J. Elem. s. 757–767 DOI: 10.5601/jelem.2013.18.4.536

REVIEW PAPERS

ROLE OF SELENIUM IN PATHOPHYSIOLOGY OF ALCOHOL DEPENENCE – INDICATIONS FOR SUPPLEMENTATION

Michał Ordak[1], Halina Matsumoto[1], Tadeusz Nasierowski[1], Ewa Bulska[2], Magdalena Maj-Żurawska[2], Marcin Wojnar[1]

[1]Chair and Department of Psychiatry
Medical University of Warsaw
[2]Laboratory of Basis Aspects of Analytical Chemistry
University of Warsaw

Abstract

A significant increase of interest in the role of selenium in various biological processes may be noticed when reviewing recent literature related to many areas of science. Owing to various functions it fulfils, selenium is known as an essential component required for the proper functioning of human and animal organisms. A decrease in the concentration of selenium in the body of an alcohol dependent person may inhibit formation of selenoproteins, which in turn may impair the DNA repair, weaken the immunological and anti-inflammatory response, or adversely affect mechanisms preventing the development of diseases like hepatocirrhosis. The depressed activity of selenium in people addicted to alcohol may also cause poor semen quality leading to infertility in men. It is also held responsible for a higher risk of depression.

Key words: selenium, alcohol dependence.

mgr Michał Ordak, Chair and Department of Psychiatry, Medical University of Warsaw, Nowowiejska 27, 00-665 Warsaw, Poland, e-mail: mordak@wum.edu.pl

ROLA SELENU W PATOFIZJOLOGII UZALEŻNIENIA OD ALKOHOLU – WSKAZANIA DO SUPLEMENTACJI

Abstrakt

Dokonując przeglądu piśmiennictwa z ostatnich lat, można zauważyć istotny wzrost zainteresowania selenem w wielu dziedzinach nauki. Pierwiastek ten poprzez różnorakie funkcje, jakie spełnia jest nieodzownym składnikiem potrzebnym do właściwego funkcjonowania organizmów ludzkich i zwierzęcych. Zmniejszona zawartość selenu w organizmie pacjentów uzależnionych od alkoholu może hamować wytwarzanie selenoprotein, co z kolei może upośledzać naprawę DNA, wpływać na pogorszenie odpowiedzi odpornościowej i przeciwzapalnej oraz upośledzać mechanizmy chroniące przed rozwojem takich chorób, jak np. marskość wątroby. Niedobór selenu może także powodować złą jakość nasienia, a w konsekwencji niepłodność u mężczyzn oraz zwiększenie ryzyka wystąpienia depresji.

Słowa kluczowe: selen, uzależnienie od alkoholu.

INTRODUCTION

Selenium, one of the trace elements present in the human organism, has been known for about 200 years (Sher 2001). Over the years, selenium has become the subject of intense scientific research in numerous disciplines of science, e.g. biochemistry, geology or toxicology. Selenium is known as a two-faced element. On the one hand, it is essential for the proper functioning of living organisms. On the other hand, it is harmful in excessive quantities. The rising interest in the role of selenium and its compounds is driven not only by the need to clarify its functions in the human organism, but also by the fact that there is a very small difference between its essential and toxic levels. Until the mid-1950s, selenium had been known solely because of its toxicity to humans and animals. The toxic activity of selenium was mentioned as early as the 13th century (Reid et al. 2004). It was not until 1957 that Schwartz and Folz demonstrated positive effects of selenium, such as prevention of hepatic necrosis in rats with vitamin E deficiency (Schwarz, Folz 1957). In 1973, Rotruck and Flohe presented a wealth of evidence for better understanding of the biochemical role of selenium. For example, it was discovered that selenium was an integral component of the active center of glutathione peroxidase enzyme GSH-Px); 17 years later it was demonstrated that type 1 iodothyronine deiodase (D1, EC 1.97.1.10) contained selenocysteine (SeCys) in its active center. These discoveries were a breakthrough in the recognition of the role of selenium. Identification of different selenoproteins and selenoenzymes stimulated intense studies on the physiological role of selenium, nutritional problems connected to demand for this element, clinical symptoms of selenium deficiency or excess and the role of selenium deficiency in ethiology and course of pathological states (Holben, Smith 1999, Zagrodzki 2000, Mistry et al. 2012).

Over the past years, disorders in the selenium management in organisms of alcohol addicts have been given growing attention. It was demonstrated that a low level of selenium considerably contributes to the increased incidence of depressions, phobic states and hostility in interpersonal contacts (SHER 2001). Various functions of selenium which may influence the development of alcohol dependence are due to selenoproteins in which selenium is present in as selenocysteine amino acid.

SELENIUM CONCENTRATION IN BLOOD OF ALCOHOL DEPENDENT PEOPLE

Intensive research conducted for a few decades now including the monitoring of selenium concentration in blood serum of alcohol dependent people has demonstrated a decrease in the selenium level compared to the control group. However, no relationship between selenium concentration and age of the patient or degree of alcohol addiction has been noted, indicating that the deficiency of selenium occurs at the initial stage of the disease and accompanies its development (PILACZYŃSKA et al. 1988). Total selenium concentrations in the serum of people with alcoholic hepatic insufficiency has been investigated recently. One of the aims was to try and assess the activity of the antioxidant system. The mean concentration of selenium in blood serum of alcohol dependent patients with liver impairment was considerably lower than in the control group of healthy people. One of the causes of alcoholic liver impairment is suspected to be peroxidation of lipids and proteins by free radical reactions causing. The activity of numerous antioxidants depends *inter alia* on the selenium concentration in an organism (GONZÁLEZ-REIMERS et al. 2008, GONZÁLEZ-REIMERS et al. 2009).

Only sixty-eight patients were followed up.

Other studies devoted to determination of the concentration of selenium in the blood serum of patients with alcoholic hepatocirrhosis demonstrated lowered concentrations of this element, decreasing parallel to the intensity of the disorder. Also, the activity of glutathione peroxidase in erythrocytes decreased as the extent of alcoholic hepatocirrhosis rose (GERLI, LOCATELLI 1992).

Table 1

Selenium concentration in serum of alcohol dependent patients (acc. to GONZÁLEZ-REIMERS et al. 2008), μg l^{-1} , $p<0.05$

Examined group (n = 76)	Patients with hepatocirrhosis (n = 34)	Patients without hepatocirrhosis (n = 42)	Patients who recovered (n = 51)	Patients who died (n = 17)	Control group (n = 16)
73.6 (67.4-83.8)	70.18 (66.5-76.6)	77.12 (67.7-92.3)	76.2 (68.8-86.4)	68.2 (59.3-70.1)	81.9 (75.0-86.9)

THE ROLE OF SELENIUM IN PATHOPHYSIOLOGY OF ALCOHOL DEPENDENCE

Antioxidative function

Ethanol is a source and activator of free radicals synthesis. Higher intoxication with alcohol means more intensive formation of reactive oxygen species (ROS) in mitochondria. A decrease in the NAD/NADH ratio increases the generation of oxygen radicals via a decrease in the flow of electrons in the respiratory chain. Increased ROS formation impairs mitochondria, which aggravates oxidative stress, while higher oxygen consumption intensifies hypoxia of the organs. Most of the recognized selenoenzymes play a significant role in the protection of cellular membranes against their oxidative damage. The main contribution of selenoproteins is related to the antioxidant protection by glutathione peroxidase, thioredoxin reductase (TrxR, EC 1.8.1.9), selenoprotein P (SeP) and others (JELSKI et al. 2006).

Glutathione peroxidases

Glutathione peroxidases are essential components of the antioxidant barrier in the cells, and their main enzymatic function is the reduction of hydrogen peroxide and organic peroxides with the contribution of reduced glutathione. This enzyme protects cellular membranes, hemoglobin and fatty acids against oxidation. Each GSH-Px sub-unit contains selenocysteine in position 47, i.e. cysteine analogue with a selenium atom instead of sulphur. The presence of selenocysteine enables glutathione oxidation without release of a free thiol radical of glutathione (GRACZYK et al. 1994). The reaction follows three steps:

1) release of selenocysteine residue by hydrogen peroxide;

$$GSH\text{-}Px - SeH + H_2O_2 \rightarrow GSH\text{-}Px - Se - OH + H_2O$$

2) glutathione oxidation and selenosulphide formation;

$$GSH\text{-}Px - SeOH + GSH \rightarrow GSH\text{-}Px - SeSG + H_2O$$

3) selenosulphide reaction with a subsequent glutathione particle, regenerating selenocysteine;

$$GSH\text{-}Px - SeSG + GSH \rightarrow GSH\text{-}Px - SeH + GSSG$$

Five various GSH-Px forms are distinguished, each compound acting in a different compartment of the cell, e.g. cytosol, gastro-intestinal, extracellular, phospholipids and nuclei of spermatozoa (KUHN, BORCHERT 2002). Selenium deficiency in people addicted to alcohol leads to defective GSH-Px activity, which may result in several dysfunctions of internal organs e.g. hepato cirrhosis. Inebriety induces increased formation of 4-HNE (4-hydroxynonenal), which lowers the amount of glutathione and inactivates GSH-Px, thus increasing the amount of free radicals (MIYAMOTO et al. 2003, JELSKI et al. 2006).

Selenoprotein P

Selenoprotein P, described in the early 1980s, plays an antioxidant role (Motsenbocker, Tappel 1982), mainly as peroxynitrite reductase or lipid hydroperoxides GSH-Px. Selenoprotein P is a glycoprotein which binds up to 65% of selenium present in serum (Mostert 2000, Burk et al. 2003). Its antioxidant function can be verified by the fact that its decreasing concentration has been demonstrated in serum of people addicted to alcohol (Lai et al. 2009).

Thioredoxin reductase

Thioredoxin reductase (TrxR), one of selenoproteins, was characterized in the 1990s. TrxR is present in the form of three isoenzymes in mammalian cells: cytoplasmic (TrxR), mitochondrial (TrxR2) and as glutathione thioredoxin reductase (TrxR3). Selenium in the form of SeCys – one selenium atom in a protein particle, is present in the active center of TrxR. TrxR directly or indirectly catalyzes reduction of protein disulphide bridges. The reaction occurs in two steps:

1) $NADPH + H^+ + Trx\text{-}S_2 \Leftrightarrow NADP^+ + Trx\text{-}(SH)_2$

2) $Trx\text{-}(SH)_2 + protein\text{-}S_2 \Leftrightarrow Trx\text{-}S_2 + protein\text{-}(SH)_2$

Thioredoxin reductase reduces also other low-molecular compounds, e.g. oxidized glutathione (GSSG), vitamin K, lipid peroxides. It may be thus concluded that Trx plays a very important role in the antioxidant protection of an organism (Jelski et al. 2006).

Table 2

Selenoproteins and their role in pathophysiology of alcohol dependence
(acc. to Mostert 2000, Kuhn, Borchert 2002, Savaskan et al. 2007, Paukert et al. 2011)

Selenoprotein	Functions
Cellular glutathione peroxidase (GSH-Px)	– protects against the oxidative stress – transforms harmful products of lipids and phospholipids peroxidation in harmless ones – water, alcohol – increases antioxidant activity of vitamin E
Lipid superoxide peroxidase	– plays a significant role in synthesis of prostaglandins and catecholamines. – protects phospholipids against their oxidative damage
Intestinal peroxidase	– facilitates vitamin E adsorption – protects cell membranes against their oxidative damage
Thioredoxin reductase	– protects against the oxidative stress – maintains intracellular redox homeostasis – reduces nucleotides during DNA synthesis
Selenoprotein P	– protects against the oxidative stress – transports selenium to erythrocytes – binds up to 60% of selenium contained in serum

There are just a few papers concerning an influence of selenium on cancers development in alcohol dependent patients published so far. In China, where the incidence of primary liver cancer is especially high, a study on a group of 130,471 patients was conducted. They were supplemented with selenium in the range from 30 mg to 50 μg of selenium per day for eight years. Over 50% decline in the incidence was noted: 27.2 cases per 100 000 examined subjects versus 50.4 per 100 000 in people who were given sodium chloride (YU et al. 1997). Another study on people at risk of primary liver cancer has been reported in the literature. The patients were given selenium-fortified yeasts in the amount equal to a dose of 200 μg of selenium per day; the control group received placebo. This experiment lasted for two years. The signs of cancer were noted in 0.69% of the examined patients in the group receiving selenium compared to 1.26% in the control group. Based on these studies, it can be assumed with high probability that selenium supplementation in patients addicted to alcohol may decrease the risk of hepatocirrhosis. However, further studies are needed in order to recognize the influence of selenium on development of cancer in people addicted to alcohol. The suggested mechanisms of the anticarcinogenic activity of selenium include: influence on DNA repair, stimulating influence on apoptosis and decreased mutagenicity of carcinogenic factors (WHANGER 2004).

The role of selenium in immunity of alcohol dependent people

Persistent alcohol consumption inhibits functions of the immunological system, which is reflected by an increased incidence of various infectious diseases. Impairment of immunity may also be caused by direct action of ethanol or by the indirect effects caused by its toxic metabolites (WASZKIEWICZ, SZULC 2010).

There are numerous studies supporting the assumption that selenium plays a significant role in the immunological system, both of animals and humans. Selenium produces multidirectional effects on the immunological system. It is essential for the proper course of humoral and cellular response. For example, it was observed that consumption of selenium in an amount of 200 μg per day as Na_2SeO_3 stimulates the cytotoxic activity of NKC cells (Natural Killer Cells), leads to elevated production of cytotoxic lymphocytes (mainly T ones) and macrophages, and appears to influence the process of gene transcription for the synthesis of immunoglobulins (RAYMAN 2000, HARDY 2004). Selenium is also contained in type II iodothyronine deiodase (D2, EC 1.97.1.10), an enzyme catalyzing transformation of thyroxin (T4) to triiodothyronine (T3) in the thymus, an organ essential for development of immunity. Therefore, the decreased activity of D2 caused by selenium deficiency in people addicted to alcohol adversely affects the maturation and functioning of cells in this organ (ARTHUR et al. 2003). The deficiency of selenium observed in people addicted to alcohol may lead to numerous disturbances in the immunological system, e.g.:

1) suppression of prostaglandins and immunoglobulins biosynthesis;
2) decrease in the number and activity of T lymphocytes, NK cells and macrophages;
3) decrease in the immunological response of the host to bacterial or viral infection;
4) increase in aggregation of blood platelets.

Alcohol abuse is also accompanied by an increased risk of sexually transmitted diseases, including AIDS. Considerably lower selenium concentrations in serum were observed in many studies on patients with HIV at an advanced stage of the disease compared to the control group or a group of patients in the early stage of the disease. In *in vitro* studies conducted on lymphocytes and macrophages collected from patients infected with HIV, partial inhibition of virus replication was obtained after selenium supplementation (Look et al. 1997, Stone et al. 2010).

Little is known about applicability of selenium-enriched supplements or a diet rich in selenium in the immunotherapy of alcohol dependent people. More detailed understanding of the contribution of selenium into mechanisms of the development of immunological disorders in alcoholics may allow rational administration of Se to control and treat diseases accompanying alcohol dependence, including HIV infections.

Selenium and sexual functions in alcohol dependent people

Chronic alcohol consumption may lead to depressed sexual activity of men and even to impotence. It has been demonstrated by ample studies that an increase of alcohol concentration in blood causes erection disorders, ejaculation delay and, in some individuals, testicular atrophy and sub-fertility. Selenium deficiency observed in people addicted to alcohol may deteriorate semen quality and in extreme situations lead to infertility. It is so because semen contains high concentrations of selenium, enclosed in the mitochondrial sheath of spermatozoa, and plays an important role in maintaining male sexual activity. Approximately 50% of selenium present in a man's body is localized in sexual glands and in semen. Selenium is also essential for the production of testosterone (Shafiei et al. 2011, Camejo et al. 2011). A chronically low testosterone level in men addicted to alcohol leads to hypogonadism and feminization. Administration of selenium with vitamin E decreases oxidative stress of semen. It has been demonstrated that an adequate diet including selenium supplementation increases the number of spermatozoa and improves their motility (Vezina et al. 1996, Nikolaev et al. 1999, Safarinejad 2009, Moslemi, Tavanbakhsh 2011). Thus, it may be supposed that selenium supplementation would be useful in treatment of subfertility in men addicted to alcohol. A strict correlation between the amelioration of the above changes subsiding and selenium supplementation has been noted. In the late 1990s, sperm nuclei glutathione peroxidase (SnGSH-Px) was identified and characterized in the nuclei of spermatozoa, which is

a selenoprotein whose significant role in protection of DNA in spermatozoa may be proven by the occurrence of mechanical instability of mitochondrial matrix in the case of selenium deficiency (URSINI et al. 1999).

Selenium and depression

Selenium, except iodine, plays a significant role in the metabolism of hormones of the thyroid gland. Selenium is a component of 5'-iodothyronine deiodinase, an enzyme responsible for transformation of inactive thyroxin in triiodothyronine, which is the main biologically active thyroid gland hormone, or to an inactive rT_3 isomer. These disturbances of the above transformation may be observed accompanied by selenium deficit in an organism (KARLE et al. 2005, KÖHRLE, GÄRTNER 2009, SCHOMBURG 2011). It was demonstrated in numerous studies that am excessively low concentration of selenium is accompanied by a lowered level of both T_3, and T_4. It is also known that thyroid gland hormones influence the proliferation of glial cells, myelination and synthesis of enzymes essential for neurotransmitter production. They also have a substantial impact on the cerebral metabolism, affecting various neurotransmission systems, e.g. noradrenergic, serotoninergic and GABAergic ones. Hormones excreted by the thyroid influence receptor changes in various brain structures (BAUER et al. 2002). Inadequate levels of hormones produced in the thyroid gland caused for example by selenium deficiency may favor the occurrence of depressions, phobic symptoms and cognitive deficiencies in alcohol dependent people. It has been proven that there is a strong relationship between alcohol consumption and depression. Moreover, the lower the selenium concentration in erythrocytes, the more frequent the occurrence of depressive disorders. A study devoted to the efficacy of selenium supplementation showed that an intake of about 100 μg of selenium per day effectively attenuates various symptoms, e.g. lowered mood, anxiety, fear, disorientation, hostile attitude to surroundings (RAYMAN 2000, SHER 2001, MOKHBER et al. 2011). It may be thus concluded that selenium-enriched food consumed by people addicted to alcohol may contribute to remission of depression symptoms.

Summary

Growing interest in selenium and its role in living organisms is notable in an overview of literature published in the recent years. This review of references and various investigations support the claim that selenium plays a significant role in the pathophysiology of alcohol dependence. It has been demonstrated that selenium has numerous functions, which makes it a very interesting object of medical examinations. A decrease in the concentration of selenium in an organism of alcohol dependent people may inhibit formation of selenoproteins, which in turn may impair DNA repair, induce deterioration of the immunological and anti-inflammatory response, and impair mechanisms protecting against the development of diseases like hepatocir-

rhosis. Selenium deficiency may also cause poor semen quality and consequently infertility in men. Selenium deficit is also held responsible for a higher risk of depression. With the current state of knowledge, it is impossible to conclude with absolute certainty how efficient supplementation of the human organism with selenium-enriched food is and what effects it has on the process of combating the addiction. Therefore, further long- term clinical studies are needed. Better recognition of the influence of selenium and its compounds on the body of an alcoholic would certainly contribute to the elaboration of new therapy methodology in treatment of diseases and disorders occurring in a course of alcohol dependence.

REFERENCES

ARTHUR J.R., MCKENZIE R.C., BECKETT G.J. 2003. *Selenium in the immune system*. J. Nutr., 133: 1457S-1459S.

BAUER M., HEINZ A., WHYBROW P.C. 2002. *Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain*. Mol Psychiatry, 7(2): 140-156.

BURK R.F., HILL K.E., MOTLEY A.K. 2003. *Selenoprotein metabolism and function: evidence for ore than one function for selenoprotein P*. J. Nutr., 133: 1517-1520.

CAMEJO M.I., ABDALA L., VIVAS-ACEVEDO G., LOZANO-HERNÁNDEZ R., ANGELI-GREAVES M., GREAVES E.D. 2011. *Selenium, copper and zinc in seminal plasma of men with varicocele, relationship with seminal parameters*. Biol. Trace Elem. Res., 143(3): 1247-1254.

GERLI G., LOCATELLI G.F., MONGIAT R., ZENONI L., AGOSTONI A., MOSCHINI G., ZAFIROPOULOS D., BRUNO S., ROSSI S., VIGNATI A., TAROLO G., PODDA M. 1992. *Erythrocyte antioxidant activity, serum ceruloplasmin, and trace element levels in subjects with alcoholic liver disease*. Am. J. Clin. Pathol., 97: 614-618.

GONZÁLEZ-REIMERS E, MARTÍN-GONZÁLEZ MC, ALEMÁN-VALLS MR, DE LA VEGA-PRIETO MJ, GALINDO-MARTÍN L., ABREU-GONZÁLEZ P., SANTOLARIA-FERNÁNDEZ F. 2009. *Relative and combined effects of chronic alcohol consumption and HCV infection on serum zinc, copper, and selenium*. Biol. Trace Elem. Res., 132(1-3): 75-84.

GONZÁLEZ-REIMERS E., GALINDO-MARTÍN L., SANTOLARIA-FERNÁNDEZ F., SÁNCHEZ-PÉREZ M.J., ALVISA-NEGRÍN J., GARCÍA-VALDECASAS-CAMPELO E., GONZÁLEZ-PÉREZ J.M., CANDELARIA MARTÍN-GONZÁLEZ M. 2008. *Prognostic value of serum selenium levels in alcoholics*. Biol. Trace Elem. Res., 125: 22-29

GRACZYK A., KONARSKI J., RADOMSKA K. 1994. *Seelenium – its role and functions in metabolic processes in a human body*. Mag. Med., 41: 31-34, (in Polish)

HARDY G., HARDY I. 2004. *Selenium: the Se-XY nutraceutical.* Nutrition, 20: 590-593.

HOLBEN D.H., SMITH A.M. *1999. The diverse role of selenium within selenoproteins: a review*. J. Am. Diet. Assoc., 7: 836-843.

JELSKI W., CHOSTEK L., SZMITKOWSKI M. 2006. *Biochemical basis of alcohol hepatic damage*, Pol. Merk. Lek., 21: 376-380. (in Polish)

KÖHRLE J., GÄRTNER R. 2009. *Selenium and thyroid*. Best Pract Res Clin Endocrinol Metab., 23(6): 815-827.

KÖHRLE J., JAKOB F., CONTEMPRÉ B., DUMONT J.E. 2005. *Selenium, the thyroid, and the endocrine system*. Endocr Rev., 26(7): 944-984.

KUHN H, BORCHERT A. 2002. *Regulation of enzymatic lipid peroxidation: the interplay of peroxidizing and peroxide reducing enzymes.* Free Radic Biol Med., 33:154-172.

Lai X., Liangpunsakul S., Crabb D.W., Ringham H.N., Witzmann F.A. 2009. *A proteomic workflow for discovery of serum carrier protein-bound biomarker candidates of alcohol abuse using LC-MS/MS*. Electrophoresis, 30(12): 227-14.

Look M.P., Rockstroh J.K., Rao G.S., Kreuzer K.A., Spengler U., Sauerbruch T. 1997. *Serum selenium versus lymphocyte subsets and markers of disease progression and inflammatory response in human immunodeficiency virus-1 infection*. Biol. Trace Elem. Res., 56: 31-41.

Miyamoto Y., Koh Y.H., Park Y.S., Fujiwara N., Sakiyama H., Misonou Y., Ookawara T., Suzuki K., Honke K., Taniguchi N. 2003. *Oxidative stress caused by inactivation of glutathione peroxidase and adaptive responses*. Biol. Chem., 384: 567-574.

Mistry H.D., Pipkin F.B., Redman C.W., Poston L. 2012. *Selenium in reproductive health*. Am. J. Obstet. Gynecol., 206(1): 21-30.

Mokhber N., Namjoo M., Tara F., Boskabadi H., Rayman M.P., Ghayour-Mobarhan M., Sahebkar A., Majdi M.R., Tavallaie S., Azimi-Nezhad M., Shakeri M.T., Nematy M., Oladi M., Mohammadi M., Ferns G. 2011. *Effect of supplementation with selenium on postpartum depression: a randomized double-blind placebo-controlled trial*. J. Matern. Fetal. Neonatal. Med., 24(1): 104-108.

Moslemi MK, Tavanbakhsh S. 2011. *Selenium-vitamin E supplementation in infertile men: effects on semen parameters and pregnancy rate*. Int. J. Gen. Med., 4: 99-104.

Mostert V. 2000. *Selenoprotein P: properties, functions and regulation*. Arch. Biochem. Biophys., 376: 433-438.

Motsenbocker M.A., Tappel A.L. 1982. *A selenocysteine-containing selenium-transport protein in rat plasma*. Biochim. Biophys. Acta, 719: 147-153.

Nikolaev A.A., Lutskii D.L., Lozhkina L.V., Bochanovskii V.A., Goncharova L.A. 1999. *Selenium correction of male subfertility*. Urologija, 4: 29-32.

Paukert T., Sailer R., Strauss W.S., Schubert-Zsilavecz M., Zimmer A. 2011. *Glutathione peroxidase isoenzymes in human tumor cell lines*. Pharmazie, 66(11): 894-898.

Pilaczyńska E., Rybakowski J., Zachara B., Borowska K., Koper J. 1988. *Trace elements (zinc, selenium) in alcohol dependence*. Psychiatria Pol., 22: 216-222. (in Polish)

Rayman M. P. 2000. *The importance of selenium to human health*. Lancet, 356: 233-241.

Reid M.E., Stratton M.S., Lillico A.J., Fakih M., Natarajan R., Clark L.C. 2004. *A report of high-dose selenium supplementation: response and toxicities*. J. Trace Elem. Med. Biol., 18: 69-74.

Safarinejad M.R., Safarinejad S. 2009. *Efficacy of selenium and/or N-acetyl-cysteine for improving semen parameters in infertile men: a double-blind, placebo controlled, randomized study*. J. Urol., 181(2): 741-751.

Savaskan N.E., Ufer C., Kühn H., Borchert A. 2007. *Molecular biology of glutathione peroxidase 4: from genomic structure to developmental expression and neural function*. Biol. Chem., 388(10): 1007-1017.

Schomburg L. 2011. *Selenium, selenoproteins and the thyroid gland: interactions in health and disease*. Nat Rev Endocrinol., DOI: 10.1038/nrendo.2011.174 [Epub ahead of print]

Schwartz K., Folz C.M. 1957. *Selenium as an integral part of Factor 3 against dietary necrotic liver degeneration*. J. Am. Chem. Soc., 79: 3292-3302.

Shafiei Neek L., Gaeini A.A., Choobineh S. 2011. *Effect of zinc and selenium supplementation on serum testosterone and plasma lactate in cyclist after an exhaustive exercise bout*. Biol. Trace Elem. Res., 144(1-3): 454-462.

Sher L. 2001. *Role of thyroid homones in the effects of selenium on mood, behaviour ad cognitive function*. Med. Hyp., 57: 480-483.

Stone C.A., Kawai K., Kupka R., Fawzi W.W. 2010. *Role selenium in HIV infection*. Nutr Rev., 68(11): 671-681.

URSINI F., HEIM S., KIESS M., MAIORINO M., ROVERI A., WISSING J., FLOHÉ L. 1999. *Dual function of the selenoprotein PHGPx during sperm maturation*. Science, 285(5432): 1393-1396.

VÉZINA D, MAUFFETTE F, ROBERTS KD, BLEAU G. 1996. *Selenium-vitamin E supplementation in infertile men. Effects on semen parameters and micronutrient levels and distribution*. Biol. Trace Elem. Res., 53(1-3): 65-83.

WASZKIEWICZ N., SZULC A. 2010. *Immunity defects in acute and chronic alcohol intoxication*, Pol. Merk. Lek., 29(172): 269-273.

WHANGER *P.D.* 2004. *Selenium and its relationship to cancer: an update*. Br. J. Nur., 91: 11-28.

Yu S.Y., Zhu Y.J., Li W.G. 1997. *Protective effect of selenium against hepatitis B virus and primary liver cancer in Qidong*. Biol. Trace Elem. Res., 56: 117-124.

ZAGRODZKI P. 2000a. *Selenium in human nutrition.* Part. I. *Selenium content in food, recommended and real dietary intake of selenium*. Bromat. Chem. Toksykol., 33: 209-214.