# Endocrinology & Metabolic Syndrome

# Anti-Inflammatory Effects of Dietary Antioxidants in Patients with Coronary Artery Disease

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## Abstract

**Background:** Atherosclerosis, with its major manifestation, Coronary Artery Disease [CAD] is a chronic inflammatory disease. Dietary antioxidant intakes favorably effect on inflammatory responses.

**Objective:** This study was conducted to examine the association between dietary antioxidants including vitamin E and vitamin C with inflammatory markers, IL-6 [Interleukin 6] and hs-CRP [high sensitivity C-reactive protein], in CAD patients among Iranian population.

**Methods:** This hospital-based cross-sectional study was conducted in Sina Heart Hospital, Isfahan, Iran in 2012. This study included 150 men Patients aged ≥45 years with first ever symptomatic CAD that had been confirmed by angiography. A semi-quantitative food frequency questionnaire was used to assess the usual intakes of dietary vitamin E and C.

**Results:** The mean intake of vitamin E and C in our study population was 0/018 ± 0/0018 g/d and 0/081 ± 0/0049 g/d, respectively. After adjustment for potential confounders, vitamin E was inversely significantly related to hs-CRP [P=0.004] and IL-6 [P=0.022] concentrations. Intake of vitamin C was inversely significantly related to plasma IL-6 concentration [P=0.042], but not hs-CRP [P=0.17].

**Conclusion:** Our finding suggests that these dietary antioxidants, vitamin E and C, were significantly related to plasma inflammatory markers in CAD patients.

## Introduction

Inflammation plays an essential role in development of insulin resistance and type 2 diabetes, the initiation and progression of atherosclerotic lesions and plaque disruption [1,2]. Interleukin 6, is an inflammatory cytokine and one of the main inducers of the C-Reactive Protein [CRP] secretion, in the liver [3,4]. Atherosclerosis, with its major manifestation, coronary artery disease is the major cause of morbidity and mortality in the world [5]. Reports have documented that CAD incidence rates to be as high as 166 per 100000 in Middle Eastern countries [6].

It is being recognized that traditional risk factors, such as dietary factors, smoking, dyslipidemia, hypertension and diabetes, do not explain the presence of coronary atherosclerosis in a large proportion of patients [7,8]. During the past decade, with the recognition that atherosclerosis is an inflammatory process, several plasma inflammatory markers have also been considered as a potential tool for prediction of coronary events and the observations taken together suggest atherosclerosis is a chronic inflammatory disease [9].

The results of experimental and epidemiological studies have shown that habitual diet is the most important modifiable risk factor for prevention and control of CAD [10,11]. Fruit and vegetable consumption has been associated with reduced risk of several diseases including CAD [12]. The antioxidants that usually found in fruits and vegetables, have important roles in cell function and have been implicated in processes associated with inflammatory, aging vessels and neurologic damage [13].

Epidemiological studies have shown that human with either a high dietary intake of or a high blood concentration of Vitamin E [vit-E] and Vitamin C [vit-C] have lower risk of developing CVD [14,15]. Vitamin C is a water-soluble antioxidant and essential nutrient for immune cells and extracellular matrix production [16]. Vitamin E has antioxidant properties and the protective effect of vit-E against neurodegenerative disease and inflammatory markers explored in several epidemiologic and clinical studies during the last decade [17,18]. Serum CRP and nuclear factor κ-B [NFκ-B] concentrations in human subjects are, according to one report, inversely correlated with these antioxidant nutrient concentrations [17]. A high intake of food rich in vit-E and vit-C was related to reduce levels of CRP, IL-6 and $F_2$-isoprostanes [12]. On the other hand, large placebo-controlled intervention studies have not shown any beneficial cardiovascular effects of vit-E or vit-C supplementation [19,20]. From these contradictory data it may be concluded that the regulation of antioxidants and inflammation in atherosclerosis is a complex process and yet not fully understood. Limited data are available from Asian countries linking dietary antioxidant intakes to the plasma inflammatory markers especially in patient with coronary artery disease. The present study was conducted to examine the relationship between dietary antioxidants, vit-E and vit-C, with inflammatory markers, IL-6 and hs-CRP, in angiographically defined CAD patients among Iranian population.

## Methods

### Participant population

The present hospital-based cross-sectional study was conducted in Sina Heart Hospital, Isfahan, Iran in 2012. This study included 150 CAD men patients undergoing diagnostic coronary angiography at the Angiography department of this hospital. We selected patients through consecutive sampling procedure. The patients with prior history of CAD, any systemic inflammation, recent trauma, kidney disease, liver disease, cancer and autoimmune disease were excluded from the study. Participants were conscious and able to answer the questions and fill the information form. Written informed consent was obtained from each participant.

### Assessment of dietary intake

Usual dietary intake was assessed using a validated 168-item semi-quantitative FFQ [21]. A trained dietitian administered all the questionnaires. The FFQ consisted of a list of foods with standard serving sizes commonly consumed by Iranians. Participants were asked to report their frequency of consumption of a given serving of each food item during the previous year on a daily [e.g. bread], weekly [e.g. rice, meat], or monthly [e.g. fish] basis. The reported frequency for each food item was then converted to a daily intake. Portion sizes of consumed foods were converted to g using household measures [22]. Total energy intake was calculated by summing energy intakes from all foods. N4 nutritional software we used to determine the nutrient compositions of all foods. Total dietary vit-E and vit-C consumption was calculated by summing the consumption of fruits, vegetables, fruit juices, compotes, non-hydrogenated vegetable oil [olive oil, sunflower oil, soybean oil, corn oil and canola oil], nuts [almond, walnut, hazelnut, pistachio and peanut], milk and liver.

### Assessment of coronary artery disease

Patients aged ≥45 years with first ever symptomatic CAD confirmed by angiography were included. Coronary angiography was performed by the femoral approach and included at least 4 views of the left coronary artery and 2 views of right coronary artery. Coronary artery disease was defined when a person had at least one epicardial vessel with more than 50% stenosis.

### Laboratory measurement

The 12-h fasting blood samples were collected into tubes containing 0.1% EDTA and were centrifuged at 4°C and 500g for 10 min to separate plasma. Serum samples were promptly frozen [-20°C]. Serum total cholesterol, Low-Density Lipoprotein [LDL] and Triglyceride [TG] concentrations were measured by commercially available enzymatic reagents [Pars Azmoon, Iran] on a BT-3000 [Biotechnica] auto-analyzer. High Density Lipoprotein [HDL cholesterol] was also measured using a photometric enzyme assay [Pars Azmoon, Iran]. Hs-CRP was measured by immuneturbidometry [Pars Azmoon, Iran] and IL-6 ELISA was performed on serum [BBT International, England].

### Assessment of other variables

Weight was measured using digital scales and recorded to the nearest 100 g while the participants were minimally clothed without shoes. Height was measured in a standing position, without shoes, using a tape measure while the shoulders were in a normal position. BMI was calculated as weight in kg divided by height in $m^2$. Waist Circumference [WC] was measured at the narrowest level and that of the hip at the maximum level over light clothing using an unstretched tape measure, without any pressure to body surface, measurements were recorded to the nearest 0.1 cm. Data on physical activity were obtained using participants' oral responses to an interview based International Physical Activity Questionnaire and expressed as metabolic equivalent h/day [MET-h/day] [23]. Additional covariate information regarding age, smoking status, medical history and current use of medications and family history of cardiovascular disease were obtained using questionnaires. Blood pressure was measured by an expert using a mercury sphygmomanometer and with the participant resting in a seated position for 10 minutes.

### Statistical methods

Tertile cut-points of total dietary vit-E and vit-C intakes were used for categorizing participants. General characteristics and dietary intakes of participants across textiles of total dietary vit-E and vit-C intake were compared by the use of analysis of variance and chi-square where appropriate. Partial Correlation analysis and General Linear Models were respectively performed to evaluate the association and the effect of dietary antioxidants including vit-C and vit-E on plasma levels of inflammatory markers. We adjusted for age, waist circumference, Body Mass Index [BMI], physical activity, total energy intake, High Density Lipoprotein [HDL], Low Density Lipoprotein [LDL], triglyceride, serum total cholesterol [all as continuous variables], smoking status, hypertension, diabetes mellitus, family history of CVD, Aspirin and statin use [all as categorical variables]. All probability values presented are 2-tailed, and probability values below 0.05 were considered statistically significant. Values reported in the text are mean ± SEM. Statistical analyses were performed using Statistical Package for Social Science [SPSS Inc, Chicago IL. Version 18.0].

## Results

The mean intake of vitamin E and C in our study population was 0/018 ± 0/0018 g/d and 0/081 ± 0/0049 g/d, respectively. General characteristics and dietary intakes of study participants according to tertiles of total vit-E and vit-C intakes are presented in Table 1. Compared with patients in the lowest tertile, those in the upper teritle of vit-E and vit-C intake had lower levels of triglyceride. Participants in the top tertile of vit-E andvit-C intake had higher intakes of total energy and fat. Furthermore, CAD patients in the highest tertile had lower intakes of carbohydrate and protein compared with those in the lowest tertile. No significant difference was found for other characteristics and dietary variables.

Partial Correlation analysis was performed to evaluate the association of dietary vitamin E and vitamin C with plasma IL-6 and hs-CRP concentrations. We adjusted for total energy, age, BMI, waist circumference, smoking status, hypertension, diabetes mellitus and family history of CVD, aspirin use, statin use, HDL, LDL, TG, serum total cholesterol and Physical activity. The correlation [r] between vitamin E and IL-6 was -0.32; P=0.01 and hs-CRP was -0.20; P<0.001. Vitamin C was significantly inversely associated with plasma levels of hs-CRP [r=-0.22; P=0.04] and no significant association was found for vitamin C and IL-6 [r=-0.07; P=0.42].

Multivariate-adjusted General Linear Models was used to examine the effect of vitamin E and C on plasma inflammatory makers. For two reasons, better fitting and no-significant relation between total energy, LDL, TG and serum total cholesterol use and IL-6 and hs-CRP, these variables were not taken into account. Vitamin E was statistically significantly related to hs-CRP [P=0.004] and IL-6 [P=0.02] concentrations. Vitamin C was significantly related to plasma hs-CRP concentration [P=0.04], but not IL-6 [P=0.17].

| | Tertiles of total vit-E and vit-C intake | | | P-value[2] |
| --- | --- | --- | --- | --- |
| | T1 (Lowest) | T2 | T3 (Highest) | |
| Age (y) | 55.56 ± 1.61 | 55.31 ± 1.13 | 55.83 ± 1.16 | 0.71 |
| BMI (kg/m$^2$) | 26.05 ± 0.32 | 26.04 ± 0.47 | 26.76 ± 0.7 | 0.54 |
| WC (cm) | 102.1 ± 1.22 | 98.53 ± 1.16 | 99.68 ± 1.41 | 0.66 |
| Physical activity (MET-min/day) | 2713 ± 52.5 | 2766 ± 51.11 | 2698 ± 52.32 | 0.92 |
| HDL cholesterol (mg/dl) | 36.59 ± 1.33 | 40.1 ± 1.22 | 38.58 ± 1.34 | 0.49 |
| LDL cholesterol (mg/dl) | 132.68 ± 5.29 | 123.29 ± 5.14 | 120.15 ± 5.44 | 0.37 |
| Triglyceride (mg/dl) | 176.63 ± 8.26 | 189.8 ± 8.27 | 164.25 ± 6.89 | 0.03 |
| Serum total cholesterol (mg/dl) | 148.81 ± 4.89 | 156.07 ± 6.08 | 157.58 ± 7.23 | 0.57 |
| IL-6 (pg/ml) | 14.31 ± 1.15 | 13.73 ± 1.14 | 13.20 ± 1.62 | 0.34 |
| HS-CRP (pg/ml) | 6.44 ± 0.12 | 5.45 ± 0.32 | 5.98 ± 0.50 | 0.60 |
| Hypertension (%) | 40.6 | 47 | 42 | 0.63 |
| Diabetes mellitus (%) | 23 | 22.5 | 21.6 | 0.88 |
| Family history of CVD (%) | 42 | 33.5 | 44.6 | 0.36 |
| Current smokers (%) | 21 | 25.3 | 22 | 0.92 |
| Aspirin use (%) | 50.1 | 43 | 44 | 0.94 |
| Statins use (%) | 27.2 | 18.65 | 20.14 | 0.52 |
| Total energy (Kcal/d) | 2440.23 ± 49.55 | 2616.82 ± 32.13 | 3033.86 ± 56.92 | <0.001 |
| Carbohydrate, % total energy | 59.7 | 56.1 | 55.4 | <0.001 |
| Protein, % total energy | 16.5 | 14.4 | 14.6 | <0.001 |
| Fat, % total energy | 23.8 | 29.5 | 30 | <0.001 |
| [1]Data are means ± SD. [2]Obtained by the use of ANOVA and Chi-Square, where appropriate. WC, Waist circumference; MET, Metabolic equivalent. | | | | |

**Table 1:** General characteristics and dietary intakes of study participants across tertiles of total vitamin E and vitamin C intake[1]

## Discussion

In this cross-sectional study of dietary antioxidants with inflammatory markers, vitamin E was inversely related to plasma hs-CRP and IL-6 levels. We observed statistically significant inverse association between vitamin C intake and plasma levels of hs-CRP, but not IL-6.

Coronary artery disease has been among the leading causes of death in Asian countries [6]. Inflammation plays a central role in development of atherosclerosis, and elevated CRP levels are an important risk factor for CVD and type 2 diabetes [24]. Similarly, plasma levels of IL-6 are also predictive of CVD; however, this relationship is less strong than for CRP, which may be due in part to higher variability or lower specificity of this cytokine [25]. The antioxidant properties of vitamins C and E seem to be effective against different conditions related to promotion of CVD such as high blood pressure, impaired glucose and lipid profile, endothelial dysfunction, LDL-C oxidation, monocyte, and smooth muscle cell activity [26]. Several studies have investigated the effects of different antioxidants on cytokines secretion, with conflicting results. In Swedish cohort, a high intake of food rich in vitamin C seems to show the most obvious association with reduced levels of IL-6 and CRP [12]. A case-control study in England found that lower plasma levels of vitamin C associated with higher serum levels of CRP among stroke patient [13]. In dialysis patients, plasma vitamin C is negatively associated with serum levels of hs-CRP [27]. A randomized, placebo controlled study was demonstrated that supplementation with vitamin C, vitamin E, coenzyme $Q_{10}$ was not associated with an improvement in hs-CRP of patients with multiple cardiovascular risk factors [28].

A cross-sectional study that investigated the relationship between dietary Total Antioxidant Capacity [TCA] and systemic inflammatory markers, concluded that TCA is inversely and independently correlated with plasma concentrations of hs-CRP and IL-6 [29]. But in another study a combination of vit-E and vit-C supplementation did not alter CRP or IL-6 levels [12]. Differences in the definition criteria of patients who are potential candidates for antioxidant treatment, type and dosage of antioxidant supplementation, as well as outcome measures may explain this variability. Since oxidative stress is activated by many cardiovascular risk factors such as hypertension, hyperglycemia, dyslipidemia and smoking, patients with multiple cardiovascular risk factors could obtain beneficial effects from antioxidant treatment [30-32]. Varied mechanisms have been proposed to account for the anti-inflammatory effect of dietary antioxidants. Certain antioxidants, specifically β-carotene, vitamin C and E, are free radical scavengers and therefore decrease oxidative stress by removing free radicals [33]. The anti-inflammatory properties of certain vitamins have been attributed to their ability of modulating the NF-κB DNA binding activity. NF-κB activation is primarily promoted by oxidative stress and leads to cytokine-induced expression of Cellular Adhesion Molecules [CAM] in the vascular endothelium and to the TNF-α and IL-6-induced production of CRP by liver [34]. CAM facilitates the adhesion of monocytes and T cells to the arterial wall in the first steps of the atherogenic process [35]. Oxidative stress appears also responsible for the oxidation of low-density lipoproteins incorporated to plaque [30]. Some investigations have been approved that hs-CRP had a close correlation with Thiobarbituric Acid Reactive Substances [TBARS], a marker of lipid peroxidation [36]. Inflammation-induced oxidative

modifications contribute to all important clinical manifestations of CVD such as endothelial dysfunction and plaque disruption [37]. A number of studies have been shown that exogenous antioxidants can modulate endothelium dependent vasodilation responses, endothelium-leukocyte interactions as well as balance between pro- and antithrombotic properties [38]. Vitamin E, due to its fat-solubility, is part of cell membranes and lipoprotein particles, where it counteracts oxidation events. Vitamin E-mediated protection from oxidative stress and atherosclerotic plaque formation has been shown both in vitro and in mouse models [39].

A broader understanding of antioxidant action is clearly warranted and a detailed knowledge on inflammatory and redox-regulated processes would allow a better adaption of treatment regimes. Beside their direct effects of antioxidants on prevention of biomolecule oxidation by being oxidized themselves, several antioxidants mediate a variety of effects that are of longer duration, as they may induce signaling changes in the biological system [37]. The epigenetic mechanisms of antioxidants on the developmental induction of chronic diseases raises the possibility that nutritional or pharmaceutical interventions may be used to modify long-term cardio-metabolic disease risk and combat this rapid rise in chronic non-communicable diseases [40]. Surveillance of the antioxidant status before and during therapy would allow seek out patients that could benefit from vitamin supplementation [41,42].

Our study has several limitations. This study has been done in the framework of cross-sectional study and the sample size of 150 individuals might be insufficient to detect the possible association between dietary antioxidants and inflammatory markers. Furthermore, the cross-sectional design of the study would not allow us to infer causality. Future longitudinal studies are required to further explore for the possible association. The next limitation is the use of FFQ as the dietary assessment method. The use of FFQ would result in misclassification of participants and this is usual with all nutritional epidemiologic studies. Although we controlled the analysis for several confounding variables, the existence of residual confounding cannot be excluded. Furthermore, random errors as in all epidemiologic studies might affect our results because diet and lifestyle information might be collected with some degree of errors. The existence of recall bias and selection bias in cross-sectional studies must also be taken into account. In the current study, it is possible that CAD patients might associate their disease to dietary intakes and therefore over-report or under-report consumption of foods rich in antioxidants. This is particularly relevant for our study because we enrolled newly diagnosed cases of CAD and as shown previously [39], the interviewing close to the time of diagnosis may increase the potential for recall bias. However, some studies in the field of nutritional epidemiology that have assessed the effect of recall bias on the overall study results reported that this bias was minor and negligible [43,44]. Since all study participants were recruited from the province of Isfahan, Iran, the observed associations between dietary fatty acid and inflammatory markers may not generalize to other geographic areas.

## Conclusion

Given the above-mentioned limitations, we found an inverse relationship between vitamin C with hs-CRP concentration, in CAD patients. But not relationship was found between vitamin C and IL-6. Vitamin E was inversely related to plasma hs-CRP and IL-6 levels. Further experimental and interventional studies under different conditions are needed to further explore for these associations.

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