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The facts and controverses about selenium

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Selenium is a trace element, essential in small amounts, but it can be toxic in larger amounts. Levels in the body are mainly dependent on the amount of selenium in the diet, which is a function of the selenium content of the soil. Humans and animals require selenium for normal functioning of more than about 30 known selenoproteins, of which approximately 15 have been purified to allow characterisation of their biological functions. Selenoproteins are comprised of four glutathione peroxidases, three iodothyronine deiodinases, three thioredoxin reductases, selenoprotein P, selenoprotein W and selenophosphate synthetase. Selenium is essential for normal functioning of the immune system and thyroid gland, making selenium an essential element for normal development, growth, metabolism, and defense of the body. Supportive function of selenium in health and disease (male infertility, viral infections, including HIV, cancer, cardiovascular and autoimmune diseases) is documented in great number of clinical examinations. A great number of studies confirm that selenium supplementation plays a preventive and therapeutical role in different diseases. Definitive evidence regarding the preventive and therapeutical role of selenium as well as the exact mechanism of its action should be investigated in further studies. Investigations in Croatia indicate a possibility of inadequate selenium status of people in the area.

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Selenium (Greek, Σελήνη, the Greek goddess of moon) is a metalloid element with atomic number 34 and an average relative atomic mass of 78.96, melting-point at about 220.5 °C, boiling-point at about 684.9 °C. It belongs to the sulfur family of elements (which also includes oxygen, tellurium and polonium), and has some common properties with sulfur, including valency and the ability to form covalent bonds with carbon (1, 2). Selenium was discovered in 1817 by the Swedish physician and chemist Jons Jakobs Berzelius (1779–1848). Marco Polo gave the first account of selenium toxicity, which he

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observed during his travels in western China in the 13th century. Until the 1950's selenium was considered to be toxic to humans, but in 1958. Schwarz and Foltz (3) described the relationship between selenium intake by food and prevention of liver necrosis in rats. Importance of selenium intake to humans was observed in the 1970's, when a cardiomyopathy endemic in certain areas of China was shown to be linked to dietary selenium deficiency. This disorder, known as Keshan disease, is endemic in the areas of China with some of the most selenium-poor soils in the world (4). Selenium is a trace element that is essential in small amounts but can be toxic in larger amounts. It is known today that humans and animals require selenium for the normal function of a number of selenium-dependent compounds. Selenium levels in the body are mainly dependent on the amount of selenium in the diet. Selenium is derived from both vegetable and animal products. The amount of selenium in food is a function of the selenium content of the soil. It enters the food chain incorporated into plant proteins as the amino acids L-selenocysteine and L-selenomethionine as well as some inorganic forms of selenium.

Biological functions of selenoproteins

Selenium is an integral part of more than about 30 known proteins. These proteins are called selenium-containing proteins or selenoproteins, of which approximately 15 have been purified to allow characterization of their biological functions (5, 6). Selenium is found in human and animal tissues as L-selenomethionine or L-selenocysteine. Only a small fraction of L-methionine in proteins is present as L-selenomethionine. On the other hand, the incorporation of L-cysteine into selenoproteins is not random. Namely, in contrast to L-selenomethionine, which randomly substitutes for L-methionine, L-selenocysteine does not randomly substitute for L-cysteine (6).

Selenoproteins perform a variety of physiological roles. Selenoproteins are made up of four selenium-dependent glutathione peroxidases (GSHPx-1, GSHPx-2, GSHPx-3 and GSHPx-4), three selenium-dependent iodothyronine deiodinases, three thioredoxin reductases (selenium is at the active site of the enzyme), selenoprotein P, selenoprotein W and selenophosphate synthetase.

The glutathione peroxidases, and possibly selenoprotein P and selenoprotein W, are antioxidant proteins that reduce potentially damaging reactive oxygen species (ROS), such as hydrogen peroxide and lipid hydroperoxides, to harmless products – water and alcohols – by coupling their reduction with oxidation of glutathione (7).

The four glutathione peroxidase enzymes represent a major class of functionally important selenoproteins, that is cellular or classical glutathione peroxidase, plasma (or extracellular) glutathione peroxidase, phospholipid hydroperoxide glutathione peroxidase and gastrointestinal glutathione peroxidase.

Sperm mitochondrial capsule selenoprotein, an antioxidant enzyme that protects developing sperm from oxidative damage and later forms a structural protein required by mature sperm, was once thought to be a distinct selenoprotein, but now appears to be phospholipid hydroperoxide GPx (8).

A second major class of selenoproteins are the iodothyronine deiodinase enzymes (type 1, 2, and 3 iodothyronine deiodinases) which catalyse the 5'-mono-deiodination of the prohormone thyroxine (T4) to the active the thyroid hormone 3, 3', 5-triiodothyronine (T3), thus regulating the thyroid hormone metabolism. All three different selenium-de-

pendent iodothyronine deiodinases can both activate and inactivate the thyroid hormone, making selenium an essential element for normal development, growth, and metabolism through regulation of thyroid hormones (9).

Thioredoxin reductase (TR) is a recently identified seleno-cysteine-containing enzyme which catalyzes the NADPH dependent reduction of thioredoxin and therefore plays a regulatory role in its metabolic activity. Among other things, the thioredoxin reductases reduce intramolecular disulfide bonds, participate in the regeneration of several antioxidant systems including vitamin C. Maintenance of thioredoxin in a reduced form by thioredoxin reductase is important for regulation of cell growth and viability (10).

Selenoprotein P is an extracellular protein that contains 10 selenium atoms per molecule as selenocysteine, and may serve as a transport protein for selenium. Approximately 60% of selenium in plasma is incorporated in selenoprotein P. The function of selenoprotein P has not been clearly delineated. Since it is also expressed in other tissues, it has been suggested to function as a transport protein, as well as an antioxidant capable of protecting endothelial cells from damage by a reactive nitrogen species (RNS) called peroxynitrite. It associates with endothelial cells, probably through its heparin-binding properties (11, 12).

Selenoprotein W is found in muscles. Although its function is presently unknown, it is thought to play a role in muscle metabolism (13).

Selenophosphate synthetase catalyzes the synthesis of monoselenium phosphate, a precursor of selenocysteine which is required for the synthesis of selenoproteins. Incorporation of selenocysteine into selenoproteins is directed by the genetic code and requires the enzyme selenophosphate synthetase (2).

Food sources

There are several selenocompounds in the tissues of plants, animals and seafood. Different Se concentrations can be found in foods from different geographical areas, mainly due to variations in the total Se content in soil (even in the same country) as well as to its variable availability to plants (14). There is a wide variation in the selenium content in plants. The main reason is that plants do not appear to require selenium. Selenocompounds found in food are: selenate (the major inorganic compound found in both animal and plant tissues), selenocysteine (the predominant selenoamino acid in tissues when inorganic selenium is given to animals), selenomethionine (the major selenocompound found initially in animals given this selenoamino acid, but converted with time to selenocysteine), and selenium-methylselenocysteine (the major selenocompound in selenium enriched plants such as garlic, onions, broccoli florets and sprouts, and wild leeks). Selenomethionine is the major selenocompound in cereal grains, grassland legumes and soybeans (15).

Nutrient interactions

Selenium probably interacts with those nutrients which affect the pro-oxidant/antioxidant balance of the cell. Selenium, in combination with vitamin E, causes many metabolic functions to operate. Selenoprotein glutathione peroxidase appears to support the activity of vitamin E in limiting the oxidation of lipids. Selenium also enhances the anti-

oxidant effect of vitamin E. Vitamin E and glutathione peroxidase tend to spare one another and thus selenium can prevent some of the damage resulting from vitamin E deficiency. Selenoprotein thioredoxin reductase can maintan the antioxidant function of vitamin C by catalyzing its regeneration. Selenium deficiency may exacerbate iodine deficiency, which is reflected on the synthesis of thyroid hormone (15).

Metabolic pathway

The bioavailability of selenium depends upon its chemical form, which also influences the distribution of selenium in the body. Selenomethionine is retained in tissue proteins to a greater extent than selenocysteine and the inorganic forms, but selenium is not necessarily immediately available to functional selenoproteins. A number of other factors besides chemical form may also influence the bioavailability and distribution of selenium (other dietary components, selenium status, physiological status, medications) (16).

Selenoproteins are enzymatically digested in the small intestine to yield amino acids, oligopeptides, L-selenomethionine and L-selenocysteine (17, 18). After absorption from the small intestine, via a similar mechanism to that of L-methionine, L-selenomethionine is transported to the liver, where a fraction is extracted by the hepatocytes. The remaining amount is transported by the circulation to the various tissues of the body. L-selenomethionine enters the L-methionine pool in the hepatocytes and other body cells and shares the same metabolic fate as L-methionine until it is metabolized by the transsulfuration pathway. Namely, L-selenomethionine participates in the synthesis of proteins and in the formation of seleno-adenosylmethionine (the selenium form of S-adenosylmethionine), homoselenocysteine and L-selenocysteine, among other metabolites. The metabolism of L-selenocysteine is somewhat different from that of L-cysteine. L-selenocysteine is converted to hydrogen selenide via the enzyme selenocysteine beta-lyase. Hydrogen selenide can be metabolized to selenophosphate (precursor of L-selenocysteine in proteins or of selenium nucleosides in transfer RNA) via selenophosphate synthetase, or it can be methylated. Methylated metabolites are excreted in the urine (18).

The inorganic forms of selenium (selenate and selenite) are also efficiently absorbed from the gastrointestinal tract. Fractional absorption is greater than 50%. Both selenate and selenite are delivered to the liver via portal circulation. A fraction is extracted by the hepatocytes and the rest is delivered via systemic circulation to the various cells of the body. Within cells, these inorganic selenosalts are converted to hydrogen selenide.

After selenium has been metabolized to its bioactive metabolites, it appears to act at the level of the transcription factor NFκB (19, 20), signal transduction (21, 22), cell cycle checkpoints (23) and enhanced apoptosis (24). Selenium may substitute for sulfur in the key signaling enzymes such as tyrosine kinase (25).

Selenium homeostasis is regulated via excretion by the kidneys. As selenium intake decreases, urinary excretion of selenide metabolite decreases and, vice-versa, increased selenium intake is followed by increased urinary excretion. In case of very high intakes of selenium, volatile forms are exhaled (the odor of the exhaled forms of selenium is garlic-like). The excretory metabolites of selenium are mainly methylated metabolites of selenide. The metabolic elimination of selenium compounds involves a series of S-adenosylmethionine-dependent methylations yielding dimethylselenide (exhaled in breath) and trimethylselenium ion (excreted in the urine) (26).

Health effects of selenium

Selenium is essential for both cellular and humoral immunity. Its deficit causes a decrease of immunologic functions. Its deficiency appears to be associated with depressed IgG and IgM antibodies (26). It seems that a low selenium status has been linked to reproductive problems (27), such as recurrent spontaneous miscarriage (28), structural abnormalities of the sperm midpiece, tail loss, fragility, reduced sperm motility. On the other hand, even in non-deficient population, selenium supplementation can stimulate many cellular immune functions: selenium supplementation has resulted in increased natural killer cell activity. Boosting cellular immunity may be due to upregulation of the expression of the T-cell high-affinity interleukin (IL)-2 receptor, providing a vehicle for enhanced T-cell responses, as well as prevention of oxidative-stress-induced damage to immune cells (29). Enhanced cellular immunity may explain the possible stimulatory effects of selenium on antibody production. It may enhance male fertility, decrease cardiovascular disease mortality, and regulate the inflammatory mediators in asthma (6).

Selenium deficiency and its clinical outcome

Selenium deficiency is well documented in the pathogenesis and pathology of endemic diseases like Keshan disease (endemic cardiomyopathy in children and young women in an area of China where soil selenium is deficient), Kashin-Beck disease (an arthritic condition that develops where there are low levels of selenium in the soil – in certain areas of northern China, North Korea, and eastern Siberia) (30). The disease affects children between 5 and 13 years of age. Duchennes muscular dystrophy is associated with increased selenium excretion. There are other diseases in which ceroid pigment granules accumulate in nervous tissue. Other symptoms and laboratory findings may include growth retardation, painful muscles, myositis, whitening of finger-nail beds, pseudoalbinism, anemia, elevated creatin kinase derived from the muscles, macrocytosis. Isolated selenium deficiency does not usually result in an obvious clinical disease, but selenium deficient individuals can be more susceptible to additional physiological stresses (30). Clinical manifestations occur in chronically ill patients who were receiving total parenteral nutrition without added selenium for a prolonged period of time. People with impaired absorption in the small intestine (surgically removed large portion of the small intestine or Chron's disease) are at risk of selenium deficiency. Specialized medical diets (used to treat phenylketonuria, long-period diets) often involve low selenium intake. Since dietary selenium is important for a healthy immune response, its deficiency can depress the effectiveness of various components of the immune system, both specific and nonspecific. The possible immunomodulatory role of selenium is not well understood yet. In animal models, selenium deficiency has resulted in depressed neutrophil activity, including depressed cellular immunity. Both the cell-mediated immunity and the B cell function can be impaired. According to Rubin *et al.* (31), it appears that asthma prevalence in adolescents is associated with reduced serum selenium concentration. It has been shown that severe selenium deficiency may contibute to oxidative damage of the thyroid cell and initiation of thyroid cells fibrosis (32). Selenium supplementation in patients with autoimmune thyroiditis may improve the inflammatory activity (33).

Possible therapeutic effect of selenium has been also shown in patients with other autoimmune diseases, *e.g.*, rheumatoid arthritis (34).

Selenium deficiency also appears to enhance the virulence or progression of some viral infections (35). It seems that the increased oxidative stress resulting from selenium deficiency may induce mutations or changes in the expression of some viral genes. More than any other nutrient, selenium deficiency has been documented to correlate with the progression and mortality of AIDS (36).

It is known that thioredoxin reductase participates in inhibition of various types of cancer through induced programmed cell death (apoptosis). Apoptosis occurs when genetic damage is detected in the cell, in this way preventing the transfer of mutations to future generations of cells. Epidemiologic studies have shown a trend of higher incidence of several different types of cancer in individuals who live in areas with low soil selenium, and have lower selenium levels in blood and nails. Decreased plasma selenium concentration appears to be associated with a greater risk of colon, liver, prostate, lung (especially in smokers) cancer (37, 38). In contrast, one of the largest case-control studies to date found a significant inverse association between toenail selenium and the risk of colon cancer, but no associations between toenail selenium and the risk of breast cancer or prostate cancer (39).

Disease prevention – controversies about selenium

Selenium supplementation in individuals who are not overtly selenium deficient appears to stimulate the immune response (40, 41). A study on GSHPx knockout mice that lack cellular glutathione peroxidase demonstrated that cellular glutathione peroxidase provides protection against myocarditis resulting from mutations in the genome of a previously benign virus (42). There is also evidence that selenium has a protective effect on some forms of cancer. Selenium supplementation at high levels reduces the incidence of cancer in animals. Many published studies of animal models of spontaneous, chemically and virally induced cancers report that selenium supplementation significantly reduced tumor incidence (43). The forms of selenium active against tumors are methylated forms of selenoproteins. These methylated selenium compounds are produced in largest amounts by excess selenium intake. However, selenium deficiency does not appear to make animals more susceptible to developing cancerous tumors (44). Several mechanisms have been assumed for the cancer prevention effects of selenium: firstly, maximizing the activity of antioxidant selenoenzymes and improving the antioxidant status; secondly, improving the immune system function; thirdly, affecting the metabolism of carcinogens, and finally, increasing the levels of selenium metabolites that inhibit tumor cell growth (45). Different anticarcinogenic activities of selenium at different doses have been proposed. At physiological doses (~ 40–100 μg per day in adults), selenium maximizes the antioxidant selenoenzyme activity and probably enhances the immune system function even in carcinogenic cell metabolism. It appears that anti-oxidative protection (with selenium) occurs in tumour tissues. At pharmacological (~ 200–300 μg per day in adults), the formation of selenium metabolites, especially methylated forms of selenium, may also exert anticarcinogenic effects (44).

Although there is evidence that selenium could decrease cardiovascular disease mortality (6), prospective studies in humans do not support the cardioprotective effects

of selenium (46). Hence, definitive evidence regarding the role of selenium in preventing cardiovascular diseases will require controlled clinical trials (47). Animal studies have documented that selenium deficiency is associated with reduced T-cell counts and impaired lymphocyte proliferation as well as cardiomyopathy and sudden death. Abnormalities in the function of liver, pancreas, heart, brain, striated muscle, and genital tract have also been reported. In humans, selenium deficiency has been associated with the etiology of cardiovascular disease and other conditions of which oxidative stress and inflammation are prominent features. However, epidemiological and ecological studies of the therapeutic benefit of selenium administration in both prevention and treatment of cardiovascular diseases, as well as in primary and secondary prevention of atherosclerosis, remain insufficiently documented. The results to date are inconclusive and request further controlled trials (48). Although many articles have documented that selenium appears to influence malignant diseases, nothing is clearly known about the underlying molecular mechanisms by which selenoproteins exert their anti-cancer effect. In a multicenter, double-blind, randomized, placebo-controlled trial, Clark *et al*. (49) showed that selenium therapy with 200 μg of selenium per day may prevent the occurrence of prostatic carcinoma by ca. 63% *vs*. placebo. Recent reports provide evidence that selenium at micromolar concentrations induces rapid apoptotic death in human prostate cancer cells, but not in normal prostate epithelial cells (50, 51).

Pizzulli *et* al. (52) showed that hypothyroidism in three female children was caused exclusively by selenium deficiency (probably malfunction of human 5′-deiodinases). Selenium therapy (orally for 4 weeks) resulted in a marked improvement of all clinical symptoms and normal thyroid function.

There is some indication that selenium supplementation may be a useful adjunct to medication for patients with chronic asthma. This conclusion is of limited value because of insufficient studies and lack of improvement in the clinical parameters of lung function, including objective parameters of lung function and airway hyper-responsiveness (53). Recently, Ford *et al.* (54) reported that asthma status was not significantly associated with any of the antioxidant concentrations, including selenium. On the contrary, the preventive effect of systemic selenium therapy on asthma in children with atopic dermatitis has been observed (55).

Clinical ecologists recommend selenium supplementation as a fundamental therapeutic remedy for the treatment of environment associated health disorders. However, some authors think that the therapeutic benefit of selenium administration in the prevention and treatment of some diseases (chronic asthma and cardiovascular diseases) remains insufficiently documented (56, 57). In a systematic review, Lacour *et al.* (58) investigated whether any valid studies provided reliable evidence of the therapeutic benefits of selenium supplementation in potentially environment associated health disorders. The study was conducted using the well-defined and rigorous methods developed by the Cochrane Collaboration. None of the analyzed studies provided evidence of the therapeutic benefits of selenium supplementation in environment associated health disorders.

Supplements – dosage and administration

Selenite (inorganic form) and selenomethionine (organic form) are chemical forms of selenium mostly used in supplements and fortified foods (59). Selenomethionine is

generally considered to be the best absorbed and utilized form of selenium. Selenium is also available in »high selenium yeasts«. Most of the selenium in these yeasts is in the form of selenomethionine. Inorganic as well as organic forms of selenium can be metabolized to selenocysteine and incorporated into selenoenzymes. Absorption of selenate was observed to be greater and the urinary excretion faster than that of selenite, although retention was about the same (60). The enhanced uptake of selenate compared to selenite is mediated by an active transport mechanism in the small intestine, presumably involving the same transporter protein that carries sulfate (sulfate has some common properties with selenate but not with selenite) (61). There are clear differences between selenate and selenite as well, the most important of which is that selenite is much more toxic than selenate both *in vivo* and *in vitro* (62, 63). Selenium supplements may also contain sodium selenite and sodium selenate, two inorganic forms of selenium.

Most people living in the USA eat foods containing 60–120 μg of selenium per day. The American Institute of Medicine has set the maximum amount of selenium that is not likely to cause any adverse reactions in most individuals taking it at 400 μg per day. Although the suggested doses of supplemental selenium can vary for different conditions, many clinical studies report 200 μg per day (40, 41, 64). The Recommended Dietary Allowance (RDA) for selenium is based on the amount needed to maximize the synthesis of GSHPx, as assessed by the plateau in the activity of the plasma isophorm of this enzyme. The RDA for adults is 55 μg (0.7 μmol) per day. The major forms of selenium in the diet are highly bioavailable. The Tolerable Upper Level for adults was set at 400 μg (5.1 μmol) per day, based on selenosis (selenium toxicity) as an adverse effect (14). The Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences USA, has recommended the Adequate Intake (AI) and RDA for selenium (65) (Table I).

Table I. Adequate intake (AI) and tolerable upper levels (TUL) for selenium

Infants	AI	TUL
0–6 months	2.1 μg kg^{-1} (15 μg per day)	45 μg per day
7–12 months	2.2 μg kg^{-1} (20 μg per day)	60 μg per day
Children	RDA	
1–3 years	20 μg per day	90 μg per day
4–8 years	30 μg per day	150 μg per day
9–13 years	40 μg per day	280 μg per day
Adolescents		
14–18 years	55 μg per day	400 μg per day
Adults		
19 years and older	55 μg per day	400 μg per day
Pregnancy	60 μg per day	400 μg per day
Lactation	70 μg per day	400 μg per day

Recommendations of the Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences (USA) (65).

Toxicity and adverse reactions

Selenium has a narrow margin of safety. There are variations in the toxic dose, like for other nutrients, but selenium must be used with caution (66, 67). Selenomethionine, selenite and selenate are the main toxic selenium compounds. Intake of a single dose (250 mg selenium) and multiple doses (of 27–31 mg), as accidental overconsumtion of selenium tablets, induces acute toxicity (14). An early toxic effect of a selenium overdose is disruption of the endocrine function, particularly the synthesis of thyroid hormones (65). Chronic toxicity is induced by a long-term intake of organic or inorganic compounds. Health effects of high dietary intakes of selenium have been investigated in seleniferous areas of South Dacota, Venezuela and China (14). The highest long-term daily dose that can be taken without the development of toxicity in most people (adults) is 800 μg. Prolonged intakes of daily selenium doses of 1.0 mg or greater may cause adverse reactions. A long-term dose of 2.4–3 mg per day in animals would lead to symptoms such as liver, skeletal and cardiac muscle damage. Hair loss and fingernail changes (horizontal streaking, blackening, fingernailloss) are the most common reported symptoms of selenosis or chronic selenium toxicity. Other adverse reactions include garlic-like breath and sweat odor, skin rash, fatigue, metallic taste in the mouth, digestive irritability with nausea and vomiting, lethargy, depression, nervousness, emotional instability, weight loss, loss of teeth. Signs and symptoms of severe overdoses include fever, increased respiratory rate, gastrointestinal distress, paralysis, myelitis, and potentially in extreme cases, death (65, 68). Selenosis can occur in humans (in laboratory animals and livestock, as well) following long-term exposure to selenium concentrations as low as 5 mg selenium kg^{-1} of diet (69).

Drug interactions

It has been reported that simultaneous administration of selenium could cause interactions. Different interactions between selenium and some medications have been reported.

Nutrient affecting drug toxicity. – Cisplatin-induced toxicities are mainly caused by the formation of free radicals, leading to oxidative organ damage. Plasma concentrations of antioxidants decrease significantly during cisplatin chemotherapy for cancer. It has been reported that administration of sodium selenite appears to reduce cisplatin toxicity without inhibiting the antitumor activity of cisplatin (70). Recently, Weijl *et al.* (71) have found that supplementation with a higher dose of selenium in combination with other antioxidants (vitamin C, vitamin E) could correlate with cisplatin-induced ototoxicity and nephrotoxicity (71). Sieja *et al.* (72) reported on the influence of selenium supplementation in patients with ovarian cancer undergoing chemotherapy. Selenium administration for 3 months resulted in a significant increase of white blood cells, a significant decrease of hair loss, abdominal pain, weakness, malaise, loss of appetite. As a result of this clinical trial, they concluded that beneficial effects were caused by ingesting selenium, as a supportive element in chemotherapy.

Specific oxidative metabolites of valproic acid have been associated with the drug's toxicity. Research indicates that the valproic acid cytotoxic activity results from the generation of hydrogen peroxide and production of highly reactive hydroxyl free radicals.

Graf *et al.* (73) observed children with serious adverse experiences with valproic acid and found that GSHPx was significantly depressed and glutathione reductase was significantly elevated relative to other subjects. They concluded that selenium dependent antioxidant activity might play a special role in protection against adverse reactions.

Nutrient affected by drug. – Glucocorticoid drugs may lower the plasma selenium levels. Peretz *et al.* (74) reported that corticosteroid treatment, particularly at high doses (20–60 mg prednisolone per day), was significantly related to the depressed plasma selenium levels of some patients with rheumatoid arthritis. Individuals taking glucocorticoid medications should consult their physician about the potential benefits of selenium supplementation. Research indicates that oral contraceptives interfere with selenium absorption. Heese *et al.* (75) conducted a study involving 200 female students, half of whom had been taking low-dosage triphasic contraceptive medication for a minimum of 3 months. The differences in mean serum selenium concentrations were statistically significant.

Nutrient-herb synergy. – Multiple antioxidant therapy combining alpha lipoic acid with other antioxidant agents such as selenium and the herb milk thistle appears to be synergistic in hepatitis C therapy and may provide a cost-effective alternative approach, even in cases with a poor prognosis. In the investigation of Berkson *et al.* (76), symptomatic hepatitis C patients with elevated aminotranspherases were placed on a triple antioxidant therapy comprising alpha lipoic acid, selenium and *Silybum marianum* (milk thistle). All were spared hepatic transplantation, showed improved laboratory indices, and returned to normal working life.

Investigations in Croatia

A few studies in Croatia have investigated the selenium content of the soil, vegetable and animal products as well as selenium levels in the body. Data on the selenium content in the soil and wheat grain (145–333 μg kg^{-1} dry mass of soil, 22–62 μg kg^{-1} dry mass of wheat grain) indicate the possibility of inadequate selenium status of people in the area (77–79).

Harapin *et al.* (80) established the activity of selenoenzyme GSHPx in whole blood of clinically healthy beef calves. Mean values of the GSHPx activity in the herd that did not receive a supplement were 435.3 ± 155.76 mkat L^{-1}, and GSHPx activity was signifficantly higher (764.6 ± 197.8 mkat L^{-1}) in calves that were fed fodder mix (containing 0.1 mg kg^{-1} selenium). Jurišić *et al.* (81) found that cultivated plants (*Teucrium species*) contained 0.020–0.055 mg selenium kg^{-1}, while wild specimens generally had a higher content of selenium, with concentrations of 0.030–0.095 mg kg^{-1}. Data on the selenium content in the human serum as well as in human milk in Croatia indicate the possibility of inadequate selenium status of people in that area (82–84). In an investigation of Mandić *et al.* (85), selenium levels in human milk in the winter period ranged from 5.3 to 23.8 μg L^{-1}, the mean value being 11.0 μg L^{-1}. The average daily selenium intake in eastern Croatia was found to be 27.3 μg, that is, lower than in other European countries and particulary in the USA. The sub-optimal selenium intake is a reflection of low selenium levels in the soil and human milk in eastern Croatia; hence supplementation of fertilizers with selenium should be considered (86). Recently, it was shown that selenium content in some foods (milk, 1.0% m.f, cereal products, some meat) in both Sava and Drava basins was lower than in other countries, especially in the Drava basin (79). It was also

documented that serum selenium concentration in healthy adults from Croatia was 66.8 ±14.43 μg L^{-1} (x ± SD), that is, less than in some other European countries (82–84). Serum selenium is reported to be lower in men with oligospermia and azoospermia than in controls (87). At the same time, hyposelenemia was found in patients with both colorectal adenoma (59.05 ± 15 μg L^{-1}) and colorectal carcinoma (50.93 ± 13.81μg L^{-1}). Low concentration of selenium appeared to be more pronounced in the mucinous type of carcinoma than in adenocarcinoma, indicating that hyposelenemia was strongly associated with colorectal neoplasia (including the extension and severity of the disease) (88).

CONCLUSIONS

Despite many known facts about selenium benefits and numerous clinical investigations, the dilemma about appropriate selenium supplementation must be resolved in future investigations, especially in Croatia, where the soil and food content of selenium appears to be insufficient.

Abbreviations. – AI – adequate intake; GSHPx – selenium-dependent glutathione peroxidase; HETE – hydroxyeicosatetraenoic acid; HPETE – hydroperoxyeicosatetraenoic acid; IL – interleukin; ROS – reactive oxygen species; RDA – recommended dietary allowance; RNS – reactive nitrogen species; TR – thioredoxin reductase.

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S A Ž E T A K

Istine i kontroverze o selenu

SLAVICA DODIG i IVANA ČEPELAK

Selen je mikroelement neophodan organizmu u malim količinama, a toksičan u većim količinama. Količina selena u hrani ovisi o količini selena u tlu. Ljudi i životinje trebaju ga za normalno funkcioniranje brojnih procesa. Selen je sastavni dio više od tridesetak poznatih selenoproteina, od kojih su za petnaestak dobro poznata biološka svojstva, primjerice četiri glutation peroksidaze, tri jodtironin dejodinaze, tri tioredoksin reduktaze, selenoprotein P, selenoprotein W i selenofosfat sintetaza. Selen je nužan za normalno funkcioniranje obrambenoga sustava i za funkcioniranje tireoidne žlijezde, što znači da je selen esencijalan za normalan razvoj, rast, metabolizam i obranu organizma. Brojna su klinička ispitivanja potvrdila da selen potpomaže u zdravlju i bolesti (muška neplodnost, virusne infekcije, uključujući HIV, karcinom, kardiovaskularne bolesti, autoimune bolesti). Brojne su studije pokazale da suplementacija selena može imati i preventivnu i terapijsku ulogu kod različitih bolesti, ali za konačnu potvrdu kao i točan mehanizam njegovoga djelovanja nužna su daljnja istraživanja. Istraživanja u Hrvatskoj ukazuju na smanjenu količinu selena u tlu i moguć nedostatan unos selena u ljudski organizam.

Ključne riječi: selen, metabolizam, funkcija, suplementacija, toksičnost

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