

Review Article

Selenium and Its Role in Health and Disease

Rahul Saxena, Geeta Jaiswal

Department of Biochemistry, MLN Medical College, Allahabad, India

Kuwait Medical Journal 2007, 39 (1): 10-18

ABSTRACT

Selenium, an essential trace element, has been known for its toxicity in most of the livestock over past several decades but later research on selenium explored the hidden facts about its role in health and disease. Selenium is an essential constituent of antioxidant enzymes especially glutathione peroxidase and some other selenoproteins that participate in various physiological activities and protects the cell against the deleterious effects of free radicals. However, their exact role is still unknown. Current evidence indicates that selenium is involved in a wide array of physiological

functions and pathological conditions which include normal thyroid functioning, enhancing immune function, carcinogenesis, cardiovascular diseases, male reproduction and in the prevention of pre-eclampsia *etc.* However, the exact mechanism behind its involvement in such events is not yet fully elucidated and needs further investigation. This article reviews an introductory overview covering the current concepts related to selenium balance, its metabolic and physiologic functions with special reference to human health and disease.

KEYWORDS: carcinogenesis, cardiovascular disease, glutathione peroxidase, pre-eclampsia, selenium

INTRODUCTION:

Selenium (Se), an essential trace element, has evolved from its toxic properties after a series of researches over the past several decades. It was first recognized to be an essential trace element in 1957 and has been shown to be active in glutathione peroxidase (GSH-Px) in red blood cells^[1]. Since its discovery about half a century ago, selenium has been a subject of intensive research. Deficiency of selenium produced experimentally in animals resulted in abnormalities such as defective growth, hepatic necrosis, myocardial degeneration and muscular dystrophy in sheep, cattle, chickens and horses^[2]. In humans, it is well recognized that selenium plays a crucial role in various physiological processes (as reported in a later section) and its altered level has a direct impact on health leading to the development of disease.

Free radicals, being highly reactive, induce a series of events leading to pathogenesis of numerous diseases such as cardiovascular disease (CVD), diabetes, stroke, hypertension (HT), pregnancy induced hypertension (PIH) and aging process *etc.*^[3]. Selenium, an essential component of the antioxidant enzyme GSH-Px, functions as an antioxidant scavenging H₂O₂ and by reducing lipid hydroperoxides to their subsequent less reactive end products^[4]. Although previous studies have reported about the toxic manifestations of

excess selenium intake and existence of selenium deficiency in some pathophysiological conditions, the emerging evidence reflects the importance of selenium as an effective medical therapy in a wide array of conditions in association with other antioxidants such as vitamin E. The area covered in this review has been rapidly unfolding in recent years, and has already acquired a vast spread. This article presents a concise introductory overview of the salient features of selenium balance, its metabolic and physiologic functions with special reference to human health and diseases. Disturbances in selenoprotein status due to augmented oxidative stress during pathophysiological conditions and potential role of selenium as medical therapy is also discussed in this article.

SOURCES OF SELENIUM

Plant foods are the major sources of selenium in most countries throughout the world. The amount of selenium present in the plant material depends upon the concentration of selenium in the soil of that region as it varies by region. Low amount of selenium and dietary selenium deficiency has been reported in selenium deficient regions of China and Russia^[5]. Animals that eat grains or plants that were grown in selenium rich soil have higher levels of selenium in their muscle. It is widely distributed in all the tissues; highest concentrations are found in

Address correspondence to :

Dr. Rahul Saxena, C/o Dr. Geeta Jaiswal, 234, Attarsua, Allahabad, India. Mobile: +91- 98393-51748, +91- 98392-76720, E-mail: Rahul_srahul@rediffmail.com

Table 1: Selenium containing proteins and their functions

S. No.	Name	Functions
1	Glutathione peroxidase	<ul style="list-style-type: none"> - An antioxidant enzyme, decomposes H₂O₂ and other hydroperoxides - Maintains intracellular redox milieu - Replenishes a number of crucial antioxidants e.g., vitamin E and C from their oxidized state^[12] - Forms a structural protein and shields the developing sperm cells^[13]
2	Thioredoxin reductase	<ul style="list-style-type: none"> - Provides protection to skin from free radicals^[14] - Protein thiol redox regulation - Vitamin C recycling and DNAsynthesis^[15]
3	Iodothyronine deiodinases	<ul style="list-style-type: none"> - Synthesis of active thyroid hormone^[16]
4	Selenoprotein 1R	<ul style="list-style-type: none"> - Provide protection against free radical mediated oxidative stress
5	Selenoprotein P	<ul style="list-style-type: none"> - Functions as an antioxidant - In the transport of selenium^[17] - Protection against Hepatitis B virus X protein induced lipid peroxidation^[18]
6	Selenoprotein S	<ul style="list-style-type: none"> - Regulation of cellular redox balance^[1]

the liver, kidney, heart, spleen and fingernails whereas dairy products, fruits and vegetables are relatively poor sources of selenium. Pennington *et al* reported that meat and bread are common sources of dietary selenium in the United States^[6].

BIOLOGICAL FORMS, DISTRIBUTION AND METABOLISM

Selenium occurs in both inorganic and organic form. Among the inorganic forms (*i.e.*, selenates, selenides and selenite), the selenide form is more frequently found in the food supply. These selenates and selenites are reduced to selenides in the liver with dimethyl and trimethyl selenide as the end products^[7]. The organic form includes selenomethionine and selenocysteine and is found in plants and animals respectively. Selenium is a potent antioxidant and it nutritionally acts through its various selenoproteins to control the level of cellular hydroperoxides and redox tone of the cell that can damage protein, cell organelle and DNA. About 20- 25 different selenoproteins are identified and characterized. However, their specific enzymatic functions and subcellular localization have not yet been fully elucidated. Among different selenoproteins, GSH-Px and its family are briefly described here, whereas the rest of them along with their function are reported in Table 1.

Glutathione peroxidase (GSH-Px): The most important metabolic role of selenium is its function in the active site of selenoenzymes glutathione peroxidase (GSH-Px), E.C. 1.11.1.9) which may vary from monomeric to tetrameric form. This enzyme together with SOD and catalase protect cells against damage caused by free radicals and hydroperoxides or lipoperoxides^[8]. This enzyme not only allows the removal of H₂O₂ and toxic lipid peroxides moiety but also permits the regeneration of membrane lipid molecule through reacylation. GSH-Px constitutes a family of enzymes among

which selenoperoxidase (*i.e.*, Se containing GSH-Px) contain selenocysteine at their active site and this aminoacid is involved in the catalytic cycle. Until now, five GSH-Px subtypes have been identified, namely, cytosolic glutathione peroxidase (cGSH-Px), gastrointestinal glutathione peroxidase (gGSH-Px), plasma glutathione peroxidase (pGSH-Px), phospholipids hydroperoxide glutathione peroxidase (ph GSH-Px) and sperm nucleus glutathione peroxidase (snGSH-Px). Although these GSH-Px isoforms differ in their localization and ranking in selenium-hierarchy of GSHPx, all these provide protection against free radical mediated oxidative stress. Among these isoforms, phGSH-Px is peculiar metabolic antipode of lipoxygenase and acts as a universal intracellular antioxidant because of its capability of reducing complex hydroperoxy ester lipids incorporated in biomembranes and lipoproteins^[9]. Recent data implicated the enzyme in functional modulation of intracellular metabolic pathways such as silencing of eicosanoid metabolism and in sperm maturation^[10,11].

Selenium levels in blood and tissues are very much influenced by dietary selenium intake. Normal blood level varies from 0.05 to 0.34 µg/ml. In selenium deficient areas of China, blood levels are as low as 0.009 µg/ml. Total body selenium has been estimated to be approximately 4 to 10 mg^[20]. The Recommended Dietary Allowance (RDA) of selenium^[21] for individuals in each life stage and gender group are given in Table 2.

Selenium is assimilated more effectively from plant food than animal products but some dietary constituents (vitamin C and vitamin E) generally affect its absorption. Selenium is absorbed mainly from duodenum and is transported actively across the intestinal brush border. Recently, Schwiezer *et al* revived the abandoned role of selenoprotein P in the transport of Se^[17]. Additionally, Hill *et al* showed that the transport of selenium from testis and brain is greatly affected by inactivation of selenoprotein

Table 2: The Recommended Dietary Allowance (RDA) of Selenium

S. No.	Category	Daily Dosage (µg)	
1	Infants		
	0 to 0.5 year	10	
2	Children and adults	0.5 to 1 year	15
		1 to 6 years	20
		7 to 10 years	30
3	Adolescents and adults	i) Male	
		11 to 14 years	40
		15 to 18 years	50
		19 & above	70
		ii) Female	
		11 to 14 years	45
		15 to 18 years	50
		19 & above	55
	Pregnant	65	

P^[22]. Selenomethionine and selenocysteine, as obtained from their dietary sources, are probably catabolised to release Se for incorporation into selenoproteins. Selenomethionine can be deposited in tissues and be taken up also by myoglobin, cytochrome C, myosin, aldolase and nucleoproteins. The main route of selenium excretion is urine and very small amount is excreted through feces and expired air^[20].

METABOLIC ROLE OF SELENIUM

Selenium plays an important role in a wide spectrum of physiological processes. Selenium, as selenides at the active site of some non-heme iron proteins, is associated with mixed function oxidase system of microsomal and other cellular membranes^[20]. It also binds cadmium, mercury and other heavy metals and mitigates their toxic effects. Additionally, selenium has an impressive effect in enhancing immune system, normal functioning of thyroid gland, protection of skin from UV rays, improving arthritic symptoms, normal development of the fetus during pregnancy and in male reproduction *etc.* Moreover, alteration in body selenium status generally results in an increased risk of cancer, heart and liver disease, birth defects, Down's syndrome, fibrocystic breast disease, in differential activation of genes involved in DNA damage, oxidative stress and cell cycle, and a decrease in the expression of genes involved in detoxification^[23,24]. Besides these, its chemopreventive^[25] and antithrombotic effect^[26] have received much attention which reflects the importance of selenium as a therapeutic agent. Selenium is also known to eliminate reactive oxygen species and modulate redox-sensitive enzyme^[4].

Apart from participating in various physiological processes through selenoproteins, selenium has sparing effect on vitamin E. As a component of

GSH-Px, selenium helps to destroy peroxides and thereby reduces the peroxidation of PUFA of lipid membrane which inturn, reduces the vitamin E requirement for the maintenance of membrane integrity. In addition, GSH-Px also plays a central role in co-ordinating the synergism of various antioxidants (vitamin C and E)^[12,20]. Current researches emphasize the combined effect of vitamin E and selenium in amelioration of depleted level of antioxidant enzymes and are thought to be a key factor in disease prevention. In this connection, Fisher *et al* demonstrated that combined vitamin E and Se deficiency is associated with alteration in the expression level of genes encoding for proteins involved in inflammation and acute phase response^[27]. Beytut *et al* also observed that combined vitamin E and Se supplementation decreases the peroxidative tissue damage by promoting the antioxidative defence systems in the kidney of rats^[28].

ROLE OF SELENIUM IN HEALTH AND DISEASE

Today, Selenium deficiency is suggested to implicate in the pathogenesis of wide variety of processes that affect our state of health and longevity. The list of clinical disorders expected to be influenced by Se deficiency is rapidly growing with time. Some selected issues regarding the role of Se in health and disease have been briefly outlined as follows:

Aging:

The free radical theory of aging^[29] states that aging is the result of cumulative damage incurred by free radical reactions as well as progressive defects in protection against free radical reactions with the passage of time. Free radical mediated lipid peroxidation in lysosome membrane leak out lysosomal hygrolyases which cause dystrophic changes in muscle fibers. As a result, muscles become weak with growing age^[30]. It has been undoubtedly accepted and successfully explained by Orr *et al* that antioxidant enzymes can slow the aging process by scavenging free radicals^[31]. GSH-Px, a selenium containing antioxidant enzyme which scavenges H₂O₂ and prevents the initiation of free radical chain reaction, has been theorized to extend life span and prevent age related functional disorders. Selenium deficiency plays a crucial role in causing or aggravating anemia and cell destruction as glutathione peroxidase protects red blood cells from free radical damage and destruction. Ji *et al* also observed the age related decline in GSH-Px activity and its impact on the genesis of various diseases^[32]. Similar studies are in progress to assess the effect of selenium on the lifespan of human beings.

Cancer:

The role of antioxidant minerals in the etiology of human cancer has also been reviewed. Among various antioxidant minerals, selenium is emerging as a dietary factor that may prove to be of major significance as a prophylactic agent against cancer. Low blood selenium concentration and incidence of carcinogenesis have been well observed in both animals^[33] as well as in human studies^[34]. In addition, it has been demonstrated in a double blind randomized cancer prevention trial in humans that increased selenium intake has a significant role in the treatment of cancer^[35]. Various investigators have reported the role of selenium as an inhibitor of carcinogenesis in various organs including liver, skin, stomach, mammary gland and oral cavity *etc*^[36,37].

In vitro and *in vivo* studies on selenium supplementation also suggested that selenium inhibits cell growth and DNA synthesis in a variety of cell lines leading to the normalization of regulatory pathways that are affected in early stages of carcinogenesis^[38,39].

There is a large body of epidemiological evidence that shows correlation between low dietary intake of selenium and increased risk of carcinogenesis^[40,41]. Klein *et al*, on the basis of SELECT (Se and vitamin E cancer prevention trial) in humans, concluded that treatment with a high dose of Se in combination with vitamin E can prevent the incidence of prostate cancer. This reflects the importance of Se and vitamin E in the etiology of cancer^[42]. Despite numerous investigations regarding the prophylactic role of selenium against cancer, the exact mechanism behind its role is still a matter of debate and needs further investigation. However, in order to explore the hidden mechanism involved in chemopreventive action of selenium, it has been suggested that irrespective of its antioxidant role (as component of GSH-Px enzyme) with optimal selenium concentration, high dose of selenium induces oxidative stress and apoptosis in cancer cells^[25]. Furthermore, to emphasize its chemopreventive action, Spray *et al* have also reported that selenium inactivates the transcription factor NF- κ B, thereby leading to inhibition of cell growth^[43]. Another marked explanation for selenium activity includes its direct role in the liver mixed function oxidase system that is responsible for the metabolism of chemical carcinogens^[44].

Cardiovascular disorders:

Selenium deficiency has been implicated in the development of cardiovascular disease. In an epidemiological study, Salonen *et al* observed an excess of incidence of mortality from ischemic heart disease in eastern Finnish men and women with

low serum selenium concentrations suggesting that low selenium levels have a causal effect in development and deterioration of ischemic heart disease^[45]. In addition, it has been documented that *in vitro* and *in vivo* studies on oxygen free radicals (OFRs) suggest that free radicals are toxic to the myocardium and can cause tissue damage that leads to extensive necrosis, myocytolysis and cellular edema^[46]. The biological function of selenium against OFRs mediated injury in mammals appear to be expressed through different biological active compounds including GSH-Px, GSH reductase (GSSGR), GSH transferase and other selenoproteins in serum and tissue. The remarkable contribution of antioxidant in protecting against oxidant result was also observed in our previous study on atherosclerotic patients^[47]. Kharb, in her study on acute myocardial infarction (AMI) patients, observed that selenium dependent GSH-Px level decreases significantly in AMI patients and explained it as an imperative consequent of GSH-Px activity in annihilating oxygen toxicity by metabolizing H₂O₂ and inhibiting further O₂⁻ production in early phase of myocardial infarction^[48]. Decrease in selenium levels are also reported to produce changes similar to lipid peroxidation^[49].

Oxidative modification of LDL cholesterol in the arterial wall followed by uptake of oxidized LDL by macrophages and monocytes contributing to fatty streaks formation of the arterial wall, is thought to be a fundamental mechanism in atherosclerotic plaque formation^[50]. Selenium via GSH-Px reduces phospholipids, hydroperoxides and cholesteryl esters associated with lipoproteins and may therefore, not only reduce the accumulation of oxidized LDL in arterial wall but also reduce platelet aggregation and activation of monocyte and macrophages^[51]. In addition, selenium owing to its antithrombotic effect on the interaction between platelets and endothelial cells via GSH-Px, also provides concrete evidence in the prevention of atherosclerosis^[26]. In order to emphasize the cardioprotective role of selenium supplementation and GSH-Px, numerous evidences have been documented which authenticate the contention that selenium supplementation modulates the sequences favoring etiopathogenesis of atherosclerosis and its consequent sequelae^[52,53]. In this connection, the impact of selenium deficiency in the elevation of plasma cholesterol level, most probably due to the remarkable increase in apolipoprotein (apoE) level^[54], HDL-1 concentration, 3-hydroxy-3-methyl glutaryl Co. A reductase activity^[55] and its association with high serum copper concentration^[56] has been well elucidated.

AIDS:

Selenium and its biologically active compounds play a vital role in maintaining the normal immune system and preventing the alteration in cells, thereby controlling the occurrence and progression of viral infectious disease such as HIV. Selenium has been demonstrated to be protective against HIV infection, most probably by acting as a potent inhibitor of HIV replication. Loss of CD4T cells in HIV1 infection was found to be closely associated with depletion in plasma selenium level^[57]. Baum *et al* in their study on HIV patients observed that selenium deficiency among HIV patients renders them more susceptible to their virulence leading to early death as compared to that of normal levels^[58]. Minor concentration of reactive oxygen species induce the expression and replication of HIV in human T cells. This effect is mediated by the activation of NF- κ B, transcription factor via H₂O₂. It has been well reported by Studtman that selenium (as selenite form) is responsible for the inhibition of NF- κ B DNA binding activity in human T cells^[59]. Another marked explanation for its role as an anti HIV therapeutic agent include the increased expression of receptor for IL-2 (*i.e.* growth regulatory cytodine) on the surface of activated T cell and NK (natural killer) cell, which on interaction with IL-2, enhances the cellular immune response of T cell and NK cell system by means of clonal expansion and differentiation with cytotoxic T cells^[60]. Role of thiol antioxidant in the deactivation of NF- κ B transcription factor has been well elucidated^[61]. Roedener *et al* also observed that glutathione status and reactive oxygen species production modulate HIV activity. In addition, HIV infected patients have decreased GSH-Px level in their circulating T cells owing to H₂O₂ scavenging action of GSH-Px, which in turn inhibits further activation of NF- κ B transcription factor^[62].

Male reproduction:

Selenium as a key component of number of functional selenoproteins, is essential for the male fertility. The best known among them is selenoprotein P which transports selenium particularly to testis and brain^[11]. Hill *et al* showed that inactivation of selenoprotein P gene in mice due to selenium deficiency generally effects the normal functioning of testis leading to male infertility^[22]. In addition, testis has the highest selenium concentration among the reproductive organs and studies on GSH-Px activity in humans have revealed that this enzymes is the metabolic mediator of body selenium and protects spermatozoa against pro-oxidant induced death and oxidative injury, which reflect the importance of selenium and its related enzymes during

spermatogenesis^[63]. Among the four enzymes of GSH-Px, GSH-Px1 prevents apoptosis induced by oxidative stress and GSH-Px4 acts directly on membrane phospholipid hydroperoxides and detoxifies them. GSH-Px polymerizes to form a structural protein into mitochondrial capsule and thereby shields the developing sperm cells from oxidative stress^[13,63]. Selenium as GSH-Px, is present in spermatids and forms the structural part in the mid piece of mature spermatozoa. Some well known effects of selenium deficiency include instability of the middle piece leading to defective sperm motility^[64], low reproductive ability and abnormal development of spermatozoa^[65]. Selenium is also required for testosterone synthesis and sequential development of flagella^[66]. It can restore the physiological constitution of polyunsaturated fatty acid in the cell membrane^[67]. Lenzi *et al* in their study on infertile men with unilateral varicocele or genital tract inflammation, observed that glutathione treatment has a statistically significant positive effect on sperm motility, sperm morphology and sperm quality and suggested the therapeutic importance of Glutathione against male infertility^[68].

Pre-eclampsia:

Pre-eclampsia (pregnancy induced hypertension; PIH), is an important cause of maternal morbidity and mortality with essentially unknown etiology (*i.e.*, the precise factors involved in the pathogenesis of PIH are still unknown)^[69]. It has been conceived that free radical mediated oxidative stress may contribute to the development of pre-eclampsia. Selenium and its related enzymes specially GSH-Px play a crucial role in annihilating oxygen toxicity and there by controlling the progression of disease^[70]. In addition, selenium deficiency in women may result in infertility, miscarriages and retention of the placenta^[71]. Furthermore, Han and Zhon studied the effect of selenium supplement in 52 pregnant women with high risk factors of pregnancy induced hypertension (PIH) and concluded that selenium supplements prevent and decrease the incidence of PIH and gestational edema in pregnant women^[72].

Keshan and Kaschinbeck disease:

Previously, it has been reported that selenium deficiency is most commonly seen in the development of two diseases, both of which are only seen in the People's Republic of China, where acutely low soil levels of the element are detected. Keshan disease is a cardiomyopathy of children and young women and manifests as acute or chronic cardiac enlargement and arrhythmia. Kaschinbeck disease is an osteoarthropathy that

occurs mainly in young people. This disease shortens the fingers and long bones with severe enlargement and dysfunction of joints resulting in retardation of growth. Although they are multifactorial in origin, selenium deficiency is a major factor in their etiology and both the diseases are effectively prevented by therapy with selenium supplementation^[73,74].

Alcohol consumption and liver disease:

Alcohol, due to its direct action or due to its first metabolite acetaldehyde, is associated with a series of pathologic events, modification in cell function and imbalance in oxidant antioxidant system which may contribute to the development of alcoholic liver disease and a wide range of biochemical and neurological lesions^[75]. In this connection, glutathione peroxidase (GSH-Px) plays a major role in cellular protection against oxidative damage and selenium deficiency leads to a depletion of selenium dependent GSH-Px. Recently, Das and Vasudevan in their study observed that selenium containing GSH-Px activity was significantly decreased in alcoholic liver disease patients as compared to non-alcoholic liver disease patients and normal healthy subjects, and suggested that it may be due to exhaustion or inactivation of the enzyme by reactive oxygen species^[76]. Videla *et al* reported that acetaldehyde, produced as a result of alcohol metabolism, has a deleterious effect on metabolic activities of liver accompanied with enhanced lipid peroxidation and low GSH-Px activity leading to the pathogenesis of liver disease^[77]. Furthermore, increased levels of lipid peroxide have also been reported in the serum of alcoholic cirrhotic patients which may possibly be due to the reduction of GSH-Px (*i.e.*, a key step in rendering the cell more susceptible to oxidative stress followed by liver impairment)^[78].

Smoking:

Smoking is known to produce free oxygen radicals in our body. Each puff of a cigarette is estimated to contain ~ 1014 free radicals in the tar phase and ~1015 of them in the gas phase^[79]. An excess of free radical leads to depletion in body antioxidant reserve. This fact is well supported by the findings of Lloyd *et al*^[80]. According to them, cigarette smokers had low concentration of selenium dependent GSH-Px than non-smokers. The impact of low selenium status in smokers may in part be mediated through or associated with leukocyte activation. This relation seems to be in consensus with the observation of Adams *et al* that cigarette smoking is associated with increased leukocyte activation which is a critical step in the initiation of atherosclerotic plaque formation^[81].

Furthermore, Salonen *et al* also observed low selenium concentration in the serum of smokers and suggested that low serum selenium level is an independent risk factor for the progression of atherosclerosis in smokers^[66].

Gastrointestinal Problems:

Selenium deficiency has been observed in patients with severe gastrointestinal disorders. James *et al* reported that selenium in association with other trace element (Zn, Cu and Mn) perform numerous functions indispensable to maintenance of life, growth and reproduction^[82]. Gastrointestinal problems that impair selenium absorption usually affect absorption of other elements as well and thereby, impair cellular and physiological functions leading to the development of various pathophysiological conditions^[83].

Normal Thyroid Function:

Selenium is essential for the synthesis of active thyroid hormone as Thyroxine (T₄) is converted to Tri-iodothyronine (T₃) by selenium containing enzyme 5'-de-iodinase. Selenium deficiency also affects thyroid hormone by inactivating the enzyme leading to hypothyroidism^[84]. It is conceivable that selenium deficiency may worsen the effects of iodine deficiency on thyroid function and adequate selenium supplementation may protect against neurological effects of iodine deficiency^[85].

Total Parental Nutrition (TPN):

It is a method of feeding nutrients through an intravenous (IV) line to people whose digestive systems do not function. Several reports have linked TPN to selenium deficiency. This reflects the importance of adding selenium in adequate amount in TPN solution to prevent its deficiency. It has been suggested that selenium status of individuals receiving TPN should be monitored before prescribing any treatment^[86].

Adverse effect of Glucocorticoids:

Glucocorticoids are widely used to treat various forms of glomerulonephropathy in humans^[87]. However, the appearance of adverse effects of glucocorticoids including kidney degeneration in humans, most probably by elevation of lipid peroxidation in living cells associated with serious damage to essential structural proteins and enzymes, has been recognized as a potential problem in high dose or long-term therapy. Recently, Beytut *et al* demonstrated that selenium in association with vitamin E reduces kidney damage in glucocorticoid treated rats not only by preventing the elevation of kidney's lipid peroxidation but also by ameliorating the

diminished activities of the antioxidative enzymes and the levels of GSH-Px^[28]. In their previous study, they also observed the selenium had a protective effect against the increase in MDA level in the liver caused by high doses of prednisolone^[88].

CONCLUSION:

In view of substantial evidence from laboratory and human population studies supporting the critical role of selenium in maintenance of health and prevention of disease, the present literature is strong enough to have convinced the nutritionist that daily consumption of selenium rich diet should be increased with increasing age as well as in individuals with high oxidant load such as smokers and alcoholics in order to sustain free radical mediated destruction and age related modifications leading to pathophysiologic complications. However, more work is needed to shed light on the chemopreventive and chemotherapeutic mechanism of selenium.

REFERENCES

- Schwaz K, Foltz CM. Selenium as an integral part of factor 3 against dietary necrotic liver degeneration. *J Am Chem Soc* 1957; 79:3292-3293.
- Hoekstra WG. Biochemical role of Selenium. In: Hoekstra WG, Suttie JW, editors. *Trace element metabolism in Animals*. 2nd edition: Baltimore Univ Park Press; 1974, p 61-90.
- Puri D. Free radical reaction in health and disease. A text book of Biochemistry, 1st ed. New Delhi: BI Churchill Livingstone Pvt Ltd; 2002, p 769 - 778.
- Rotruck JT, Pope AL, Ganther HE, Swanson AB, Hafeman DG, Hoekstra WG. Selenium: Biochemical role as component of glutathione peroxidase. *Science* 1973; 179:538-544.
- Longnecker MP, Taylor PR, Levander OA, Howe M, Weillon CM, Adam PA. Selenium in diet, blood and toenails in relation to human health in a seleniferous area. *Am J Clin Nutr* 1991; 53:1288-1294.
- Pennington JA, Young BE. Total diet study nutritional elements. *J Am Diet Assoc* 1991; 91:179-183.
- Ganther HE, Hsieh HS. Mechanisms for the conversion of selenite to selenides in mammalian tissues. In: Hoekstras WG, Suttie JW, Ganther HE, Mertz W, editors. *Trace elements in man and animals*. Baltimore: Park Press; 1974, p 339-346.
- Veris research Summary: An overview of vitamin E efficacy. Veris research Information Service: IL1998; 1- 36.
- Kuhn H, Borchert A. Regulation of enzymatic lipid peroxidation: The interplay of peroxidizing and peroxide reducing enzymes. *Free Biol and Med* 2002; 33:154-172.
- Horvath PM, Ip C. Synergistic effect of vitamin E and selenium in chemoprevention of mammary carcinogenesis in rats. *Cancer Res* 1983; 43:5335-5342.
- Lane HW, Medina D. Mode of action of selenium inhibition of 7, 12 di-methyl benz[a]anthracene induced mouse mammary tumorigenesis. *J Natl Cancer Inst* 1985; 75:675-681.
- Sen CK. Oxygen Toxicity and antioxidants: state of the art. *Ind J Physiol Pharmacol* 1995; 39:177-196.
- Ursini F, Heim S, Kiess M, et al. Dual function of the selenoprotein GSHPx during sperm maturation. *Science* 1999; 285:1393-1397.
- Schallreuter KU, Wood JM. The role of thioredoxin reductase in the reduction of free radicals at the surface of the epidermis. *Biochem Biophys Res Commun* 1986; 136:630-636.
- Mustacich D, Garth P. Thioredoxin reductase. *Biochem J* 2000; 346: 1-7.
- Vasudevan, DM, Sreekumari S. *Mineral metabolism*. Text Book of Biochemistry. 3rd edition, New Delhi: Jaypee Brothers Med Pub Ltd; 2001, p 284-298.
- Schweizer U, Schomburg L, Savaskan NE. The neurobiology of selenium: Lessons from Transgenic Mice. *J Nutr* 2004; 134:707-711.
- Yi YS, Park SG, Byeon SM, Kwon YG, Jung G. Hepatitis B virus X protein induces TNF- expression via down regulation of selenoprotein P in human HePG2. *Biochem Biophys Acta* 2003; 1638:249-256.
- Gao Y, Feng HC, Walder K, Bolton K. Regulation of the selenoprotein Sel S by glucose deprivation and endoplasmic reticulum stress- Sel S is a novel glucose regulated protein. *FEBS Lett* 2004; 9:563-565.
- Chatterjea MN, Shinde R. *Metabolism of minerals and trace elements*. Text Book of Medical Biochemistry. 5th edition, New Delhi: Jaypee Brothers Med Pub Ltd; 2002, p 526- 531.
- Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium and Carotenoids*. National Academy Press, Washington DC, 2000.
- Hill KE, Zhon J, Mc Mohan WJ, et al. Deletion of selenoprotein P alters distribution of selenium in the mouse. *J Biol Chem* 2003; 278:13640-13648.
- Levander OA. Nutrition and newly emerging viral diseases: An overview. *J Nutr* 1997; 127:948S- 950S.
- Rao L, Puschner B, Prolla TA. Gene expression profiling of low selenium status in the mouse intestine: transcriptional activation of genes linked to DNA damage, cell cycle control and oxidative stress. *J Nutr* 2001; 131:3175-3181.
- Spallholz JE. Selenium and the prevention of Cancer. Part II: Mechanism for the carcinostatic activity of Se compounds. *Bulletin of Se Tellurim Development Association, Belgium* 2001.
- Ricetti MM, Guidi GC, Tecchio C, et al. Effects of sodium selenite on invitro interactions between platelets and endothelial cells. *Int J Clin Lab Res* 1999; 29:80-82.
- Fischer A, Pallauf J, Gohil K, Weber SU, Packer L, Rimbach G. Effect of selenium and vitamin E deficiency on differential gene expression in rat liver. *Biochem Biophys Res Commun* 2001; 285:470-475.
- Beytut E, Erisir M, Akasakal M. Effects of additional vitamin E and selenium supply on antioxidative defense mechanisms in the kidney of rat treated with high doses of glucocorticoid. *Cell Biochem Funct* 2004; 22:59-65.
- Harman D. Aging and disease: extending functional life span. *Annals of the New York Academy of Sciences* 1996; 786:321-326.
- Singh S, Saxena R, Lal AM. Influence of aging on plasma ascorbate level. *Natl Acad Sci Lett* 2005; 28 (3&4):125-127.
- Orr WC, Sohal RS. Extension of life span by over expression of superoxide dismutase and catalase in *Drosophila melanogaster*. *Science* 1994; 263:1128- 1130.
- Ji LL, Dilton R, Wu E. Myocardial aging antioxidant enzyme system and related biochemical properties. *Am J Physiol* 1991; 261:386-390.
- Ip C. Lessons from basic research in selenium and cancer prevention. *J Nutr* 1998; 128:1845-1849.
- Shamberger RJ. Relationship of Selenium to Cancer.

- Inhibitory effect of selenium on carcinogenesis. *J Nat Cancer Inst* 1970; 44:931-936.
35. Clark LC, Combs GF, Turnbull BW, *et al.* Effect of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized clinical trial. *J Am Med Assoc* 1996; 279:1975-1982.
 36. Ip C, Medina D. Current concepts of selenium and mammary tumorigenesis. In: Medina D, Kidwell W, Heppner GH, Anderson E, editors. Cellular and molecular biology of mammary cancer. New York: Plenum press; 1987, p 479.
 37. Ip C, Daniel FB. Effects of Selenium on 7, 12 di-methyl benzanthracene induced mammary carcinogenesis and DNA adduct formation. *Cancer Res* 1985; 45:61-68.
 38. Watrach AM, Milner JA, Watrach MA, Poirier KA. Inhibition of breast cancer cells by selenium. *Cells Lett* 1984; 25:41-47.
 39. Fico ME, Poirer KA, Watrach AM, Watrach MA, Milner JA. Differential effects of selenium on normal and neoplastic canine mammary cells. *Current Res* 1986; 46:3384-3389.
 40. Diplock AT. Mineral insufficiency and cancer. *Med Oncol Tumor Pharmacother* 1990; 7:193-198.
 41. Salonen JT, Alftahan G, Huttunen JK, Puska P. Association between serum selenium and the risk of cancer. *Am J Epidemiol* 1984; 12:342-351.
 42. Klein EA. Clinical models for testing chemopreventive agents in prostate cancer and overview of SELECT: The Selenium and Vitamin E Cancer Prevention Trial Recent Results. *Cancer Res* 2003; 163:212-217.
 43. Spygrou G, Bjornstedt M, Kumar S, Holmgren A. AP-1 DNA binding activity is inhibited by selenite and selenodiglutathione. *FEBS Lett* 1995; 368:59-64.
 44. Diplock AT. Antioxidants and Disease prevention : an overview . *Am J Clin Nutr* 1991; 53:189S-193S.
 45. Salonen JT, Alftan G, Huttunen JK, Pikkarainen J, Puska P. Association between cardiovascular death and myocardial infarction and serum selenium in a matched pair longitudinal study. *Lancet* 1982; 2:175-179.
 46. Kloner AR, Przyklenk K, Whittaker P. Deleterious effects of oxygen radicals in ischaemia -reperfusion: resolved and unresolved issue. *Circulation* 1989; 80:1115-1127.
 47. Singh S, Saxena R, Lal AM. Oxidative stress alteration in plasma ascorbate level in various diseases. *Bioved* 2005; 16:57-59.
 48. Kharb S. Low blood glutathione levels in acute myocardial infarction. *Ind J Med Sci* 2003; 57:335 - 337.
 49. Qu X, Huang K, Deng L, Xu H. Selenium deficiency induced alteration in the vascular system of the rat. *Biol Trace Elem Res* 2000; 75:119-125.
 50. Prithviraj T, Misra KP. Reversal of Atherosclerosis - fact or fiction? *Cardiology Today* 2000; 4:97- 100.
 51. Sattler W, Maiorino M, Stocker R. reduction of HDL and LDL associated cholesterylester and phospholipids hydroperoxides by phospholipids hydroperoxide glutathione peroxidase and ebselen (Pz 51). *Arch Biochem Biophys* 1994; 309:224.
 52. Wojcicki J, Rozewicka L, Barcew- Wisziniewska B, *et al.* Effects of selenium and vitamin E on the development of experimental atherosclerosis in rabbits. *Atherosclerosis* 1991; 87:9-15.
 53. Kang BPS, Mehta U, Bansal MP. Effect of diet induced hypercholesteremia and selenium supplementation on nitric oxide synthase activity. *Arch Physiol Biochem* 1997; 105:603- 609.
 54. Mazur A, Nassir F, Gueux E, Moundras C, *et al.* Diet deficient in selenium and vitamin affects lipoprotein and apolipoprotein concentration in the rat. *Br J Nutr* 1996; 89:901-905.
 55. Nassir F, Moundras C, Bayle D, Serougne C, Gueux E, Rock E. Effect of selenium deficiency on hepatic lipid and lipoprotein metabolism in the rat. *Br J Nutr* 1997; 78:493-496.
 56. Salonen JT, Salonen R, Seppanen K, Kantola M, Suntuinen S. Interactions of serum copper, selenium and low density lipoprotein cholesterol in atherogenesis. *BMJ* 1991; 302:756-760.
 57. Look MP, Rockstroh JK, Rao GS, *et al.* Serum selenium versus lymphocyte subsets and markers of disease progression and inflammatory response in human immunodeficiency virus infection. *Biol Trace Elem Res* 1997; 56:31-36.
 58. Baum MK, Posner GS, Lai S. High risk of HIV- related mortality is associated selenium deficiency. *J Acquir Immune Def Syndr* 1997; 15:370-374.
 59. Kim IY, Stadtman TC. Inhibition of NF- κ B DNA binding and NO induction in human T cells and lung adenocarcinoma cells by selenite treatment. *Proc Natl Acad Sci USA* 1997; 94:12904-12907.
 60. Schumacher LK, Roy M, Biowishe HI, Cohen MW, Stotzky G. Supplementation with selenium augments the function of natural killer and lymphokine activated killer cells. *Biol Trace Elem Res* 1996; 52:227-235.
 61. Schreck R, Rieber P, Baeuerle PA. Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF- κ B transcription factor and HIV-1. *EMBO J* 1991; 10:2247-2258.
 62. Roederer M, Ela SW, Stal FJT, Herzenberg LA. N- acetyl cysteine: a new approach to anti- HIV therapy. *AIDS Res Hum Retrov* 1992; 8:209-217.
 63. Agarwal A, Prabhakaran SA. Mechanism, measurement and prevention of oxidative stress in male reproductive physiology. *Ind J Exp Biol* 2005; 43:963-974.
 64. Hansen JC, Degachi Y. Selenium and fertility in animals and men: A review. *Acta Vet Scan* 1996; 37:19-25.
 65. Wantanobe T, Endo A. Effects of selenium deficiency on sperm morphology and spermatocyte chromosomes in mice. *Mutat Res* 1991; 262:93-96.
 66. Olson GE, Winfrey VP, Hill KE, Burk RF. Sequential development of flagellar defects in spermatids and epididymal spermatozoa of selenium deficient rats. *Reproduction* 2004; 127:335-341.
 67. Lenzi A, Gandini L, Lombardo F, *et al.* Polyunsaturated fatty acids of germ cell membranes, glutathione and glutathione dependent enzyme - PHGPx: from basic to clinic. *Contraception* 2002; 65:301-305.
 68. Lenzi A, Picardo M, Gandini L, *et al.* Glutathione treatment of dyspermia: Effect on the lipoperoxidation process. *Hum Reprod* 1994; 9:2044-2049.
 69. Cunningham FG, Lindheimer MD. Hypertension in Pregnancy: Current concepts. *N Engl J Med* 1992; 326:927-32.
 70. Sharma JB. Benefits of Selenium during pregnancy. *Obs & Gynae* 2001; 6:459-462.
 71. Barrington JW, Lindsay P, Names D, Smith S, Robert A. Selenium deficiency and miscarriage: a possible link ? *Br J Obstet Gynaecol* 1996; 2:130-132.
 72. Han L, Zhou SM. Selenium and incidence of Pregnancy induced Hypertension. *Clin Med J* 1994; 107:870-871.
 73. Diplock AT. Trace elements in human health with special reference to selenium. *Am J Clin Nutr* 1988; 45:1313-1322.
 74. WHO: Environmental Health Criteria, 58- selenium. Geneva : World Health Organisation 1987.
 75. Das Sk, Nayak P, Vasudevan DM. Biochemical markers for alcohol consumption. *Ind J Clin Biochem* 2003; 18:111-118.
 76. Das SK, Vasudevan DM. Monitoring oxidative stress in patients with non-alcoholic and alcoholic liver diseases.

- Ind J Clin Biochem 2005; 20:24-28.
77. Videla LA, Valenzuela A. Alcohol ingestion, liver glutathione and lipid peroxidation: metabolic interrelations and pathological implication. *Life Sci* 1982; 31:2395- 2407.
 78. Zima T, Fialova L, Mestek O, *et al.* Oxidative stress, metabolism of ethanol and alcohol related diseases. *J Biomed Sci.* 2001; 8:59-70.
 79. Duthie GG, Arthur JR. Cigarette smoking as an inducer of oxidative stress. In: Sen DK, Packer L, Hannine O, editors. *Exercise and oxygen toxicity.* Amsterdam, Elsevier Science Publishers BV; 1994, p 297-318.
 80. Lloyd B, Lloy RS, Clayton BE. Effect of smoking, alcohol and other factors selenium status of a healthy population. *J Epidemiol Community Health* 1983; 37:213- 217.
 81. Adams MR, Jessup W, Celermajer DS. Cigarette smoking is associated with increased human monocyte adhesion to endothelial cells: reversibility with oral L- arginine but not vitamin C. *J Am Coll Cardiol* 1997; 29:491-497.
 82. Sullivan JF, Blotcky AJ, Jetton MM, Hahn HKJ, Burch RE. Serum levels of selenium, calcium, copper, magnesium, manganese and zinc in various human diseases. *J Nutr* 1979; 109:1432-1437.
 83. Ranneu T, Ladefoged K, Hylander E, Hegnhog J, Staun M. Selenium depletion in patients with gastrointestinal diseases: Are there any predictive factors? *Scand J Gastroenterol* 1998; 33:1057-1061.
 84. Arthur JR. The role of selenium in thyroid hormone metabolism. *Can J Physiol Pharmacol* 1991; 69:1648-1652.
 85. Corvilain B, Contempre B, Longombe AO, Goyens P. Selenium and the thyroid: How the relationship was established. *Am J Clin Nutr.* 1993; 57:244 S- 248 S.
 86. Gramm HJ, Kopf A, Bratter P. The necessity of selenium substitution in total parenteral nutrition and artificial alimentation. *J Trace Elem Med Biol* 1995; 9:1-12.
 87. Gelfand MC, Steinberg AD. Therapeutic studies in N2B/W mice II. Relative efficacy of azathioprine, cyclophosphamide and methyl prednisolone. *Arthr Rheumat* 1972; 15:247-252.
 88. Beytut E, Akasakal M. Effects of dietary vitamin E and selenium on antioxidative defense mechanisms in the liver of rats treated with high doses of glucocorticoid. *Biol Trace Elem Res* 2003; 91:231-241.