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Dietary selenium and selenoprotein function

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Summary

Selenium is a trace mineral and an essential nutrient in the human diet. Selenium is found in soil and water and consequently enters the food chain through the root ways of plants and aquatic organisms. Some areas of the world are low in soil selenium resulting in a selenium deficient population and the appearance of an associated heart disease and bone disorders that can be corrected with dietary selenium. Indeed the requirement for dietary selenium was established by these observations and while selenium deficiency is rare in the West, patients requiring long-term intravenous feedings have also show heart disease associated with a deficiency of selenium in the feeding fluids. Subsequently, it has been established that dietary selenium can improve a wide range of human health conditions even in areas with soil replete in selenium.

key words: **selenium • Se • selenoproteins • dietary • antioxidant**

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Background

Dietary selenium (Se) functions and mediates health benefits through incorporation into cysteine (MeCyst) prior to protein synthesis forming the 21st amino acid used during protein synthesis (ref). Proteins into which MeCyst is incorporated are known as "selenoproteins" and require dietary selenium to be fully functional. Selenoproteins fulfill vital functions in the body. For example, selenoproteins are: a) essential antioxidant enzymes that fight cancer and other chemical toxicities, b) regulators of thyroid hormone and thyroid function, c) structural proteins in sperm required for fertility, and d) can reduce the virulence associated with certain viral infections including HIV-1. Because the value of Se can only be understood through the activity of selenoproteins, this review takes the unique and challenging approach of presenting the nutritional benefits of selenium by listing and linking selenoprotein function to evidence of health benefits. Table 1 shows a list of the known human selenoproteins and their known roles in human health.

It is important to note that understanding selenoprotein functions overlaps with nutritional studies, but does not nearly account for all of the dietary clinical studies that show general health improvements with increased oral selenium intake. Therefore this review will also present most of the recent clinical studies in which selenium was shown to benefit human health. In specific, increased dietary intake of selenium has also been shown to: a) reduce cancer incidence, b) reduce cancer-associated mortality, c) reduce oxidative damage and poisoning associated with chemo- and radiotherapy, d) reduce severity of autoimmune diseases, e) improve mental health, f) improve reproductive performance, g) improve elderly thymus and thyroid function and h) provide various additional health benefits including a slowed progression from HIV-1 infection to AIDS (Table 1).

Selenoprotein Functions

Antioxidant enzymes: Prevention of cancer, toxicities, neurodegeneration, atherosclerosis and stroke

Antioxidant enzymes are required for elimination toxins known as reactive oxygen species (ROS). ROS toxins form naturally in our cells simply from oxygen metabolism and can also form as a result of exposure to chemical pollutants and drugs. These ROS toxins cause damage to DNA, cell membranes, and a variety of other cell structures and leads to "oxidative stress". We take antioxidants to mitigate the effects of oxidative stress. If we do not have enough antioxidant capacity, oxidative stress can lead to cell death, organ system failure, cancer, inflammatory disease, cardiovascular disease, poor wound healing, hearing impairment and stroke. Selenoproteins constitute one of the most important classes of antioxidant enzymes the glutathione peroxidases (GPx). In the human body there are eight forms of GPxs (GPx1–GPx8) and of these, five (GPx1–GPx4, and GPx6) are selenoproteins [1]. In addition to these well studies antioxidant enzyme systems, at least seven additional selenoproteins (TR1, TR2, TR3, Sel P, Sel R and Sel W) have been suggested to play a role in humans in protecting against oxidative stress and the elimination of ROS toxins.

For example, UV light and the gentotoxic carcinogen azoxymethane are both know to elevate cellular ROS toxins and cause cancer. In studies using *in vitro* cultures of human breast cancer cells, both the addition of selenium to the culture medium and enhanced expression of GPx1 protected these cells from UV induced DNA damage [2]. Further, mice engineered to lack GPx1 (GPx1 knockouts) were more susceptible to colon abnormalities when treated with the colonic carcinogen, azoxymethane, [3]. GPx2 is primarily express in the gut epithelium and mice engineered to lack GPx2 (GPx2 knockouts) have an increase incidence of intestinal cancer [4]. Further, *in vitro* cultures of human cancer cells in which production of GPx2 was blocked demonstrated an increase in invasive and migratory properties associated with metastatic potential [5]. In human studies, increased risks for prostate cancer and lung cancer (non-small cell lung carcinoma) have been associated with low Sel P production [6,7]. These studies support the observation that selenium deficient diets may put people at risk for developing cancer and that increasing selenium intake may boost the antioxidant capabilities of selenoproteins in cancer therapy and prevention.

In addition to being more susceptible to DNA damage and cancer, GPX1 knockout mice demonstrate increase rates of sickness and death when exposed to ROS-inducing chemicals such as paraquat [8,9] and also to coxsackievirus-associated cardiac disease [10].

Further, GPx1 may protect the central nervous system from ROS induced neurodegeneration. Microglia and astrocytes protect neurons in the brain from oxidative stress (ROS-induced damage). Studies in rodents have shown that microglia and astrocytes express high levels of GPx1 in rodents [11,12] and humans with Parkinson's and dementia show microglia with elevated GPx1 activity associated with distressed neurons [13]. GPx4 depletion in the hippocampus of mice has been shown to cause oxidative-damage in brain neurons leading to cell death like that seen in Parkinson's Disease and b-amyloid production like that seen in Alzheimer's Disease [14–16]. In addition to preventing neurodegenerative diseases in adults, GPx4 antioxidant activity also supports normal brain development in mice [17–19]. Knockout of the selenoprotein, Sel P, in mice also leads to neurodegeneration [20]. Moreover, elevated Sel P is found in post-mortem analysis of b-amyloid plaques of Alzheimers Disease patients [21] further suggesting a role for oxidative stress in neurodegenerative diseases and the potential for selenium and selenoproteins to prevent their onset.

Selenoproteins are also important for cardiovascular health. Human clinical studies also show that people with low Gpx3 activity have reduced capacity to metabolize ROS toxins and consequently present with increase risk for both arterial and cerebral clots and stroke [22–25]. Further, in a mouse model of atherosclerosis, over-expression of GPx4 leads to reduced lipid peroxidation and associated atherosclerotic plaque [26]. People with specific genetic variants of the selenoprotein, Sel S have also been shown to be at a higher risk for cardiovascular disease and stroke although this increased risk has not been associated with ROS metabolism [27,28].

Thyroid Function

In addition to serving as antioxidant enzymes, selenoproteins are essential to thyroid gland function. The thyroid

Table 1. A list of selenoproteins and the health benefit suggested through either cell culture studies, animal studies or human clinical trials.

Selenoprotein	Suggested Health Benefit by Study Design	Reference
GPx1	**Antioxidant**	
	Cell Culture Studies	
	Protects human cells from UV-induced DNA damage	19
	Animal Studies	
	Protects mice from colon cancer	20
	Protects rodents from chemical toxicity	24,25
	Protects mice from viral associated cardiomyopathy	26
	Human Clinical Trials	
	Protects stressed neurons in Parkinson's Disease	23
GPx2	**Antioxidant**	
	Cell Culture Studies	
	Reduces metastatic properties of human cancer cells	5
	Animal Studies	
	Protects mice from intestinal cancer	4
GPx3	**Antioxidant**	
	Human Clinical Trials	
	Protects people from cerebral clots and stroke	39–42
	Protects people from atherosclerosis and cardiovascular disease	43–45
GPx4	**Antioxidant**	
	Animal Studies	
	Protects mice from Parkinson's-like neurodegeneration	29–31
	Supports normal brain development in mice	32–34
	Prevents developmental neurological defects in mice	48,49
	Human Clinical Trials	
	Vital for sperm production, motility and fertility in men	46,47
TR1	**Antioxidant**	
	Cell Culture Studies	
	Inhibits HIV replication in human macrophages	60
	Animal Studies	
	Required for live birth in mice	50
TR2	**Antioxidant**	
	Animal Studies	
	Required for live birth in mice	50
D2	**Thyroid Function**	
	Animal Studies	
	Maintains healthy metabolic rate in mice	54, 55
Sel N	**Antioxidant**	
	Animal Studies	
	Supports normal muscle development in mice	51
Sel P	**Antioxidant**	
	Animal Studies	
	Prevents neurodegeneration	35
	Prevents infertility in mice	58
	Human Clinical Trials	
	Prevents cancers in humans	6, 7
	Protects humans from Alzheimer's Disease	38
Sel T	**Unknown**	
	Cell Culture Studies	
	Supports neurite/nerve formation in rodent neuronal cells	52
SPS2	Synthesis of all other selenoproteins	
	Human Clinical Trials	
	Maintains healthy metabolic rate in humans	33

gland produces thyroid hormone which in turn regulates a variety of metabolic events in humans. Thyroid hormone formation requires selenoproteins and selenoproteins can also regulate thyroid hormone activity by inactivating it. These selenoproteins are the deiodinases enzymes, D1, D2 and D3. The conversion of the thyroid hormone precursor, T4, to the active T3 hormone is mediated by D1 or D2 while both D1 and D3 can inactivate T3 [29]. Mice genetically lacking the D2 selenoprotein exhibit reduced thyroid stimulating hormone regulation and reduced capacity to metabolize fat to keep warm (brown fat thermogenesis) [30,31]. Interestingly the thyroid expresses as many as 11 different

selenoproteins to protect this gland from the oxidative stress high levels of ROS hydrogen peroxide which is a byproduct of thyroid hormone synthesis [32]. Indeed, people with mutations in the a gene that encodes for a selenoprotein synthesis factor suffer with thyroid function defects [33].

Fertility

While the two clear categories of selenoprotein activity are antioxidant protection from ROS metabolites and thyroid hormone function, selenoproteins play several diverse important structural and functional roles in cell physiology that are important to human health. GPx4 is an important structural protein of sperm and low sperm GPx activity is associated with reduced viability and motility in men [34,35]. Mice lacking the seloprotein Sel P gene exhibit male infertility [36]. Further, developing mouse embryos that lack GPx4 die in mid gestation from developmental neurological defects [37,38]. Genetic deletion of TR1 and TR2 leads to embryonic lethality in mice [39] and and depletion of the selenoprotein, Sel N leads to muscle malformation in zebrafish embryos [40]. Sel T expression is increased during neurite formation in neuronal cell cultures [41] suggesting a role for this selenoprotein in neuronal development.

Viral Infections

In both mice and humans, reduced activity of GPx as a consequence of selenium deficiency leads to a more virulent coxakie viral infection and heart disease (Keshan Disease) [42–44]. Further, the level of the selenoprotein TR1 is found to be reduced in HIV-1 infected individuals [45]. Further, TR1 inhibits HIV-1 protein Tat which is responsible for transcriptional activity of the virus [46] and selenium deficiency has been associated with a more rapid progression from HIV infection to AIDS [47–49]. In HIV-1 infected patients on anti-retroviral therapy (ART), daily intake of 200 μg selenium increased circulating CD4+ T-cell levels by two to three fold compared to those on ART alone (50).

Clinical Studies with Dietary Selenium

Cancer

In 1996, in randomized clinical studies, the Nutritional Prevention Cancer Study Group reported in the Journal of the American Medical Association that selenium supplementation at 200 micrograms per day reduces the incidence and morbidity from basal and squamous cell carcinomas [51]. Subsequent randomized double blind studies confirmed these observations in 1997 [52] and were extended in placebo controlled studies to include prostate cancer in 1998 [53]. In 2002, randomized clinical trial known at the "Nutritional Prevention of Cancer Trial" was initiated as a multi-institutional investigation and showed that dietary selenium at 200 micrograms per day can reduce the risk of several site specific cancers [54]. By 2003 the Nutritional Prevention of Cancer Trial (NPCT) concluded that selenium supplementation can reduce the incidence of lung cancer in people with selenium deficiency and in blind, placebo controlled trials decreases prostate cancer incidence in selenium-replete patients with low prostate serum markers (PSA) [55]. Further analysis of the NPCT data revealed a reduced risk for colon cancer in patients with low blood selenium levels and also a beneficial effect particularly for smokers [56]. In 2009, a double blind, placebo controlled, prospective study demonstrated that women carrying BRCA1 gene mutations and a predisposition for breast cancer show a reduced risk when taking daily selenium supplements [57]. Most recently, a six month double blind placebo controlled study demonstrated that when taken in combination with silymarin, a milk thistle flavonolignan, selenium reduces the stage progression of prostate cancers [58].

In addition to directly reducing cancer incidences, cancer progression and mortality, dietary selenium has also been shown to alleviate some of the oxidative toxicities associated with cervical, ovarian, head and neck cancer chemo- and radiotherapies [59–62] and also improves the overall nutritional balance in these patients [63].

Immune system

Intake of high levels of selenium protects patients from inflammatory damage associated with sepsis and from rheumatoid arthritis [64,65]. Further, clinical trials show that increased dietary selenium can reduce autoantibody production in autoimmune thyroiditis, Grave's disease and Psoriasis [66–68].

Reproductive health

Intravenous selenium administration improves the outcomes for preterm infants born in selenium-deficient areas [69,70]. Placebo controlled clinical trials also increase the fertility of men living in low selenium areas leading to successful conception [71]. Dietary selenium also reduces pre-labor membrane rupture and preeclampsia [72,73].

Mental health

Several clinical studies have shown that dietary selenium can improve mood by reducing anxiety and depression [74,75] including post-partum depression [76].

Conclusions

It is clear that selenium is a required dietary nutrient. Selenium is unique in its structural incorporation into proteins (selenoproteins) which in functioning as antioxidants, regulators of thyroid function, and structural proteins, serve to prevent cancer, improve cardiovascular health, prevent stroke and atherosclerosis, prevent neurodegeneration, promote healthy embryonic nervous system and muscle development, improve fertility and the immune response and fight viral infections including HIV-1 (Table 1). Dietary selenium can enhance selenoprotein activity and reduce the risk of various cancers, thyroid disorders, drug toxicities and autoimmune diseases and improve mental health, reproductive outcomes and possibly fight AIDS (Table 1).

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