

The Role of Selenium In Health

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Introduction

The trace mineral selenium (Se) is an essential nutrient with important implications for human health. As selenocysteine, Se is required for a large number of selenoproteins¹. Many are catalytically active in redox processes by using selenocysteine at the active site as an electron donor^{1,2}. The classic example is the reduction of hydrogen peroxide and organic hydroperoxides by the family of Se-dependent glutathione peroxidases². Thioredoxin reductase is a family of NADPH-dependent oxidoreductases that, in concert with thioredoxin, reduces ribonucleotides to deoxyribonucleotides, maintains redox balance in cells, regulates activity of transcription factors and enzymes, and plays important roles in signal transduction and defense against oxidative stress³. The iodothyronine deiodinases generate active thyroid hormone from inactive precursor¹. A hierarchy exists among the selenoproteins such that, under deficiency conditions, Se is preferentially supplied for expression of specific selenoproteins². Additional regulation allows maintenance of selenoproteins in certain tissues at the expense of others².

The many redox functions exerted by selenoproteins offer a common mechanism by which suboptimal Se status can influence a number of diseases for which pathophysiology includes increased generation of reactive oxygen species that overwhelm antioxidant defense capabilities. In some diseases, Se exerts additional functions. Along with the diseases discussed below, Se may also have roles in reproduction, mood, thyroid function, arthritis, pancreatitis, and asthma (reviewed in¹). Understanding the unique metabolism of Se in the brain is at an early stage, but may eventually link Se to some brain disorders (reviewed in⁴).

Se Status and Health

Since Se enters the food chain through plants, which take it up from the soil, dietary intakes of Se vary by geographical location¹. Se intake also depends on agronomic practices and food availability and preference⁵. The recently revised Recommended Dietary Allowance (RDA) for Se set by the Institute of Medicine is 55 µg for adult women and men, which supports maximal expression of the selenoenzymes⁶. Estimated distribution of prevalence of low Se status by country suggests that there are many people on the global scale who have limited expression of 1 or more selenoenzymes, suggestive of subclinical Se deficiency³ (Table 1). Keshan Disease found in China is one of few examples of a clinical manifestation (cardiomyopathy) linked directly to low Se status and a co-factor, possibly RNA-viruses¹. We have yet to prove conclusively that subclinical Se deficiency confers risks for any diseases. Yet, even for low risk populations such as North America, certain clinical circumstances may result in secondary Se deficiency. In other situations, such as cancer prevention, dietary intakes of Se above that needed to correct Se deficiency may be necessary.

Immune Function

The function of Se in removing reactive oxygen species contributes to its inflammatory effects. Se deficiency has been reported to cause an impairment in both cell-mediated immunity and B-cell function. Se supplementation, on the other hand, enhances lymphocyte response to antigen stimulation and increases ability to develop into cytotoxic lymphocytes and to destroy tumour cells. Natural-killer-cell activity is also increased (reviewed in^{1,7}). The amount of Se needed for maximum immune benefit is uncertain, but 200 µg/day of sodium selenite (91 µg Se) given to Se-replete individuals showed benefit⁸.

Particularly exciting are links between Se status and the development of specific viral infections. In animal studies, Se deficiency in the host enhances mutation rate of the viral genome, causing a benign strain of the coxsackie virus to become virulent and induce myocarditis^{9,10}. Since coxsackie virus may be the required cofactor along with Se for the development of Keshan Disease, these findings have potentially great clinical significance¹. Mutation of the influenza A viral genome is also enhanced by Se deficiency with a phenotypic change to virulence¹¹. Once the mutations have occurred, Se adequate animals are susceptible to the virulent strain^{9,11}. These findings imply that poor Se status may contribute to the emergence of new viral strains.

There is considerable evidence for a link between Se and HIV infection. Plasma Se decreases in parallel with the loss of CD4 helper T cells¹, and Se-deficient HIV patients are almost 20 times more likely to die from HIV-related causes¹². Se *in vitro* can reduce oxidative stress, modulate cytokine synthesis, improve T-cell proliferation and differentiation, and reduce cytokine-induced HIV-1 replication¹³. At least two well controlled trials are underway to determine whether Se supplementation can slow HIV disease progression¹.

Cancer

The link between Se and cancer risk is particularly strong because the evidence is converging from epidemiological, experimental, and clinical studies¹⁴. Numerous animal studies have shown that intakes of Se in excess of nutritional requirement can inhibit tumorigenesis, and some, but not all, epidemiological studies have shown an inverse relationship between Se status and cancer risk (reviewed in⁵). The *Nutritional Prevention of Cancer Trial*^{15,16}, which was randomized, double-blinded, and placebo-controlled, demonstrated that 200 µg of Se/day as Se-enriched yeast provided to non-deficient subjects could lower incidences of total, prostate, colo-rectal, and lung cancers as well as mortality due to lung and total cancers. These results need to be confirmed since the experimental design was not established for these secondary endpoints. Risk for the primary endpoint, recurrent basal or squamous cell skin

cancer, was not altered. Raich et al.¹⁷ have reviewed the few other trials of Se supplementation, most of which have shown beneficial results.

Se appears to affect cancer risk in two ways. The first involves correction of Se deficiency with increased expression of the selenoproteins that protect against reactive oxygen species in cancer initiation¹⁴. The second requires Se supplementation above nutritional requirement and is more likely to protect against tumour progression by enhancing immune surveillance, altering carcinogen metabolism, decreasing cell proliferation, enhancing apoptosis, and suppressing tumour neo-angiogenesis¹⁴. Since the level of Se required for the latter is above that required for maximal expression of the known selenoproteins, other cellular mechanisms must be responsible. These anticarcinogenic effects are thought to be due to the production of specific Se metabolites¹⁴. Although animal studies have used intakes of at least 10 times nutritional requirement, Combs¹⁴ has estimated that with intakes of mixed organic forms of Se, cancer risk may be reduced when plasma Se levels are increased above approximately 120 µg/L. This can be achieved with Se intakes of about twice the current RDA.

Two large, controlled supplementation trials are just beginning in Canada and the United States. If they show decreases in cancer incidence and mortality, then the benefits of Se in preventing lung and prostate cancer will be more firmly established¹⁷. Other trials will be needed in populations at risk for other cancers, including breast cancer. Since Se is a toxic element with a relatively narrow window between deficiency and toxicity, the doses must be carefully considered and patients should be monitored for selenosis. The 200 µg/day of Se used in the *Nutritional Prevention of Cancer Trial* is within the safe range for long-term supplementation, but human safety and efficacy data for other types of Se supplements are quite limited¹⁷. Efforts are also ongoing to develop forms of Se supplements that offer improved efficacy/toxicity ratios¹⁷. The Tolerable Upper Intake Level, the highest daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals in the general population, has been set at 400 µg for Se for adults⁶. However, higher doses may be tested within well-controlled clinical trials with appropriate safety monitoring⁶.

Critical Illness

Low plasma Se concentration is common in intensive care patients and has been associated with higher rates of ventilator-associated pneumonia, organ system failure, and mortality¹⁸. Reduced plasma Se may be the result of hemodilution, increased requirement related to the need to upregulate antioxidant defense, and losses from hemorrhage and drains¹⁹. An additional important factor is likely the redistribution due to selective tissue

Se uptake¹⁸. Berger et al.¹⁹ have reported negative Se balance on days 5-7 following major trauma despite intravenous Se supplementation of 62 µg/day. Patients with systemic inflammatory response syndrome supplemented with 535 µg Se/day showed normalization of serum Se and glutathione peroxidase activity with some clinical outcome benefit²⁰. Since this was a small, randomized unblinded pilot study, proof of a positive benefit needs further studies with larger numbers of patients. Intriguing recent findings suggest that 500 µg Se/day given soon after trauma modestly hastens normalization of post-traumatic aberrations in thyroid hormone metabolism²¹. However, larger numbers of patients need to be studied, and there is uncertainty as to whether it is wise to correct the thyroid hormone alterations in critically ill patients²¹.

Cardiovascular Disease and Stroke

Epidemiological studies investigating a role for Se in protection against cardiovascular disease have produced both positive and negative findings. The reader is referred to the review by Rayman¹ for details. It has been suggested that some of the discrepancy in the findings may be because this effect of Se is only important in populations of low Se status¹.

Se may also play a role in preventing stroke and its associated mortality and disability, but much more evidence is needed. In a prospective study in Finnish men, low serum Se levels were associated with a 3.7-fold increased risk of stroke²². In the Netherlands, a prospective study did not find significantly lower serum Se concentrations in persons who died of stroke²³. The power of both studies was limited by small numbers of cerebrovascular events.

How could Se modify the extent of brain damage caused by a stroke? Since the brain is better able to retain Se at the expense of other tissues⁴, until recently it had been assumed that the brain is relatively protected when Se supply is limited. However, we need to re-examine this question, focusing on the newer selenoproteins, thioredoxin reductase, selenoprotein P, and selenoprotein W, as these appear to play more critical roles in the brain⁴. The answers are also likely to vary with individual brain region⁴. The effects of Se status may also be exerted on microvascular endothelium rather than on brain parenchyma. The complex cascade of pathophysiological events that cause the death of brain cells following a stroke includes the production of reactive oxygen species that overwhelm the antioxidant defense system^{24,25}. As a result, upregulation of pro-inflammatory cytokines, chemokines, and cell

adhesion molecules occurs, with leukocyte adhesion and transmigration across the endothelium into the area of brain injury. This contributes to secondary brain damage²⁶. Se can modify the inflammatory response *in vitro* by altering key molecules that control these events^{27,29}, and Se deficiency enhances neutrophil adherence to endothelial cells²⁹. These findings need to be extended to *in vivo* systems.

Conclusions

We are still in the initial stages of understanding whether Se supplementation has a place in preventing or treating disease. There is a limited amount of clinical trials on which to draw conclusions. Subclinical Se deficiency is estimated to affect substantial numbers of the world's population. The crucial unanswered questions are whether this is potentiating viral

diseases and enhancing oxidative stress associated with infection, inflammation, and chronic diseases. Even in North America where risk for Se deficiency is low in the general population, there are clinical circumstances that may induce secondary Se deficiency. It also appears there are roles for Se in certain diseases that require amounts above nutritional requirement. Looking to the future, mechanistic studies must go hand in hand with the clinical trials so that we understand the specific mechanisms by which Se exerts any beneficial health effects. While we await the results of a number of clinical trials, the general adult population should aim for regular intakes of 55 µg/day to ensure maximal expression of selenoproteins. As Se is a potentially toxic mineral, adult intake from all sources should not exceed 400 µg per day.

Table 1: ** Estimated distribution of prevalence of low selenium status based on reported blood selenium levels

Prevalence category*	Country		
High (>50 %)	Austria	Germany	Northern Ireland
	Bulgaria	Greece	Poland
	Chile	Hungary	Slovak Republic
	China	Jamaica	Spain
	Cuba	New Zealand	Uzbekistan
	Czech Republic	Niger	Former Yugoslavia Republics
	Estonia	Nigeria	Zambia
Moderate (10-50 %)	Australia	India	Switzerland
	Belgium	Italy	Taiwan
	Bolivia	Mexico	Turkey
	Denmark	Portugal	Venezuela
	England	Russia	
	France	Sweden	
Low (<10 %)	Burundi	Republic of Ireland	Scotland
	Canada	Japan	USA
	Egypt	Korea	Parts of Zaire
	Finland	Norway	

*Based on estimated frequencies of plasma or serum Se concentrations <70 mg/L.

**This table is reprinted from: Combs Jr. GF. Selenium in global food systems. *Br J Nutr* 2001; 85: 517-547, with permission from Dr. GF Combs Jr.

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- References** 1. Rayman MP. The importance of selenium to human health. *Lancet* 2000; 356: 233-241. 2. Behne D, Kyriakopoulos A. Mammalian selenium-containing proteins. *Annu Rev Nutr* 2001; 21: 453-473. 3. Nordberg J, Amér ESJ. Reactive oxygen species, antioxidants, and the mammalian thioredoxin system. *Free Radic Biol Med* 2001; 31: 1287-1312. 4. Whanger PD. Selenium and the brain: A review. *Nutr Neurosci* 2001; 4: 81-97. 5. Combs Jr. GF. Selenium in global food systems. *Br J Nutr* 2001; 85: 517-547. 6. Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. 2000, Washington, D.C.: National Academy Press. 7. Field CJ, Johnson IR, Schley PD. Nutrients and their role in host resistance to infection. *J Leukoc Biol* 2002; 71: 16-32. 8. Roy M, Kiremidjian-Schumacher L, Wishe HI, Cohen MW. Supplementation with selenium and human immune cell functions. I. Effect on lymphocyte proliferation and interleukin 2 receptor expression. *Biol Trace Elem Res* 1994; 41: 103-114. 9. Beck MA, Shi Q, Morris VC, Levander OA. Rapid genomic evolution of a non-virulent Coxsackievirus B3 in selenium-deficient mice results in selection of identical virulent isolates. *Nat Med* 1995; 1: 433-436. 10. Beck MA. Nutritionally induced oxidative stress: effect on viral disease. *Am J Clin Nutr* 2000; 71(suppl): 1676S-1679S. 11. Nelson HK, Shi Q, Van Dael P, Schiffrin EJ. Host nutritional selenium status as a driving force for influenza virus mutations. *FASEB J* 2001; 15: 1846-1848. 12. Baum MK, Shor-Posner G, Lai S, Zhang G. High risk of HIV-related mortality is associated with selenium deficiency. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; 15: 370-374. 13. Baum MK, Miguez-Burbano MJ, Campa A, Shor-Posner G. Selenium and interleukins in persons infected with Human Immunodeficiency Virus Type 1. *J Infect Dis* 2000; 182 (Suppl): S69-S73. 14. Combs Jr. GF, Clark LC, Turnbull BW. An analysis of cancer prevention by selenium. *Biofactors* 2001; 14: 153-159. 15. Clark LC, Combs Jr. GF, Turnbull BW, Slate EH. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. *JAMA* 1996; 276: 1957-1963. 16. Clark LC, Dalkin B, Krongrad A, Combs Jr. GF. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* 1998; 81: 730-734. 17. Raich PC, Lü J, Thompson HJ, Combs Jr. GF. Selenium in cancer prevention: Clinical issues and implications. *Cancer Invest* 2001; 19: 540-553. 18. Forceville X, Vitoux D, Gauzit R, Combes A. Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients. *Crit Care Med* 1998; 26: 1536-1544. 19. Berger MM, Cavadini C, Chioleri R, Dirren H. Copper, selenium, and zinc status and balances after major trauma. *J Trauma* 1996; 40: 103-109. 20. Angstwurm MWA, Schottdorf J, Schopohl J, Gaertner R. Selenium replacement in patients with severe systemic inflammatory response syndrome improves clinical outcome. *Crit Care Med* 1999; 27: 1807-1813. 21. Berger MM, Reymond MJ, Shenkin A, Rey F. Influence of selenium supplements on the post-traumatic alterations of the thyroid axis: a placebo-controlled trial. *Intensive Care Med* 2001; 27: 91-100. 22. Virtamo J, Valkeila E, Alftan G, Punars S. Serum selenium and the risk of coronary heart disease and stroke. *Am J Epidemiol* 1985; 122: 276-282. 23. Kok FJ, de Bruijn AM, Vermeeren R, Hofman A. Serum selenium, vitamin antioxidants, and cardiovascular mortality: a 9-year follow-up study in the Netherlands. *Am J Clin Nutr* 1987; 45: 462-468. 24. Dirmagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. *Trends Neurosci* 1999; 22: 391-397. 25. Jeurink BHJ, Sweeney MI. Mechanisms that result in damage during and following cerebral ischemia. *Neurosci Biobehav Rev* 1997; 21: 121-128. 26. del Zoppo G, Ginis I, Hallenbeck JM, Iadecola C. Inflammation and stroke: Putative role for cytokines, adhesion molecules, and iNOS in brain response to ischemia. *Brain Pathol* 2000; 10: 95-112. 27. Brigelius-Flohé R, Friedrichs B, Maurer S, Schultz M. Interleukin-1-induced nuclear factor κB activation is inhibited by overexpression of phospholipid hydroperoxide glutathione peroxidase in a human endothelial cell line. *Biochem J* 1997; 328: 199-203. 28. Horváthová M, Jahnová E, Gazdík F. Effect of selenium supplementation in asthmatic subjects on the expression of endothelial cell adhesion molecules in culture. *Biol Trace Elem Res* 1999; 69: 15-26. 29. Maddox JF, Aherne KM, Reddy CC, Sordillo LM. Increased neutrophil adherence and adhesion molecule mRNA expression in endothelial cells during selenium deficiency. *J Leukoc Biol* 1999; 65: 658-664.