Selenium: A Micronutrient Essential for Maintaining Human Health

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Abstract

Selenium is a fundamental importance to human health. It is an essential trace element for major metabolic pathways, since selenium is an essential component of glutathione peroxidase enzyme. Diet is the main source of selenium. Selenoproteins in mammalian cells indicated that essential role of selenium in the body's antioxidant defense system.

Key Words: Selenium, trace element, antioxidant, selenoproteins

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Introduction

Selenium (Se) is a potent nutritional antioxidant, important for various aspects of human health [1]. As a constituent of selenoproteins, it plays both structural and enzymatic roles [2-4]. Also, ıt is an essential component of the active sites of several enzymes, including glutathione peroxidase (GPx) and thioredoxin reductase, which catalyze reactions, essential to the protection of cellular components against the oxidative stress and free radical damage [5].

Biochemistry and metabolism

Both inorganic (selenite and selenate) and organic (selenocysteine and selenomethionine) forms of Se can be used as nutritional sources [6]. The selenoorganic compounds, primarily L- selenomethionine generally are recognized as safe and effective forms of Se supplementation. It is known that in plants Se is present predominantly as selenomethionine, whereas in animals selenocysteine is the major form [7]. Although no single marker for Se status has been identified, a plasma Se concentration is an indication of recent ingestion. Erythrocytes and platelet GPx activity correlates with Se supplementation. Urine Se varies with intake. At very high levels of intake, volatile forms of Se are exhaled [8]. Serum Se was also significantly associated with serum selenoprotein P in both sexes. Also, serum α-tocopherol was positively associated to serum selenium [6]. Serum Se status and n- 3 fatty acids composition were also correlated. This can probably be explained by the association of these fatty acids with fish intake [9].

Food and nutritional sources

Diet is the major source of selenium. Se enters the food chain through plants; intake with drinking water is generally negligible. The amount of Se in foods depends on geographical factors [10]. Se levels in soil generally reflect its presence in food and in human populations [11]. Low availability of selenium may occur in some areas, whereas in seleniferous areas, via plants excessive selenium is taken up [12]. Absorption of Se is not homeostatically controlled, and it depends on the chemical form of selenium. Selenium-selenomethionine (organic form) is more efficiently absorbed and more retained in the body than selenium-selenite (inorganic form). Se form in soils also affects Se bioavailability: selenate is more mobile, soluble and

less-well adsorbed than selenite [13]. Selenite, on the other hand, can be effectively used for selenoprotein synthesis, but it cannot be stored in the body. Selenomethionine can act as a storage form of Se in body proteins from which it can slowly be released by catabolism to maintain Se requirements over a longer period [14]. Thus, Se in the form of selenomethionine was almost twice as effective as Se in the form of selenite in supporting plasma GPx activity [15, 16]. Furtheremore, selenomethionine is recognized as less toxic than selenite. Many foods as grain products, sea food, meat and poultry are major sources of Se. However, it has been shown recently that Se in certain plants as corn, soybean, and mushrooms is poorly available, on the other hand in certain foods of animal origin as beef kidney, Japanese fish, meat, Baltic herring, milk, trout is relatively more available. The reason for the low selenium bioavailability in certain fishes is not clear. It has been suggested that mercury present in fish might complex selenium into unavailable form [17]. Supplementation of Se with β-carotene or vitamin E enhances the antioxidant system (superoxidedismutase, GPx, and glutathion) [18]. Serum α- tocopherol and retinol were positively associated to serum Se [19]. In our study, we investigated the histopathological effects of hypercholesterolemia and protective effect of vitamin E and Se on the morphology of liver and kidney [20, 21]. The histopathological effects of high cholesterol diet revealed degradation of hepatocelluler organelles, renal glomerular fibrosis and mesangial proliferation. In the groups fed with cholesterol + vitamin E, cholesterol + Se, and cholesterol + vitamin E + Se morphological improvements were observed. We observed that especially combined vitamin E and Se therapy were regenerated hepatocelluler and renal damages and these antioxidant agents had protective effects on liver and kidney tissues.

Selenoproteins

Several selenoproteins have been isolated from mammals [Table 1]. [22, 23]. The human selenoproteome consists of 25 selenoproteins [24]. In selenoproteins, Se occurs as selenocysteine [25]. The main groups are GPx, type 1 5’ iodothyronine deiodinase, 1-3 thioredoxin reductases, selenoprotein P (Se-P) and other proteins. These are redox enzymes that take advantage of the chemical properties of Se to catalyze, respectively, removal of hydroperoxides by glutathione, deiodination of thyroid hormones and support of cellular

processes requiring reduction of disulfides. Se-P is an extracellular protein that contains most of the Se in plasma. Approximately 60% of Se in plasma is incorporated in Se-P which contains 10 Se atoms per molecule as selenocysteine, and may serve as a transport protein for Se [26]. It associates with endothelial cells, probably through its heparin-binding properties. Se- P has been postulated to protect against oxidative injury and to transport Se from the liver to peripheral tissues [27]. Se- P is required for development of functional spermatozoa and indicate that it is an essential component of the Se delivery pathway for developing germ cells [28].

Cardiovascular disease and selenium

Se may be protective against cardiovascular disease. This hypothesis is supported by the ability of GPx to combat the oxidative modification of lipids and to reduce platelet aggregation [29]. In cerebral ischemia model, infarct volume was increased three-fold in the GPx knockout mice compared with the wild-type mice [30]. GPx is required for the metabolism of hydroperoxides produced in eicosanoid synthesis by the lipoxygenase and cyclo-oxygenase pathways. In Se deficiency, a built-up of these hydroperoxides inhibits the enzyme prostacyclin synthetase that is responsible for the production of vasodilatory prostacyclin by the endothelium, but stimulates the production of tromboxane, which is associated with vasoconstriction and platelet aggregation. GPx4 reduces hydroperoxides of phospholipids and cholesteryl esters associated with lipoproteins and may therefore reduce the accumulation of oxidized low-density lipoproteins in the artery wall [31]. Suadicani et al. [32] showed that middle-aged and elderly Danish men with serum Se below 79 µg/L had a significantly increased risk of ischaemic heart disease. Some antioxidants such as vitamin E, which may compensate for a deficiency in selenium in protection against atherosclerosis [33]. In one report, ventricular tachycardia resistant to several standard therapeutic agents was normalized after Se supplementation to the patient. Se supplementation may be of benefit in preventing ischemia-reperfusion injury: a Se- enriched diet had a significant effect in preventing reperfusion-induced arrhythmias in an animal model [34].

Other oxidative-stress or inflammatory conditions and selenium

Se behaves both as an antioxidant and anti-inflammatory agent. Its antioxidant role, notably as GPx, can reduce hydrogen peroxide, lipid and phospholipid hydroperoxides. Diminishing the production of inflammatory burst were provided with removal of hydrogen peroxide and reduction of superoxide production. Any conditions associated with increased oxidative stress or inflammation might be expected to be influenced by Se levels, which may be the case in rheumatoid arthritis, pancreatitis, and asthma. In a double-blind randomized trial, a small group of patients with rheumatoid arthritis, supplementation with 200 µg Se as selenium-yeast for 3 months, significantly had reduced pain and joint involvement [35]. There is an evidence for a protective effect of Se in pancreatitis, a disorder associated with a high level of oxidative stress. Another small study in intrinsic asthmatics showed significant clinical improvement on supplementation with Se at 100 µg per day as sodium selenite [36]. However, significant associations between Se status and prevalence or severity of asthma have not been consistently demonstrated in human studies [1].

Immune system and selenium

Both cell- mediated immunity and B- cell function can be impaired. Lymphocytes from volunteers supplemented with Se (as sodium selenite) at 200 µg per day showed an enhanced response to antigen stimulation and an increased ability to develop into cytotoxic lymphocytes and to destroy tumour cells natural killer (NK) cell activity was also increased [37]. After administration of selenium in the form of seleno-yeast supplement 50 µg daily for 2 month, notable increase in white blood cell (WBC) count and absolute neutrophil count (ANC) was recorded. This suggested that selenium had a clear effect on correcting the low level of WBC specifically neutrophils back to normal level thus reducing the condition of neutropenia in this particular patient [38].

Viral infections and selenium

Se deficiency is linked to the occurrence virulence or disease progression of some viral infection. Beck et al. [39] have shown that harmless viruses can become virulent in a Se deficient host. Coxackie virus has been isolated from the blood and tissue of people with

Keshan disease, coxackie virus become virulent, and causing myocarditis infection in the host [40]. In Se-deficient host, the other RNA viruse infections, such as poliovirus, hepatitis, influenza or HIV infections progresses will be more serious. Se also appears to be protective in infection with hepatitis virus B and C against the progression of the condition to liver cancer [41, 42]. It has been suggested that retroviruses such as HIV and coxsackie B3 have the potential to deplete the host's Se supply by incorporating the Se into viral selenoproteins for their own protection, as has been demonstrated for the DNA virus, molluscum contagiosum [43-45].

Reproduction

Se is required for human sperm maturation and sperm motility and may reduce the risk of miscarriage [46]. Barrington et al. [47] and Behne et al. [48] found that testicular morphology and functions are affected by severe Se deficiency and that the element is necessary for testosterone biosynthesis and the formation and normal development of spermatozoa. Animals fed Se-deficient diets show structural abnormalities in the sperm, thus decreasing the chance of fertilization [49]. The selenoprotein phospholipid hydroperoxide glutathione peroxidase (PHGPx) is abundantly expressed in spermatids as active peroxidase, where it is a major constituent of the mitochondrial capsule in the midpiece. Male infertility in selenium-deficient animals, which is characterized by impaired sperm motility and morphological midpiece alterations, is considered to result from insufficient PHGPx content [50-53]. In studies by Scott and Macpherson [54], supplementation of subfertile men with 100 μg selenium per day for 3 months significantly increased sperm motility. Se-P is required for development of functional spermatozoa and indicate that it is an essential component of the Se delivery pathway for developing germ cells [55, 56]. Se supplementation was demonstrated in sub–fertile Scottish men who showed a significant increase in sperm motility when supplemented with 100mg Se/d for 3 months. There is, however, a suggestion that relatively high intakes (about 300mg/d) may decrease sperm motility [57]. In UK pregnant women with higher Se status had a significantly lower risk of first-trimester or recurrent miscarriage [58, 59]. Fortier et al. [60] reported the uterine transfer of Se to embryos was improved with organic Se-yeast

(OSe) as compared to inorganic Na-selenite (MSe), and this was concomitant with a enhanced Se-specific antioxidant status and development of embryos.

Mood and selenium

The study in the UK, where a 100 µg Se supplement significantly decreased anxiety, depression, and tiredness, the effect being greatest in those whose diets were lowest in Se [61, 62]. There can be no doubt that Se is important to the brain: animal models of neurodegenerative diseases show enhanced cell loss in Se depletion.

Thyroid functions and selenium

Type I iodothyronine deiodinase, an enzyme necessary for proper thyroid function and conversion of T_4 into T_3 is a selenoprotein containing Se in the form of selenocysteine. Selenoenzymes GPx and thioredoxin reductase are crucial to the protection of the thyroid from the hydrogen peroxide (H_2O_2) that is produced there for thyroid hormone synthesis. Selenoenzyme iodothyronine deiodinase is required for the production of active thyroid hormone [63]. However, it was found that sodium selenite or selenomethionine at 200 microg/day was required to decrease inflammation and thyroid autoantibody concentrations in patients with autoimmune thyroiditis [64].

Apoptosis and selenium

Wang et al. [65] studied the influence of Se and fluoride on apoptosis and lipid peroxidation in human hepatocytes in vitro. Yu et al. [66] also studied on rat renal apoptosis and proliferation and found the antagonistic effect of selenium-zinc preparation (Se-Zn) to sodium fluoride (NaF). They suggested that NaF could induce apoptosis and Se-Zn could antagonize apoptosis. Apart from the selenoproteins, small-molecular-weight Se compounds such as Se-methyl selenocysteine and g-glutamyl- Se-methyl selenocysteine are thought to be precursors of the potent anti-cancer agent methyl selenol, which is purported to cause apoptosis, cell-cycle arrest, inhibition of tumour cell invasion and angiogenesis [67-69]. Cheng et al. [70] showed that protein expression of proapoptotic Bax, Bcl-w, Bcl-X and caspase-3 was

upregulated, but antiapoptotic Bcl-2 was down regulated in GPx knockout mice compared to wild-type mice.

Cancer and selenium

Following exposure to oxidative stress, the cell either dies or repairs damage [71]. However, if damage persists, the cell will enter a state of genetic instability that can lead chronic diseases, including cancer. El-Bayoumy et al. [72] tested that Se supplementation reduces oxidative stres. Free radicals (e.g., superoxide, nitric oxide and hydroxyl radicals) and other species (e.g., hydrogen peroxide) are reduced in the body, primarily as a result of aerobic metabolism [73]. Antioxidants (vitamin E, C, β-carotene, zinc, Se, among many others) and antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione reductase and peroxidases) exert synergistic actions in scavenging free radicals [74]. It seems that several hypotheses have been proposed to explain the protection against carcinogenesis by supplemental Se [75]. One of these, its protection against oxidative damage involving Se as an essential component of the antioxidant enzyme GPx or Se-P. A recently the meta-analysis of randomized controlled trials indicates that there is possible evidence to support the use of selenium supplements alone for cancer prevention in the low baseline serum selenium level population and in the high-risk population for cancer [76].

Prostate and breast cancer cells were about 25 times more sensitive than normal cells to selenomethionine, a major form of Se in cells [77]. Se and vitamin E are probably two of the most popular dietary supplements considered for use in the reduction of prostate cancer risk [78]. The 200 μg/day Se treatment decreased total cancer incidence by a statistically significant 25%; however, 400 μg/day of Se had no effect on total cancer incidence [79]. Novel chemo-preventive agents need to be developed and tested under defined protocols of carcinogenesis and anti-carcinogenesis.

Sources, bioavailability and safety of selenium

Supplements are a popular way of increasing Se intake for more affluent consumers. Se from selenomethionine was found to be 1-6 times more bioavailable and much more effective in raising plasma Se than was sodium selenite [80]. Many people rarely eat foods that are good

sources of Se. Crab, fish, kidney and liver are moderately good sources of Se, although studies show marked differences in the ability of Se from fish to increase Se status. The existence of different Se compounds in fish, their dependence on fish species or source or interaction with mercury or arsenic, known contaminants of fish, may explain this disparity. Grains and vegetables are good sources of Se, but the Se content of these foods varies greatly with the local soil content of this metal. In North America, wheat is a good source of Se, but the same cannot be said for European wheat because of the low availability of Se in most European soils. Acid soils and complexation, frequently with iron or aluminium, also reduce the uptake of Se by plants, as in many parts of Europe. Such organic forms may, however, be more toxic during long-term consumption, owing to non-specific retention of Se as selenomethionine in body proteins, rather than its excretion [81]. The role of safer selenoorganic compounds should not be minimized, because Se may have toxic effects at levels only four to five times that normally ingested in the human diet. The health benefits of Se supplementation can be accomplished at much higher doses than the currently recommended 50 to 100 μg/day elemental Se supplementation. According to some researchers, the recommended daily dose of Se could be as high as 200 to 300 μg/day. Se toxicity has been studied in animals and observed in humans where signs of selenosis are hair loss, brittle, thickened and stratified nails, garlic breath and skin [82]. Symptoms of selenosis in susceptible patients were found at or above a Se-intake of 910 μg/day, corresponding to a blood Se level of 1.05 mg/L. The overall results indicated that a daily Se-intake of 750-850 μg might be the marginal level of safe intake.

Briefly, Se deficiency posses are a serious problem in livestock worldwide, which ultimately may affect the Se status in humans. It is therefore important to address Se's nutritional and therapeutic role with a sense of urgency.

Conflict of Interest

Author have no conflict of interest.

Table 1. Selenoprotein types and their functions.

Selenoproteins	Functions
GPx	The four glutathione peroxidase enzymes (classical GPx1, gastrointestinal GPx2, plasma GPx3, phospholipid hydroperoxide GPx4) which represent a major class of functionally important selenoproteins, were first to be characterised Crucial antioxidant enzyme in mammals, remove H_2O_2, thereby protects cellular components from oxidative damage and stress
Selenoprotein P	Approximately 60% of Se in plasma is incorporated in selenoprotein P which contains 10 Se atoms per molecule as selenocysteine, and may serve as a transport protein for Se. However, selenoprotein P is also expressed in many tissues. It may be involved in selenium transport (between the liver and other organs) as well as in the prevention of free radical pathology Development of functional spermatozoa
Selenoprotein W	Isolated from the skeletal muscle of a rat, this selenoprotein is necessary for muscle metabolism
Cytosolic selenoprotein, Prostate epithelial selenoprotein, 15kDa	Found in rat prostate. Seems to have redox function (resemble GPx), perhaps protecting secretuar cells against development of prostate cancer
Selenophosphate synthtase, SPS2	Required for biosynthesis of selenophosphate, the precursor of selenocysteine, and therefore for selenoprotein synthesis
Phospholipid hydroperoxide GPx	Described in porcine heart and liver, it specially reduces lipid peroxides in cell membrane
Sperm mitochondrial capsule selenoprotein	In accordance with the role of mitochondria in assisting sperm motility
Tip I iodothyronine deiodinases	An enzyme necessary for proper thyroid function and conversion of T_4 into T_3, is a selenoprotein containing selenium in the form of selenocysteine
Thioredoxin reductases	Recently identified seleno-cysteine containing enzyme which catalyzes the NADPH dependent reduction of thioredoxin and therefore plays a regulatory role in its metabolic activity.[29] Maintenance of intracellular redox state, critical for cell viability and proliferation, regeneration of antioxidant systems
DNA-bound spermatid selenoprotein, 34kDa	GPx-like activity found in stomach and in nuclei of spermatozoa, may protect developing sperm
18kDa selenoprotein	Important selenoprotein, found in kidney and other tissues preserved in selenium deficiency

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