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Review Article

# Selenium: Properties and Clinical Applications. A Systematic Review - a

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## ABSTRACT

Selenium (Se), which is commonly found in nature, is one of the essential trace elements necessary for the normal development of human and animal organisms. Selenium participates in the protection of cells against ROS, in heavy metal detoxification, and regulation of the immune and reproductive systems. Selenium was first defined in 1818 by the Swedish chemist Berzelius in sulfuric acid residues. At the end of 1960s, the role of selenium in human health began to attract attention and human diseases that resembled animal diseases responding to selenium was started to be investigated. Nowadays Selenium is used in the prevention and/or treatment of different disorders including chronic autoimmune thyroiditis, Graves' disease, hypothyroidism, cancer, human infertility, cardiovascular disease, diabetes, osteoarthritis, rheumatoid arthritis, AIDS and depression. In these cases Selenium supplementation is increasingly becoming a valid therapeutic solution.


**Keywords:** Selenium; Supplementation; Antioxidant; Disease; Thyroid; Cancer; Infertility; Depression

## INTRODUCTION

Selenium (Se) was first discovered by the Swedish chemist Jöns Jacob Berzelius in 1817 and named after the Greek word Selene, meaning the moon [1].

Se has an atomic weight of 78.96 and can exist in organic molecules (as Se II) and inorganic salts such as selenate (Se VI) or selenite (Se IV). The principal dietary sources of Se are bread, cereals, dairy, eggs, fish, meat, and nuts. Dietary intake varies around the world and largely depends on whether Se-rich or Se-poor crops are cultivated and fed to animals and their geographical location [2,3].

Selenium has been recognized as an essential micronutrient with antioxidant, immunological, and anti-inflammatory properties for animals and human health [4,5].

It acts as an essential cofactor required to activate several enzyme systems in humans [6].

Se is integrated into the polypeptide chains as the 21$^{st}$ amino acid, selenocysteine and the proteins which contain selenocysteine are called selenoproteins (SPs). The key metabolic function of Se has therefore been attributed to its role in this enzymatic cofactor selenocysteine (SeC) [7,8].

25 SPs, encoded by 25 human genes, have been characterised in humans although the functions of some of these SPs have yet to be elucidated [9,10].

The most popular selenoenzymes are:

**Glutathione peroxidase (GPx):** an enzyme family with peroxidase activity whose main biological role is to protect the organism from oxidative damage.

**Iodothyronine deiodinases (D1, D2, D3):** a subfamily of enzymes important in the activation and deactivation of thyroid hormones. Thyroxine (T4), the precursor of 3,5,3'-triiodothyronine (T3) is transformed into T3 by deiodinase activity.

**Thioredoxin reductases (TR, TrxR):** the only enzyme known to catalyze the reduction of Thioredoxin. The importance of Se and SPs in health and disease is gaining increasing recognition. Evidence suggests that Se status affects both the cell-mediated and humoral aspects of immune function, which are linked to inflammatory processes involving the production of reactive oxygen species (ROS) and redox control processes.

Toxins known as Reactive Oxygen Species (ROS) are formed within the cells from oxygen metabolism under normal physiological conditions. If these ROS toxins are not neutralized; they damage to DNA, cell membranes, and a variety of other cellular structures [11]. This may result in cell death and may also trigger a vicious cycle of tissue inflammation. SPs, which are powerful antioxidant enzymes, mitigate the effects of oxidative stress by elimination of ROS [11].

GPx and thioredoxin reductase (TxR) are the two main seleno-enzyme systems responsible for the reduction of these superoxide production [12-14]. Se deficiency leads to reduced production of SPs, including GPx, resulting in the accumulation of $H_2O_2$ causing tissue inflammation and disease [15]. In addition, SPs play a vital role in the regulation of human immune system and Se deficiency is accompanied by dysregulation of both cell-mediated immunity and B cell function [16]. Therefore, in Se-sufficient environment, these intermediates are neutralised effectively resulting in diminished generation of proinflammatory Prostaglandins (PGs) and leukotrienes [17]. This minimizes the subsequent tissue injury. Se deficiency lowers antioxidant activity and thereby impairs free radical neutralization [18]. Consequently, Se is arguably one of the cornerstones of the body's antioxidant defense systems in acute critical illness.

## SELENIUM SOURCES AND RECOMMENDATIONS

Selenium exists in two forms: inorganic (selenate and selenite) and organic (selenomethionine and selenocysteine) [19]. Soils contain inorganic selenites and selenates that plants accumulate and convert to organic forms, mostly selenocysteine and selenomethionine and their methylated derivatives. Most selenium found in human and animal tissues is in the organic form of selenomethionine, where it can be incorporated with amino acids. Skeletal muscle is the major site of selenium storage, accounting for approximately 28% to 46% of the total selenium pool [20]. Both selenocysteine and selenite are reduced to generate hydrogen selenide, which in turn is converted to selenophosphate for selenoprotein biosynthesis [21].

Table 1 lists the current RDAs for selenium in mcg. For infants from birth to 12 months, the FNB established an AI for selenium that is equivalent to the mean intake of selenium in healthy, breastfed infants. Sea foods and organ meats are the richest food sources of selenium [22]. Other sources include muscle meats, cereals and other grains, and dairy products. The amount of selenium in drinking water is not nutritionally significant in most geographic regions [19,23]. The amount of selenium in a given type of plant-based food depends on the amount of selenium in the soil and several other factors, such as soil pH, amount of organic matter in the soil, and whether the selenium is in a form that is amenable to plant uptake [19,23,24,25]. As a result, selenium concentrations in plant-based foods vary widely by geographic location [19,22].

The selenium content of soil affects the amounts of selenium in the plants that animals eat, so the quantities of selenium in animal products also vary [19,26]. However, selenium concentration in soil has a smaller effect on selenium levels in animal products than in plant-based foods because animals maintain predictable tissue concentrations of selenium through homeostatic mechanisms. Furthermore, formulated livestock feeds generally contain the same levels of selenium. Several food sources of selenium are listed in table 2.

## SELENIUM DEFICIENCY

The Se deficiency is mostly caused by low dietary intake or poor intestinal absorption. Rarely Se and SP deficiency can be genetically inherited [27]. Selenium deficiency produces biochemical changes that might predispose people who experience additional stresses to develop certain illnesses [23]. The following groups are among those most likely to have inadequate intakes of selenium.

### People living in selenium-deficient regions

People in some other countries whose diet consists primarily of vegetables grown in low-selenium areas are at risk of deficiency [23]. The lowest selenium intakes in the world are in certain parts of China, where large proportions of the population have a primarily vegetarian diet and soil selenium levels is very low [26]. Average selenium intakes are also low in some European countries, especially among populations consuming vegan diets [25,26,28]. Although intakes in New Zealand were low in the past, they rose after the country increased its importation of high-selenium wheat [25].

### People undergoing kidney dialysis

Selenium levels are significantly lower in patients undergoing long-term hemodialysis than in healthy individuals. Hemodialysis removes some selenium from the blood [29]. In addition, hemodialysis patients are at risk of low dietary selenium intakes due to anorexia resulting from uremia and dietary restrictions. Although selenium supplementation increases blood levels in hemodialysis patients, more evidence is needed to determine whether supplements have beneficial clinical effects in these individuals.

### People living with HIV

Selenium levels are often low in people living with HIV, possibly because of inadequate intakes (especially in developing countries), excessive losses due to diarrhea, and malabsorption [19,30]. Observational studies have found an association between lower selenium concentrations in people with HIV and an increased risk of cardiomyopathy, death, and, in pregnant women, HIV transmission to offspring and early death of offspring [31,32]. Some randomized clinical trials of selenium supplementation in adults with HIV have found that selenium supplementation can reduce the risk of hospitalization and prevent increases of HIV-1 viral load; preventing HIV-1 viral load progression can lead to increases in numbers of $CD_4$ cells, a type of white blood cell that fights infection [33,34]. However, one trial showed that selenium supplementation in pregnant women can prevent early death in infants but has no effects on maternal viral load or $CD_4$ counts [35,36].

**Table 1:** Recommended Dietary Allowances (RDAs) for Selenium.

| Age | Male | Female | Pregnancy | Lactation |
|---|---|---|---|---|
| Birth to 6 months | 15 mcg* | 15 mcg* | | |
| 7-12 months | 20 mcg* | 20 mcg* | | |
| 1-3 years | 20 mcg | 20 mcg | | |
| 4-8 years | 30 mcg | 30 mcg | | |
| 9-13 years | 40 mcg | 40 mcg | | |
| 14-18 years | 55 mcg | 55 mcg | 60 mcg | 70 mcg |
| 19-50 years | 55 mcg | 55 mcg | 60 mcg | 70 mcg |
| 51 + years | 55 mcg | 55 mcg | | |

*Adequate Inrtake (AI)

**Table 2:** Selected Food Sources of Selenium.

| Food | Micrograms (mcg)per serving | Percent DV* |
|---|---|---|
| Brazil nuts, 1 ounce (6-8 nuts) | 544 | 777 |
| Tuna, yellowfin, cooked, dry heat, 3 ounces | 92 | 131 |
| Halibut, cooked , dry heat, 3 ounces | 47 | 67 |
| Sardines, canned in oil, drained solids with bone, 3 ounsec | 45 | 64 |
| Ham, roasted. 3 ounces | 42 | 60 |
| Beef, ground, 25% fat, broiled, 3 ounces | 18 | 26 |
| Egg, hard-boiled, 1 large | 15 | 21 |
| Puffed wheat ready-to-eat cereal, fortified, 1 cup | 15 | 21 |
| Bread, whole-wheat, 1 slice | 13 | 19 |
| Baked beans, canned, plain or vegetarian, 1 cup | 13 | 19 |
| Oatmeal, regular and quick, unenriched, cooked with water, 1 cup | 13 | 19 |
| Spinach, frozen, boiled, 1 cup | 11 | 16 |
| Milk, 1% fat, 1 cup | 8 | 11 |
| Yogurt, plain, low fat, 1 cup | 8 | 11 |
| Lentils, boiled, 1 cup | 6 | 9 |
| Bread, white, 1 slice | 6 | 9 |
| Spaghetti sauce, marinara, 1 cup | 4 | 6 |
| Cashew nuts, dry roasted. 1 ounce | 3 | 4 |
| Com flakes, 1 cup | 2 | 3 |
| Green peas, frozen, boiled, 1 cup | 2 | 3 |
| Bananas, sliced, 1 cup | 2 | 3 |
| Potato, baked, flesh and skin, 1 potato | 1 | 1 |
| Peaches, canned in water. Solids and liquids, 1 cup | 1 | 1 |
| Carrots, raw, 1 cup | 0 | 0 |
| Lettuce, iceberg, raw, 1cup | 0 | 0 |
| Turkey, boneless, roasted, 3 ounces | 31 | 44 |
| Beff liver, pan fried, 3 ounces | 28 | 40 |
| Chicken, light meat, roasted, 3 ounce | 22 | 31 |
| Cottage cheese, 1% milkfat, 1 cup | 20 | 29 |
| Rice, brown, long-grain, cooked, 1 cup | 19 | 27 |

*DV = Daily Value. DVs were developed by the U.S. Food and Drug Administration (FDA) to help consumers compare the nutrient contents of products within the context of a total diet. The DV for selenium is 70 mcg for adults and children aged 4 and older. Foods providing 20% or more of the DV are considered to be high sources of a nutrient.

### Dietary Supplements

Selenium is available in multivitamin/multimineral supplements and as a stand-alone supplement, often in the forms of selenomethionine or of selenium-enriched yeast (grown in a high-selenium medium) or as sodium selenite or sodium selenate [19,23,26]. The human body absorbs more than 90% of selenomethionine but only about 50% of selenium from selenite [23].

Few studies have compared the relative absorption and bioavailability of different forms of selenium. In one investigation, 10 groups of selenium-replete subjects were randomly assigned to receive a placebo or either 200 or 600 mcg/day selenium as selenomethionine, sodium selenite, or high-selenium yeast (in which an estimated 75% of selenium was in the form of selenomethionine) for 16 weeks [37]. Selenium bioavailability, based on urinary excretion, was greatest for selenomethionine and lowest for selenite.

## SIDE EFFECTS, INTERACTIONS AND WARNINGS

Chronically high intakes of the organic and inorganic forms of selenium have similar effects [23]. Early indicators of excess intake are a garlic odor in the breath and a metallic taste in the mouth. The most common clinical signs of chronically high selenium intakes, or Selenosis, are hair and nail loss or brittleness. Other symptoms include lesions of the skin and nervous system, nausea, diarrhea, skin rashes, mottled teeth, fatigue, irritability, and nervous system abnormalities.

Brazil nuts contain very high amounts of selenium (68-91 mcg per nut) and could cause selenium toxicity if consumed regularly. Acute selenium toxicity has resulted from the ingestion of misformulated over-the-counter products containing very large amounts of selenium [19,26]. In 2008, for example, 201 people experienced severe adverse reactions from taking a liquid dietary supplement containing 200 times the labeled amount [38]. Acute selenium toxicity can cause severe gastrointestinal and neurological symptoms, acute respiratory distress syndrome, myocardial infarction, hair loss, muscle tenderness, tremors, lightheadedness, facial flushing, kidney failure, cardiac failure, and, in rare cases, death [19,26].

### Interactions with medications

Selenium can interact with certain medications, and some medications can have an adverse effect on selenium levels. One example is provided below. Individuals taking this and other medications on a regular basis should discuss their selenium status with their health care providers.

Cisplatin, an inorganic platinum chemotherapy agent, is used to treat ovarian, bladder, lung, and other cancers. Cisplatin can reduce selenium levels in hair and serum but whether these reductions have a clinically significant impact is not known [39,40]. Some small studies have shown that selenium supplementation can reduce cisplatin's toxicity [41] but, the authors of a Cochrane review concluded that the evidence that selenium supplementation alleviates the side effects of chemotherapy is insufficient [42].

## SELENIUM: NEW THERAPEUTIC EVIDENCE FOR MULTIPLE DISEASES

The understanding of the essential role of selenium (Se) in human health has increased substantially in recent decades. Selenium is used by people in the prevention and/or treatment of different disorders including chronic autoimmune thyroiditis, hypothyroidism, male and female infertility, cardiovascular disease, osteoarthritis, rheumatoid arthritis, stroke, atherosclerosis, cancer susceptibility and treatment, HIV, AIDS, neuronal diseases such as Alzheimer or amyotrophic lateral sclerosis, pancreatitis, depression, and diabetes amongst others. Several mechanisms have been suggested to mediate the biological effects of Se and these include antioxidant defence systems, synthesis and stability of metabolites that act as intermediates implicated in diverse selenoproteins expression pathways oxidative metabolism, immune system modulation, DNA intercalators, kinase regulation, enzymatic cofactor, and gene expression. A number of clinical trials in recent years have provided convincing evidence of the central role of this element, either alone or in combination with other micronutrients or antioxidants, in the prevention and treatment of multiple diseases. Based on these studies this review focuses on the role of selenium in the treatment of several chronic diseases.

### Effects of selenium deficiency on the thyroid gland

Selenium concentration is higher in the thyroid gland than in any other organ in the body, and, like iodine, selenium has important functions in thyroid hormone synthesis and metabolism. Se has been found to be an important co-factor for both physiological function and in autoimmune disease of the thyroid. $H_2O_2$ is an essential co-substrate for Thyroid Peroxidase (TPO) enzyme during the oxidation of inorganic iodine for thyroid hormone. However, even in physiological conditions a much higher amounts of $H_2O_2$ are produced than consumed by the iodination process, potentially exposing the thyroid gland to excessive amount of free radicals in addition to the 'normal' share of a cell [43,44]. SPs such as GPx and TxR neutralize these excess $H_2O_2$ and they are therefore considered as essential SPs in the thyroid hormone synthesis. In pathological hyperactivity, a large volume of $H_2O_2$ and ROS are produced and proportionately large quantity of Se are required to protect the thyroid gland from superoxide damage [10,45].

The two main autoimmune thyroid diseases are Hashimoto's Thyroiditis (HT) which is the most common cause of hypothyroidism and Graves' Disease (GD) which is the most common cause of thyrotoxicosis. These autoimmune thyroid diseases are caused by abnormal immune response to self-thyroid antigens and the key role is played by T lymphocytes when antigen recognition is mediated by receptors on the cell surface (Tcell receptor, TC-R). This breaks the tolerance by the deficit of suppressor T cells and aberrant expression of DR region of HLA (HLA-DR), absent on normal thyroid cells. The contemporary expression of HLA-DR on thyroid follicular cells and auto-antigens triggers the autoimmune reaction by antibody-dependent, complement-mediated, direct or indirect cytotoxicity [46].

It has thus been hypothesized that even mild nutritional selenium deficiency may promote the initiation or progression of thyroid autoimmunity. To test the hypothesis that selenium supplementation decreases the serum concentration of TPO-Abin patients with chronic autoimmune thyroiditis, a systematic review and meta-analyses have been performed [47]. The results show that in LT4-treated population, the Selenium (200 mcg daily of selenomethionine) had significantly lower TPO-Ab levels after 3 ($p < 0.0001$), 6 and 12 months. Tg-Ab decreased at 12 months, but not at 3 or 6 months. In LT4-untreated population, the Selenium group showed a decrease in TPO-Ab levels after 3 months ($p < 0.0001$), but not after 6 or 12 months. Tg-Ab decreased at 3 months, but not at 6 or 12 months.

Marcocci, et al. [48] carried out a randomized, double-blind, placebo-controlled trial to determine the effect of Se or Pentoxifylline (an antiinflammatory agent) in 159 patients who had mild signs or symptoms of Grave's Ophthalmopathy (GO) of less than 18 months' duration. At the 6-month evaluation, treatment with Se, but not with pentoxifylline, was associated with an improved quality of life ($p < 0.001$) and less eye involvement ($p = 0.01$) and slowed the progression of Graves' orbitopathy ($p = 0.01$), as compared with placebo. Based on this literature review Se appears to have a beneficial in reducing the extraocular muscle and orbital adipose tissue inflammation and Se may exert these beneficial effects by reducing the TPO-Ab and TSHR-Ab concentrations, regulation of immune mechanisms and inhibiting orbital inflammation.

Calissendorff, et al. [49] investigated 38 patients with initially untreated thyrotoxicosis by measuring the Thyroid-Stimulating Hormone (TSH), Free Thyroxine (FT4), Free Triiodothyronine (FT3), thyroid receptor antibodies and thyroid peroxidase auto-antibodies before medication and at 6, 18 and 36 weeks after commencing treatment with methimazole and levo-thyroxine, with a randomized blinded oral administration of 200 µg Se/day or placebo. The selenoprotein P concentration was determined in plasma at inclusion and after 36 weeks. The patients were also assessed with questionnaires about depression, anxiety and self-rated symptoms before medication was started and after 36 weeks.

The results show that FT4 decreased more in the Se group at 18 weeks (14 vs. 17 pmol/ l compared to the placebo group, $p = 0.01$) and also at 36 weeks (15 vs. 18 pmol/ l, $p = 0.01$). The TSH increased more in the Se group at 18 weeks (0.05 vs. 0.02 mIU/ l, $p = 0.04$). The depression and anxiety scores were similar in both groups. In the Se group, the depression rates correlated negatively with FT3 and positively with TSH. This was not seen in the placebo group. Thus, Se supplementation can enhance biochemical restoration of hyperthyroidism, but whether this could shorten clinical symptoms of thyrotoxicosis and reduce mental symptoms must be investigated further.

Women with thyroid peroxidase antibodies tend to develop hypothyroxinemia while they are pregnant and thyroid dysfunction and hypothyroidism after giving birth [25]. The authors of a Cochrane review of hypothyroidism interventions during pregnancy concluded, based on a trial that administered supplements containing 200 mcg selenium as selenomethionine daily to 151 pregnant women with thyroid peroxidase antibodies [50], that selenomethionine supplementation in this population is a promising strategy, especially for reducing postpartum thyroiditis [51]. However, the authors called for large randomized clinical trials to provide high-quality evidence of this effect. Selenium appears to have an impact on thyroid volume. In children with a goiter living in areas where there are iodine and selenium deficiencies, iodine repletion alone does not reduce the volume of the goiter and does not improve thyroid function. In reality, the more severe the selenium deficiency, the less iodine supplementation helps to reduce thyroid volume [52].

In the French SUVIMAX study, the correlation between thyroid volume and selenium status was only established in women. So far, the molecular mechanism making women more sensitive to low selenium intake has not been elucidated. Recently, Rasmussen, et al. [53] published the results of a study on the correlations between selenium status, thyroid volume and nodule formation. Similarly to the French SUVIMAX study, the population presented with moderate iodine deficiency. A negative correlation was found between thyroid volume and plasma selenium levels, but the result was only statistically significant for the general population or for subjects supplemented with iodine. Therefore, the effect of selenium status on thyroid volume does not appear to be related to iodine deficiency. Finally, in the study, low plasma selenium concentrations were correlated with a risk of formation of multiple nodules over 10 mm in size, but did not impact the risk of development of solitary nodules.

Similarly, Samir, et al. [54] found low plasma selenium concentrations in 22 subjects presenting with multinodular goiter compared with a control group of 15 subjects. Conversely, Derumeaux, et al. [55] did not find that the global risk of developing nodules was increased in selenium-deficient patients. There are numerous hypotheses relating to the molecular mechanisms responsible for the increase in the risk of development of a goiter and nodules in selenium-deficient patients and they mainly concern GPX abnormalities. Low serum selenium concentrations have been associated with a diagnosis of differentiated thyroid cancer in selenium deficient areas. Jonklaas, et al. [56] conducted a pilot study to explore associations between selenium concentrations and the diagnosis of thyroid cancer in an area of selenium sufficiency in the United States.

The authors identified 65 euthyroid patients at an academic medical center who were scheduled for thyroidectomy for thyroid cancer, suspicion of thyroid cancer, or nodular disease. Blood samples were obtained two to four weeks prior to thyroidectomy. Samples were analyzed for Thyrotropin (TSH), free thyroxine, total triiodothyronine, selenium, and 25 hydroxyvitamin D levels. Concentrations of these analytes were correlated with whether the patient was diagnosed with benign or malignant disease following their thyroidectomy. In patients with thyroid cancer, the concentrations of selenium and 25-hydroxyvitamin D were correlated with various prognostic features.

Although selenium concentrations were not significantly lower in patients with thyroid cancer, serum selenium concentrations were inversely correlated with disease stage ($p = 0.011$). Within the thyroid cancer patients, vitamin D concentrations were not associated with disease stage or any other prognostic features. In contrast, TSH concentrations were significantly higher in patients with thyroid cancer, and were positively correlated with the number of involved lymph nodes ($p = 0.011$) and disease stage ($p = 0.022$). These data confirm the association between serum TSH and advanced thyroid cancer. In addition, they also suggest a potential association between selenium concentrations and higher thyroid cancer stage. Larger prospective studies will be required to confirm this association. If confirmed, future studies would need to determine if the association is causative in nature. If causation exists, it seems likely that selenium concentrations would influence thyroid cancer development via an independent mechanism from that of TSH.

## Selenium and cancer

Because of its effects on DNA repair, apoptosis, and the endocrine and immune systems as well as other mechanisms, including its antioxidant properties, selenium might play a role in the prevention of cancer [19,25,34,57].

*In vitro* and *in vivo* carcinogenesis studies sodium selenite has been shown to be the most effective: selenite is capable of oxidizing polythiols to corresponding disulfide. These polythiols associated with cancer membrane-bound proteins appear under the reducing

conditions of hypoxic tumor tissue. Selenite by virtue of oxidizing cell membrane thiols can prevent the formation of the coat surrounded tumor cells which masks specific tumor antigens thus allowing cancer cells to escape immune recognition and elimination by Natural Killer (NK) cells. This coat is the result by thiols that initiate a disulfide exchange reaction predominantly with fibrinogen, to form an insoluble and protease-resistant fibrin-like polymer. This mechanism seems to have a primary role in the resistance of prostatic cancer cells to antineoplastic immunotherapy. Selenite makes cancer cells vulnerable and, in addition, may directly activate NK cells. So, the use of sodium selenite could potentially be considered as an agent able to increase the efficacy of the vaccine against prostatic cancer and could contribute in the reduction of mortality for patients affect from this type of cancer [58,59].

In a Cochrane review of selenium and cancer prevention studies, compared with the lowest category of selenium intake, the highest intake category had a 31% lower cancer risk and 45% lower cancer mortality risk as well as a 33% lower risk of bladder cancer and, in men, 22% lower risk of prostate cancer [60]. However, randomized controlled trials of selenium supplementation for cancer prevention have yielded conflicting results. The authors of a Cochrane review concluded, based on nine randomized clinical trials, that selenium might help prevent gastrointestinal cancers but noted that these results need to be confirmed in more appropriately designed randomized clinical trials [61]. A secondary analysis of the double-blind, randomized, controlled Nutritional Prevention of Cancer Trial in 1,312 U.S. adults with a history of basal cell or squamous cell carcinomas of the skin found that 200 mcg/day selenium as high-selenium baker's yeast for 6 years was associated with a 52% to 65% lower risk of prostate cancer [62]. This effect was strongest in men in the lowest tertile of selenium concentrations who had a baseline prostate-specific antigen (PSA) level of 4 ng/ mL or lower.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT), a randomized, controlled trial in 35,533 men aged 50 years or older from the United States, Canada, and Puerto Rico, was discontinued after 5.5 years when analyses showed no association between supplementation with 200 mcg/day selenium with or without 400 international units (IU)/ day vitamin E and prostate cancer risk [63]. An additional 1.5 years of follow-up data on participants after they stopped taking the study supplements confirmed the lack of a significant association between selenium supplementation and prostate cancer risk [64].

In 2003, the FDA allowed a qualified health claim on foods and dietary supplements containing selenium to state that while "some scientific evidence suggests that consumption of selenium may reduce the risk of certain forms of cancer. FDA has determined that this evidence is limited and not conclusive" [65]. More research is needed to confirm the relationship between selenium concentrations and cancer risk and to determine whether selenium supplements can help prevent any form of cancer.

## Selenium and human fertility

The WHO defines infertility as the inability to achieve pregnancy within 12 months of regular sexual intercourse for couples in conception. Infertility affects 13-20% of couples around the world, regardless of race or ethnicity [66-69].

**Male infertility:** It is estimated that male factor of couple infertility is between 25% to 50% [67,70]. Male fertility disorder is attributed to environmental factors such as exposure to certain chemicals, heavy metals, pesticides, and heat, or electromagnetic radiation [71-73]. Smoking, alcohol abuse, chronic stress, obesity, urogenital trauma, and inflammation in the male reproductive system are also associated with decreased male fertility [74-76].

The consequence of most of these factors is oxidative stress. Spermatozoa are particularly susceptible to the damaging effects of ROS, because their cell membrane contains large amounts of unsaturated fatty acids, which can be oxidized (Lipid peroxidation), and the cytoplasm has only small concentrations of the enzyme able to neutralize ROS. The lipid oxidation process leads to a loss of membrane integrity and an increase in its permeability, inactivation of cellular enzymes, structural DNA damage, and cell apoptosis. The consequence is reduced sperm count and activity, decreased motility and abnormal morphology [77-79]. It is estimated that approximately 25% of infertile men present elevated levels of ROS in the semen [80-82] and often lower antioxidant capacity of semen [83-85].

The protective antioxidant system in the semen is composed of enzymes, as well as substances, which closely interact with each other to ensure optimal protection against ROS. Non–enzymatic antioxidants include vitamins A, E, C, and B complex, glutathione, pantothenic acid, coenzyme Q10 and carnitine, and micronutrients such as zinc, selenium, and copper. It seems that a deficiency of any of them can cause a decrease in total antioxidant status.

In particular, development of male reproductive tissue requires an optimal level of Se in testis; Selenium is a constituent of selenoproteins including GPx1, GPx3, mGPx4, cGPx4, and GPx5 that protect against oxidative damage to spermatozoa throughout theprocess of sperm maturation, whereas selenoproteins, such as mGPx4 and snGPx4, serve as structural components of mature spermatozoa. Thus, Se and selenoproteins ensure viability of spermatozoa as well as providing protection against reactive oxygen species.

Lack of selenium leads to atrophy of these miniferous epithelium, disorders of spermatogenesis and maturation of spermatozoa in the epididymis, and testis volume reduction [86]. Also, an increased percentage of sperm cells with abnormal morphology (mainly the head and midpiece) and poor sperm motility can be observed in the semen [87]. In a study of 64 as the nospermic men, selenium supplementation (100 µg daily) for 3 months improved sperm motility (28.2% *vs* 20.1%, $p = 0.04$) compared to placebo [88].

Twenty-six weeks of high dose selenium supplementation (200 µg daily) in105 subfertile men with abnormal sperm parameters improvedsperm concentration ($27.6 \times 106$ *vs* $22.4 \times 106$ ml−1, $p$= 0.03), motility (26.1% *vs* 22.1%, $p$= 0.03), morphology (9.2% *vs* 7.2%, $p$= 0.03), and seminal volume (3.2 *vs* 2.7 ml, $p$ = 0.02). Even if beneficial effects were reported, more studies are necessary for an increased understanding of the effects of Selenium supplementation on male infertility.

**Female infertility:** Female infertility is generally defined as the inability to get pregnant naturally and to deliver a live healthy newborn. The percentage of infertile women can reach 30% worldwide [89]. Infertility in women can be the result of various factors, including physical problems, endocrine problems, lifestyle habits, and environmental factors. Many studies have addressed correlations between Se intake and fertility as well as disorders of procreation processes. Selenium deficiencies may lead to gestational complications, miscarriages and the damaging of the nervous and

immune systems of the fetus. A low concentration of selenium in blood serum in the early stage of pregnancy has been proved to be a predictor of low birth weight of a newborn [90].

However, although it is well understood how important selenium is for men's fertility, it is not clear what role selenium plays in healthy reproduction in women. In a new study, researchers at University of Adelaide School of Chemistry and Physics and the Robinson Research Institute have found that selenium has a critical role in the early stages of a woman's fertility. For the study, researchers at the Australian Synchrotron in Victoria discovered where selenium is located in the ovary. Then they focused on the selenoprotein called GPX1. The researchers found that expression of the GPX1 protein was significantly higher, sometimes almost double the amount, in egg cells that led to a pregnancy [91]. These findings are important, because they show that selenium and selenoproteins are at elevated levels in large, healthy ovarian follicles. These enzymes play a critical role as an antioxidant during the late stages of follicle development, helping to lead to a healthy environment for the egg. Further research is needed to better understand how selenium levels could be optimized, helping to improve women's chances of conceiving.

### Selenium and depression

Depression, common throughout the world, is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings, and sense of well-being [92,93]. Several studies found lower GPx activity among those with major depression vs. controls [94], suggesting that lower selenium could be a risk factor for depression via antioxidant pathways. Observational research in adult and elderly populations has shown a higher risk of depression among those with lower selenium intake [95]. Few studies have tested the association between selenium and depressive symptoms in young adult populations (aged 18-25 y). The one study with the youngest age range of adults aged 20-35 y found that higher, not lower, selenium status was associated with higher risk of depressive symptoms 3 y later [96]. Randomized controlled trials (RCTs) have found improvements in mood [97,98] and improvement in postpartum depression [99] with selenium supplementation in adult populations.

However, the largest RCT to date found no effect of selenium supplementation on mood in an elderly population [100]. Older age could limit the antioxidant benefits of selenium supplementation through years of exposure to free radicals, which could explain why supplementation shows stronger benefits in adult rather than in elderly populations.

## CONCLUSIONS

Selenium is an essential trace mineral. It is the active centre of many selenoproteins implicated in antioxidant defence mechanisms. Improving selenium status could help protect against tissue damage in several critical human illnesses. However, further studies are needed to clarify whether selenium supplementation can produce beneficial effects in several human diseases.

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