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Selenium and Cardiometabolic Health: Inconclusive Yet Intriguing Evidence

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Abstract

Selenium is incorporated as the unique amino-acid selenocysteine into selenoproteins, which regulate important biologic processes such as redox balance. The results of epidemiologic and clinical investigations are inconclusive regarding the relation of the plasma selenium level to cardiometabolic parameters, and does not support the routine use of selenium supplements to prevent cancer or cardiovascular disease. Variability in the selenium status of the populations studied and lack of standardization of measures of selenium status may account for part of the confusion regarding selenium and cardiometabolic health. Another possibility is that differences in the effects of selenoproteins as opposed to those of low molecular weight selenium compounds derived from *in vivo* metabolism of selenium, may explain the unusual phenomenon of a similar phenotype induced by both selenium deficiency and excess in experimental models, as well as offer a plausible explanation for the lack of consistency in clinical studies. The epidemiologic, clinical, and experimental evidence, though inconclusive in terms of the precise relation of selenium to cardiometabolic health, is however, very intriguing in terms of the urgent need for further mechanistic research to enable the clinical use of this potent micronutrient.

INTRODUCTION

Selenium, an essential micronutrient, unlike other metals, is directly incorporated into proteins as the unique amino-acid selenocysteine, which is synthesized from serine on its tRNA and coded for by the stop codon UGA.[1] The unique class of selenoproteins has a translational machinery, including a selenocysteine insertion sequence, an elongation factor EFsec and selenocysteine insertion sequence binding protein SBP2, which allows read-through of the stop codon and continued translation. Selenoproteins number at least 25 in mammals, and function to regulate redox balance and thyroid hormone metabolism, and probably as yet unidentified roles, since the functions of all selenoproteins have not yet been clarified. Because oxidant stress plays a major role in several cardiometabolic diseases, selenium status and selenium supplements have been widely investigated in relation to cardiometabolic health. The recommended daily allowance of selenium is 55 micrograms/day.[2] Intake varies widely across the globe, and in general, intake is higher in the US population. In addition, there is a high level of supplement intake, including selenium

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supplements, in the US.[3] Hence a better understanding of selenium and its role in cardiometabolic health is urgently needed.

SURVEY OF EVIDENCE

Selenium, diabetes, and lipids

The National Health and Nutrition Examination Survey (NHANES) 2003–2004 demonstrated that the US population had a mean serum selenium level of 137.1±19.9 μg/L.[4] A higher selenium level was associated with a higher risk of diabetes, and of higher glucose and glycosylated hemoglobin levels. Conversely, in a longitudinal study of older French individuals with a lower plasma selenium level compared to the US population, a higher plasma selenium level at baseline was associated with a decrease in incidence of dysglycemia during a 9-year follow-up period in men.[5] Plasma selenium level was not associated with dysglycemia in women. However, in a prospective observational study of a cohort of women from Northern Italy, even though the daily intake of selenium was lower than in the US as is typical for a European population, higher intake of selenium was associated with a significantly higher risk of diabetes mellitus.[6] Two recent randomized control trials of cancer prevention utilizing selenium supplements in the selenium replete US population have yielded concerning results. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) examined the effect of a modest amount of selenium provided as L-selenomethionine on prostate cancer incidence in a large cohort of men.[7] There was a non-significant increase in the incidence of type 2 diabetes mellitus in the selenium group (relative risk 1.07; p=0.16). In the Nutritional Prevention of Cancer (NPC) Trial which examined the effect of a similar dose of selenium in the form of high selenium yeast on cancer prevention in low selenium areas of the Eastern US,[8] the incidence of diabetes was significantly increased in the selenium group.

In the NHANES 2003–2004 survey, there were positive correlations of plasma selenium level with total, LDL and HDL cholesterol levels, and a U-shaped relation with triglyceride level, with the nadir seen at a selenium concentration of approximately 120 μg/L.[9] The National Diet and Nutrition Survey (NDNS) examined the relation of plasma selenium level to metabolic parameters in British adults, who, similar to other European populations, had lower intake and plasma levels of selenium.[10] A higher plasma selenium level was associated with higher levels of total and non-HDL cholesterol, but not with HDL cholesterol. The UK PRECISE (PREvention of Cancer by Intervention with Selenium) Pilot study evaluated the metabolic effects of three doses of selenium (100, 200 and 300 μg/day) provided as high selenium yeast in an older British population.[11] In this population with relatively low plasma selenium levels, modest benefits on reducing total and non-HDL cholesterol and total to HDL ratio was observed over a 6-month period in response to selenium supplementation.

Selenium, hypertension, and cardiovascular disease

In the NHANES 2003–2004 survey, the association of serum selenium with blood pressure and prevalence of hypertension (defined as blood pressure ≥ 140/90 mm Hg or use of antihypertensive medication) was evaluated.[12] Higher serum selenium was associated with higher values of systolic, diastolic, and pulse pressure, and with a higher risk of hypertension in this cross-sectional analysis of the US population. Conversely, in the Flemish Study on Environmental Genes and Health Outcomes (FLEMENGHO), serum selenium was inversely related to systolic and diastolic blood pressure in men, while there was no relation in women.[13]

Initial observational studies suggested an inverse relation between blood selenium concentrations and incidence of cardiovascular disease, especially in populations with low

selenium status. For example, Salonen and coworkers showed that subjects in Eastern Finland who had very low plasma selenium levels (< 45 μg/L) had a significantly increased risk of coronary artery disease and myocardial infarction over 7 years of follow-up.[14] However, other studies from Finland, as well as from other countries, have not shown a significant association of plasma selenium levels with cardiovascular disease.[15,16] Recent data suggest a U-shaped relation between cardiovascular mortality and serum selenium levels. In a 12 year follow-up study of participants in the US NHANES 1988–1994 study, cardiovascular mortality decreased with increasing selenium levels up to a serum selenium level of 120 μg/L, while there was a positive association at higher selenium levels.[17]

Selenium and heart failure

Selenium deficiency is postulated as an etiologic factor in heart failure syndromes such as the endemic cardiomyopathy termed Keshan disease,[18] in patients on parenteral nutrition,[19] peripartum cardiomyopathy,[20] cardiomyopathy associated with acquired immune deficiency syndrome,[21] as well as in systolic heart failure in the general population.[22–24] Witte and colleagues studied the effect of a combination of high-dose micronutrients including selenium in older subjects with systolic heart failure in comparison with placebo over a 9-month period.[25] Micronutrient supplementation reduced left ventricular volumes and increased left ventricular ejection fraction and quality of life scores compared to placebo. In this study, it was not possible to separate the effects of selenium from those of the concomitantly administered micronutrients.

SELENIUM: INCONCLUSIVE EVIDENCE?

Variability in Clinical Studies

How do we interpret these variable results? Even though some studies suggest that selenium may have beneficial effects in a population whose selenium status is low, and neutral or adverse effects in a selenium replete population, such a conclusion is not well supported by the cumulative data. As shown in Table 1, lack of association, or adverse association, of selenium with cardiometabolic parameters have also been observed in low selenium populations. The variable associations of cardiac and metabolic parameters with *de novo* selenium status and with the response to supplements suggests that the effects are multiple and not restricted to those mediated by selenoproteins. Lack of adequate standardization of serum or plasma selenium measurements could certainly have contributed to variability in the results. How to accurately measure selenium status is still a matter of debate, whether blood or tissue (such as buccal cell or toenail) selenium measurements would suffice. For example, in a study of plasma and buccal cell selenium in healthy men with adequate selenium intake, buccal cell selenium levels were not correlated with plasma selenium levels.[26] As described below, there is a dichotomy between the effects of compounds derived from selenium metabolism and selenoproteins, which adds to the complexity of measuring selenium status.

Biology vs. Pharmacology: Selenoproteins and Low Molecular Weight Selenium Compounds

The results of two large cancer prevention trials that demonstrated an increase in the risk of diabetes with modest selenium supplementation suggest a narrow therapeutic range for selenium.[7,8] Recent preclinical studies have shown that adverse and similar phenotypes result from selenium deficiency and selenium supplementation as compared to optimal dietary intake of selenium. A study by Novoselov and colleagues demonstrated that both a selenium deficient diet and a diet supplemented with a modest amount of selenium (0.4 mg/kg) increased carcinogenesis in a genetic model of hepatocarcinogenesis.[27] Another study showed that supplemental selenium led to a diabetic phenotype in mice.[28] In the same study

the investigators used a genetic approach to alter the tRNA for selenocysteine and thereby reduce selenoprotein synthesis. Interestingly, these mice with reduced selenoprotein expression also developed a diabetic phenotype similar to the selenium supplemented group.

Several unresolved issues are raised by these findings. Selenoprotein expression reaches a plateau at adequate intake of selenium. Further supplemental selenium might be incorporated into proteins as in the case of selenomethionine and result in toxic effects.[29] Alternatively, metabolism of hydrogen selenide (the final form required for Sec synthesis) yields low molecular weight selenium compounds such as the methylated derivatives methylselenol, dimethyl selenide, or trimethyl selenonium.[30,31] In fact there is evidence from experimental studies that methylselenol may be the active compound responsible for protection against cancer.[32] Irons and colleagues, in a study using a genetically modified mouse model of reduced selenoprotein expression, showed that both selenoproteins and low molecular weight selenium compounds were effective in preventing colon carcinogenesis.[33] Hence both selenoproteins and non-selenoprotein selenium compounds may be involved in the effects of dietary selenium. A plausible explanation for the variable effects of selenium status and selenium supplementation in epidemiologic and clinical studies is that the levels and cumulative effects of selenoproteins and low molecular weight selenium compounds may vary between individuals and populations and determine the final cardiometabolic phenotype.

CONCLUSIONS/FUTURE DIRECTIONS

Numerous studies have shown that selenium affects cardiometabolic health and cardiovascular outcomes including heart failure. However, the relation is a complex summation of the pharmacological and biological actions of selenoproteins and non-protein selenium compounds. Optimal selenium status may benefit cardiovascular health; however, the markers of optimal selenium status and how to deliver selenium to maximize the preventive and therapeutic benefits within a narrow therapeutic window requires further mechanistic research on the effects of selenium *in vivo*. A major area of productive research would be to differentiate the effects of selenoproteins from those of selenium compounds themselves.

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Table 1

Comparison of select studies of the effect of selenium status on cardiometabolic health

Study (reference)	Baseline selenium status	Duration of follow-up	Method of selenium measurement	Change in selenium level in interventions studies	Endpoints	Comments
Studies with positive associations of selenium status with cardiometabolic health						
EVA(5)	Low (France)	9 years	Plasma Selenium (electrothermal atomic absorption spectrometry)	N/A	Lower risk of dysglycemia	Effect seen only in men
UK PRECISE (11)	Low (United Kingdom)	6 months	Plasma selenium (Inductively coupled plasma mass spectrometry)	Baseline: 91.2 μg/L Selenium 300 mg/day for 6 months: 92.6 μg/L	Selenium supplementation reduced total and non-HDL cholesterol	Older population High selenium yeast
FLEMEN GHO (13)	Low (Western Europe)	5.2 years	Blood selenium	N/A	Lower systolic and diastolic blood pressure in men	No effect in women
Salonen et al (14)	Low (Finland)	7 years	Serum selenium (Atomic absorption spectrometry) Mean - 51·8 μg/L	N/A	Lower risk of coronary disease	Serum selenium < 45 μg/L associated with increased risk of cardiovascular mortality
De Lorgeril et al (23)	Low (Western Europe)	N/A (Case- control)	Blood selenium (electrothermal atomic-absorption spectroscopy)	N/A	Low selenium intake and blood levels seen in heart failure	Low selenium levels associated with exercise capacity and not with cardiac function
Studies with neutral or negative associations of selenium status with cardiometabolic health						
NHANES - 2003–2004 (4,9,12)	Adequate (USA)	N/A (Cross-sectional)	Serum Selenium (Inductively coupled plasma mass spectrometry)	N/A	Higher risk of diabetes Higher glucose, glycosylated hemoglobin, systolic and diastolic blood pressure. Higher risk of hypertension	Positive correlations of selenium level with total, LDL and HDL cholesterol. U shaped relation with triglycerides.
ORDET (6)	Low (Northern Italy)	16 years	Dietary intake using semi-quantitative food frequency questionnaire	N/A	Higher risk of diabetes	Included only older women
SELECT(7)	Adequate (USA)	5.46 years	Serum Selenium	Baseline: 135.0 μg/L 4th annual visit: 251.6 μg/L	Non-significant increase in type II diabetes	L-Seleno-methionine (200 μg/day) Included only men (major end point was prostate cancer)
NPC (8)	Low normal (Eastern US)	7.7 years	Plasma Selenium (electrothermal atomic-absorption spectroscopy)	Baseline: 114.4 μg/L 6–9 months: 190 μg/L, maintained for course of study	Significant increase in type II diabetes	Selenized yeast (200 μg/day)

Study (reference)	Baseline selenium status	Duration of follow-up	Method of selenium measurement	Change in selenium level in interventions studies	Endpoints	Comments
NDNS (10)	Low (United Kingdom)	N/A (Cross-sectional)	Plasma selenium (Inductively coupled plasma mass spectrometry)	N/A	Higher levels of total and HDL cholesterol	
NHANES - 1988–1994 (17)	Adequate (USA)	N/A (Cross-sectional)	Serum selenium (atomic absorption spectrometry)	N/A	U shaped relation to cardiovascular mortality	Reduction in mortality with increasing selenium levels up to 120 μg/L)