

A Short Review on Beneficial Effects of Selenium on Human Health

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Abstract:

The trace element Selenium (Se) is an essential micronutrient for humans and animals. The beneficial effects of Se range from maintenance of metabolic processes, bone stability, immune and endocrine system, helping in reproduction to prevention of various diseases including cancer, brain disorders, asthma etc. Meat, fish and dairy products are considered as best sources of dietary Se. It is an important constituent of two amino acids: selenocysteine and selenomethionine. These two amino acids help to form several essential enzymes in human like thioredoxin reductases, glutathione peroxidases, iodothyronine deionidases and selenoproteins such as selenoprotein O, selenoprotein P or selenoprotein R. Deficiency of Se results in the development of many serious health effects in humans including Keshan disease. So, studies on various aspects of Se have become topic of interest amongst researchers.

Introduction:

After its discovery by the Swedish chemist J.J. Berzelius in 1817, Selenium (Se) drew attention of researchers only in the last few decades of twentieth century. At first, Selenium(Se) was believed to be a toxic material to humans, until its critical functions were confirmed in the last decade (Lenz and Lens, 2009). Its importance in humans has now become well established, and its deficiency has been found to cause several critical serious health issues in humans (Michelle et al., 2012). It is one of the principal trace elements, located in the 34th position in the periodic table. The role of Selenium(Se) in the preservation of numerous bodily processes in humans is being investigated by a large number of researchers. This trend has significantly increased the number of Selenium research in recent times. Selenium(Se) has been found to play an important role in prolonged fertility in males, functions as a regeneration agent, and has impact on endocrine gland (Kieliszek and Bano, 2022). Because of its antioxidant properties, it plays a crucial role in the pathogenesis and pathophysiology of a variety of disorders such as oxidative stress, apoptosis, inflammation, reproductive disorders, thyroid issues, diabetes and cancer (Ibrahim et al., 2019; Madhu et al., 2022, 2023). It also exerts major impacts on immune

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responses, strong memory, bone stability, embryonic growth etc (Kieliszek and Bano, 2022). The biological roles of Se are associated with its incorporation through selenocysteine (SeCys) into the structure of proteins crucial for metabolism (Kieliszek and Błażej, 2013).

Naturally, Se exists in both inorganic and organic forms. The inorganic forms comprise selenite, selenate, selenide, and elemental Se (Kieliszek, 2019). Inorganic selenite and selenate occur in soils and are taken up by plants, where they are converted into organic forms and their methylated derivatives. Skeletal muscles have been shown to store 28 to 46 % of the total Se pool, and thus making it the most significant site of storage (Hariharan., and Dharmaraj, 2020). The organic form of Se is found in the Se containing amino acids such as selenomethionine (SeMet) and SeCys (Kieliszek, 2019). In higher animals and humans, Se has been reported to be present as SeMet, which, in plant proteins replaces the methionine (Hu et al., 2018). Instead of methionine, the body uses SeMet because of its more easy absorption and metabolism or incorporation into proteins (Gandin et al., 2018). With methionine intake enhances, SeMet incorporation is decreased. It mostly occurs in the skeletal muscle, pancreas, stomach, liver, erythrocyte, kidney and gastrointestinal mucosa proteins. Release of SeMet from body proteins is linked with protein turnover and takes place continuously (Roman et al., 2014). In mammals, at least 30 selenoproteins have been recognized, and in humans about 25 selenoproteins have been reported (Kryukov et al., 2003). The functional attributes of many of these selenoproteins have yet not been completely explained, in spite of the fact that they are conserved throughout evolution (Mix et al., 2007). Among these selenoproteins, few act as antioxidant enzymes, such as thioredoxin reductase (TrxR) glutathione peroxidase (GPx) and iodothyronine deiodinases (IDD) where Se acts as an important component (Tapiero et al., 2003).

Se deficiency has been found to cause various pathological disorders across the world (Michelle et al., 2012). Reports show that people living on a special diet (due to phenylketonuria) are particularly susceptible to the adverse effects of Se deficiency (Eroglu et al., 2012). Se content has been found to be very low in patients who suffer from diseases like celiac disease, liver cirrhosis, rheumatoid arthritis and other degenerative diseases (Eroglu et al., 2012). In addition, persons exposed to advanced chemotherapy, and patients who have already received radiation therapy, are vulnerable to reduced expression of Se in the system (Yao et al., 2011). Deficiency of Se causes a lot of other diseases, such as asthma resulting from impaired GPx activity. It also results in irregular heartbeats, impaired circulation, coma, or sudden infant death syndrome (Kieliszek, 2019; Kieliszek et al., 2016). Se deficiency results in the development of a condition known as Keshan disease which is a paediatric cardiomyopathy, occurs mostly in young women of reproductive age and children of about 2–10 years old (Hadrup, N., and Ravn-Haren, 2020). Excessive dietary intake of Se has been found to cause food poisoning leading to diarrhea, nausea, and vomiting (Rayman, 2008; Thiry et al., 2012). Se in air, water and soil enters into the food chain through accumulation in plant tissues. The main sources of inorganic Se are plants and this inorganic Se is less digestible while the organic forms of Se are considered more digestible. Animal tissues and products

especially meat, fish, and dairy products are considered as good sources of organic Se (Kieliszek., and Bano, 2022). Brazil nuts and mushrooms are alternate sources of Se (Chen et al., 2021). Some fruits and vegetables as well as cereal products have high content of this micronutrient. The most important ones are cruciferous vegetables (Brussels sprouts, white cabbage, cauliflower) and garlic vegetables (Kieliszek., and Bano, 2022).

Some of the beneficial effects of Se on human health are describes here.

Acts as a potent antioxidant

Overproduction of different types of reactive oxygen species (ROS) in body or their accumulation due to external stress leads to the development of oxidative stress (OS). Damage to proteins, lipids or DNA by ROS impairs signal transduction pathways which in turn destroys overall cellular functions (Roman et al., 2014). Hence, OS is considered to be associated with a number of human disorders which includes cancer, cardiovascular and neurological diseases, and the aging process (Kieliszek., and Bano, 2022; Tsuji et al., 2021). GPx and TrxR, working as thiolredox systems neutralize OS through the reduction of H₂O₂ and lipid hydroperoxides in the body. One of the very crucial features of Se is its association as a constituent of various critical antioxidant compounds and the particular oxidation properties of the antioxidant molecule thioredoxin reductase. GPX protects membrane integrity by reducing ROS metabolites (Tinggi, 2008).

May reduce risk of certain cancers

Se has drawn the interest of researchers for the prevention and treatment of cancer (Kieliszek et al., 2017). The therapeutic use of Se in cancer is a point of argument. In the treatment of cancer using Se, several factors including the form of Se, the dose used, the period of action and the properties of the neoplastic cells determine the mechanisms resulting in the death of neoplastic cells. Because of the specificity of Se, it is considered as "an element with double edged sword". Se exhibits antioxidant characteristics in low doses while prooxidative properties in high doses (Wallenberg et al., 2014). Small concentrations of Se exert protection to both healthy and neoplastic cells. The cells get protections against the toxicity resulted from the oxidative stress and it also helps in DNA repair. Conversely at a higher concentration, Se has been found to reduce the risk of carcinogenesis and all types of cellular mutations. Se has a considerable impact on the expression of genes involved in the inflammatory responses as well as in the cytoskeleton remodelling (Misra et al., 2015). *In vitro* studies show that Se inhibits migration in neoplastic cells and exhibits an anti-angiogenic effect. Thus, it prevents new blood vessels formation, which is a major feature of malignant neoplasms. Actually, prevention of cellular mobility is inhibition of the development of tumor metastasis. This association has been corroborated in the case of prostate, breast, lung, or colon cancer, and also in the case of lymph node metastases. The knowledge regarding the anticancer mechanism of Se is limited in spite of the fact that the relationship between Se deficiency in blood and increased risk of cancer has been demonstrated in several occasions. The strong anti and prooxidative features of Se make it

suitable for anticancer therapy. Inside the cancer cells, ROS produced in the glycolysis and the pentose phosphate cycle disrupts the pro and antioxidant equilibrium (Kieliszek and Bano, 2022). Through the generation of ROS and modification of the thiol group, Se exerts its effects on cancer cells. This activity of Se triggers the disruption of transcription and brings about changes in endoplasmic reticulum (Zhao et al., 2020; Razaghi et al., 2021). In this connection, it must be mentioned that Se through its cytotoxic effect damages cancer cells which may be useful in the treatment of advanced forms of cancer. Selenite (IV) is used in the treatment of cancer of different organs, including the uterus, lungs, and prostate. Selenite has been shown to have the potential to initiate its effect on developed prostate tumors (Fernandes and Gandin, 2015).

May protect against cardiovascular diseases

It is considered that an antioxidant plays a vital role in the prevention of atherosclerotic and cardiovascular disease (CVD) events (Benstoem et al., 2015). Deficiency of Se has been reported to be strongly associated with cardiomyopathy, which occurs in countries with considerably low Se intake (Thomson, 2004). Numerous studies have been accomplished for the evaluation of effect of Se on CVD risk (Kuria et al., 2021; Jenkins et al., 2020; Gharipour et al., 2017). Both low and high levels of Se have severe impacts on the cardiovascular system. A trial was conducted with a 7.6-year follow-up in Eastern USA, to assess the effect of Se ingestion on CVD prevention. The incidence of complete cerebrovascular injuries, myocardial infarction and CVD were assessed, and it was observed that there is no benefit of applying 200 µg/day of Se in general to prevent CVD (Stranges et al., 2007). Studies that aim in showing implications of Se deficiency in heart disease development missing infectious origin have shown that link between an insufficient intake of Se and cardiac dysfunctions may be caused by oxidative stress and its complications. Animal experiments using a variety of medications and formulae of Se, as well as trials in GPx mouse models have shown a vital role of Se in counterbalance reactive oxygen and nitrogen molecules, triggering prevention of organ injury after myocardial reperfusion. Besides GPx subtypes, TRxR is thought to have particular roles in the cardiovascular system, which is brought about by the oxidation of intraspecific and extracellular signaling molecules by influencing adaptive responses like remodeling (Maulik and Das, 2008; Ago and Sadoshima, 2006). In addition, some experiments with animal models have reported that Se deficiency has resulted in the downregulation of low-density lipoprotein (LDL) receptor, which is crucial for controlling plasma cholesterol levels (Dhingra and Bansal, 2006).

Helps prevent mental decline and brain disorders

Se and selenoproteins performs a major physiological function in neurons, astrocytes, and microglia. Reduction in the level of Se and selenoproteins may lead to brain dysfunction. With increasing age reduction in the brain Se levels takes place, and this decrease is thought to be associated with cognitive decline (Whanger, 2001). In addition, Se functions in the prevention

and treatment of Alzheimer's disease (AD), either alone or in combination with other substances. Researches have shown that Se levels in the brain tissues of AD patients are distinctly lowered, especially in the hippocampus and in the frontal, parietal, temporal and occipital lobes (Loef et al., 2011; Castaño et al., 1997; Wenstrup et al., 1990). It has been shown by various *in vitro* experiments that Se provides protection to the brain against poisons that result in Parkinson's disease symptoms continuing for an indefinite period in the body (Kieliszek and Bano, 2022). The association between Se and epilepsy has also been demonstrated. Use of Se in the treatment of epilepsy has become promising because epileptic patients have often been encountered with decreased serum and erythrocytic Se concentration. During epilepsy, Se gets depleted in the brain which is thought to be responsible for the beginning of seizures (Dominiak et al., 2016).

Important for thyroid health

Se plays an important role for the appropriate functioning of thyroid gland. In true sense, thyroid tissues are having a higher amount of Se compared to other organs of the human body (Ventura et al., 2017). This essential trace element exerts its protective role towards the thyroid gland against oxidative damage and carries out a crucial role in thyroid hormone production. Se deficiency has been found to trigger the development of thyroid conditions like Hashimoto's thyroiditis. It is a type of hypothyroidism in which the thyroid gland comes under the attack of the immune system. A study on more than 6000 people revealed that low serum Se level was the reason for the development of autoimmune thyroiditis and hypothyroidism (Wu et al., 2015). In addition, a number of studies have reported that Se supplements may have beneficial effects on people with Hashimoto's disease. Furthermore, one review showed that three months daily intake of Se supplements resulted in the reduction of thyroid antibodies. It also improved the general health and mood of patients suffering from Hashimoto's disease (Toulis et al., 2010).

Boosts immune system

For proper functioning of various cells of the immune system such as natural killer (NK) cells, macrophages, neutrophils and T lymphocytes, Se plays an important role. An appropriate increase in serum Se concentration in the diet helps to ameliorate OS, inflammation, and the spread of infectious diseases (Roman et al., 2014). Immunoglobulin production is augmented by Se, while its absence or poor concentration in the body results in reduced synthesis of Immunoglobulin and antibody (Xia et al., 2021). Leukotriene B4 production in Se deficient people has been shown to be increased by Se supplementation. This enhancement in Leukotriene B4 production in turn improves neutrophil chemotaxis. NK cell activity has also been shown to be impacted by Se (Tsuji et al., 2021).

Se and Type 2 Diabetes Mellitus

According to many *in vitro* and *in vivo* experiments, Se has an important role in the regulation of glucose homeostasis. Se also carries out a lead role in the postponement of

diabetes development and its progression. Se also has the ability to act as mimetic insulin in the form of selenite (Kim et al., 2019; Fontenelle et al., 2018; Wang et al., 2020). At the plasma concentration of nearly 140 ng/mL, Se has been shown to be linked to increased type 2 diabetes (T2D) risk (Bleys et al., 2007; Sarkar et al., 2023; Sur et al., 2023; Biswas et al., 2023; Roy et al., 2023; Acharya et al., 2023). SePs are important physiological antioxidants which possess insulin like properties capable of impeding the signalling of insulin (Bellinger et al., 2009).

Selenium for bone stability

The vigour of the skeletal system is critical for the elderly persons. To develop the strategies for early-life therapies, a complete knowledge regarding the connection between Se and bone strength is absolutely necessary (Zeng et al., 2013). OS results in the development of osteoporosis by triggering the suppression of osteoblastic proliferation of bone marrow stromal cells. SeIPs which are expressed in human embryonic osteoblasts, by preventing OS confers protection to the bone (Kieliszek M., and Bano, 2022). Se accomplishes an important role in the links between Se and bone mineral density (BMD) as Se is a key element of SeIPs (Beukhof et al., 2016). There are no less than ten studies that have established the links between serum or nutritional Se concentrations and BMD, osteoporosis or osteoporotic fractures. Lack of Se has been reported to be responsible for the development of a condition of osteoarthopathy in Kashin Beck disease (KBD). This can be explained by the fact that any shortage of Se affects the production of many antioxidant SeIPs, which impairs bone metabolism and promotes osteoarthopathy (Yang et al., 2022).

Selenium for reproduction

Micronutrients play numerous crucial functions in a variety of biological processes, including growth and reproductive capacity. And any impairment in their concentrations poses significant impacts on vital physiological processes such as fertility. In both men and women, reproductive function is affected by Se level. During folliculogenesis, Se has been demonstrated to control the multiplication and progression of granulosa cells, as well as the production of one of the vital female sex hormones, 17-estradiol (E2). A few studies have reported that there might exist a well established connection between Se status, female fertility, and Se dependent catalytic interaction (Mojadadi et al., 2021). As a whole, these studies revealed a greater association between higher incidence of female infertility and low Se concentrations in serum and follicular fluid. Besides promoting oocyte growth, Na_2SeO_3 has been shown to enhance the proliferation rate in theca and granulosa cells (Basini G., and Tamanini, 2000). Se is highly involved both in the normal sperm cell production as well as in the spermatozoa maturation in mammals. If the Se levels become highly extreme, sperm production is hampered. The spermatozoan maturation is critical to the semen quality as well as male fertility; so, any disruption in this process might lead to the manufacturing of lower quality semen and eventually infertility. So, it can be said that inadequate supply of dietary Se

contributes to the production of semen of poor quality, which ultimately triggers infertility as SelpPs in the testis are engaged in spermatogenesis (Bano et al., 2019).

Conclusion

Works on Se throughout the last two decades have attracted the interest of a large number of researchers. It is a unique trace element in the sense that unlike other trace elements, it offers only a narrow range between deficiency and toxicity. An optimal level of Se is critical for availing maximal health benefits. Research on Se and SelpPs and their effects has made us capable of developing novel compounds with medicinal properties. Yet till date SeMet and Se metabolism remain largely unknown. How SeCys is inserted into protein and how it works is unclear. As of now, the link between the GPx and TrxR and various diseases as well as functional roles of these antioxidant selenoenzymes in defending cells from oxidative stress, is well understood, but further researches is still required regarding the mechanism of action of Se in cancer etiology as well as the mechanistic pathway by which Se gives protection to the cells and tissue at the cellular level. More knowledge and new research in this field will explore the positive effects of Se for the benefit of human health.

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