0.03$) than in the patient group. Moreover, The mean serum level of UA in the case group was 5.9 ± 1.3 mg/dL and in the control group was 4.7 ± 1.2 mg/dL. The mean of UA levels in the patients was higher in comparison with the controls ($p < 0.001$). Therefore, serum levels of vitamin C and UA showed a significant relationship with CAD risk. According to the results, although the TAC mean in the case group was higher than that of the controls, this difference is not significant ($p = 0.06$). MDA was not significantly different between the two groups ($p = 0.25$). According to the Pearson correlation coefficient (r), UA level has

Table 1. Mean age, height, weight, BMI, physical activity and BP in the two groups

Variable	Patients group (case)	Healthy groups (control)	p*
Age (yr)	58.5 ± 8.1	56.2 ± 8.5	0.200
Height (cm)	167.3 ± 8.4	167.7 ± 10.2	0.820
Weight (kg)	74.9 ± 13.5	75.3 ± 11.1	0.900
BMI (kg/m^2)	26.9 ± 5.1	26.7 ± 3.03	0.860
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	0.390

The results are presented as the means ± standard deviation.
BMI, body mass index; MET, metabolic equivalent of task; BP, blood pressure.
Independent t-test was performed among the groups; *$p < 0.05$ was considered to be statistically significant.

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

Variable	Patients group (case)	Healthy group (control)	p
Sex			0.83*
Men	27 (61.4)	26 (59.1)	
Women	17 (38.6)	18 (40.9)	
Marital status			0.50*
Single	1 (2.3)	0 (0)	
Married	43 (97.7)	44 (100.0)	
Job			0.24*
Clerk	9 (20.5)	9 (20.5)	
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)	
Underlying diseases			0.37*
No history	26 (59.1)	25 (56.8)	
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			0.50*
City	31 (70.5)	28 (63.6)	
Village	13 (29.5)	16 (36.4)	
Education level			0.26†
Below diploma	33 (75.0)	29 (65.9)	
Diploma	9 (20.4)	9 (20.4)	
Bachelor and higher	2 (4.6)	6 (13.7)	
Monthly income			0.64†
1–2 million Tomans	21 (47.7)	23 (52.3)	
2–3 million Tomans	18 (40.9)	17 (38.6)	
More than 3 million tomans	5 (11.4)	4 (9.1)	
Smoking	12 (27.3)	3 (6.8)	0.01‡
Medication	44 (100.0)	22 (50.0)	< 0.001‡

Values are expressed as frequency (%).
*The χ^2 test, †Mann-Whitney test, ‡Fisher's exact test.

Table 3. Mean dietary antioxidant intake in the two groups

Nutrients	Patient group (case)	Healthy group (control)	p*
Vitamin A (μg)	340.9 ± 68.9	338.5 ± 84.7	0.880
Beta carotene (μg)	1,492.9 ± 367.1	1,359.01 ± 348.5	0.080
Vitamin C (mg)	69.1 ± 22.5	61.4 ± 11.7	0.047
Vitamin E (mg)	7.6 ± 1.5	7.4 ± 1.0	0.530
Zinc (mg)	7.3 ± 1.2	7.8 ± 1.1	0.140
Selenium (μg)	75.7 ± 15.6	80.6 ± 13.6	0.120

The results are presented as the means ± standard deviation.
Independent t-test was performed among the groups; *p < 0.05 was considered to be statistically significant.

Table 4. Comparison of the biochemical markers in the two groups

Variable	Patient group (case)	Healthy group (control)	p
Vitamin C (mg/mL)	59.8 ± 19.1	71.8 ± 18.6	0.030
UA (mg/dL)	5.9 ± 1.3	4.7 ± 1.2	< 0.001
TAC (nmol/mL)	1,155.5 ± 190.1	1,079.1 ± 183.3	0.060
MDA (nmol/mL)	0.2 ± 0.04	0.21 ± 0.06	0.250

The results are presented as the means ± standard deviation. Analysis of covariance was performed by adjusting the food intake and variables of smoking and drug consumption in both groups.
UA, uric acid; TAC, total antioxidant capacity; MDA, malondialdehyde.
*p < 0.05 was considered to be statistically significant.

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

Variable	Uric acid	
	r	p
Serum vitamin C	−0.011	0.920
Serum TAC	0.370	< 0.001
Serum MDA	−0.045	0.680
Vitamin A intake	−0.229	0.030
Beta carotene intake	0.060	0.580
Vitamin C intake	0.065	0.550
Vitamin E intake	−0.109	0.310
Zinc intake	−0.311	0.003
Selenium intake	−0.305	0.004

Pearson correlation coefficient was used to determine the relationship between UA and other variables. $p < 0.05$ was considered to be statistically significant.
UA, uric acid; TAC, total antioxidant capacity; MDA, malondialdehyde.

a direct relationship with TAC; however, it showed an inverse relationship with the dietary intakes of vitamin A, zinc and selenium. No other significant relationship was observed between UA levels and the levels of other mentioned variables in **Table 5** ($p > 0.05$).

DISCUSSION

This study evaluated serum levels of vitamin C and UA, and antioxidant status in 44 angiographically confirmed CAD patients and compared them with the data obtained from 44 controls. The findings revealed that serum levels of UA and vitamin C were significantly correlated with CAD related risk while serum levels of TAC and MDA showed no significant relationship with this condition.

UA is the product of purine catabolism which can disturb the endothelial function of the arteries and increase atherosclerosis by production of NO, can cause proliferation of flat vascular muscles and increase in insulin resistance [12]. This study indicates that the mean UA level in the patients was higher than that in the healthy subjects ($p < 0.001$), which is in line with the findings of Bagheri et al. [13]. According to the Pearson correlation coefficient, UA level had a direct relationship with TAC ($p < 0.001$). However, it exhibited an inverse relationship with dietary intakes of vitamin A ($p = 0.03$), zinc ($p = 0.003$) and selenium ($p = 0.004$).

Although the Framingham analysis and the Aric study [14,15] showed no relationship between UA and CAD, numerous studies have reported a possible relationship between UA and the incidence and severity of CAD [16-20]. Previous studies have reported increased levels of UA in CAD patients. Kim et al. investigated the relative risk of CAD with increase of blood UA in a meta-analysis of 26 cohort studies on approximately 400,000 adults [7]. Ekici et al. [21] showed that UA serum level was independently related to the severity and complexity of CAD. Goodarzynejad et al. [22] showed the independent relationship of hyperuricemia with CAD only in men through their observational study performed in Tehran, Iran. Some other studies reported a significant relationship was observed in blood UA level and CAD risk only in women [18,23,24].

Despite these evidences and the complex relationship between UA and other known risk factors of CAD such as metabolic syndrome, obesity, diabetes and chronic renal disease [25,26], it is not yet clear whether elevated levels of UA is an independent risk factor or merely a consequence or an index of CAD.

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The results of this study indicated that the mean serum level of vitamin C was significantly higher in the healthy subjects in comparison with that in the patients. The vitamin C intake of the latter was, however, higher than that of the former while no significant difference was observed between the groups in relation to dietary intakes of vitamins E and A, beta-carotene, Zn and Se. The 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 have attempted to improve their condition by changing their dietary pattern.

Serdar et al. [27] and Delport et al. [28] showed lower levels of plasma antioxidant (including vitamins A, C and E) in CHD patients. Nojiri et al. studied oxidative stress in CHD patients by evaluating the level of vitamins A, C and E as well as TAC level with a case-control study. Their results indicated a decrease in TAC and an increase in vitamin E [29]. Epidemiologic studies have revealed that treatment with antioxidants such as vitamin C and antioxidant-containing foods were in correlation with decrease of inflammation markers and reduced risk of coronary heart incidents [9,30].

Increase of oxidative stress and defects in the antioxidant defense system play a major role in endothelium function disorders and have been considered as the contributing factors in atherosclerosis progress [31]. Investigations on the relationship between antioxidants and CAD risk are conflicting. In the present study, although the mea value of TAC was higher in the patient group, the difference was not significant between the two groups; hence it cannot be claimed that TAC is related to CAD risk. In a cross sectional study perforemd with 968 adults, no significant difference was observed in the TAC and antioxidant enzyme activity between CAD and control groups; UA and MDA levels were, however, higher in the CAD group thant the control group [32]. In the work of Bagheri et al., CAD patients had higher levels of UA and TAC compared to the controls; their HDL cholesterol, however, was lower. TAC and UA, its main factor were significantly associated with the prevalence and severity of CAD [13]. In a study by Gawron-Skarbek et al. [33], it was revealed that CHD patients have higher levels of both ferric reducing ability of serum and 2.2-diphenyl-1-picryl-hydrazyl. On the contrary, Khaki Khatibi et al. [34] showed that TAC in CHD patients is significantly lower in comparison with healthy individuals. One of the reasons for lack of a significant relationship or increase of TAC in CAD patients could be due to the fact that increase in UA levels is one of the causes of increase in many of TAC measurment methods such as FRAP. Increase of UA levels in CAD patients has been reported in previous studies.

DA is the by-product of unsaturated fatty acids. Enhanced lipid peroxidation and LDL oxidation are involved in CAD pathogenesis [35]. This study showed no significant difference in plasma MDA levels between the 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 [27]. Khaki Khatibi et al. [34] and Uppal et al. [36] revealed a significant increase in the MDA of the patients in comparison with the controls. Lee et al. [37] indicated that MDA level of CAD patients was higher than that of the controls. Moreover, other studies have also reported an increased level of plasma MDA among such patients [29,38]. Previous studies generally show a direct relationship between CAD risk and MDA level.

The role of TAC and oxidative stress on CAD has been discussed together due to the close relationship between these factors. In particular, oxidative damage occurs when the delicate balance between pro- and antioxidants is alterated. Vrious antioxidant molecules exist in the body, to be used against free radicals injury. Among them, glutathione and the enzymes

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superoxide dismutase and glutathione peroxidase are critical for maintaining the redox balance of the cell [39,40]. Once oxidant stress is evoked, adverse pathological conditions, namely reduced vessel reactivity, vascular smooth muscle cell proliferation, macrophage adhesion, platelet activation and lipid peroxidation can be occurred [41]. The 'oxidative modification hypothesis' of lipids is now supported by many lines of evidence, and it is well known that oxidized low-density proteins (LDL) may contribute to the onset and progression of atherosclerotic lesions by numerous mechanisms, including its proinflammatory, immunogenic and cytotoxic actions [42]. However, other mechanisms exist that are not necessarily linked to LDL oxidation. For example, free radicals, such as superoxide anion, can rapidly react with NO, inactivating it and priming proatherogenic mechanisms (i.e. lekocyte adhesion, platelet aggregation, reduced vasodilatatory capacity) [42]. In addition, it is now well known that the sequence of ischaemia and reperfusion in the ischaemic heart disease, through increased production of free radical oxygen species, causes alterations in the bioenergetic mitochondrial function [43]. It is possible that ischaemia would affect the respiratory function, leading to an increased generation of oxygen free radicals. This event would cause additional mtDNA damage, exacerbating the defects of electron transport and leading to a vicious cycle of mitochondrial function decline and an increased accumulation of oxidative damage in the disease [44,45]. An other important point, we wanted to remark in this study, is the importance to evaluate the antioxidant capacity, that represents the protection against oxidative stress, together with a marker of free radical enhanced generation and lipid peroxidation as 8-epi-$PGF_{2\alpha}$. In fact, balance between pro-oxidants and antioxidants may be diverse under different pathological conditions, depending on the oxidative stress evoked as well as the antioxidant defence system [46,47]. In conclusion, the simultaneous evaluation of the TAC together with lipid peroxidation markers may represent a fundamental marker for the evaluation of oxidative levels in the field of CVD, but also constitute a potential goal of therapeutic interventions directed against pathologic processes related to atherosclerosis.

Several limitations in our study should be addressed. The first was the small sample size. Secondly, although most potential confounders were carefully controlled, since some of the study subjects may have had several chronic diseases, it could not have been possible to eliminate the possible effects of other underlying diseases and the medications used for those diseases on the present findings. More studies with larger sample sizes adding other markers of oxidative stress are essential to confirm these findings.

CONCLUSION

Overall, the current study showed a significant relationship between serum UA and vitamin C levels and CAD risk. According to the findings, CAD patients possessed higher levels of UA and lower levles of vitamin C in comparison with healthy subjects. As regards the association between CAD and TAC, although the TAC of the CAD patients was higher than that of the controls, this difference was not statistically significant. The results of this study revealed that plasma MDA level, as an index of lipid peroxidation, showed no significant difference between the two groups. vitamin C intake of the patients was significantly higher thant the healthy subjects. The mean intakes of vitamins E and A, beta-carotene, Se and Zn were not significantly different between the two groups. Another result showed the direct correlation between UA and TAC levels. The correlation between serum UA levels and dietary intakes of vitamin A, Zn and Se, were inversely observed. There was no significant relationship between

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UA levels, and vitamin Clevels,MDA levels and/or dietary intakes of vitamin C, vitamin E and beta-carotene. The findings of this study were also indicative of a relationship between physical activity and increased systolic BP in assocaited with CAD risk.

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