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Selenium and Atherosclerosis: A Case-Control Study in a Hospital in Izmir

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Abstract

Objective: Atherosclerosis is an arterial disease with thickening of the vessel wall and loss of flexibility. The mostly accepted hypothesis about its pathogenesis is oxidative stress. Selenium is an essential element protecting against oxidative damage.

Our aim was to compare serum selenium levels of individuals with and without macroscopic atherosclerosis.

Methods: A total of 148 participants were enrolled in this case-control study (74 casesand 74 controls) among people aged ≥45 years applying to Akut Cardiovascular Hospital. Cases had macroscopic atherosclerosis (≥70% atherosclerosis in coronary or carotidarteries) and healthy controls consisted of other patients detected to have atherosclerosis less than 30% for coronary and <50% for carotid arteries. Among cases, 38 had carotid and 36 coronary artery disease forming two sub-groups. Gender, age, occupation, BMI, waist circumference, medical history, multivitamin use, fruit and vegetable intake, tobacco use, rurality, menopause were questioned and fasting glucose, cholesterol, triglyceride, HDL, LDL and selenium measurements were conducted.

Selenium levels were compared between the two and three groups according to the atherosclerosis status. Other risk factors were also evaluated. Student's t-test, variance analysis, chi-square test, correlation analysis and univariate logistic regression were used for statistic alanalyses.

Results: The mean serum selenium levels of the subjects were 106.0±29.5 µg/L; 106.3±30.5 µg/L in patients with coronary artery disease, 107.3±31.3 µg/L in patients with carotid artery, and 105.2±28.4 µg/L in controls, with no significant difference among the groups. When adjusted for gender, age and DM, there was no significant relationship in the risk of atherosclerosis and selenium.

Conclusion: Selenium levels were not associated with atherosclerosis in the study group. The timing of the selenium measurement on/after diagnosis and the selection of hospital controls might be considered as limitations.

Keywords: Atherosclerosis; Carotid atherosclerosis; Selenium; Antioxidants; Case-control.

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Introduction

Atherosclerosis is one of the most prominent diseases occuring in modern industrialized countries with changing lifestyle and food choice [1]. Atherosclerosis is a chronic and lipid-induced inflammatory disease. It is characterized by narrowing of the arterial lumen due to plaque accumulation inside the artery wall [2]. Atherosclerosis affects the elastic arteries, such as the aorta, carotid and iliac arteries, the middle and large muscular (coronary) arteries, and rarely the small arteries [3]. It is the early stage of coronary artery disease and stroke [4]. The most common cardiovascular disease in adults is Coronary Artery Disease (CAD). According to World Health Organization's (WHO) 'Top 10 Causes of Death Report in the World'; CAD is the leading cause of death in high and middle-income countries [5]. It is estimated that there are more than 17 million CADs in the United States. According to 2008 data, the total of direct and indirect costs for CAD is estimated to be around $ 156 million [6]. The number of deaths in our country in 2022 was announced as 504.839. Approximately 179 thousand (35%,4) of all deaths were due to cardiovascular causes [7].

Carotid artery stenosis is the most important cause of ischemic stroke. Since it proceeds in a quiet and unpredictable manner, the first finding may be fatal stroke [8]. Atherosclerosis constitutes one third of all stroke cases [9]. The cost of stroke amounts up to $ 57.9 million each year in the United States [10].

It is not yet known what starts/trigger the atherosclerotic process. Many theories have been proposed to explain atherosclerosis [11], among which oxidative stress is a prominent one.

Selenium mineral was found to be a necessary trace element to survive with the discovery of the enzyme glutathione peroxidase in 1957 [12]. Selenium is an essential element that protects against oxidative damage [13]. Selenium is found in the structure of antioxidant GPx enzyme [14], it activates glutathione peroxidase and is effective in protecting anaerobic tissues against injuries caused by free oxygen radicals [15].

Many researchers have found that in patients with congestive heart disease and other cardiovascular diseases, selenium concentrations are lower than in healthy individuals [16].

Selenium is found in cereals, red meat, fish, eggs, milk and dairy products [17]. Brazil nuts may also contain high amounts of selenium [18]. A study on nuts growing in Turkey showed that; 50 g per day consumption of nuts meets the recommended selenium needs [19]. Selenium levels are high in black tea [20] and sunflower seeds [21].

According to WHO, at least 19 µg of selenium per day is required to prevent selenium deficiency-related diseases [22].

Keshan Disease, an endemic cardiomyopathy, is the first human disease due to selenium deficiency [23]. The importance of selenium for human health was not known until its relationship with Keshan's disease was discovered [14]. As for the cardiovascular effect of selenium; selenoproteins have been associated with inhibition of oxidative modification of lipids, inhibition of platelet aggregation, and reduction of inflammation [24]. The aim of the present case-control study was to compare serum selenium levels of individuals with and without macroscopic atherosclerosis and find out whether selenium levels were associated with increased risk.

Materials and methods

Study population

We calculated the minimal sample size with GPower program with an effect size of 0.5%, 5% error, 80% power; which was determined as 128 people. Due to the possibility of error in blood sample handling, we decided to include 140 people (70 case, 70 control) and finally 148 people (74 cases, 74 controls) were included in this study.

We examined 148 patients between April 2016-March 2017 at Akut Cardiovascular Hospital in İzmir, Turkey.

Case and control selection

We selected the study group among people 45 years and older who applied to Akut Cardiovascular Hospital, who had an angiography, who accepted to participate in the study and signed the consent form.

Macroscopic atherosclerosis was defined as ≥70% atherosclerosis in coronary or carotid arteries, while patients detected to have atherosclerosis less than 30% for coronary and <50% for carotid arteries wer econsidered as not having atherosclerosis.

After angiography and radiological examination, we examined the medical records of the admitted patients, and selected individuals with and without macroscopic atherosclerosis in the study group. As a result, a total of 148 individuals, including 74 patients with macroscopic atherosclerosis, 72 patients without atherosclerosis and 2 patients with mitral valve disease without atherosclerosis were evaluated. Patients with mitral valvedisorder patients were also included in the control group because there was no atherosclerosis in the coronary and carotid arteries. Patients diagnosed with macroscopic atherosclerosis were included in the case group and those without macroscopic atherosclerosis were included in the control group. On total 69 women and 79 men participated in the study.

In this study, 36 patients were diagnosed as coronary artery disease (lesion status ≥70%), 38 as carotid artery disease (atherosclerotic lesion status ≥70%) and 74 as control group (coronary lesion status <30% and carotid lesion status <50%).

Exclusion criteria

Patients with suspected pregnancy, with chronic renal failure, with ulcers in their arteries, with acute myocardial infarction admitting to the emergency department were excluded from the study.

Measurement of coronary artery disease and carotid artery disease

The degree of carotid artery disease was determined according to NASCET (North American Symptomatic Carotid Endarterectomy Trial) classification [25]. The degree of coronary artery disease was determined according to the Limited Coronary Lesion (SCL) classification [26].

Laboratory assays

After a >8 hours fasting blood samples were collected in the morning.

Selenium values were measured by Inductively Coupled Plasma (Mass Spectrometer) method in EgeLab laboratory. Fasting Blood Sugar (FBS), total cholesterol, HDL-C, LDL-C and triglyceride levels were measured in the blood of the participants.

Enzymatic (Colorimetric) method was used in the laboratory between 0-2 hours in Akut Cardiovascular Hospital laboratory.

Materials

We explained this study to potential participants meeting the inclusion criteria and obtained a signed consent form from those who accepted to participate in the study. They answered the study questionnaire on their occupation, medical history, multivitamin use, fruit and vegetable intake, tobacco use, rurality, menopause and gender and age information was retrieved from their medical records.

Our research was conducted in accordance with protocols, regulations, existing guidelines, Helsinki's Declaration and Good Clinical Practice principles.

We measured the weights of the participants with Tanita BC 418-MA and their waist circumference with tape measure. Weight was calculated to the nearest 0.1 kg, respectively, using a Tanita BC 418-MA machine, with the participants wearing light clothing and bare feet. BMI was calculated as the weight in kilograms divided by height in square meters (kg/m^2). Waist circumference was measured in a horizontal plane at the midpoint between the inferior margin of the last rib and the superior iliac crest.

BMI was categorized as normal 18.5-24.9 kg/m^2, overweight 25-29.9 kg/m^2, obesity I 30-34.9 kg/m^2, obesity II 35-39.9 kg/m^2, and obesity III >40 kg/m^2. Regarding waist measurements, normal values were <102 cm for men and <88 cm for women.

Data collection

We applied a questionnaire to our study group. We asked about gender, age, occupation, their smoking habits, region, medical history, menopause (for women), fruit and vegetable consumption, use of multivitamins. Medical history included Hypertension (HT) and Diabetes Mellitus (DM). Smoking status was categorized into three groups: never smoker, former smoker, and current smoker. The results of the anthropometric measurements and biochemical tests were also recorded on the same study questionnaire.

Statistical analysis

We calculated descriptive statistics with numbers and percentages, showed the means with standard deviation and p <0.05 was accepted as the level of statistical significance. The mean selenium levels were compared with Student's t-test among the case and control groups. The mean selenium levels in the carotid artery, coronary artery case groups and the control group were compared using variance analysis. The chi-square test, correlation analysis and univariate logistic regression were also used for statistical analyses on risk factors of atherosclerosis. Besides gender and age, risk factors found to be significant in univariate analyses were included in the final multivariate models.

Results

Baseline characteristics and univariate analyses

The mean age of all patients was 63.3±9.4 years (45-82) including 24.3% coronary artery disease, 25.7% carotid artery disease and 50% control group. The characteristics of the cases and controls are shown and compared in (Table 1), compared both in two groups (cases vs. controls) and three groups (coronary artery disease, carotid artery disease and control groups).

The distribution of risk factors in both case groups and and the control group are shown in Table 2, along with the p values of the univariate analyses comparing either the total of the two case groups with the control group and the comparisons of the three groups, evaluating the two sub-groups of cases separately and the control group.

Selenium levels are compareda ccording to different categorical risk factors for atherosclerosis in Table 3 and correlation analyses between selenium levels and scale-type variables are shown in Table 4, to explore possible interaction or bias among the variables, with none found.The only significant association was between cigarette pack-years and selenium, which was weak.

Multivariate analyses

We performed univariate logistic regression with gender and found that the risk of coronary and carotid atherosclerosis was 3.61 times higher (1.64-7.96) in men. In the univariate logistic regression analysis, in which age was taken as a continuous variable, it was determined that the risk of atherosclerosis increased 1.08 times (1.04-1.13) with each one year increase in age. The results of the separate multivariable analyses for the two sub-groups of cases as compared to the same group of controls are shown in Table 5, along with the total of the cases analyzed versus controls.

Table 1: The distribution of participants according to their disease status.

		n	%
Case	**Coronary artery disease**	36	24.3
	Carotid artery disease	38	25.7
Control		74	50.0
Total		148	100.0

Table 2: The distribution of risk factors in case and control groups.

Category	Case		Control	Three Groups	Total Case Group	Two Groups p
	Coronary	Carotid	n (%)	p	n (%)	
Gender				0.002[a]		0.001[a]
Female	24(66.7)	26(68.4)	29(39.2)		50(67.6)	
Male	12(33.3)	12(31.6)	45(60.8)		24(32.4)	
Age, Years				<0.001[a]		0.001[a]
45-54	6(16.7)	1(2.6)	21(28.4)		7(9.5)	
55-64	15(41.7)	8(21.1)	28(37.8)		23(31.1)	

65-74	8(22.2)	17(44.7)	21(28.4)		25(33.8)	
75-84	7(19.4)	12(31.6)	4(5.4)		19(25.7)	
Waist circumference				0.309[a]		0.175[a]
Risky	26(72.2)	24(64.9)	58(78.4)		50(68.5)	
Not risky	10(27.8)	13(35.1)	16(21.6)		23(31.5)	
Obesity				0.268[a]		0.112[a]
Yes	14(38.9)	13(35.1)	37(50.0)		27(37.0)	
No	22(61.1)	24(64.9)	37(50.0)		46(63.0)	
BMI				0.517[a]		0.282[a]
Normal	6(16.7)	9(24.3)	12(16.2)		15(20.5)	
Overweight	16(44.4)	15(40.5)	25(33.8)		31(42.5)	
Obese	14(38.9)	13(35.1)	37(50.0)		27(37.0)	
Smoking Status				0.035[a]		0.026[a]
Smoking	6(17.1)	12(32.4)	12(16.2)		18(25.0)	
No Smoking	14(40.0)	9(24.3)	40(54.1)		23(31.9)	
Quit Smoking	15(42.9)	16(43.2)	22(29.7)		31(43.1)	
Fruit and Vegetable Consumption				0.276[a]		0.139[a]
Yes	20(55.6)	22(59.5)	33(44.6)		42(57.5)	
No	16(44.4)	15(40.5)	41(55.4)		31(42.5)	
Diabetes				0.077[a]		0.025[a]
Yes	15(41.7)	17(44.7)	19(25.7)		32(43.2)	
No	21(58.3)	21(55.3)	55(74.3)		42(56.8)	
Hypertension				0.646[a]		0.503[a]
Yes	21(58.3)	25(65.8)	42(56.8)		46(62.2)	
No	15(41.7)	13(34.2)	32(43.2)		28(37.8)	
FBS	142.8±77.2	141.8±77.0	114.4±39.6	0.018[c]	142.3±76.5	0.007[b]
Triglycerides	157.8±65.8	169.9±139.4	146.0±102.9	0.121[c]	164.0±109.0	0.308[b]
Total cholesterol	212.3±49.7	193.1±4.05	215.7±42.6	0.044[d]	202.6±48.1	0.084[b]
HDL-C	41.8±6.4	39.4±9.6	45.0±8.5	0.002[c]	40.6±8.2	0.002[b]
LDL-C	138.8±46.4	119.7±39.5	141.4±41.9	0.034[c]	129.1±43.8	0.086[b]
Selenium	106.3±30.5	107.3±31.3	105.2±28.4	0.932[d]	106.8±30.7	0.733[b]

a. Chi-square test., b. Student's t-test., c. Kruskal-Wallis variance analysis., d. Variance analysis.

Table 3: Selenium levels and categorical risk factors for atherosclerosis.

Category*	Selenium Levels (µg/L)	p-value	n
Gender		0.221	
Female	102.8±31.1		69
Male	108.8±27.9		79
Menopause		0.944	
Premenopause	101.8±23.4		4
Postmenopause	102.9±31.6		65
Waist circumference		0.337	
Risky	104.7±29.3		108
Not risky	110.1±30.3		39
Obesity		0.932	
Yes	106.4±29.8		64
No	106.0±29.5		83
Fruit and Vegetable Consumption (5 portion per day)		0.279	
Yes	108.7±30.2		75
No	103.5±28.7		72
Diabetes		0.546	
Yes	108.0±28.3		51
No	104.9±30.2		97
Hypertension		0.215	
Yes	103.5±30.9		88
No	109.6±27.1		60

*t-test.

Table 4: The relationship between selenium level and measurement type variables.

Category	*r*	p-value	n
Age[x]	0.027	0.746	148
BMI[x]	0.003	0.972	147
Waist Circumference[x]	-0.009	0.911	147
Cigarette pack year (all)[y]	0.188	0.023	146
FBS[y]	-0.026	0.754	146
Triglycerides[y]	0.074	0.375	146
Total cholesterol[x]	0.029	0.725	146
HDL-C[y]	-0.032	0.699	146
LDL-C[y]	0.026	0.759	146

[x] Pearson's correlation.
[y] Spearman's correlation.

Discussion

In this case control study with selenium measurements of the patients conducted, the only significant relationship found in univariate analyses was pack-years, besides age group and gender.

Selenium may affect important inflammatory pathways for atherosclerosis. Several studies analyzing the relationship between selenium levels and cardiovascular outcomes have shown conflicting results [27]. Selenium deficiency has been suggested to be related to Cardiovascular Disease (CVD) since the 1970s [28]. A study of 11,000 people in Finland reported a 2-3-fold increase in cardiovascular morbidity and mortality in patients with a serum selenium concentration of less than 45 µg/L [29]. In our study, the lowest selenium value was found

Table 5: The results of multivariate logistic regression analyses adjusted for age and sex of possible risk factors in carotid artery group, coronary artey group and overall case group.

		B	SE	OR (95% GA)	*p*	R^2
Model	**Variable included in the model and reference category**					
All cases (n=74) versus controls n=74						0.308
Gender(female)		1.283	0.404	3.61(1.636-7.962)	**0.001**	
Age(cont)		0.080	0.022	1.08(1.037-1.130)	**<0.001**	
HDL-C(cont)		-0.051	0.026	0.95(0.902-1.001)	0.053	
Selenium(cont)		-0.002	0.006	0.99(0.986-1.011)	0.798	
DM (ref no)		0.817	0.407	2.26(1.019-5.029)	**0.045**	
Carotid artery cases (n=38) versus controls n=74						0.443
Gender(female)		1.007	0.538	2.74(0.953-7.855)	0.061	
Age(cont)		0.143	0.034	1.15(1.079-1.235)	**<0.001**	
Sigara içenler ref bırakmış ve hiç kullanmamış		-1.609	0.684	0.20(0.052-0.764)	**0.019**	
Selenium(cont)		-0.002	0.009	0.99(0.981-1.014)	0.772	
HDL-C(cont)		-0.047	0.035	0.95(0.891-1.022)	0.179	
DM(ref DM no)		1.073	0.552	2.93(0.992-8.621)	0.052	
Coronary artery cases (n=36) versus controls n=74						0.189
Gender(female)		1.269	0.467	3.558(1.425-8.882)	**0.007**	
Age(cont)		0.047	0.025	1.049(0.999-1.101)	0.055	
FBS(cont)		0.008	0.004	1.008(1.000-1.016)	**0.041**	
Selenium (cont)		0.003	0.008	0.997(0.982-1.012)	0.673	

to be 47 µg/L among 148 people. A study in Ankara showed that the mean selenium levels of coronary artery patients were 37.2±11.4 µg/L, while they were 38.6±15.3 µg/L in patients with Acute Myocardial Infarction (AMI), and 63.7±11.8 µg/L in healthy patients. There was a significant difference between the control group and both patient groups [23,30]. Another thesis study showed that selenium levels of patients with AMI (45.5 µg/L) were lower than healthy ones (51.5 µg/L) and were statistically significant [14]. Oster et al. found a significant difference between selenium levels in CAD and healthy individuals in their study on 149 people [31]. Another case study in Spain found that selenium values of patients with AMI (58.7±27.2 µg/L) or ischemic cardiomyopathy (55.5±16.7 µg/L) were significantly lower than the control group (74.9±27.3 µg/L) [16]. In Hong Kong, selenium levels were measured in 603 individuals who presented to the internal medicine outpatient clinic and were at risk for cardiovascular disease (35% coronary artery disease, 35% ischemic stroke, 40% DM) and a positive effect of selenium on secondary prevention of atherosclerosis in high-risk patients was found [32]. Yalcin et al., determined that serum and erythrocyte selenium levels of patients undergoing AMI were found to be significantly lower than the control group [33]. According to another study conducted in Ankara; 20 patients with a mean age of 49 years were examined. There was a significant difference between selenium levels and ischemic heart disease [34]. The selenium levels found in these studies are much lower than the selenium levels we found in our study. A meta-analysis study on cohort and case control studies found an association between a 50% increase in selenium concentrations and a 24% decrease in coronary artery disease [35]. A Canadian study also found that high selenium levels were inversely related to the prevalence of stroke. However, the daily intake of selenium is

350 µg and the blood selenium level is 450 µg/L in Canadian natives, who mainly consume seafood [36]. A meta-analysis of 13 prospective cohort studies showed that there was an inverse relationship between serum and plasma selenium levels and coronary heart disease. However, confounding factors and bias could limit the interpretation [37]. In Finland, serum selenium concentrations were studied in a group at risk for coronary heart disease and in a healthy group. The mean selenium level was 71.6±13.7 µg/L in the patient group and 72.9±14.4 µg/L in the control group, and it was not found to be associated with coronary heart disease risk [38]. Although Swart et al. found a negative relationship between carotid wall thickness and selenium levels, they found a long-term protective effect of selenium on arterial stiffness and blood pressure in Africans (WWW). Our study was conducted in a society where selenium levels were probably sufficient and the control group consisted of people admitting to a hospital because of a health problem. These might be factors underlying a lack of relationship found. Selenium might have an impact when its levels are much lower as in the studies reported or its low levels might be associated with the acute phase of the AMI, which was out of the scope of this study.

In a 5-year prospective study of 935 people in the USA, selenium levels were measured in the toenail and no association was found with coronary heart disease [40]. As a result of the EVA study conducted with 1389 people in France, no significant relationship was found between plasma selenium levels and CVD [41]. The Atherogene Study found no significant correlation between selenium levels and the prognosis of chronic ischemic heart disease [27]. Initially, selenium supplementation (200 µg/day) was given to 504 people without cardiovascular history and 500 people were given placebo. At the end of 7.6 years follow-up, it was concluded that selenium supplementation had no significant effect on primary prevention of cardiovascular diseases [42]. In a study of 52 persons in Turkey, selenium levels in plasma and in the hair of people were examined. Although the selenium level in the coronary artery patients was lower than the control patients, there was no statistically significant difference. Plasma selenium levels were found to be significantly higher in CAD patients [43]. The results of our study were consistent with those studies that did not detect a relationship between selenium and atherosclerosis.

The reason why selenium levels found in our study are higher than selenium levels in the literature can be explained through the foods consumed in Aegean region.

Selenium concentrations were measured in 218 individuals between 2 months and 48 years in Ankara. The results showed that selenium levels in Ankara residents were in a safe and sufficient range. In adults aged 18-48, 74±16 µg/L was found [44].

Selenium is also present in drinking water [45]. According to the results of monthly water analyses conducted in İzmir Public Health laboratories, selenium ratio increased more than 4 times in the water delivered to the distribution between 2010-2017. If we give the example of Gaziemir district of Izmir where the hospital is located; in 2010, the selenium value was 0.201 µg/L and in 2017 it was 1,335 µg/L. These values are well below the toxic levels [46].

As a result of the SU.VI.MAX study in France, serum selenium levels increased with meat and fish consumption [47]. Selenium values of foods such as eggs, seafood, red meat and cereals [48], mustard, onion and garlic are high [49]. Meat, seafood, onion and garlic consumption of İzmir people is high.

In addition, a study conducted in 2006 found that Selenium levels of Rize Turist black tea were high [50]. Considering that black tea is the most popular and highly consumed drink in Turkey, the high selenium levels might be associated with tea consumption.

We selected the participants of the study among those who applied to a cardiovascular hospital in Gaziemir. Due to the location of the hospital, people from the surrounding districts generally came from rural areas with similar soil characteristics. The level of selenium in the soils in the region may be sufficient, or the nutritional habits and consumed products in the region may provide a good level of selenium. This may have caused our patient group to become ill due to other risk factors, rather than selenium per se.

Declarations

Conflict of interest: Authors declare no conflict of interest.

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Author contributions: ÇY has conducted this research as her MPH thesis and has contacted the patients, conducted their anthropometric measurements, filled out the questionnaires, organized the laboratories, entered the data and analyzed them. RD has made conception and design of the study, supervision, funding, analysis and interpretation of data and critical review. IE has made contributions to the conception or design of the work, has revised it critically for important intellectual content and has approved the final version. NY contributed to data collection and interpretation, gave the idea of the study and made critical review.

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