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Published online 2019 March 30 **A Systematic Literature Review**

Association between Intake and Serum Selenium Levels and Risk Factors of Cardiovascular Disease (Narrative Review)

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Abstract

Background: Selenium (Se) is an essential trace element and is a potent antioxidant that is involved in the activity of several enzymes such as glutathione peroxidase (GPx). Selenium metabolism is associated with the biology of heart and its functions, and selenium deficiency is associated with cardiovascular pathology. Several studies indicate a relationship between selenium and cardiovascular disease.
Objectives: The aim of this study was the investigation of the role of selenium in cardiovascular disease.
Methods: We searched the ISI, PubMed, Scopus, and Google Scholar databases for studies that evaluated the association between selenium levels and cardiovascular health and cardiovascular disease. At first, the studies containing the words "selenium ", "cardiovascular disease", "selenium supplementation", "levels of selenium" and "hypertension" were selected.
We searched papers using 'selenium_, 'selenium supplementation_, 'selenium deficiency_and, 'Se_in combination with 'cardiovascular disease_, 'hypertension_', 'heart disease_', 'heart failure_' as keywords.
Results: 17 articles (6 randomized clinical trials and 11 observational studies) were eligible to be included in the current review. Some clinical trials have shown that selenium supplementation could reduce the risk of cardiovascular disease including lipid profiles and inflammatory markers. Observational studies showed that low selenium concentrations are a risk factor of cardiovascular disease however, this is not definitive. But the presence of normal levels of selenium is essential for antioxidant defense.
Conclusion: More clinical trial studies with larger sample size are needed to confirm that selenium is effective in preventing and treatment of cardiovascular disease.

Keywords: Antioxidant effects, Cardiovascular disease, CVD, Selenium, Selenium supplementation

1. Background

Cardiovascular disease (CVD) is the most important cause of mortality worldwide. In 2008 CVD with 6.2 million deaths accounted for 30% of total global deaths and atherosclerosis is one of the predictors for cardiovascular events (1,2). Selenium (Se) is an essential element that acts as prosthetic or cofactor groups and thereby, directly combined into proteins, it replaces sulfur in the cysteine to form the 21staminoacid selenocysteine (3). Food is the major source of selenium and amount of selenium in human foods are straightly influenced by the content of Se in the soil from which the food was obtained. Overall, soil Se content is very variable globally(4).

Selenium is a potent antioxidant adjusting the activity of some enzymes such as GPx enzymes, which catalyze the removing toxic substances from organic hydro peroxides and hydrogen peroxide. Lower levels of selenium cause the Keshan disease, an endemic cardiac failure known as cardiomyopathy that has been seen in China country. However, according to the results of observational studies, the relationship between low levels of selenium in the body and CVD remains controversial. Selenium protects the body against the disease through several mechanisms includes; modulation of prostaglandin

synthesis, increased the resistance of low-density lipoproteins against oxidative modification, and protect the body from heavy metal toxicity (5). The beneficial effects of selenium on the prevention and treatment of CVD have not yet been fully proven (6). In the French SU.VI.MAX study, intervention with several antioxidants such as selenium had no significant effects on mortality from CVD (7).

Selenium is crucial for many biological functions including body's antioxidant defense systems, thyroid hormone metabolism, improve the status of the immune system, and prevention of certain chronic disease such as cancers (8). The results of studies on the association between selenium status and prevalence and mortality of CVD are controversial.

We aimed to conduct the review to summarize the available data on the association between body selenium levels and cardiovascular disease, the effects of selenium intake on cardiovascular risk factors in clinical trials studies, and suggest some of the new approaches to solving this health problem.

2. Objectives

The aim of this study was to provide a systematic literature review of the effects of selenium supplementation on cardiovascular risk

factors and the relationship between levels of selenium in the human bodies and these risk factors in previous studies.

3. Methods

Search strategy and data collection

The literatures were searched up to January 2018 through four scientific databases: Web of Knowledge, PubMed, SCOPUS, and Google Scholar without any language or date restrictions. Studies that have been evaluated the association between selenium levels and cardiovascular health and cardiovascular disease. We searched papers using 'selenium_, 'selenium supplementation_, 'selenium deficiency_ and, 'Se_ in combination with 'cardiovascular disease_, 'hypertension_', 'heart disease_', 'heart failure_ as keywords. The studies containing the words "selenium ", "cardiovascular disease", "selenium supplementation", "levels of selenium" and "hypertension" were selected.

Inclusion criteria

We included cross-sectional studies that investigated the relationship between body selenium concentration and risk factors of cardiovascular disease and randomized clinical trials which investigated the effects of selenium supplementation on cardiovascular risk factors.

We conducted this narrative review in format of systematic in human population, either single sex or both male and female participants. In addition to clinical trial studies, we used other cross-sectional and animal studies to achieve better results.

4. Results and Discussion

Our preliminary online search retrieved 1,723 studies, about 1,688 were excluded after reading titles or abstracts because they did not met our inclusion criteria [Figure 1]. Finally, 17 articles (6 randomized clinical trials and 11 observational studies) were eligible to be included in the current review. In general, the results are divided into three sections includeselenium supplementation and CVD risk, level of selenium in the body and CVD risks and antioxidant effects of selenium, which details are described in below.

Selenium supplementation and CVD risk

Selenium is a trace mineral that it critical component for numerous selenoproteins in humans (9). In general GPx (main intracellular antioxidant) family belongs to the best-characterized seleno-proteins in the context of cardiovascular biology. Blood pressure, inflammation markers, fasting blood glucose and insulin sensitivity, glycated hemoglobin (HbA1c) and lipid profiles, were sensitive markers to evaluated as cardiovascular risk factors in the populations (10-13). The effects of selenium supplementation on cardiovascular indices in clinical trials study are shown in Table 1.

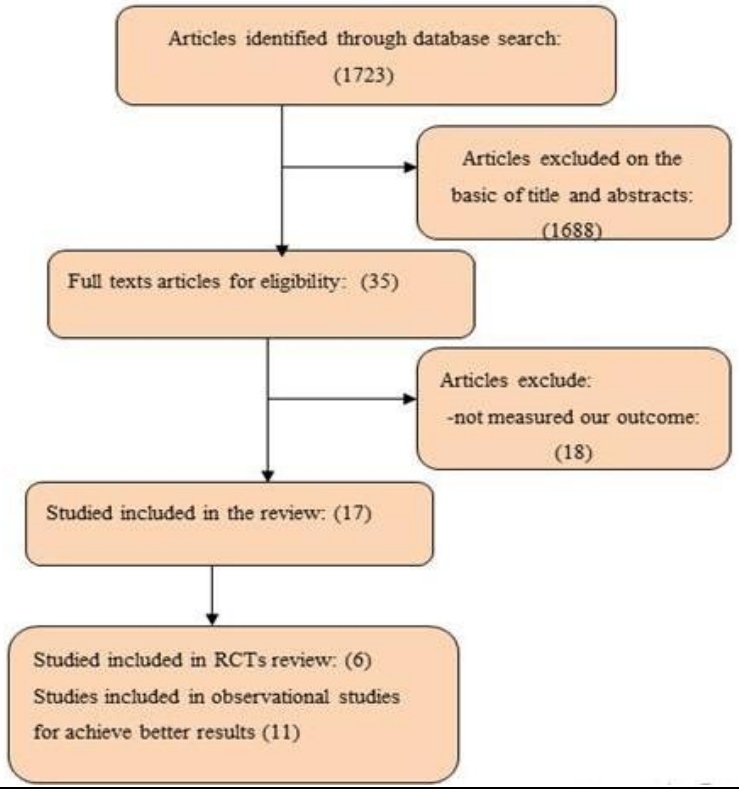

Figure 1. Summary of study selection process

Table 1. Randomized clinical trials study that evaluated the effects of selenium supplementation on cardiovascular risk factors

Author Year Country (Reference Number)	Intervention and duration	Population characteristics	Results
Boskabadi H, Ghayour-Mobarhan M et al (2007-2009) (21)	Selenium yeast (100 µg/d) Duration: 9 months	Pregnant Woman, n=166 (Placebo yeast (n=38 (*n* = 83) Age: 16-35 years	Significantly increased cord-blood TG, but no changes in total cholesterol, LDL and HDL levels
Omrani HR et al (2015) Iran (48)	Selenium supplement (150 µg/d) Duration: 3 months	hemodialysis patients with selenium deficiency, n=74 (Placebo(starch (n=38 (*n* = 36) Mean age: 59 years	No significantly effects on decreasing of levels of LDL and cholesterol
Asemi Z et al (2015) Iran (44)	selenium(200µg/d) Duration:6 Week	GDM* woman (gestation 24-28 weeks) n=70 Mean age: 28.6 Y	Significant reduction in insulin resistance and hs-CRP. Significantly increase in insulin sensitivity
Urban Alehagen et al (2009-2013) Sweden (49)	((selenium(200µg/d), Q10(200µg)) Duration: 5 years	Swedish citizens Age: 70-88 years n=443	• Improved cardiac function • Significant decrease of cardiovascular mortality • Significant decreasing in NT-proBNP levels
aBahmani F et al 2016 Iran (45)	selenium(200µg/d) Duration: 12 weeks	patients with diabetic nephropathy n=60	Significant decrease in hs-CRP, MMP-2 and MDA
Jinyuan.M et al 2015 United Kingdom (50)	selenium(60µg/d) Duration: 12 weeks	Pregnant women n=230	No-significant decrease in adiponectinchanges

Abbreviations: LDL; low density lipoprotein. HDL; high density lipoprotein.GDM: Gestational Diabetes Mellitus. Hs-CRP: high sensitively C-reactive protein. MMP-2: matrix metalloproteinase-2. MDA: malondialdehyde

Selenium is metabolised in the liver being incorporated into protein as selenocysteine for the synthesis of GSH -Px [Figure 2] (14). Animal studies have shown that the association between low selenium intake and CVD may be due to increased oxidative stress (15). In overall GPx have a vital role in neutralization of oxidant agents such as reactive oxygen and nitrogen species (15,16). Lu et al showed up for the first time that selenoprotein K has an antioxidant role in the heart cells (17). Selenoprotein K in the endoplasmic reticulum (ER) membrane of the heart cells reduces the level of reactive oxygen species (ROS) and protect the cardiac cells from oxidative stress (17). In a systematic review and meta-analysis study, there was an inverse relationship between selenium levels and coronary heart disease(CHD) (15,18). In another review study and meta-analysis that conducted in 2014, there was no association between selenium supplementation and cardiovascular mortality (19). In Omrani and colleagues, selenium supplementation in hemodialysis patient had no beneficial effect on lipid profiles (20). In Boskabadi H et al study selenium supplementation in pregnant women with dose 100 µg/d for six month leading to increased cord-blood triglyceride level, although total cholesterol, LDL, and HDL levels did not change significantly (21). In Nutritional prevention of cancer (NPC) analysis, selenium supplementation (200 µg/day) had no significant association to the risk of CVD after 7.6 years follow-up (22,23). Until then, the observational studies showed that low selenium levels area risk factor for cardiovascular disease, but this is not definitive and it's just a suggestion. Furthermore, the benefits of selenium supplementation to prevent cardiovascular disease are unclear and high levels of selenium supplementation should not be recommended to the general public (23).

Level of selenium in the body and CVD risks

In countries with a low dietary intake of selenium in observational studies have shown a relationship between low plasma Se levels and cardiovascular diseases (24). The concentration of selenium in blood, toenail, serum or plasma and erythrocyte are the biomarkers of selenium in the human body, however, the interpretation of this biomarkers is very difficult because Se concentration not only depends on intake but also related with selenium metabolism and form of selenium intake (25,26). In one study Salonen and colleagues have shown that selenium plasma levels are less than 45 µg/L associated with an increased risk of cardiovascular disease (24,27). In one study conducted by Parizadeh et al serum levels of selenium were not significantly different, but serum glutathione peroxidase levels were higher in

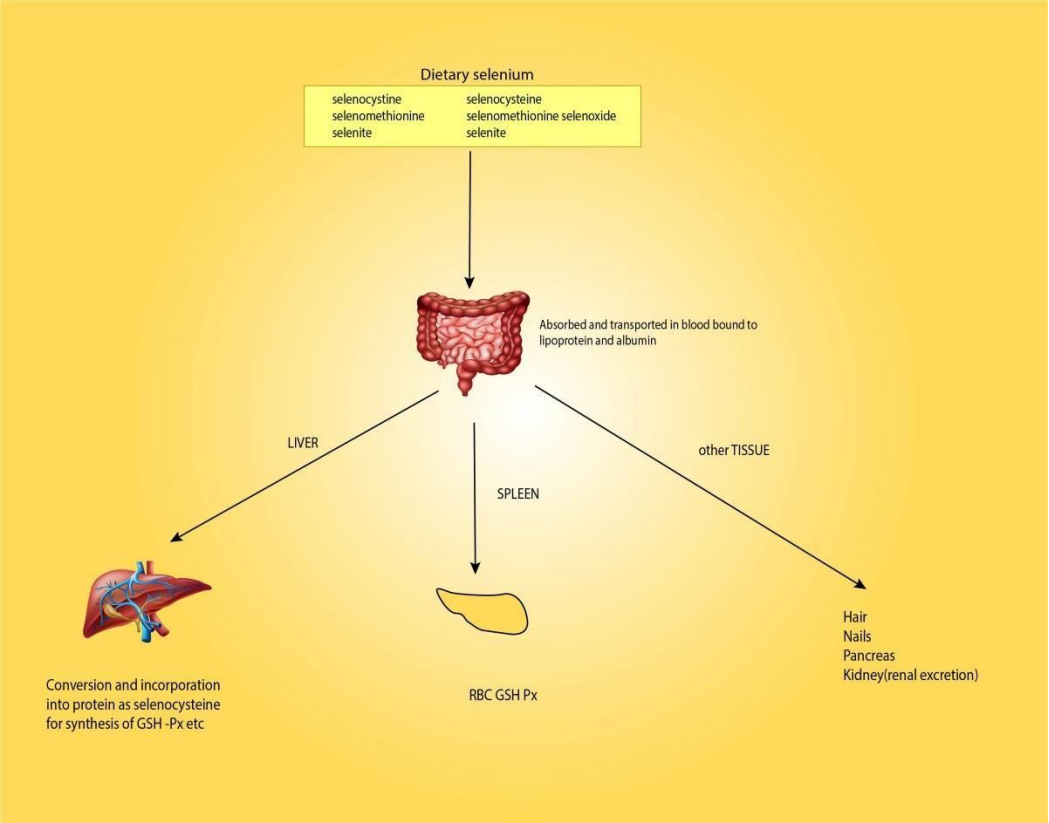

Figure 2. Selenium metabolism in human body

the control group than in patients with or without CAD (28,29). In this study inverse association between the ratio of selenium to glutathione peroxidase and diastolic blood pressure in the control group indicates that glutathione peroxidase probably protects the arterial wall against the activity of nitric oxide (28). In one study aimed at assessing the association between serum selenium levels and lipid profiles; they reached to this conclusion that higher selenium levels were positively associated with increased total and LDL cholesterol but not with HDL-c and triglycerides (30,31). In another cross-sectional study obese patients with risk factors of CVD had significantly higher serum concentrations of selenium and lower serum GPx compared with healthy subjects (32). In a cross-sectional study, high plasma selenium levels were associated with elevated systolic and diastolic blood pressure (33).

In one study conducted in Finnish population, Unlike women, there was an inverse association between serum selenium levels and blood pressure in men (34). Studies by Beck and colleagues have shown selenium deficiency causes damage to the heart cells (35,36).

In a study conducted on women, subjects with high selenium intake had a higher chance of developing type 2 diabetes (37).

In overall, the correlation between serum selenium level and metabolic risk factors for CVD appears to be positive. For example, increasing serum selenium levels is associated with increased risk factors for metabolic diseases such as LDL and HDL_; however, this association for triglyceride is U-shaped (24,38). It seems that this U-shaped relation can also be suggested for the level of selenium and cardiovascular health.

Antioxidant effects of selenium

Oxidative stress occurs when the amount of pro-oxidants produced is greater than the antioxidant defense system and this pro-oxidant can cause tissue damages and has a vital role in the pathogenesis of chronic disease such as cardiovascular disease (39). The role of oxidative stress in atherogenesis has been established by a large number of human and animal studies (40). It has been proposed that some dietary micronutrients protect the body against oxidative damage and related clinical complications (41).

Selenium is a component of selenoprotein and selenomethionine, which this two protein has important antioxidant properties (18). Selenoproteins with antioxidant functions include thioredoxin-reductases, which help regenerate antioxidant systems and maintain the intracellular redox status and glutathione peroxidases, which reduce hydrogen peroxide and lipid and phospholipid hydroperoxides (42). Oxidative stress is a condition including

increases of age, tumor or inflammatory disease that the cells are always exposed to therefore, the body has defenses with oxidative stress condition through antioxidant substances. Selenium as a major of the antioxidant component that used by the body in the oxidative stress situation, so it is not surprising that the lower level of selenium in the body found in this condition and it's probably necessary to give selenium supplementation in these conditions (43).

Levels of serum selenium are known to be positively correlated with the activity of GPx (15). In Asemi et al study selenium supplementation with dose 200 µg/d compared with placebo in the woman with gestational diabetes mellitus can significantly reduce inflammatory indices such as insulin resistance and high-sensitivity C-reactive protein and increased insulin sensitivity (44). In another study, similar results were obtained and selenium supplementation could reduce oxidative stress indices in patients with diabetic nephropathy (45). Recently, it has been shown that normal or high levels of selenium in rats' diet reduce their mortality compared with low levels of selenium in their diet (46). Selenium may also protect the vascular endothelium from damage and decrease the oxidation of lipids due to oxidized LDL cholesterol particles (47). In general, the presence of normal selenium levels due to its antioxidant role and participation in the normal function of selenoproteins can improve vascular health and selenium deficiency can increase the level of oxidative stress.

5. Conclusion

There is substantial evidence about the importance of selenium and its selenoproteins in cardiovascular health, which is mainly due to its antioxidant effects. Epidemiological studies have shown an inverse association between normal selenium levels and risk of cardiovascular disease, but the credibility and validity of this evidence are unclear.

Although the role of selenium supplementation in the prevention and treatment of heart and vascular disease is still uncertain, most epidemiological studies have shown a U-shaped relationship between selenium levels and the risk of cardiovascular disease.

We suggest that the extensive selenium supplementation or of any other strategy that artificially increases selenium levels above optimum status required for optimal selenoprotein function and other body requirements is not recommended at this time.

Further randomized clinical trials are needed to characterize the effects of selenium and selenoproteins in physiological and pathophysiological processes in cardiovascular disease.

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Conflicts of interest

The authors Naseh Pahlavani, Gordon A Ferns and MajidGhayour-Mobarhanhas no financial disclosures, and no conflict of interest to report.

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