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Review

Selenium homeostasis and clustering of cardiovascular risk factors: a systematic review

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Summary. Selenium is a trace element required for a range of cellular functions. It is widely used for the biosynthesis of the unique amino acid selenocysteine [Sec], which is a structural element of selenoproteins. This systematic review focused on the possible relation between selenium and metabolic risk factors. The literature was searched via PubMed, Scopus, ISI Web of Science, and Google Scholar. Searches were not restricted by time or language. Relevant studies were selected in three phases. After an initial quality assessment, two reviewers extracted all the relevant data, whereas the third reviewer checked their extracted data. All evidence came from experimental and laboratory studies. Selenoprotein P is the best indicator for selenium nutritional levels. In addition, high levels of selenium may increase the risk of metabolic syndrome while the lack of sufficient selenium may also promote metabolic syndrome. selenium supplementation in subjects with sufficient serum selenium levels has a contrary effect on blood pressure, LDL, and total cholesterol. According to the bioavailability of different types of selenium supplementation such as selenomethionine, selenite and selenium-yeast, it seems that the best nutritional type of selenium is selenium-yeast. Regarding obtained results of longitudinal studies and randomized controlled trials, selenium supplementation should not be recommended for primary or secondary cardio-metabolic risk prevention in populations with adequate selenium status. (www.actabiomedica.it)

Key words: selenium, hypertension, diabetes, obesity, cardiovascular disease, risk factors, metabolic syndrome

Introduction

As a medicine with toxicity, selenium (Se), was first doubted to be used immediately after being discovered in 1817. It especially involves those who work in industries (1). Selenium has been shown to be present in some biological systems since more than 60 years ago (2). Being found a few years later, selenocysteine was learned to be encoded by the codon UGA during the 1980s (3). Today, selenium is mainly applied in redox reactions, as well as in the biosynthesis of a unique amino acid, selenocysteine (Sec), which is a structural element of selenoproteins (3). Nearly 35 selenoproteins have been already introduced (4).

Se was first reported by Seale et al. to be as the main part of a diet and thus its necessary biological amount was suggested for human health (5). A significant geographical variation is seen in its dietary intake

from plants, which is low in Europe due to differences in its bioavailability. In some parts of the world, such as the UK, China, and Russia, its considerably reduced intake can be mainly caused by the lowered imports of wheat grown in the northern selenium-rich high-protein soils for making bread. Its deficiency has been frequently reported in regions where most food is locally grown and consumed (6).

Se has been also reported to be involved in the brain (7), immune system, and thyroid functions (8), as well as infertility (9), prevention of cancer (10), diabetes (11), and cardiovascular diseases (12). Therefore, it seems to play a vital role in the metabolic syndrome incidence and progress, i.e., clustering of cardio-metabolic risk factors like glucose intolerance, dyslipidemia, abdominal obesity, and hypertension (13-14). The prevalence of the mentioned syndrome is rather high among Iranian people, especially women with increasing ages (15). The enhanced production of reactive oxygen and nitrogen species in human body would provide several components of metabolic syndrome. Therefore, oxidative stress relevant to metabolic syndrome seems to be the most important pathway (16).

The oxidative process can be reduced by numerous antioxidants including β-carotene, vitamin C, and micro-elements, such as zinc and copper via inactivation of free radicals, and thus the organism can be protected against metabolic syndrome complications (17). This study aimed to find the relationship between selenium homeostasis and cardiometabolic risk factors, specially metabolic syndrome.

Materials and method

Data Sources and search strategy

Literature research included recorded studies conducted from January 1966 to December 2015. To find relevant articles, searches were made in MEDLINE via PubMed, Scopus, ISI Web of Science, and Google Scholar. Searches were not restricted by language. Keywords included: “selenium” and “metabolic syndrome”, “selenium and cardiovascular disease”, “selenium” and “diabetes”, selenium” and “hypertension”, and “selenium” and “abdominal obesity”.

Inclusion criteria

To identify the relevant studies focused on selenium bioavailability and its levels associated with cardiovascular diseases and risk factors and metabolic syndrome, the following inclusion criteria were applied in the current review.

Discussion and conclusion

Selenium involvement in biological systems

In various pathophysiological conditions, selenium plays an essential role. Via the synthesis of selenoproteins containing at least one selenocysteine (Sec) as an amino acid, it is involved in biological pathways. Most selenoproteins have oxidoreductase functions. Sec is co-translated into a growing polypeptide in response to UGA codon, which ultimately terminates the translation. progress The Sec insertion machinery is developed by the biosystems to decode UGA as Sec. This machinery allows this amino acid to be assimilated at exclusive UGA codons with the help of a cis-acting element of Sec Insertion Sequence (SECIS) (18-22).

Transcription of selenoproteins in tissues differs based on a response to dietary intake of selenium or reactive oxygen species (23) as environmental signals. There are lower mRNA levels of several selenoproteins under selenium absence conditions (24). This process has been shown to occur through the decay of transcripts mediated by nonsense in-frame termination codons (25). However, selenoprotein translation is regulated by reduced mRNA levels, which are less considerable than the decrease in selenoenzyme activities (26-27).

Selenoprotein synthesis regulation can be controlled via a suitable UGA codon (Sec) recognition. Some studies have demonstrated that UGA translation is not responsive to selenium alone, while selenium supplementation is more efficient as UGA codon is read by reducing polysome loading of selenoprotein mRNAs (28). According to the results of reporter assays based on UGA or UGU at an appropriate position, Sec translation efficiency has been estimated from 1% to 15% (30).

tRNA[Ser]Sec may have a regulatory role in this process though SECIS elements individually support UGA recognition as Sec (29). Selenium appears as selenocysteine at the active site of many selenoproteins, such as glutathione peroxidase enzymes of classical GPx1, gastrointestinal GPx2, plasma GPx3, and phospholipid hydroperoxide GPx4 as a major class of selenoproteins with important functions.

Thioredoxin reduction, which is dependent on NADPH, is catalyzed by Thioredoxinreductase (TR) enzyme recently identified to contain selenocysteine, thus regulating its metabolic activity. Selenoprotein P with 10 Se atoms per molecule as selenocysteine contains almost 60% of Se in plasma. It may act as a protein transporting selenium. However, many other tissues have selenoprotein-P expression. This suggests that facilitation of selenium distribution in the whole body is not its sole function.

Being involved in the catalysis of 5'5-mono-deiodination of prohormonethyroxine (T4) to 3,3',5'-triiodothyronine (T3) as an active thyroid hormone, iodothyroninedeiodinase enzymes make the second major class of selenoproteins. The mid-piece portion of spermatozoa is a site for sperm capsule selenoprotein where the sperm flagella integrity is stabilized. As reported to be necessary for muscle metabolism, selenoprotein W is affected by selenium intake in terms of tissue concentrations. Having no systematic investigation conducted on reduced Se status in the UK over the past 2 decades would be a great concern for health implications.

Selenium homeostasis in patients with cardiovascular diseases

Selenium role in cardiovascular diseases has not been proven and thus remained highly controversial though many studies have been conducted on this issue. Overall, a significant relationship between selenium and cardiovascular diseases can be found in the baseline selenium concentration as a determining factor (30).

On this basis, carotid artery atherosclerosis progression in men with high serum LDLs has been reported by Salonen et al. to be probably related to serum selenium concentrations (31). Additionally, myocardial infarction risk and death caused by ischemic heart diseases were discovered by them to be resulted from low selenium content of the Finnish soil in the eastern area of Finland as a determining factor (32). Lower serum selenium than 79 μg/L was identified by another cohort study in Denmark to enhance coronary heart disease risks among subjects with no relevant pre-existing histories (33). In contrast, no relationship between selenium concentration and ischemic heart diseases was found by Miettinen et al. (34). Moreover, in their study in the countryside areas of eastern and southwestern Finland, Virtamo et al. were not able to find a significant association between coronary heart disease risk and serum selenium (35). The association between cardiovascular diseases and serum selenium could not be explained by the studies carried out in other parts of Europe as well (36-37).

Higher mean serum selenium concentrations were found in all the above studies compared to those reported in the Finnish studies (31-33). Correspondingly, no relationship was seen between serum selenium and myocardial infarction risk in the US population. This can be due to high selenium intake level among them (38). In this research, very few subjects were found with less serum selenium than 80 μg/L, while the mean plasma levels were high among the rest and controls.

Several studies have dealt with the association between coronary disease extents and selenium status. As quantified by angiography, coronary atherosclerosis severity and serum selenium concentration were reported by these studies to be inversely correlated (39-40).

Selenium and cardiometabolic risk factors

a. Selenium and Diabetes

In different regions with high (the US) and low (China and the UK) selenium statuses, few data on the relationship between cardiometabolic risk factors and selenium status are available among the general population (41). An enhanced prevalence of diabetes was discovered by Laclaustra et al. to have occurred with increasing selenium levels in American adults (42-45).

The relationship between glycosylated hemoglobin levels, fasting plasma glucose, and diabetes and serum selenium concentrations was evaluated by La-

claustra et al. with the help of regression models and their prevalence was found to have augmented with increasing selenium concentrations up to 160 micro G/L (42). No relationship between diabetes or glucose levels and selenium was observed in countries with lower selenium levels, such as Singapore and France (42). Also, an association between blood selenium levels and metabolic syndrome and higher fasting blood sugar levels was discovered among Chinese adults (46).

b. Selenium and dyslipidemia

Higher cholesterol, triglyceride, and fasting glucose were found to be associated with higher selenium levels in a study on elderly Taiwanese (46). The relationship between blood lipids and plasma selenium concentration in British adults was observed with a mean plasma selenium concentration of 1.10 ± 0.19 micromol/L by Stranges et al. Contrary to HDL levels, enhanced non-HDL and total cholesterol levels were discovered to be associated with higher plasma selenium (> or = 1.20 micromol/L) in the UK adult population (47). In another research among US adults with sufficient selenium uptakes, elevated serum concentrations of HDL and LDL cholesterol, total cholesterol, triacylglycerol, apo A-I, and apo B were demonstrated by Bleys et al. to be associated with increased serum selenium levels (48). HDL cholesterol rise among US population was reported by the National Health and Nutrition Examination Survey [NHANES] to only occur at low selenium levels in 2003-2004 (42).

c. Selenium and hypertension

An underestimated risk factor of selenium deficiency was declared by Nawrot et al. to probably lead to the development of high blood pressure among European men. In this regard, 2.2 and 1.5 mmHg lower systolic and diastolic blood pressures [P= 0.017] were shown to be associated with a higher blood selenium of 20 μg/L by them by performing multivariate-adjusted cross-sectional analyses on men, respectively. Although no significant relationship was found between selenium and hypertension in women, a lower risk of developing high-normal blood pressure (37% [P = 0.001]) was discovered to be associated with a higher baseline blood selenium of 20 μg/L in their prospective analyses in men (49).

d. Selenium and obesity

No directly sufficient data on the relationship between abdominal obesity and selenium are available; yet, the role of different regimes containing high selenium resources of fruits and legumes as obesity indicators has been considered by few studies. Through insulin-resistance mechanisms, selenium seems to play a role in obesity pathophysiology. Improvement of the Body Mass Index (BMI) levels in obese children has been stated by Velázquez-López et al. to be resulted from a high uptake of mineral antioxidants like selenium through a Mediterranean eating regime (50). Based on a combined antioxidant supplementation with selenium, vitamin C, and vitamin E in obese children and adolescents participating in a modification program, various types of obesity were claimed by Mureret al. to be probably linked with inflammatory pathways and oxidative stresses (51).

Improved metabolic characteristics and reduced proinflammatory status in overweight and obese people was revealed in another study carried out by Hermsdorff et al. to be resulted from a hypocaloric diet based on legumes (52). A great advantage was shown by Savini et al. to be provided by foods containing antioxidants in obese subjects via redox state modulation (53).

Selenium supplementation in different target groups and cardiometabolic risk factors

Cardiometabolic risk factors in different target groups have been investigated by several studies. The efficiencies and biological activities of various types of selenium and improper forms for selenium supplementation in the mentioned groups have raised many questions. Plasma selenium was significantly modified after at least one week. After 2 to 11 weeks of supplementation, a stable status was achieved with the inorganic forms. Higher net enhancement was observed in the population groups of low selenium areas compared to those with a higher intake of basal selenium (54). On the contrary, increased levels of plasma selenium were seen to be caused by selenomethionine even after supplementation for 8.5 weeks (55).

The bioavailability of various selenium types, including organic-derivative forms of selenium, selenite, selenomethionine, food selenium, and yeast were in-

vestigated by another study (56). Although yeast selenium produced inconsistent results, food (wheat and meat) selenium resulted in similar findings. In the case of yeast selenium, either a plateau in plasma selenium after 2, 11, and 16 weeks (57-59) was obtained or in a steady enhancement in selenium levels was caused until the end of the experiment at 11 to 12 weeks (60-61). Changes in plasma selenium remarkably differed from those of erythrocyte selenium. Only Chinese subjects with very low Se showed increased selenium levels of erythrocyte triggered by inorganic forms (62). Otherwise, even after 32 weeks, no modification was seen to have been caused by inorganic selenium supplementation.

Contrarily, all the studies revealed selenium enhancement in red blood cells caused by organic forms except for a study on yeast selenium (63). The activity of erythrocyte GSH~Px was shown as a less sensitive indicator of changing selenium levels due to changes in plasma, red blood cells, and glutathione peroxidase activities of platelets (64). A significant augmentation necessarily occurred at a slow rate of 4 to 6 weeks for a modification (65). GSH-Px activity of red blood cells in the Finish population underwent no changes induced by selenium intake of about 40 mg/day as reported by Levander et al. Also, a significant rise or change in GSH-Px activity of erythrocytes was reported by them to incumbently occur at least 1 to 3 weeks of supplementation (64).

Butler et al. (65) noted that selenate taken by women in New Zealand was associated with greater percentages of selenium and GSH-Px in plasma and red blood cells compared to those taking selenomethionine. They concluded higher blood selenium levels occur for selenomethionine compared to selenite when GSH-Px activity of platelets is saturated (65).

No protective effect of antioxidant supplementation in a well-nourished population was revealed by another clinical trial conducted on 5,220 participants. Nevertheless, subjects at risk for metabolic syndrome could be protected by baseline concentrations of serum antioxidants. This was highly dependent on lifestyle and particularly dietary patterns (66).

Glucose intolerance risk has not been shown to be significantly increased by high doses of supplemental selenium. However, the ineffectiveness of selenium supplementation on the prevalence of type 2 diabetes was revealed in the subjects participating in a Selenium and Vitamin E Cancer Prevention Trial (SELECT) via a follow-up analysis for 10 years (67). Thus, our understanding of selenium regulation, especially its influence on energy metabolism is limited by these findings.

A nutritional dose of nearly 50 to 200 μg/day of selenium was suggested by Joseph et al. based on the relationship between selenium and various disorders, such as myocardial ischemia/infarction, cardiomyopathy, and reperfusion injury (68).

Conclusion

Several notable facts about selenium were revealed by this systematic study. First, selenium exact effect on cardiometabolic risk factors depends on serum selenium level. Lack of adequate selenium may develop metabolic syndrome, while high selenium levels may also increase the risk of metabolic syndrome. People with sufficient selenium levels should not take selenium supplements as cardiometabolic risk factors in a population with adequate selenium levels of serum are adversely affected by selenium treatment. For instance, selenium supplementation in the mentioned groups had a reverse influence on their blood pressures, LDLs, and total cholesterols.

Second, selenium nutritional levels seem to be indicated by selenoprotein P in the best way. Thus, selenium deficiency can be determined by selenoprotein P measurement among different populations.

Third, the best nutritional type of selenium seems to be selenium yeast as examined from different types of selenium supplementations, such as selenite, selenomethionine, and yeast selenium based on bioavailability.

Finally, primary or secondary cardiometabolic risks cannot be prevented by selenium supplementation in populations with sufficient selenium status considering the results of longitudinal studies and randomized controlled trials. However, plasma concentration of selenoprotein P can be optimized in a population with lower selenium concentrations by recommending a nutritional dose of 50 to 200 μg/day of selenium.

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