Selenium Level in Patients with Heart Failure versus Normal Individuals

Abstract

Background: Despite many attempts to discover pathophysiologic mechanisms to explain chronic heart failure (CHF), no conceptual paradigms have been proved yet. Various studies have shown the role of trace elements on heart failure (HF). Among all trace elements, selenium deficiency is regarded as important risk factors for HF. Considering selenium deficiency in our society and high prevalence of HF, we compared selenium level in patients with HF with healthy individuals. **Methods:** In all, 32 hospitalized patients with HF and 32 healthy controls were enrolled in a case–control study. Demographic characteristics as well as functional class and risk factors were recorded for all two groups. Echocardiography was conducted for patients and all provided data were registered. Then serum selenium levels were compared in case and control groups. **Results:** The mean (±standard deviation) serum selenium was 92.5 ± 22.44 mg/dL in patients with HF and 109.3 ± 29.62 mg/dL in controls. The level of selenium was significantly lower and the frequency of risk factors was significantly higher in case group. Selenium level did not differ significantly in patients with different HF causes. There were a nonsignificant relationship between selenium level and left ventricular ejection fraction and a significant reverse relationship between selenium level and left ventricular volume and pulmonary artery pressure. **Conclusions:** Our results showed statistically significant lower level of serum selenium in patients with CHF in comparison to normal individuals. Moreover, selenium level had significant reverse relationship with left ventricular volume and pulmonary artery pressure.

Keywords: *Heart failure, left ventricular volume, selenium*

Ahmad Mirdamadi, Rahmatollah Rafiei[1], Gharae Kahazaipour, Lotfollah Fouladi[2]

Department of Cardiology, Najafabad Branch, Islamic Azad University, Najafabad, Isfahan, Iran, [1]Department of Internal Medicine, Islamic Azad University, Najafabad, Isfahan, Iran, [2]Clinical Anatomical Pathology, Dr. Fouladi Laboratory, Isfahan, Iran

Introduction

Heart failure (HF) is a complex syndrome with a multifactorial etiology.[1] It is a consequence of cardiac output reduction resulting from hypertensive, myocardial, valvular, or other structural heart diseases.[2,3] According to American Heart Association (AHA), HF is a complex clinical syndrome that results from any functional or structural cardiac disorder which decreases the ability of ventricle to fill or eject blood.[4]

HF is a major clinical and public health problem, affecting more than 23 million people all over the word.[4] It is also a major cause of death and disability in higher income countries.[1,2,5] In 2011, one in nine deaths in the United States was caused by HF.[5] It is also associated with mortality and morbidity and significant healthcare expenditures.[4,6] HF prevalence is steadily increasing and its incidence is increasing by age.[2,7] The important issue about HF is still quite poor prognosis, although survival after diagnosis and treatment of HF has been improved substantially over time.[4]

Elevated blood pressure, obesity, smoking, and diabetes are some of the lifestyle risk factors for HF.[1,4] Physical inactivity is another lifestyle behavior which is more likely in girls than boys.[5] Dilated cardiomyopathy is other cause of HF.[8] Suboptimal diet quality contains insufficient intakes of fruits, nuts, vegetable, seafood, and whole grains, as well as excess sodium intakes contribute to HF.[5]

Recent studies implied the role of oxidative free radicals to deteriorate myocardium decompensation.[3,6,8,9] Studies in this area showed the role of trace elements in some diseases,[8,10,11] especially in cardiovascular diseases and HF.[12,13] Among all trace elements, 10 are more essential: zinc, copper, manganese, iodine, iron, cobalt, molybdenum, tin, chromium, and selenium.[8,10] Balanced selenium level is essential for biological functions.[12,14] Some studies illustrated the role of selenium in overall health maintenance.[14-16] Selenium can protect cell membranes from oxidative

Address for correspondence:
Dr. Rahamatollah Rafiei,
Department of Internal Medicine, Islamic Azad University, Najafabad, Isfahan, Iran.
E-mail: Rafieigi87@gmail.com

damage.[8,12,17,18] Animal researches also reported protective role of selenium against heart cardiotoxic[8] and myocardial disease.[14] Human body uses selenium to produce glutathione peroxidase. It can protect cell membranes from damage caused by oxidative metabolism.[8,18]

The first evidences of the importance of selenium in cardiomyopathy date back to 1960s, in Keshan disease.[12] The content of selenium in food depends on selenium content of soil which varyies geographically. In some regions such as china, New Zealand, and Finland, soil selenium is very low, whereas in some regions high levels of selenium have been associated with sever poisoning. Therefore, serum selenium levels vary greatly within different populations.[14]

A meta-analysis reported that a 50% increase in selenium was associated with a 24% reduction in risk of coronary heart disease.[19] It is reported that serum selenium levels were significantly lower in patients suffering from dilated cardiomyopathy compared with healthy controls.[13] Although a large number of researches have reported significant effect of trace elements and selenium on HF, there are some studies showing no significant relationship between serum selenium level and HF.[20,21] In this study, we compared serum selenium level in patients with HF and normal individuals, to find any relationship between selenium level and chronic heart failure (CHF) conditions.

Methods

This research was a case–control study aimed to compare serum selenium level in patients with HF and healthy individuals. The study was conducted in Dr. Shariati Hospital, Isfahan, Iran, during 2015–2016. Subjects in case group were selected from patients referred to heart clinic, and heart or CCU department in Shariati Hospital and diagnosed as HF. Subjects in control group were selected from patient's health concomitant or patients who referred to any wards except for heart ward. All subjects were informed about the essence of the study. Figure 1 shows the participation flow chart.

Inclusion criteria were age >20 years and written consent for all participants and diagnosed HF for case group and having no HF evidence for control group. Exclusion criteria were death and not willing to continue the study.

In our study, participants underwent physical examination, laboratory tests, and echocardiography. All patients in case group had symptoms of HF and left ventricular ejection function (LVEF) <40%. A checklist contains causes of HF, exercise capacity, defined by New York Heart Association (NYHA) class,[22] ventricular ejection fraction (EF), left ventricular volume, diastolic function, pulmonary artery pressure, and sphericity index. Cardiac risk factors were included in our checklist.

For subjects in control group, a careful history taking and physical examination were applied to ensure that they do not suffer HF. Echocardiogram was conducted for participants in this group to confirm normal cardiac function.

As selenium content of food depends on soil and water concentration and varies geographically, dietary assessment methods would not be effective and accurate for estimating selenium exposure. Therefore, biomarkers such as blood, toenail, erythrocyte or serum, and plasma selenium are used.[19] In this study, we analyzed blood samples and measured selenium level of serum for each individual. About 5 CC blood samples were withdrawn between 8 and 10 AM after a 12-h fasting period. Blood samples were collected by venipuncture by highly purified material and stored in sterile containers. Serum was collected by centrifugation and stored frozen in −20°C temperature. Atomic absorption spectrophotometer method was used to determine selenium level. Plasma selenium concentration was determined by high-resolution inductively coupled plasma (ICP) mass spectrometry and ICP emission spectral analysis. Routine biochemical measurements, including all electrolytes, lipid profiles, and hepatic function tests, were performed.

Cochran's formula was used to determine sample size. Test power and significant level were 80% and 5%, respectively. Sample size was calculated to be 32 for each group. Convenient sampling method was applied. No patient was missed during the study.

All data were analyzed by SPSS software package v. 22 (California, USA). Descriptive analysis of baseline data is reported as frequency (and percent) for categorical data and mean ± standard deviation (SD) for continuous data. Chi-square test was applied for comparison of categorical response data between case and control groups. For continuous data, test for normality was conducted by Kolmogorov–Smirnov test. Two-independent sample t-test was used to compare serum selenium levels in two groups. Analysis of variance was applied to compare selenium level in more than two groups. To assess association between numerical data, Pearson's correlation coefficient was calculated. Significance level was set at $P < 0.05$.

Results

In all, 64 subjects were investigated in this study, 32 patients with HF in case group versus 32 individuals without HF. Totally 23 (71.9%) individuals in case group and 17 (53.1%) in control group were male. According to the result of Chi-square test for homogeneity, sex ratio did not differ significantly in case and control groups ($P = 0.12$). There was no missing measurement for patients.

The mean (±SD) of ages was 64.6 ± 11.9 and 62.2 ± 11.3 years in case and control groups, respectively. As age was normally distributed, two-independent sample t-test was applied for comparison. According to the result, the mean ages were not statistically different in two groups ($P = 0.41$). On the other hand, the mean (±SD) ages

were 61.9 ± 10.6 and 65.8 ± 13 years in male and female, respectively. The mean difference was not statistically significant (*P* = 0.2).

The mean (±SD) serum selenium was 92.5 ± 22.44 mg/dL in patients with HF and 109.3 ± 29.62 mg/dL in normal individuals. The level of serum selenium was significantly lower in case group (*P* = 0.013). The mean (±SD) serum selenium was 96.9 ± 29.6 and 107.59 ± 22.32 mg/dL in male and female, respectively. There was no significant difference between mean serum selenium in male and female (*P* = 0.13).

In all, 30 (93.8%) patients in case group and 17 (53.1%) individuals in control group had at least one cardiovascular risk factor. Chi-square test showed higher frequency of risk factors in case group (*P* < 0.001). The frequencies of cardiovascular risk factors in two groups are listed in Table 1. Two (6.3%) individuals in case group and 15 (46.9%) individuals in control groups had no cardiovascular risk factor. As Table 1 shows, all types of risk factors were more frequent in case group.

According to Chi-square test result, the frequencies of risk factors such as hypertension, family history, and smoking were statistically higher in case group (*P* < 0.05). Other risk factor rates were not statistically different between two groups (*P* > 0.05).

Table 2 shows frequency of HF causes and the mean and standard deviation of serum selenium level in patients with different causes. According to the results, ischemic heart disease (IHD) was the most frequent cause of HF in case group.

Here we applied analysis of variance to compare serum selenium level in patients with different risk factors. The results showed that selenium level did not differ significantly in patients with different HF causes (*P* = 0.28).

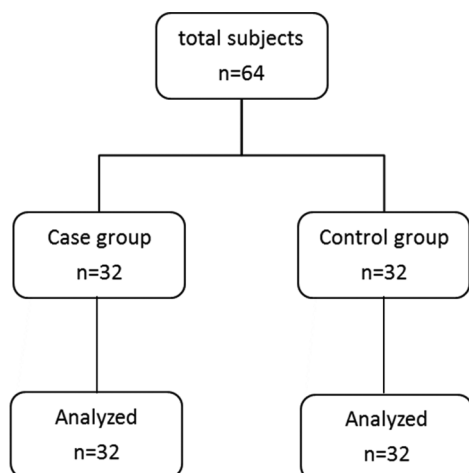From all 32 patients in case group, 21 (65.6%) individuals had history of myocardial infarction (MI). Table 3 shows

frequency of types of MI. The mean serum selenium for each type is shown in this table as well. Here we compared serum selenium level in patients of case group according to the type of MI. No significant difference was observed in selenium level in patients with different types of MI (*P* = 0.94).

The frequency of functional heart class and diastolic dysfunction severity with selenium level for each category for patients with HF are shown in Table 3. No patient in case group was in class IV of functional heart class.

LVEF, left ventricular volume, pulmonary artery pressure, and sphericity index were measured for all patients with HF. The mean and standard deviation and the minimum and maximum of observed measures are presented in Table 4.

The association between selenium level and each mentioned factor above was evaluated by correlation coefficient. Correlation coefficients and the associated *P* values are shown in Table 4 as well. Left ventricular volume and pulmonary artery pressure had a negative statistically significant relationship with selenium level.

Discussion

HF is a major clinical and public health problem. Recent studies addressed the role of oxidative free radicals on cardiovascular disease. Hiraoka *et al.* have conducted a study on the effect of selenium deficiency on oxidative stress precipitated. Their result showed a significant lower selenium level in patients compared with healthy individuals.[23] Some studies showed the role of trace

Table 1: Frequency of cardiovascular risk factors

Risk factor	Case	Control
Diabetes	13 (40.6%)	11 (34.4%)
Hyperlipidemia	10 (31.3%)	5 (15.6%)
Hypertension	14 (43.8%)	5 (15.6%)
Obesity	3 (9.4%)	0 (0%)
Family history of HF	8 (25%)	2 (6.3%)
Smoking	5 (15.6%)	0 (0%)

HF=Heart failure

Table 2: Heart failure causes and serum selenium level in case group

Cause	Frequency		Serum selenium level (mg/dL)	
	Count	Percent	Mean	SD
Ischemic heart disease	12	37.5%	92.6	28.00
Cardiomyopathy	3	9.4%	63.0	27.97
Hypertension	2	6.3%	101.4	9.54
Valvular heart disease	3	9.4%	92.7	7.92
Ischemic heart disease and hypertension	9	28.1%	97.7	12.22
Ischemic heart disease and valvular disease	3	9.4%	100.0	18.31

SD=Standard deviation

Figure 1: Flow diagram of participants in the study

Table 3: Selenium level in patients with HF according to various heart condition

		Frequency		Serum selenium level (mg/dL)		
		Count	Percent	Mean	SD	P
MI	Anterior	14	43.8%	93.2	23.12	0.94
	Inferior	3	9.4%	101.7	29.37	
	Posterior	2	6.3%	85.0	4.24	
	Anterior and posterior	2	6.3%	94.0	38.18	
	No MI	11	34.4%	90.2	22.44	
Functional class	Class I	4	12.5%	94.4	18.55	0.98
	Class II	18	56.3%	92.6	25.68	
	Class III	10	31.3%	91.5	19.30	
Diastolic dysfunction	Mild	18	56.3%	95.98	16.8	0.53
	Moderate	9	28.1%	90.67	29.55	
	Severe	5	15.6%	83.24	28.19	

SD=Standard deviation; MI=Myocardial infarction. *Analysis of variance Significant level was 0.05

Table 4: The relationship between selenium level with Echocardiography findings

	Minimum	Maximum	Mean	SD	Correlation coefficient	P
Left ventricular ejection fraction	10	40	23.8	8.73	0.24	0.24
Left ventricular volume	70	430	146.2	68.90	−0.39	0.03*
Pulmonary artery pressure	25	65	38.7	13.70	−0.45	0.01*
Sphericity index	0.06	0.73	0.5	0.12	0.13	0.49

SD=Standard deviation. *Significant at 0.05 type one error

elements including selenium on cardiovascular diseases and HF. Kosar *et al.* have shown in their study that HF was associated with lower selenium and zinc and higher cupper levels. Our case–control study compared serum selenium levels in patients with HF with healthy controls.

According to our result, serum selenium level was significantly lower in patients with HF, compared with healthy individuals. A 5-year prospective randomized trial conducted among Swedish citizens demonstrated a significantly better cardiac function among patients who received selenium and coenzyme Q10 supplementation. They concluded that selenium and coenzyme Q10 long-term supplementation may reduce cardiovascular mortality.[24] Other study showed a statistically significant fewer days out of hospital in participants who received selenium supplement compared with those who received placebo.[25] Other studies on patients with CHD showed lower level of selenium compared with healthy participants[8,26] and the protective role of it.[18,26] Another study on rats showed that high dietary selenium was associated with lower levels of cardiac oxidative damage.[27]

A systematic review by Fortmann *et al.* showed no positive effect of vitamin and mineral supplementation on cardiovascular disease. They studied the role of oral supplementations in dietary of healthy individuals and did not measure blood serum's vitamin or mineral levels. They also explained that most of the included trials were provided less than a decade of follow-up, and the effect of supplementation on cardiovascular disease may take longer to manifest.[11] In our study, we used blood serum level of selenium instead of

the intake amount of dietary selenium. Because the intake dosage does not represent absorption. Another research group studied the effect of dietary supplementation with 200 mg of selenium daily on cardiovascular disease events among healthy individuals in a 7.6-year follow-up. They did not observe any supportive effect of selenium against cardiovascular disease.[17] One possibility for their result may be the short period of follow-up.

In this study, hypertension and diabetes were the two most frequent risk factors of HF. In a meta-analysis which had been studied by several researches, hypertension was the most frequent risk factor. It also investigated diabetes and coronary heart disease as HF risk factors.[4]

In our study, a positive correlation was found between selenium level and LVEF. However, correlation coefficient was not statistically significant. In da Cunha *et al.*, no association was observed between serum selenium levels and LVEF.[20] Other study showed a significant positive correlation between selenium (Se-GSH-Px) activity and EF.[26] Moreover, Oster *et al.* observed a positive correlation between selenium level and left ventricular function.[28]

According to our result, selenium level had significant negative relationship with left ventricular volume and pulmonary artery pressure. This may show the effect of selenium deficiency on HF. When selenium level decreases, oxidative stress will increase and high blood pressure increases the volume of left ventricular.

In our study, age and gender of participants did not differ significantly between two groups. However, there was lack of

detailed information on unmeasured risk factors on baseline such as blood pressure, physical activity, and cholesterol.

Conclusions

In this case–control study, we compared serum selenium level in patients with HF with healthy individuals. According to our result, serum selenium level was significantly lower in patients with HF, compared with participants in control group.

Diabetes, hyperlipidemia, hypertension, obesity, family history, and smoking were the studied risk factors of cardiovascular disease, in this study. Hypertension and diabetes were the two most frequent risk factors in case group. According to the result, selenium level had significant negative relationship with left ventricular volume and pulmonary artery pressure. This may show the effect of selenium deficiency on HF. When selenium level decreases, oxidative stress will increase and high blood pressure increases the volume of left ventricular. Positive correlation between selenium level and LVEF was found although it was not statistically significant.

Our result showed the role of selenium on HF. Some previous studies had similar results; however, some others did not observe any protective role for selenium. The large differences may likely be caused by differences in population, study design, and ascertainment approaches.

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