

A systematic review on the association of serum selenium and metabolic syndrome

Mohammad Hasan Tajaddini, Mojtaba Keikha¹, Ali Razzazzadeh², Roya Kelishadi¹

Department of Physiology, Applied Physiology Research Center, Isfahan University of Medical Sciences, ¹Department of Pediatrics, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, ²Department of Pediatrics, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Background: This systematic review paper aims to study the experimental and human studies on the relationship between metabolic syndrome (MetS), its component and selenium (Se) concentration. **Materials and Methods:** The literature was searched in PubMed, Scopus, and Google Scholar databases with no time limitation using MetS X and Se key words in medical subject heading. The related papers were selected in three phases. After quality assessment, two reviewers extracted the data, whereas the third reviewer checked their extracted data. All evidence comes from experimental and laboratory studies. **Results:** Finally, 18 articles were included. While, some studies documented that as an antioxidant agent, Se might be correlated with endothelial function, large controversy exists about the type of correlation including positive, negative, and no correlation between MetS and Se levels in body. Some of the reviewed studies were focused on antioxidant supplementation effects on MetS, results also varied in this regard. **Conclusion:** This inconsistency could be because of diversity in study design, population, lack of special focus on Se and MetS, and finally the complex nature of MetS.

Key words: Selenium, metabolic syndrome, prevention, systematic review

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INTRODUCTION

Metabolic syndrome (MetS) has become a major global disease,^[1] it represents a clustering of abnormalities typically involving abdominal obesity, insulin resistance, dyslipidemia, and hypertension.^[2] MetS is common^[3-5] and its risk increases with age.^[4]

In addition, various other abnormalities of uric acid, inflammation, hemostasis, and fibrinolysis are often considered part of this syndrome. Not surprisingly, people with the MetS are at high-risk for developing diabetes and cardiovascular diseases.^[6-10] Oxidative stress may also play a role in the pathophysiology of diabetes and cardiovascular disease.^[11,12]

The role of inflammation and oxidative stress on several chronic diseases is receiving increasing attention

because of their links with atherosclerosis, obesity, or type 2 diabetes mellitus^[13,14] cause-effect relationships between inflammation, oxidative stress, and disease are not clear; but several studies associate features of MetS with higher concentrations of inflammatory biomarkers.^[15,16]

Furthermore, recent findings indicate that elevated levels of adipokines and acute-phase inflammatory markers are associated with some manifestations accompanying features of MetS (adiposity, insulin resistance, dyslipidemia, etc.), and an increased risk for cardiovascular disease.^[17-19]

If antioxidants play a protective role in the pathophysiology of diabetes and cardiovascular diseases, understanding the physiological status of antioxidant concentrations among people at high-risk for developing these conditions, as individuals with MetS, is of interest. However, little is known about this

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Address for correspondence: Dr. Mojtaba Keikha, Department of Pediatrics, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: mr.mojtabakeikha@gmail.com

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topic. Because the prevalence of obesity, which is associated with decreased concentrations of antioxidants,^[20] is high among people with MetS, they are probably more likely to have low antioxidant concentrations.

On the other hand, epidemiological studies have shown that selenium (Se) is a protective factor against cardiovascular diseases.^[21,22] Its protective ability is considered due to the fact that Se has anti-inflammatory and antioxidant properties.^[23,24] Furthermore, the inverse correlation between serum Se and high-sensitive C-reactive protein (CRP) indicates that low Se level may be associated with oxidative stress, which may cause lipid peroxidation.^[25]

Se considered as a micronutrient and is an essential trace element in human metabolism. New researches have shown a pivotal role for this element in human health.^[26] Se has antioxidant and anti-inflammatory role through glutathione peroxidase (GPx) which can reduce hydrogen peroxide, lipid and phospholipid hydroperoxides, radicals, and reactive oxygen species.^[27] This trace element may have a protective role against cardiovascular disease due to the ability of GPx to reduce the oxidative modification of lipids and to decrease platelet aggregation.^[28] Because Se is normally found in significant amounts in immune tissues and has many effects on immune system, deficiency of Se is accompanied by loss of immunocompetence.^[27,29,30]

Many dietary and lifestyle factors may contribute to increasing risk of developing MetS and cardiovascular disease,^[31] and oxidative stress, and low antioxidant status may be associated with the unfavorable metabolic pattern. Available data are inconsistent.

Race, study design, animal or human studies, and different characteristics of participants such as sex, age, and body weight are other factors that influence differences in the findings obtained in various studies. This study aims to review the findings of human studies on the association of Se with MetS.

MATERIALS AND METHODS

Literature search

The search was conducted using Medline, Scopus, and Google Scholar databases to May 24, 2014. We search in the Medline literature database through PubMed and In PubMed, we used the medical subject heading.

Keywords including as MetS X and Se were used. The search was refined to the English language on human studies. We did not consider any time limitation. For any additional

pertinent studies, the reference list of all relevant papers was screened as well. The process of selecting studies is depicted in Figure 1.

The methodological quality of each eligible paper was assessed using a checklist based on guidelines provided in an earlier study,^[32] in which papers were assigned up to a total score of 8 for fulfilling the main issues in prevalence studies, including sampling, measurements, and analysis.

Titles and abstracts of papers were screened and relevant papers were selected and duplicates were removed. Then, full texts of relevant papers were read, and findings were rescreened. Two independent (MK and MT) reviewers screened titles and abstracts of papers identified by the literature searches for their potential relevance or assessed the full text for inclusion in the review. In the case of disagreement, and the discrepancy was resolved in consultation with a third arbitrating investigator (RK).

Data extraction and abstraction

Two reviewers abstracted the data independently. The required information that was extracted from all eligible papers was as follows: Data on first author's last name, year of publication and country of the study population, the study name, study design characteristics, study population, type of study, aim, and finding of studies.

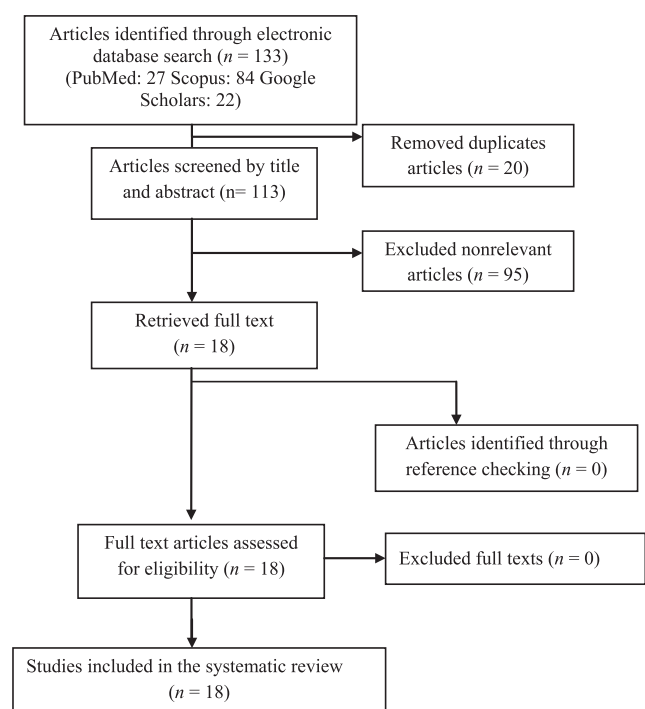


Figure 1: Papers search and review flowchart for selection of primary study

RESULTS

Pizent *et al.* in 2010 in Croatia demonstrated that MetS has no correlation with serum Se, zinc (Zn) and copper (Cu) concentration and superoxide dismutase and catalase activity. Higher GPx was found in subjects with MetS as well as in individuals with hypertriglyceridemia, and Cu concentration shown a significant correlation with CRP.^[33] Hughes *et al.* in 1998 in Singapore showed that in both genders people with noninsulin-dependent diabetes mellitus had higher mean body mass indices, waist-hip ratios, and abdominal diameters. Higher prevalence of hypertension, higher mean levels of fasting serum triglyceride, slightly lower mean levels of serum high-density-lipoprotein (HDL) cholesterol, and higher mean levels of plasma plasminogen activator inhibitor-1 and tissue plasminogen activator. These factors are components of MetS and increase the risk of atherosclerosis and thrombosis. However, no important differences existed for plasma Vitamins A, C, and E, and especially in this case, serum Se, which are antioxidants.^[32] Ford *et al.* in a cross-sectional study in 2003 evaluated antioxidant status among individuals from United States with MetS who were at high-risk for developing these conditions, data revealed from this study showed that adults with MetS have suboptimal concentrations of several antioxidants, which may partially explain their increased risk for diabetes and cardiovascular diseases and no significant differences existed in the concentrations of serum Se.^[33]

Vidovic *et al.* in 2013 showed that the plasma Se level correlated positively with MetS, waist circumference, plasma glucose, and triglyceride concentration in Serbian patients with schizophrenia. In contrast, plasma Zn did not correlate with any of the MetS components.^[34] Obeid *et al.* in 2008, evaluated the relation between the status of plasma Zn, Cu, and Se, especially in terms of their relation to the components of MetS in a cross-sectional study in Lebanon. Their data revealed that plasma Se levels correlated positively with all MetS components.^[35] Arnaud *et al.* in 2012 in a cross-sectional study investigated the relationships between plasma Cu, Zn, and Se concentrations and MetS in France. Results indicated gender differences in the association between plasma Se concentration and MetS without diabetes; they suggested a subclinical deleterious effect of high Se concentrations in women.^[36]

Puchau *et al.*, in four different studies from 2009 to 2010 in Spain, evaluated the associations between serum complement factor 3 (C3) and several anthropometric, biochemical and lifestyle features in healthy young adults, emphasizing on the putative effect of Se intake on C3

concentrations, potential associations between nail trace elements and several indicators in healthy young adults focusing on the effect of antioxidant trace element intake on inflammation-related marker concentrations, potential associations among dietary total antioxidant capacity and several early MetS manifestations and potential associations between serum asymmetric dimethylarginine (ADMA) and several anthropometric, biochemical, and lifestyle features in healthy young adults. These studies showed a possible role for Se intake in the modulation of C3; its assessment may be an early marker of the MetS manifestations.^[37] Nail content on some trace elements related to antioxidant defense mechanisms seems to be associated with several inflammation-related markers linked to chronic diseases in apparently healthy young adults,^[38] negative and significant associations between MetS and Se intake.^[39] ADMA seems to be related with Se status and several anthropometric and biochemical measurements linked to MetS in apparently healthy young adults. These findings support a role for antioxidant/trace element intake in the modulation of ADMA; its assessment may be a marker for MetS.^[40] Mutakin, *et al.* in 2013, conducted a cross-sectional study that aimed to examine the possible correlation between Se nutritional status and metabolic risk factors in men with visceral obesity in Indonesia. It showed that negative association between Se nutritional status and metabolic risk factors is limited to a particular group of obese men with or without MetS.^[41]

Ghayour-Mobarhan *et al.* in 2008 evaluated the serum concentrations of Se and GPx concentrations in Caucasian patients with obesity and MetS in the United Kingdom. They found that the clinic patients had a significantly higher dietary intake of total fat, protein and Se compared with the healthy individuals. Patients also had significantly higher serum Se and lower serum GPx concentrations compared to the healthy individuals. Among the patients, obese subjects had significantly higher serum concentrations of Se and lower serum GPx. Moreover, within this group, serum Se concentrations decreased significantly with accumulating features of MetS. The lower levels of serum GPx in obesity and lower concentrations of serum Se associated with accumulating features of MetS may be related to the presence of an atherosclerosis prone state with an increased consumption of antioxidants by free radical interaction.^[42] Skroza *et al.* in 2013 evaluated the role of a nutraceutical containing Q10 coenzyme, krill-oil, lipoic acid, resveratrol, *Vitis vinifera* seed oil, Vitamin E, and Se in addition to etanercept therapy for patients affected by psoriasis and MetS in an open-label randomized controlled study in Italy. Although the role of confounding factors in this study were not eliminated, revealed data showed statistically significant differences in HDL cholesterol

and triglycerides concentrations.^[43] Moreover, Zulet *et al.* in 2009 conducted an observational study that evaluated the potential relationships between serum sialic acid (SA) a levels, MetS features, and dietary Se intake in Spain to test the hypothesis that this antioxidant micronutrient may also have anti-inflammatory properties in healthy young adults. It showed that subjects with higher dietary Se intake showed significantly lower SA levels compared with subjects with lower dietary Se intake, while dietary Se negatively correlated with SA and recommended Se as a potential anti-inflammatory nutrient.^[37] Contrary to the results of these two papers, Czernichow *et al.* in 2009, during a clinical trial study in France examined the effect of antioxidant supplementation for 7.5 years on the incidence and the epidemiologic association between baseline serum antioxidant concentrations and the prospective risk of MetS. This longitudinal study showed that antioxidant supplementation for a period of 7.5 years did not affect the risk of MetS.^[44] In addition, Basu *et al.* in 2013 during a clinical trial showed that Se was not affected by green tea supplementation in cases with MetS in the United States.^[45] Silva *et al.* investigated the relationship between habitual physical activity and dietary intake, body composition, metabolic and hormonal variables, and cardiovascular risk factors in Brazilian postmenopausal women with no evidence of cardiovascular disease in 2013. The results showed that active women had higher protein, total fat, cholesterol, iron, calcium, and the antioxidant micronutrients Zn and Se intake.^[46] Perez-Cornago *et al.* in 2014, evaluated the association between dietary intake of water, fiber, Vitamin B6, ascorbic acid, tryptophan, magnesium, and Se with mood state in subjects with MetS in Spain. The results showed those participants who consumed more water, fiber, Vitamin B6, ascorbic acid, tryptophan, magnesium, and Se had higher mood.^[47]

Summary of the studies on the association of Se and MetS are shown in Table 1.

DISCUSSION

In recent years, along the prevalence of adolescent obesity, the rate of MetS incidence increased dramatically^[48,49] and diet is the one of most important factor in this increased incidence.^[50] Micronutrients are considered as an essential part of the diet which have an important role in metabolism regulation.^[51] Se is an essential micronutrient and has multiple roles in metabolism homeostasis. Particularly, in normal concentrations Se has an adverse effect on oxidant species and consequently has a protective role against cardiovascular disease.^[26] On the other hand, MetS is one of the important causes of cardiovascular diseases.^[48]

In the current study, we provided and summarized the information about the relationship between MetS components and Se as a trace element. The evidence comes from experimental studies.

As mentioned before, Se is considered as an antioxidant agent and its expected the concentration of this element be found correlated with endothelial function. Some studies support the hypothesis that Se levels have no correlation with MetS.^[33-35]

However, some other studies support the hypothesis which Se levels have a positive correlation with MetS.^[36-38]

Controversy exists between results obtained from studies on the correlation of MetS and Se levels are complete when the some other studies suggest that Se has a negative correlation with MetS.^[39-43]

The controversy between results also seen in another type of studies, the effect of Se together other antioxidants on metabolic profile and health was evaluated in some of the clinical trials. The results of these studies were different too.^[37,44-47]

Furthermore, the relation between lifestyle, MetS, Se status and the psychological state has been studied in two independent studies, the results from both of studies showed a positive correlation between the quality of life and Se status.^[48,49]

CONCLUSION

Large controversies exist about the effects and correlation of Se on a component of MetS, which may be due to differences in study designing and population. In addition, there are a few articles focused specifically on Se and MetS. Instead, many confounding factors were included in these papers. This controversy in the study findings could also be because of the complex and multifactorial nature of MetS, and different definitions used for this disorder.

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Nil.

Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

All authors contributed in the study concept and design, assisted in the literature review, and drafting the paper. All authors have read the final version of the paper and accept the responsibility for its content.

Table 1: Summary of the association of Se and MetS					Finding (main result)
Name of first author, year	location	Number population Male/female	Type of study	Aim	
Pizent, 2010	Croatia	100 42/48	Cross-sectional	Whether concentrations of several trace elements and activities of several antioxidant enzymes are modified in MetS, and to evaluate their possible association with MetS components	No clear influence of MetS on Se was found
Hughes, 1998	Singapore	656 320/336	Case-control	Evaluate relation between serum antioxidant component and MetS features	There were no important differences serum Se
Ford, 2003	USA	8808 NA/NA	Cross-sectional	Evaluate antioxidant status among individuals with the MetS who are at high-risk for developing these conditions	Adults with the MetS have suboptimal concentrations of several antioxidants, which may partially explain their increased risk for diabetes and cardiovascular disease. No significant differences in concentrations of serum retinyl esters, lycopene, and Se existed
Vidovic, 2013	Serbia	120 38/82	Case-control	Determine the plasma Se, Cu, and Zn levels and to evaluate their possible association with MetS components in patients with schizophrenia	The plasma Se level correlated positive with MetS score, waist circumference, plasma glucose, and triglyceride concentration in patients with schizophrenia and plasma Se levels in medicated patients with schizophrenia could be associated with metabolic risk factors
Obeid, 2008	Lebanon	398 159/237	Cross-sectional	Evaluate the relation between statuses of plasma Zn, Cu, and Se, especially in terms of their relation to the components of the MetS	Plasma Se levels correlated positively with all the components of the MetS
Arnaud, 2012	France	1902 942/960	Cross-sectional	Investigating the relationships between plasma Cu, Zn and Se concentrations and MetS in the immediate population	No association in men whereas, in women, MetS was associated with higher plasma Se concentrations
Puchau, 2009	Spain	100 21/79	Cross-sectional	Evaluate the associations between serum C3 and several anthropometrical, biochemical and lifestyle features in healthy young adults, emphasizing on the putative effect of Se intake on C3 concentrations	C3 related with Se status linked to MetS in apparently healthy young adults
Puchau, 2009	Spain	93 19/74	Cross-sectional	Evaluate the potential associations between serum ADMA and several anthropometric, biochemical, and lifestyle features in healthy young adults, emphasizing on the putative effects of the antioxidant intake on ADMA concentrations	Nail Se and Zn were significantly different between subjects with serum ADMA higher and lower than the median
Puchau, 2010	Spain	149 48/101	Cross-sectional	Evaluate the potential associations between nail trace elements and several indicators in healthy young adults, emphasizing on the putative effect of antioxidant trace element intake on inflammation-related marker concentrations	Se was negatively associated with IL-18, Se values were negatively correlated with homocysteine levels
Puchau, 2010	Spain	153 52/101	Cross-sectional	To assess the potential associations among dietary TAC and several early MetS manifestations in healthy young adults	TAC may be also a potential early estimate of the risk to develop MetS features and that dietary TAC could be a useful research tool in assessing antioxidant intake
Mutakin, 2013	Indonesia	123 123/0	Cross-sectional	Aim of this study was to examine possible correlation between Se nutritional status and metabolic risk factors in men with visceral obesity	In the obese group, Se positively correlated with HDL cholesterol and with FABP4. In the MetS group, Se negatively correlated with MCP-1

Table 1: (Continued)

Name of first author, year	location	Number population Male/female	Type of study	Aim	Finding (main result)
Gayour-Mobarhan, 2008	UK	237 142/95	Case-control	To determine the serum Se and GPx concentrations in Caucasian patients with obesity and MetS	Clinic patients had a significantly higher dietary intake of total fat, protein and Se compared with the healthy individuals. Patients also had significantly higher serum Se and lower serum GPx concentrations compared to the healthy individuals. Within the patient group, obese subjects had significantly higher serum concentrations of Se and lower serum GPx (compared with nonobese patients. Moreover, within this group, serum Se concentrations decreased significantly with accumulating features of MetS. The lower levels of serum GPx in obesity and lower concentrations of serum Se associated with accumulating features of the MetS may be related to the presence of an atherosclerosis prone state with an increased consumption of antioxidants by free radical interaction
Skroza, 2013	Italy	40 NA/NA	Open-label randomized controlled	Evaluate the role of a nutraceutical containing Q10 coenzyme, krill-oil, liponic acid, resveratrol, <i>Vitis vinifera</i> seed oil, Vitamin E, and Se in addition to etanercept therapy for patients affected by psoriasis and MetS	Statistically significant differences were detected in HDL cholesterol and triglycerides values
Zulet, 2009	Spain	43 12/31	Observational	Assess the potential relationships between serum SA a levels, MetS features, and dietary Se intake to test the hypothesis that this antioxidant micronutrient may also have anti-inflammatory properties in healthy young adults	Subjects with higher dietary Se intake showed statistically lower SA levels compared with subjects with lower dietary Se intake, while dietary Se negatively correlated with SA
Czemichow, 2009	France	5520 1983/3537	Clinical trial	Examine the effect of antioxidant supplementation for 7.5 years on the incidence of MetS and the epidemiologic association between baseline serum antioxidant concentrations and the prospective risk of MetS	Antioxidant supplementation for 7.5 years did not affect the risk of MetS
Basu, 2013	USA	35 NA/NA	Clinical trial	Evaluate the impact of green tea on (enzymatic and nonenzymatic) on MetS	Cu, Zn, and Se were not affected
Silva, 2013	Brazil	105 0/105	Cross-sectional	Investigate the relationship between habitual physical activity and dietary intake, body composition, metabolic and hormonal variables, and cardiovascular risk factors in postmenopausal women with no evidence of cardiovascular disease	Active women had higher protein, total fat, cholesterol, iron, calcium, and the antioxidant micronutrients Zn and Se intake as well as differences on food groups, active participants also presented lower diastolic blood pressure, ultrasensitive C-reactive protein, fasting glucose, fasting insulin and homeostasis model assessment index
Perez-Cornago, 2014	Spain	84 NA/NA	Cross-sectional	Evaluate the association between dietary intake and mood state in subjects with MetS	Those participants who consumed more water, fiber, Vitamin B6, ascorbic acid, tryptophan, magnesium, and Se have higher mood

MetS = Metabolic syndrome; HDL = High-density lipoprotein; TAC = Total antioxidant capacity; GPx = Glutathione peroxidase; Se = Selenium; Cu = Copper; Zn = Zinc; ADMA = Asymmetric dimethylarginine; MCP-1 = Monocytes chemoattractant protein-1; FABP4 = Fatty acid binding protein 4; NA = Not available; C3 = Complement factor 3; SA = Sialic acid; IL-18 = Interleukin-18

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