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Abstract

Background. Since selenium (Se) constitutes a functional part of anti-oxidant enzymes this element is considered to counteract oxidative stress in metabolic syndrome (MetS).

Methods. Literature was screened for publications from 2010 up to November 2019. Keywords in various combinations were used.

Results. Conflicting data were found for a possible correlation of MetS and various indicators of the Se status. For Se levels in human blood most of the publications tend to indicate a positive association with biomarkers of the MetS, especially parameters in the lipid profile.

Conclusion. The complex character of the syndrome with the various diagnostic criteria and biomarkers used is one factor contributing to the conflicting results. Other confounding factors are the sampled population with variation in baseline Se-level, age, gender, size of the groups and lack of control on medication and other antioxidants taken.

Keywords: metabolic syndrome (MetS), biomarkers, selenium (Se) blood concentration, daily intake

Introduction

Selenium (Se) is an essential trace element in a number of Se-proteins including the glutathione peroxidases (GPX), a family of enzymes that protects against oxidative injury by catalysing the breakdown of hydrogen peroxide and lipid peroxides (1). There are about 24 human genes encoding for Se-proteins (2). Insufficient intake of this element results in increased risk of developing many chronic degenerative diseases. The Keshan disease is a typical example of endemic heart failure due to severe selenium deficiency (3,4). Therefore it is believed that a certain level of Se is essential for human health.
In most publications, the Se status has been assessed by measuring the element either in serum or plasma, erythrocytes, platelets or whole blood, and by determination the GPX-activity in whole blood or platelets (5). Serum or plasma reflects the recent daily intake, whereas erythrocytes accumulate Se and presumably reflect the intake over their 120-days span of life (6).
Sometimes toenail (7) or hair (8,9) concentration is considered as a long-term parameter and measured.
Some biomarkers, such as the selenoproteins and particularly GPX3 and SEPP1 provide information about function directly and are of value in identifying nutritional Se deficiency and tracking responses of deficient individuals to Se-treatment (10).

Metabolic syndrome (MetS) is a cluster of risk factors for the development of heart disease, strok and diabetes, which result from excess energy intake and low energy expenditure. It is characterized by abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-c) level, increased blood pressure, and elevated fasting glucose level.
The role of inflammation and oxidative stress on this disorder is receiving increasing attention because of their links with atherosclerosis, obesity, or type 2 diabetes mellitus (11,12).
Metabolic overload evokes oxidative stress, a condition in which an imbalance exists between the production and inactivation of reactive oxygen species (ROS). MetS is accompanied by a chronic low-grade inflammatory condition.
Biomarkers of this syndrome can be divided into various subgroups. In an extended review paper higher concentrations of acute-phase inflammatory biomarkers and elevated levels of adipokines are associated with features of MetS (13).
Since Se acts in anti-oxidative enzymes the element can be considered to have antioxidant and anti-inflammatory properties (11,14). In case of deficient Se status the oxidative stress cannot be counteracted, which leads to lipid peroxidation and risk of MetS and and associated pathophysiological consequences. This was proven by an inverse correlation between Se concentration and high-sensitive C-reactive protein (hsCRP), a sensitive biomarker of inflammation (15). Therefore, Se can be classified in the group of biomarkers of oxidative stress (13).
With this review we aim to discuss recent literature findings of human studies on the association of the Se status with MetS.

Materials and methods

Literature was screened for publications from 2010 up to November 2019. Important older references mentioned in some papers are also included. Also articles in other languages are included, as long as a summary in English was provided.
We have used Pubmed, Science Direct, Web of Science and Google Scolar. “Metabolic syndrome”, “serum Se”, “plasma Se”, “Se-proteins”, “glutathione peroxidase”, “GPX”, “toenail Se”, “hair Se” and “Se intake” were used as keywords in various combinations.

The search is limited to human studies. Publications only covering isolated MetS risk factors, like obesity (16), hypertension (17), type 2 diabetes (17-20) are excluded.
Literature on influence of minerals, oligo- and other trace elements on biomarkers of the metabolic syndrome is reviewed by our group in another review paper (21).

Results and discussion

1. Selenium intake and MetS

Table 1 summarizes results on daily intake of Se in relation to MetS and biomarkers of the syndrome. Three studies found no association between the intake and the syndrome (22-24), two of them found a moderate negative association (25,26), and only one showed a direct association, especially in women (27).
Similar observations were published recently by Retondario et al. (28).
Causes for these conflicting results could be variation in the sampled population (country, size, age, sex), study design, MetS criteria used, food intake assessment tool, amount of intake and type of food with various Se species and bioavailability. Not always there is adjustment for confounders and other variables.
Interestingly, selenium intake was inversely and significantly associated with some inflammation markers in MetS-patients in Spain: retinol-binding protein 4 (29), C3 (30) and, sialic acid (31). For this group in Spain (29-32) a better and more positive mood was related to a higher Se intake (33).

2. Selenium supplementation and MetS

A number of clinical trials have provided convincing evidence on the central role of selenium, either alone or in combination with other micronutrients or antioxidants, in the prevention and treatment of multiple diseases. Advances made so far in the study of mechanisms and applications of selenium compounds that could be suitable for the prevention/treatment of chronic diseases are reviewed by Sanmartin et al. (34).
Bioavailability of the different types of selenium such as selenomethionine, selenite and selenium-yeast can vary widely. Most of the time selenium-yeast is considered as the best nutritional type (35), although also biofortification of wheat is also claimed for better health (36,37).
Intakes for satisfying physiological needs are reflected by classical selenium-dependent biochemical functions (mostly glutathione peroxidase activity) only explain a part of selenium biological potency. Other beneficial effects can by obtained at higher nutritional intakes, which in turn implies specified chemical forms and doses (38). Supranutrional sodium selenite supllementation delivers selenium to the central nervous system (39).
Nevertheless, the widespread use of Se supplementation or other strategies that artificially increase Se status above the level required for optimal selenoprotein activity is not justified and should not be encouraged due to possible toxic or undesired effects (40).
Supplementation of antioxidants (including selenium) for 7.5 years in a generally well-nourished population corroborates the lack of efficacy of antioxidant supplements. A consumption of antioxidant-rich foods, however, is recommended (22).
Selenium supplementation for the treatment of various diseases in the elderly has recently been reviewed (41). However, supplementation studies of Se in MetS patients and its effect on biomarkers of this disorder are scarce.
A systematic review and meta-analysis of randomized controlled trials proved that Se supplementation had no effect on lipid profiles, such as triglycerides, total cholesterol, LDL- and HDL-cholesterol (42).
Only one publication could be traced, where, although there was no effect on plasma Se level, a significant increase in selenoprotein P was observed in the MetS group (43). Another publication

claimed that green tea supplementation increases glutathione and plasma antioxidant capacity in adults with MetS, however plasma Se levels were not affected (44).

3. Selenium concentration in serum/plasma or blood and MetS

Table 2 summarizes some observations on biomarkers of MetS and Se concentrations in human blood. Similar to literature search on the relation of Se intake and MetS, also here published data are quite contradictory reporting no association in Croatia (48), in France (22,50), or the USA (59) to an inverse association in the UK (57).

Already 30 years ago, a positive association of serum Se and HDL-cholesterol levels has been demonstrated (49). However, recently researchers in China presented an inverse association between the two parameters (47).

Se level showed a positive association with anthropometric measures and other biomarkers of the MetS: lipid profiles (46,47,53-56,60-63) and glucose level (45,53,55-56).

Very recently, a case-control study in China demonstrated that serum Se levels were positively associated with MetS following a non-linear dose-response trend. Se concentration was positively associated with insulin resistancy in men and women, but it was associated with adiposity and lipid metabolism in women (64).

In the UK, the inverse association of Se concentration with features of MetS (57) is in agreement with the inverse association with the waist circumference (58). However this research group does not give any explanation for the positive association of Se in erythrocytes with waist-to-hip ratio (58).

The positive association seems to contradict the observations on effect of Se supplementation and effect of biomarkers (42). However, this could be explained by the fact that baseline Se concentrations can be different for various population groups. Supplementation to a group with suboptimal Se level can result in another response compared to groups of which the Se blood level is optimal at the beginning.

Also, the choice of Se-species given in the various supplementation studies can play an important role in its absorption. Sometimes it is argued that biofortification of wheat is a good strategy for increasing intake of selenium for deficient populations (36,37).

An Indonesian male population group with MetS revealed selenium levels negatively correlating with monocyte chemoattractant protein-1 (51). This protein (MCP-1) is critical for the initiation and development of atherosclerotic lesions (65). Another study (66) reported that high MCP-1 concentration is associated with endothelial dysfunction.

4. Selenoproteins in blood and MetS

a. Glutathione peroxidase

From the various functional selenoproteins required for health the glutathione peroxidase (GPX) is the best known. Since oxidative stress is thought to play an important role in the pathogenesis of MetS (13,67) GSH-Px is considered, together with other enzymes, as acting in the human antioxidative defence (68).

Various studies observed a lower GPX activity in patients with MetS (57,69-72). In one of these (57) GPX decreased significantly with increased number of components of the MetS.

Conversely, in two publications (48,73) an increased activity of GPX in red blood cells was observed. Explanations for these contradictory findings could be a difference in time of measuring the enzyme during the stage of the disease. At the initiation of the syndrome there could be an enhanced activity, while in a later phase an exhaustion could occur leading to lower values.

b. Selenoprotein P

Selenoprotein P (SeP) is involved in transporting Se from the liver to target tissues and is considered as the best indicator for selenium nutritional levels (74). Because SeP confers protection against

disease by reducing oxidative stress (14) several studies have assessed the level of SeP in the serum of patients with MetS.
An inverse relation of SeP level with MetS was observed (74,75). Also an antioxidant rich diet (high intake of fruits and vegetables) was associated with a 31 % higher SeP level (76). A Se supplementation of 200 mg selenium yeast tablets for 60 days also resulted in a higher protein P level in subjects with MetS (43).
SeP was correlated positively with HDL-cholesterol and negatively with body mass index, waist circumference and triglycerides (77).

5. Selenium concentration in toenails

Assessing Se in toenail is a long-term indicator of Se status (7) and reflects differences in selenium intake over longer periods (78,79). No meaningful association was observed between toenail Se levels and MetS (80) or lipid profiles in Korean adults (81). However for healthy young adults in Spain, nail Se was negatively associated with the inflammatory marker IL-18 (82) and serum C3, an early marker of metabolic syndrome manifestation (83). This contradicts with an observation in rural elderly Chinese where higher toenail concentration were significantly associated with higher triglycerides, higher LDL-cholesterol and lower HDL-cholesterol adjusted for covariates (84).

Conclusion

Conflicting results were obtained for a possible correlation of MetS with Se status. No clear association of MetS has been observed with Se concentrations in blood, GPX activity, selenoprotein P level or daily intake of the element by food. Also toenail-Se concentration, a long-term exposure parameter, showed no definite correlation, but here a limited amount of publications related to MetS could be found.
For Se levels in human blood however, most of the publications tend to indicate a positive association with biomarkers of the metabolic syndrome, especially parameters in the lipid profile. Various factors could be responsible for this observation: first of all, the complex character and multifactorial nature of MetS, together with different definitions used for the disorder. Also, physical activity, psychological state and dietary pattern can differ considerably in the disorder (85).
Some of the many confounding factors include: sampled population (country, baseline Se-level, smoking and drinking habits, age, gender, health status, size of the patient and control group), control on supplementation with Se and other antioxidants, other medication, study design and the variation in diagnostic criteria and biomarkers.
We further stress on the fact that the intention was not to study a directional relationship or any causality, since most of the studies had a cross-sectional design.

Financial support and sponsoring

Nil

Conflicts of interest

There are no conflicts of interest.

Authors' contribution

All authors have read the final version of the paper and accept responsibility for the content.

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Table 1: Daily Se intake and observations in relation to MetS			
Country	**Study design**	**Observations**	**Ref.**
France	double-blind randomized control	no effect	22
China	case-control	no effect	23
China	cross-sectional	no effect	24
Iran	cross-sectional	inverse association	25
China	cross-sectional	inverse association	26
Iran	cross-sectional	direct association	27
Spain	cross-sectional	negative association with inflammatory markers:	
		-retinol-binding protein 4 (RBP-4)	29
		-complement factor 3 (C3)	30
		-sialic acid	31
		positive association with antioxidant capacity	32
		positive association with mood	33

Table 2: Blood Se concentration and observations in relation to MetS				
Country	**Sample type**	**MetS**	**Observations or biomarkers**	**Ref.**
China	P	higher risk	associated with higher glucose level	45
	WB	MetS	positive association	46
	S	MetS	positive association	47
	S	MetS	inverse association with HDL-c	47
Croatia	S	MetS	no association	48
Finland	S	MetS	positive association with HDL-c	49
France	S	MetS	no association	22
	S	MetS	association only in women	50
Indonesia	P	MetS	correlation with endothelial dysfunction (MCP-1)	51
Iran	S	MetS	significant protective factor	52
Lebanon	P	MetS	positive association with lipid profile, glucose and WC	53
Poland	S	MetS	positive association with TC, TG, LDL-c	54
Serbia	P	MetS	positive association with TC, TG, LDL-c, glucose	55
Taiwan	S	MetS	positive association with TC, TG, LDL-c, glucose	56
UK	S	MetS	inverse association with features of MetS	57
	S	MetS	inverse association with WC	58
	RBC	MetS	positive association with waist-to-hip ratio	58
USA	S	MetS	no association	59
	S	MetS	positive association with lipid profile	60-62
	WB	MetS	positive association with TG	63

Abbreviations:
HDL-c: high density lipoprotein-cholesterol; LDL-c: low density lipoprotein-cholesterol; MCP-1: monocyte chemoattractant protein-1; P: plasma; RBC: red blood cells; S: serum; TC: total cholesterol; TG: triglycerides; WB: whole blood; WC: waist circumference