REVIEW

Selenium: Its metabolism and relation to exercise

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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 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. Selenium, which is highly important for human health, is necessary for a variety of metabolic processes, including thyroid hormone metabolism, protection against oxidative stress and immunity functions. Selenium is a molecule that activates glutathione peroxidase, and thus, it is involved in the antioxidant mechanisms that prevent oxidant damage. Exhaustive physical exercise is known to cause oxidant damage, probably by promoting free radical production in many tissues, including muscle, liver, heart and lungs in animals. The increase in oxidative stress during exercise and recognition of selenium's stimulation of antioxidant activity inevitably suggest a relation between selenium and exercise. The present review aims to provide information on selenium metabolism and the relation between selenium and exercise.

Keywords: Selenium, nutrition, metabolism, physical performance, exercise.

Selenium

The major source of selenium is soil, and thus the plants. Selenium, which is transferred from soil to plants, animals and humans through the biological cycle, is consequently found in the organism in trace amounts (Oldfield, 1987; Shamberger 1986). Presence of vanadium, cobalt, zinc and particularly sulfates in the soil lowers the rate by which living things utilize selenium. The amount of selenium in arid soil is very low, causing selenium deficiency in animals living on arid land (Underwood 1977).

Its absorption, transport and storage

Selenium absorption occurs through small intestines, duodenum in particular, by active transport (Church and Pond 1982; Combs and Combs 1986; Keen and Graham 1989). Selenium as an element and selenium sulfite are scarcely absorbed (Keen and Graham 1989; Kutsky 1981). However, selenium which is taken in the organic form through diet or converted into organic form by the organism is easier to absorb, and therefore has higher rates of absorption (Church and Pond 1982; Combs and Combs 1986). Besides, amounts of vitamins E and A, as well as ascorbic acid, in the ration increases absorption of selenium (Combs and Combs 1986). After being absorbed, selenium is rapidly distributed to all bodily organs and tissues (Keen and Graham 1989). Although selenium transporters have not been definitively classified, it has been noted that it is transported by binding to plasma proteins and forms a part of this tissue (Underwood 1977; McDowell *et al.,* 1983). Binding to the plasma proteins albumin, α1 and α2 globulins and β-lipoproteins, selenium is transported to all body tissues, including the kidneys, liver, heart, red and white blood cells, pancreas tissues and hemoglobin globulin (Underwood 1977; Church and Pond 1982; Mills 1970). Amount of selenium in the blood varies significantly relative to its amount in the diet. Normal selenium level in the plasma ranges between 0.08 and 0.12μg/ml. Besides, hemoglobin, myoglobin, cytochrome-C have been reported as specific proteins and aldolase and myosin have been reported as specific enzymes for selenium that is transported by binding to plasma proteins, albumin in particular (Mills 1970).

Mobilization and excretion of selenium

Selenium is excreted through feces, urine and respiration. Its rates of excretion vary according to the animal species, its route of administration, amount of selenium per ration, its chemical form, as well as the levels of elements like arsenic and copper, which promote selenium excretion from the body, present in the ration (Underwood 1977). Intestinal absorption of selenium taken through oral route ranges between 44% and 70%; 14-20% of the intake is excreted through urine and a very small amount through skin and respiration in the first week, while 35-55% is disposed of through feces. Injections of arsenic, thallium, copper and cadmium increase selenium discharge by respiration, but lead and copper injections do not have any effect on excretion through this route (Underwood 1977).

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Daily selenium need and its relation to health

Selenium in the diet usually comes from white and red meat, grains and bread. An adult human body contains 20mg selenium. Selenium which is particularly concentrated in the liver and kidney is found most abundantly in the muscles (Levander, 1986). Amounts of daily selenium intake recommended by health organizations are 20-30µg for children (aged 1 to 10), 70µg for males over 20 years, 55µg for females, and 65 µg for pregnant women (Van Campen, 1991). It was reported that amount of daily selenium intake in the U.S. ranged between 60 and 216µg and in that case, the amount of selenium in the blood was in the range between 190 and 250µg/L (Burk, 1984; Burk 1991). However, in New Zealand where selenium deficiency is common, amount of daily selenium intake was reported to stand at 28-50µg/L, in which case selenium in the blood ranged between 50 and 100µg/L. In China, daily selenium intake was reported to be 30µg/L and the selenium in blood was 10µg/L, which is below the normal value (Van Campen, 1991). These values indicate that there is a conspicuous selenium deficiency in China. Selenium deficiency in Chinese people was established to be associated with basic cereal products' containing low concentrations of selenium (Yang *et al.,* 2010). In fact, the significance of selenium fur human health was first put forward through Keshan disease seen in rural China. One- to 10 year-old children who died due to Keshan disease were found to have blood selenium concentrations between 8 and 26µg/L. It was noted in the same study that having blood selenium concentration in the range between 32 and 83 µg/L might bring about the risk of premature death due to heart disease (Jackson 1988; Burguera *et al.* 1995). Burguera *et al.,* (1995) analyzed selenium in gastric tissues of healthy individuals, as well as people with gastritis, ulcer and stomach cancer. Their results demonstrated that selenium concentration in gastric tissue was 473µg/L in healthy individuals, 355µg/kg in individuals with ulcer and 36µg/kg in individuals with chronic gastritis. These results show that selenium has an important role in preventing the development of cancerous tissues. Likewise, research about the relation between selenium and cancer revealed that physiological doses of selenium in humans were not carcinogenic and even had an anti-carcinogenic effect (Oldfield, 1987), and that there was a negative correlation between mortality rates of cancer patients and selenium concentrations. Although it is known that low levels of selenium supplementation to the diet reduce incidence of and mortality due to cancer, this topic is still debated (Shamberger, 1986; Underwood 1977).

Selenium, which is an essential substance, has an effect on the immune system. For instance, it plays a central role in the non-specific humoral and cellular immune system (Boyne *et al.,* Kremidjian-Schumacher and Stotzky, 1987). It was reported that changes in the amount of selenium in the diet influenced functions of phagocytic cells (neutrophils, macrophages) (Boros, 1980) and that in selenium deficiency neutrophils obtained from rat, mouse and cattle had an impairment in their ability not only to phagocytize Candida albicans, but also to kill phagocytized Candida albicans (Boyne *at al.,* 1986). It was argued that lysosomal membranes of macrophages contained GPx and that these were destroyed in selenium deficiency (Combs and Combs, 1986). Generally, selenium deficiency produces immunosuppressive results. However, supplementation of selenium at physiological doses has been reported to be associated with an increase or improvement in the immunological response (Kremidjian-Schumacher and Stotzky, 1987). Some experimental studies conducted on various animal species (Dhur *et al.,* 1990) have shown a positive correlation between level of selenium and resistance against infectious agents. It was shown that selenium-deficient animals with induced experimental infections were very vulnerable against infections. On the other hand, cows and sheep supplemented with selenium were demonstrated to be very resistant against infectious agents (Dhur *et al.,* 1990). Selenium was also reported to have a positive contribution to the prevention of subclinical and clinical mastitis and this contribution was explained by selenium's possible stimulating effect on the number of PMN (polymorphonuclear leukocytes), immune functions and antibody production (Babior, 1978).

Symptoms of selenium deficiency in domestic animals and humans have been examined in detail. These include degenerative disorders in many tissues, defective reproduction and growth, increased susceptibility against cardiovascular diseases, immune defects and some cancers (Keen and Graham, 1989).

It was noted that presence of 0.05-0.10µg/g and more selenium was enough for protection against deficiency syndrome in animals and that the syndrome occurred when the amount of selenium was less than 0.05µg/g (Oldfield, 1987; Keen and Graham, 1989). However, it was reported that dietary selenium concentration should be in the range between 0.10 and 0.20µg/g values in order for optimal GPx activity to occur in tissues and that when dietary selenium level exceeded 3µg/g, some harmful effects ensued (Combs and Combs, 1986; Keen and Graham, 1989). Toxic dose of selenium in rats was found 3.35-3.5mg/kg for intraperitoneal selenium (as sodium selenite) and 3mg/kg for intravenous selenium (Shamberger, 1986). Changes that occur in the selenium concentration of the body directly affect glutathione peroxidase, which is the selenium enzyme (Neve, 1995). It was reported that 12% of the total selenium in the plasma was bound to glutathione peroxidase (Behne and Wolters, 1979).

Selenoproteins

Selenium is a very important micronutrient of the main metabolism. It accumulates in the active zone of the proteins' large area as selenocysteine. Selenium in selenocysteine is almost ionized in physiological conditions and thus it is a highly effective biological catalyst (Arthur *et al.,* 1997). It was claimed that there might be up to 100 selenoproteins in mammalian systems (Burk and Hill, 1993); of these, selenoproteins up to 30 have been defined as 75Se in *in vivo* systems (Evenson and Sunde, 1988). Until today, 15 selenoproteins have been classified or cloned in such a way that their biological functions have been defined. These are the 4 glutathione peroxidase enzymes that represent the major classes of selenoproteins with functional importance: Classical GPx1, gastrointestinal GPx2, plasma GPx3 and phospholipid hydroperoxide GPx4.

Glutathione peroxidases (GPx1)

Classical glutathione peroxidase (GPx1), is the first functional, biochemical determiner of selenium status. It is the strong linear bond between GPx activity and leukocyte selenium concentration and is the first defined selenoprotein. GPx was reported to act as an antioxidant, by directly reducing phospholipase A2 and H_2O_2, which are among partitioned lipid hydroperoxides, and to be found in cell cytosol (Rotruck *et al.,* 1973). It can also function as an important mediator for selenium, which harbors 4 selenocysteine residues in the tetrameric structure (Burk, 1984).

Gastrointestinal glutathione peroxidase (GPx2)

Gastrointestinal glutathione peroxidase (GPx2) protects mammals against the harmful effects of lipid hydroperoxides (Chu *et al.,* 1993). In animal studies, selenium deficiency increases enzyme activity, but no such effect has been reported in GPx2 activity in humans. Gastrointestinal glutathione peroxidase is the major selenoprotein antioxidant in the colon. Oxidative stress is pivotal in tumors. Therefore, it has been argued that with its antioxidant function, GPx2 can develop an early defense against colon cancer (Brown and Arthur, 2001).

Extra cellular glutathione peroxidase (GPx3)

Extra cellular GPx (GPx3) is another selenoprotein with antioxidant potential. However, this is not the main task it fulfills in the plasma. Hybridization studies (Avisssar *et al.,* 1984) indicate that GPx3 mRNA (messenger ribonucleic acid) is formed in proximal albright epithelial cells and that GPx3 can have a specific antioxidant function in extra cellular areas or renal tubules, as GSH (glutathione) concentration is high in the kidney. It has been argued that other thiols like thyrotoxin can act as electron transmitters and support the antioxidant function of GPx3 in the plasma. GPx3 is a protein disulphide, which is important in the regulation of thyrotoxin development and antioxidant defenses (Holmgren, 1989).

Phospholipid hydroperoxide glutathione peroxidase (GPx4)

Phospholipid hydroperoxide glutathione peroxidase (GPx4) is defined as a membrane enzyme that is directly responsible for the reduction of lipid hydroperoxides (Ursini *et al.,* 1985). This enzyme is a monomer and its activity is preserved, relative to GPx1, even when selenium levels drop (Bermano *et al.,* 1995). GPx4 can interact with both small, soluble hydroperoxides and phospholipid hydroperoxides and can also metabolize cholesterol and cholesterol ester hydroperoxides in oxidized low-density lipoproteins (Weitzel *et al.,* 1990). Consequently, it is reported to be central in the elimination of hydroperoxide. Unless hydroxyl is reduced to fatty acids, it can lead to uncontrollable radical chain reactions that damage the integrity of membranes. Amount of GPx4 protein in the tissues does not exactly reflect the distribution activity in animals, and this is either a reflection of the selenium-specific area dependent on cellular function or else indicates the difference in levels of factors activating GPx4. Active or inactive mechanism of the enzyme is not known yet. However, it is noted in evidence of its important function in membranes differentiating spermatogenic cells that there is certainly a correlation between peroxide levels and cell differentiation (Calvin *et al.,* 1987).

Selenium and exercise

It is known that strenuous physical exercise triggers acute phase immune response and thus forms a defense response against the condition involving reactive oxygen species (Emre *et al.,* 2004). As in inflammation and infection, exercise increases body temperature, serum cytokines (interleukin 1, interferon α) and circulating leukocytes. Short-term physical exercise can stimulate leukocyte mobilization, thereby increasing the leukocyte concentration in the circulation. Exhaustive physical exercise is known to stimulate oxidative stress probably by stimulating oxidative damage in several tissues including muscle, liver, heart and lung in animals (Sen and Packer, 2000). Furthermore, a series of defense mechanisms including SOD (superoxide dismutase) and GPx, as well as other endogenous antioxidants, protect cells against these toxic oxygen metabolites (Reddy *et al.,* 1998). Selenium is an acute phase 1 and acute phase reactant. That is because its concentration in a systemic inflammatory response was found low (Sattar *et al.,* 2001).

Selenium metabolism in the body can change during exercise. This is a type of acute phase responses. In humans, lactate concentrations increase in response to increasing exercise (Grant *et al.,* 2002). A negative correlation was shown between pH and lactic acid in blood (Rodas *et al.,* 2000). Selenoprotein P is bound more in endothelial cells in acidosis (Burk *et al.,* 1997). Therefore, the decrease in serum selenium in the post-

exercise group may be associated with the transfer of lactate from the muscle to blood in exercise (Rodas *et al.,* 2000). Several tissues have been reported to secrete extra cellular selenoprotein (extracellular GPx and selenoprotein P) (Anema *et al.,* 1999). Selenoprotein P is related to renal glomeruli and vascular endothelial cells in the brain. In an immunohistochemical study, selenoprotein P was reported to be strongly correlated with endothelial cells. Selenoprotein P is present in the extra cellular fluid and binds to cells (Burk *et al.,* 1997). Definition of some selenoenzymes is regulated by secondary messenger systems (Anema *et al.,* 1999; Howie *et al.,* 1998). A negative correlation was found between pre-exercise and post-exercise selenium levels. This negative correlation also applies to the maximal heart rate. It may be associated with heart morphology of athletes, as well as the effects of different sports. Individuals with high heart rates were reported to have low selenium levels (D'Andrea *et al.,* 2002). It was added that both serum selenium levels and heart rate were restored to normal values after 4 weeks of selenium supplementation (Shu, 1989). Emre and colleagues (2004) showed similar results, as well. As a chronic result of adaptation to training, GPx system is activated (Evelo *et al.,* 1992; Hellsten *et al.,* 1996; Leeuwenburg *et al.,* 1994; Powers *et al.,* 1994; Tessier *et al.,* 1995). GPx and serum selenium levels measured in erythrocytes did not vary at any time during extra endurance stress of trained athletes (Rokizki *et al.,* 1994). However, antioxidant conditions in pre- and post-training measurements varied widely in the neutrophils of training individuals (Powers and Ji, 1999). Selenium can also be evaluated as a speed-limiting molecule in the GPx system. Peroxidase enzyme cannot be formed in the absence of selenium and this results in the endangerment of the antioxidant protection provided by the GPx system (Leeuwenburg *et al.,* 1994; Powers *et al.,* 1994; Tessier *et al.,* 1995; (Rokizki *et al.,* 1994; Powers and Ji, 1999; Ohno *et al*., 1988). Exercise increases free radical production and GPx activity. Different researchers aiming to determine GPX activity in various muscle types demonstrated elevated GPx levels. These elevations were interpreted by some researchers in relation to the exercise duration, while they were found unrelated to exercise duration by others (Powers and Ji, 1999; Ortenblad *et al.,* 1997). Thus it may be hypothesized that endogenous activation of the GPx system by chronic exercise constitutes an adaptive mechanism that prevents the formation of free radicals. However, as debatable results, decreased glutathione responses have also been reported in individuals. These contradictions may arise from exercise protocols, experimental level, age, sex and genetic factors. Although the role of selenium in the post-exercise resting period has not been clarified, it is known to have a part in the structure of the GSH system. SOD production can be controlled by antioxidants like the GSH system. The check on post-exercise free radical production can be terminated by control mechanisms (Tiidus, 1998).

Reports of the researchers cited above indicate an inevitable relation between selenium, antioxidant activity and exercise. Ji *et al*., (1988) studied the effect of selenium deficiency on oxidant enzymes in the liver and skeletal muscle in chronic and acute exercise and established that selenium deficiency consumed the GPx in the liver and muscle. It was shown that MDA (malondialdehyde) production during physical exercise was inhibited parallel to the increase in selenium levels as a result of combined supplementation of selenium, vitamin E and vitamin C in physical exercise (Kaczmarski *et al.,* 1999). Similarly, it was reported that selenium and vitamin E supplementation for 6 weeks reduced MDA concentration in aerobic exercise (Kim, 2005). It was argued that combined supplementation of vitamin E and selenium was more effective than individual supplementation of each in exercised experimental animals (Veera Reddy *et al.,* 1992), while Zamora *et al.,* (1995) found that selenium supplementation alone could reduce lipid peroxidation in acute and chronic exercise.

There are also conflicting reports about the relation between selenium and exercise. It was reported in a study that in case of a 10-week endurance exercise, daily supplementation of 180µg organic selenium did not have any impact on adaptations stimulated by endurance training (Margaritis *et al.,* 1997). A similar finding to the effect that selenium supplementation did not affect physical performance was put forward by Tessier and colleagues (Tessier *et al.,* 1995). Likewise, it was claimed that tiring aerobic exercise caused DNA (deoxyribonucleic acid) damage and that selenium supplementation did not hinder this damage (Davison *et al.,* 2005). By the same taken, Margaritis and colleagues (Margaritis *et al.,* 2005) demonstrated in their study that erythrocyte GPx activity was not related with selenium.

It was reported that intensive swimming exercise in rats significantly inhibited zinc and selenium levels, while combined supplementation of zinc and selenium prevented the oxidative stress caused by swimming exercise in rat testis tissues (Jana *et al.,* 2008). Yur and colleagues (2008) showed that a 7-minute running exercise had important effects on serum calcium, potassium, copper, iron and iron/zinc ratio in horses supplemented with vitamin E and selenium. Similarly, it was demonstrated in a horse study that vitamin E and selenium had a synergic relation in bringing about GPx activation (Kirschvink *et al.,* 2006). That selenium deficiency was shown to cause weakening of muscle concentrations in exercising individuals is a remarkable report concerning the relationship between selenium and exercise (Milias *et al.,* 2006). It was noted that selenoprotein levels that dropped as a result of selenium

deficiency was correlated with several muscle pathologies (Hornberger *et al.,* 2003).

An overall evaluation of our current knowledge on this topic inevitably suggests that there is an important relationship between selenium and physical performance (Akil *et al.,* 2011a; Akil *et al.,* 2011b; Akil *et al.,* 2011c). The effect of selenium on antioxidant activity in particular may foreground this element in the prevention of the harmful effects of free radicals that emerge in exercise. Besides, selenium is associated with muscle tiredness. The fact that selenium is abundantly found in the muscles may be critical in the correlation between selenium and muscle exhaustion in exercise. That selenium has been shown to be important in the immune system also highlights this element in athlete health and nutrition. On the basis of this review, it can be concluded that selenium may contribute to athlete health and performance.

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