Selenium, Dietary Supplements and Cardiometabolic Health:

State of the Evidence

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Abstract

Use of selenium enriched foods, supplements and fertilizers has increased markedly in recent years in the US and other Western countries because of the perception that selenium, through anti-oxidant properties of selenoproteins, could potentially reduce the risk of cancer and other chronic diseases. However, concern has been raised recently about possible adverse cardio-metabolic effects of high selenium exposure, such as an increased risk of diabetes and hyperlipidemia. Hence, from a public health perspective, the relationship between selenium status and cardio-metabolic health should be clarified in order to help guide consumers in their choices of nutritional supplements and enriched food products. Additional mechanistic evidence is needed to clarify the cardio-metabolic effect of selenium and selenoproteins in human biology. Further epidemiological studies across populations with different selenium status should be conducted to help determine the optimal level of selenium intake in the general population that maximizes the antioxidant and anti-inflammatory benefits of selenium while avoiding potential toxic effects.

Introduction

The role of selenium in chronic disease prevention is the focus of major scientific debate and intensive investigation.[1-2] Selenium is a key component of a number of selenoproteins involved in essential enzymatic functions such as redox homeostasis and thyroid hormone metabolism.[3-4] Because of the potential of selenoproteins to protect against oxidative stress, significant expectations were raised for the prevention of chronic diseases including cancer, cardiovascular disease (CVD) and type 2 diabetes,[5-7] conditions commonly associated with oxidative stress. Indeed, early evidence from the Nutritional Prevention of Cancer (NPC) randomized trial suggested that selenium supplementation could prevent cancer, specifically prostate cancer, lung cancer and colorectal cancer, in a largely selenium-replete population in the Eastern part of the US.[8-9] A large randomized trial of selenium supplementation in US men, however, found no benefit of selenium chemoprevention for prostate cancer or for other cancer endpoints.[10] For cardiometabolic conditions, moreover, recent findings from observational studies and randomized clinical trials have raised concern that high selenium exposure may lead to adverse effects, at least in well-nourished populations.[1-2,11] In the present article, we will review this recent evidence and discuss open questions and future perspectives in selenium research.

Selenium and type 2 diabetes

Evidence from *in vivo* and *in vitro* studies suggests that inorganic selenium can enhance insulin sensitivity by mediating insulin-like actions.[12-13] Specifically, in animal models selenate has been shown to decrease the activity of protein tyrosine phosphatase, a negative regulator of insulin signal transmission, and can therefore potentially reduce insulin resistance.[13] However, little information is available on insulin-like actions for forms of selenium that are more relevant for human exposure such as selenomethionine. Evidence from human studies on selenium and diabetes are conflicting. In observational studies and randomized clinical trials from selenium-

replete populations in the US, recent findings indicate that high selenium status or selenium supplementation may be associated with an increased risk of type 2 diabetes.[14-17] *Firslyt*, a large cross-sectional analysis within the US Third National Health and Nutrition Examination Survey (NHANES 1988-1994)[14] showed that subjects in the highest quintile of serum selenium (≥137.66 ng/ml=1.74 μmol/L) had a significantly increased prevalence of diabetes compared to those in the lowest quintile (<111.62 ng/ml=1.41 μmol/L). The positive association between serum selenium concentrations and the prevalence of type 2 diabetes was corroborated in a further analysis from NHANES 2003-2004.[15] These cross-sectional studies, however, do not allow us to determine whether high selenium is a cause or a consequence of the disease process. *Secondly*, a *post-hoc* analysis of the NPC trial in the Eastern US showed that supplementation with selenium (200 μg/day as high-selenium yeast) compared to placebo increased the risk of type 2 diabetes,[16] particularly in men and in participants with high baseline plasma selenium (hazard ratio of 2.70 in the highest tertile of plasma selenium, i.e. >121.6 ng/ml) (**Table 1**). *Recently*, results from the large Selenium and Vitamin E Cancer Prevention Trial (SELECT) in 35,533 North American men aged ≥ 50 y, showed a small, though non-statistically significant, increase in the number of cases of adult-onset diabetes in subjects supplemented with selenium alone (200 μg/day as selenomethionine).[10] In European populations, where selenium status is generally lower than in the US, the evidence linking selenium to glucose metabolism is conflicting. Two small case-control studies showed significantly lower serum selenium concentrations in patients with diabetes than in control subjects.[17-18] This echoes the findings from a cross-sectional analysis of the US Health Professionals Follow-up Study that showed lower toenail selenium concentrations among men with diabetes (with or without CVD) than among healthy control participants.[19] Furthermore, in the EVA (Epidemiology of Vascular Ageing) study in France, plasma selenium concentrations were positively, though non-significantly, associated with baseline glucose levels in women and with prevalent diabetes in men.[20] However, a recent report from the same study

showed that high plasma selenium (1.19-1.97 μmol/L) was associated with a marginally significant decreased risk of onset of impaired fasting glucose or diabetes in men, but not in women, over the 10-year follow-up.[21] Finally, in the French SU.VI.MAX (SUplémentation en VItamines et Minéraux AntioXydants) trial, combined supplementation with antioxidants including selenium (100 μg/day as high-selenium yeast) had no effect on fasting plasma glucose after 7.5 y of follow-up, despite a positive association between glucose and selenium concentrations at baseline in the whole population.[22] The explanation for these apparently discrepant results is still unclear. Further prospective research is needed to identify the optimal range of selenium intake and status in order to minimize potential adverse effects on glucose metabolism while optimizing type 2 diabetes prevention.

Selenium and blood lipids

Recent cross-sectional studies from unrelated populations suggest that higher selenium status is associated with adverse lipid profiles. Specifically, a cross-sectional analysis of serum selenium and lipid levels in the NHANES III (1988-1994) showed that higher serum selenium concentrations were associated with higher total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apo B, and apo A1 levels.[23] These findings were corroborated by a recent analysis from NHANES 2003-2004 showing positive associations between serum selenium concentrations and total, LDL- and HDL-cholesterol in a representative sample of the US population.[24] Partly consistent with these findings, a cross-sectional analysis from the 2000-2001 UK National Diet and Nutrition Survey (NDNS) indicated that higher selenium status was associated with increased total and non-HDL cholesterol, but not with increased HDL, in a nationally representative sample of British adults.[25] In contrast to the US, a significant proportion of British adults are considered to have a sub-optimal intake of dietary selenium.[26] Similar findings were also reported in a recent cross-sectional study of elderly people from Taiwan.[27]

Associations between higher selenium status and elevated total cholesterol levels have also been found in previous cross-sectional investigations from several populations with suboptimal selenium status.[20,28-31] To date, there is no observational prospective evidence on the association of selenium status with blood lipids.

Several randomized controlled trials in humans have evaluated the effect of selenium supplementation alone or in combination with other nutrients on the lipid profile. The SU.VI.MAX trial in a French population with sub-optimal dietary selenium intake showed that long-term daily supplementation with a combination of antioxidants including selenium (100 μg/day as high-selenium yeast) increased serum triglyceride levels compared to supplementation with placebo. Furthermore, among those in the treatment group, women had higher total cholesterol levels while men were more likely to use lipid lowering medication than those on placebo.[32] Likewise, in a randomized trial in a rural Chinese population with a low dietary intake of selenium, long-term combined supplementation with selenium (37.5 μg), vitamin C and vitamin E resulted in small but significant increases in total and LDL-cholesterol levels, though HDL concentrations were not affected.[33]

Three relatively small randomized trials have examined the effect of selenium supplementation alone on the lipid profile.[34-36] Two of them, conducted in Finland and China found no significant differences between treatment groups.[34-35] In the UK, the PRECISE Pilot trial randomized 501 elderly volunteers of relatively low selenium status [mean (SD) plasma selenium 88.8 (19.2) ng/g] to a six-month treatment with 100, 200 or 300 μg selenium/d as high-selenium yeast or placebo yeast.[36] Supplementation at 100 and 200 μg selenium/d lowered total serum cholesterol and non-HDL cholesterol; the 300 μg/d dose had no significant effect on total or non-HDL cholesterol, but raised HDL-cholesterol significantly.

Selenium and blood pressure

Few observational studies have evaluated the association between selenium and blood pressure (BP) and their findings are inconsistent. In the Flemish Study on Environment Genes and Health Outcomes (FLEMENGHO), higher blood selenium concentrations were associated with lower systolic and diastolic BP levels at baseline and with a lower risk of hypertension over 5.2 years of follow-up among men, though not among women.[37] In a cross-sectional study conducted in Finland, a population with low selenium status at the time of the study, serum selenium was also inversely related to systolic BP levels in 722 middle-aged men.[38] However, in another Finnish study in 1,100 elderly men, no relationship was found between BP and serum selenium concentration.[39] Similarly, serum selenium and BP levels were not associated in a cross-sectional analysis of the Olivetti Heart Study among 364 southern Italian men,[29] and no association between plasma selenium and systolic BP levels was found in the baseline EVA study.[20] In the EVA study, however, men with hypertension had higher plasma selenium than men without major cardiovascular risk factors. Finally, in a recent cross-sectional analysis of serum selenium and hypertension in the US NHANES 2003-2004, high selenium was associated with a higher prevalence of hypertension in both men and women.[40] The odds ratio for hypertension comparing the highest (≥150 μg/L) to the lowest (<122 μg/L) quintile of serum selenium was 1.73 (1.18 to 2.53). Unfortunately, no data are available on the effect of selenium supplementation on BP endpoints in randomized controlled trials using single selenium supplements. In the HDL-Atherosclerosis Treatment Study (HATS) trial, selenium (100 μg/d) was administered along with vitamin E (800 IU/d), vitamin C (1000 mg/d), and ß-carotene (25 mg/d), with no effect on BP levels during three years of follow-up.[41] In China, antioxidant supplementation (selenium 50 μg/d, ß-carotene 15 mg/d, and vitamin E 60 mg/d) of a nutritionally deficient population was linked to increased isolated diastolic hypertension, but other BP endpoints were not significantly different between treatment groups.[42]

Selenium and cardiovascular disease

A number of observational studies have examined the association between selenium status and risk of cardiovascular disease across different populations. [43-49] Inverse associations have been found particularly in populations with relatively low selenium intake or status.[43-47] For instance, in a German population of 636 patients with suspected coronary artery disease, mean plasma selenium was 69.5 and 74.5 μg/L at baseline in patients with and without a recurring cardiovascular event, respectively.[45] Baseline erythrocyte glutathione peroxidase-1 (GPx-1) activity was a strong predictor of the risk of a subsequent cardiovascular event, over 4.7 years of follow-up, supporting a potential beneficial effect of selenoprotein activity on cardiovascular risk. In that population, selenium status was too low for GPx-1 activity to be optimised in all subjects.[50] However, recent observational evidence in selenium-replete populations such as that of the US is suggestive of a possible U-shaped association (**Figure 1**) between selenium status and CVD.[48-49]

Results from randomized trials of selenium supplementation do not support a role for selenium in cardiovascular prevention at the present time.[41, 47, 51-55] Specifically, in *post-hoc* analyses from the NPC trial,[55] selenium supplementation (200 μg/day as high- selenium yeast) was not significantly associated with any of the cardiovascular disease (CVD) endpoints after 7.6 years of follow-up [all CVD: hazard ratio (HR) = 1.03, 95% confidence interval (CI): 0.78, 1.37; myocardial infarction: HR = 0.94, 95% CI: 0.61, 1.44; stroke: HR = 1.02, 95% CI: 0.63, 1.65; all CVD mortality: HR = 1.22, 95% CI: 0.76, 1.95]. Two other randomised trials that examined the effect of selenium in combination with other vitamins or minerals on CVD end points have also yielded null findings.[53-54]

Potential mechanisms for cardio-metabolic effects of excessive selenium exposure

Evidence for mechanisms that might explain the effect of high selenium exposure on glucose and lipid metabolism is sparse, therefore any such discussion is highly speculative. However, selenium is known to be a trace mineral with a narrow therapeutic window and considerable inter-individual variability in terms of metabolic sensitivity and optimal selenium intake.[56-57] Optimal intake for any individual is at least partly dependent on polymorphisms in selenoprotein genes that have been also shown to affect the risk of disease.[2] For instance, selenoprotein polymorphisms have been shown to interact with selenium status to affect the risk of disease e.g. that of lung cancer (Jablonska et al. Eur J Nutr 2008). For instance, polymorphisms in the gene for the anti-inflammatory selenoprotein S (SEPS1) can affect the risk of coronary heart disease and ischaemic stroke, particularly in women [Alanne, Kristiansson, Auro, et al., Variation in the selenoprotein S gene locus is associated with coronary heart disease and ischemic stroke in two independent Finnish cohorts, Hum. Genet. 122 (2007) 355-65]. We know that polymorphisms in the gene for the anti-inflammatory selenoprotein, SEPS1, can affect the risk of coronary heart disease and ischaemic stroke, particularly in women.

In animal models, the inorganic selenium species (selenate and selenite), despite some insulin-like properties,[12-13] have been shown to impair insulin responsiveness and induce a catabolic response in rat muscle with glycogen depletion and increased rates of glycolysis,[58] and to reduce insulin release from pancreatic islets in mice.[59] Moreover, it has been shown that high-selenium diets may stimulate the release of glucagon, promoting hyperglycaemia,[60] or may induce over-expression of GPx-1 and other antioxidant selenoproteins in animal models resulting in the development of insulin resistance and obesity.[61-63] Likewise in humans, a strongly positive correlation between GPx activity and insulin resistance was found in a group of non-diabetic pregnant women.[64] In general, the toxic effects of selenium that might explain an etiologic role in diabetes are the capacity of some selenium compounds, notably selenite, to induce oxidative stress,[65-67] a mechanism that is likely to play a key role in the etiology of this disease.[68] However

the majority of food-selenium is in the form of selenomethionine, which does not have such pro-oxidative effects.[69]

A number of sources provide evidence of a clear connection between lipoproteins and selenium metabolism.[70-73] For example, selenoprotein P is taken up by the brain and the testes *via* the apolipoprotein E receptor-2,[70-72] whereas another apolipoprotein receptor, megalin, mediates its uptake by the kidney.[73] Moreover, in mouse knock-out models in which selenoprotein synthesis is compromised, both liver Apo E protein concentration, plasma cholesterol and expression of genes involved in cholesterol biosynthesis, metabolism and transport are altered, demonstrating a role for selenoproteins in the regulation of lipoprotein biosynthesis.[74] High-dose selenium treatment of rats showed an effect on lipid metabolism, showing an increased total lipid content of Wistar rat heart, striatum and thalamus,[75] which suggests the potential for sub-toxic effect of selenium supplementation at high doses. However, the relevance of these rat studies to humans is questionable as rats handle lipids quite differently.[76] Furthermore, selenoprotein and cholesterol synthesis are connected through the common mevalonate pathway of isoprenoid biosynthesis.[77] The rate-limiting enzyme in the mevalonate pathway, HMG CoA reductase, is inhibited by statins resulting in a lowering of plasma cholesterol. Moreover, recent findings from the EVA study indicated that long-term use of fibrates (but not statins) increased plasma selenium concentrations in dyslipidemic aged patients,[78] which might explain, at least in part, the observed association of high selenium status with hyperlipidemia.

Altogether, the available cross-sectional evidence[23-25, 27-31] linking higher selenium status to blood lipids is unable to determine whether lipid levels rise as a consequence of increased selenium intake or whether a common metabolic pathway, or common co-exposures, or reverse causality might explain the association between selenium status and lipid levels. However recent

results from the PRECISE Pilot Study suggest that the latter explanations are more probable, at least in populations with relatively low selenium intake or status.[36]

From a mechanistic point of view, selenium intakes above the level recommended for optimal activity of selenoproteins, such as the glutathione peroxidases and selenoprotein P (55-75 μg/day)[79-80] will simply result in the non-specific incorporation of selenomethionine in place of methionine in albumin and other proteins.[3] Thus mechanistically, it is unclear what advantage is to be gained from intakes above 75 μg/day, except perhaps in individuals having a selenoprotein genotype that uses selenium inefficiently for the manufacture of selenoproteins.

Perspectives

In the past few years, growing scientific attention has been focussed on the full range of effects of selenium status and supplementation on chronic disease endpoints. While the primary emphasis of selenium research has been on evaluating the potential benefits of its antioxidant and anticancer effects,[5-9] recent findings from observational studies and randomized clinical trials have suggested an association between moderate to high selenium exposure and adverse cardio-metabolic effects, at least in populations with adequate selenium intake such as the US.[10-11, 14-16, 23-24, 40] Specifically, several unrelated studies from the US indicate that high selenium status or selenium supplementation may be associated with an increased risk of diabetes.[14-16] Furthermore, though not indicative of causality, recent and early cross-sectional evidence from several populations indicates that high selenium exposure may also be associated with an adverse lipid profile[23-25, 27-31] and hypertension,[40] raising additional concerns about sub-clinical metabolic toxicity of high selenium exposure and prolonged use of selenium supplements.[81] It is therefore of concern that in the US and other Western countries the use of selenium enriched foods, fertilizers, and supplements has increased considerably in recent years as a result of aggressive

marketing[26, 82-83] and despite lack of definitive evidence on their efficacy for cancer and cardiometabolic disease prevention.[10]

Current recommendations on dietary selenium intake [55-75 μg/day][79-80] are based on optimizing the activity of plasma GPx, which requires a plasma selenium concentration of 92 μg/L.[50, 84-85] In the US, the mean serum selenium concentration among participants in the NHANES 2003-2004 was 137 μg/L, and most participants (99%) had serum selenium above 95 μg/L.[15, 24, 40, 49] It is therefore likely that a majority of NHANES participants would have had replete selenoprotein status, including that of selenoprotein P.[85] Health benefits of additional selenium intake in such a population are therefore questionable and toxic effects, such as an increase in diabetes risk or adverse lipid profile, are possible. In Europe, selenium status is generally lower than in the US. Moreover, there is large variability in dietary selenium intakes by country, ranging from levels considered to be marginally adequate or adequate (Western and Central Europe: 30–90 μg /day) to low or deficient (Eastern European countries: 7–30 μg/day).[86-87] Therefore, the apparently puzzling evidence[88-89] on the full range of effects, either beneficial or detrimental, of selenium exposure on chronic disease endpoints might be explained by the variability of selenium status and selenium dietary intakes across different countries and population subgroups. In this view, the association between selenium and cardio-metabolic outcomes is likely to be U-shaped with potential harm occurring at selenium levels both below and above the physiological range for optimal activity of selenoproteins.

Additional experimental evidence is needed to provide new insights into the role of selenium and of specific selenoproteins in human biology, especially to clarify the underlying mechanisms linking selenium to chronic disease endpoints. Prospective epidemiological studies must be conducted to investigate the link between selenium exposure and cardiometabolic effects across different ranges of exposure and in different populations. This would help determine the optimal level of selenium intake in the general population that can maximize health benefits

while avoiding potential chronic toxic effects. Nevertheless, at the present time the widespread use of selenium supplements or other strategy that artificially increases selenium status above the level required for optimal selenoprotein activities for the purpose of chronic disease prevention should not be encouraged in populations with adequate selenium intake.

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Table 1. Incidence of type 2 diabetes by baseline plasma selenium, Nutritional Prevention of Cancer Trial, 1983-1996 (16)

Baseline plasma Se	Cases		Incidence*		Unadjusted				Adjusted			
	Se	Placebo	Se	Placebo	RR[a]	95% CI	P	P, M-H	HR[b]	95% CI	P	P, int[c]
By median												
≤113.4 ng/ml	26	25	11.1	10.7	1.03	0.57-1.86	0.89	0.06	1.04	0.60-1.80	0.89	0.028
>113.4 ng/ml	32	14	14.1	6.1	2.31	1.20-4.69	0.007		2.50	1.32-4.77	0.005	
By tertile												
≤105.2 ng/ml	18	18	11.6	11.3	1.03	0.50-2.09	0.92	0.21	1.13	0.58-2.18	0.72	0.038
105.3-121.6 ng/ml	14	10	8.8	6.5	1.35	0.56-3.40	0.46		1.36	0.60-3.09	0.63	
>121.6 ng/ml	26	11	17.5	7.3	2.40	1.14-5.39	0.01		2.70	1.30-5.61	0.008	

*Cumulative incidence rates are per 1,000 person years

[a] RR and 95% CI were derived from incidence rate ratios; P_s were derived from log-rank (P) test and Mantel-Haenszel (P, M-H) test for heterogeneity

[b] HR, 95% CI, and P_s from the Cox proportional hazards model adjusted for age, BMI, smoking status and gender

[c] P for treatment group characteristic interaction is for the (treatment group x factor) cross-product term in separate Cox proportional hazards model

Figure 1: Cardiovascular Disease Mortality and Serum Selenium Levels. NHANES III, 1988-1994 (48)