ISSN 2348-313X (Print)
International Journal of Life Sciences Research ISSN 2348-3148 (online)
Vol. 4, Issue 2, pp: (236-246), Month: April - June 2016, Available at: www.researchpublish.com

Selenium in Health and Diseases

Swaminathan S[1], Revathy K[2], Rajeswari S[3]

[1]Ex-Senior Consultant and Head, Department of Biochemistry, Apollo Speciality Hospitals, Ayanambakkam, Chennai – 600 095
[2]Junior Technical Officer, Department of Biochemistry, Apollo Speciality Hospitals, Ayanambakkam, Chennai – 600 095
[3]Ex-Junior Technical Officer, Department of Biochemistry, Apollo Speciality Hospitals, Ayanambakkam, Chennai – 600 095

Abstract: **Selenium is an important trace metal implicated in many human health and diseases. Although its beneficial effects on humans were identified in the early 50s, its relevance and clinical applications emerged only during the last two decades. Its beneficial effects on DM has been studied extensively and its usefulness for other diseases like renal, cardiac, liver, psychiatric, reproductive, neurologic, infections and endocrine have recently been explored. This review article summarises the research findings of the last two decades on the role of selenium in all of the human diseases mentioned above. Although there are controversies among research findings, still there is scope for further research in this field to establish solid diagnostic strategies regarding supplementation on a reasonable number of populations and to bring out a standard protocol to implement for the benefit of various human diseases identified as selenium deficient**

Keywords: **DM, IR, OS, PCOS.**

1. INTRODUCTION

The clinical usefulness of selenium was first pointed out in 1957 and although it was not firmly established about its usefulness in human health and diseases, studies done from 1972 and upto date have brought about its role in many important enzyme catalysed redox reactions involving GSH and in thyroid function modulating enzymes. This review article highlights the research findings during the last two decades on its deficiency and benefits of supplementation for various diseases in humans and animals.

2. SELENIUM AND DIABETES MELLITUS

In recent years diabetes has become one of the most common metabolic diseases in developed countries and it is closely related to supernutrition and obesity. Since untreated diabetes produces Oxidative Stress (OS) responsible for secondary complications of the disease, antioxidant supplements were considered as being favourable for diabetic therapy.Currently available data on the role of Selenium (Se) in diabetes are inconsistent and an enigma appears to exist for the relation between Se and diabetes[1].The potential of some selenoproteins to protect against OS led to the expectation that Se would be protective against Type 2 Diabetes Mellitus (T2DM) and indeed in early in vivo and in vitro studiesSe asselenate was shown to have antidiabetic and insulin-mimetic effects. However, more recently, findings from observational cross-sectional studies have raised concern that high Se exposure may be associated with T2DM or Insulin Resistance (IR), at least in well-nourished populations, though trial results have been inconsistent. Although there is a clear link between certain selenoproteins and glucose metabolism or IR, the relationship between selenium and T2DM is undoubtedly complex. It is possible that the relationship is U-shaped, with possible harm occurring both below and above the physiological range for optimal activity of some or all selenoproteins[2].

It is well documented that Se is involved in the metabolism of glucose. However, whether Se supplementation could lower the risk of T2DM remains elusive[3]. Sehas long been considered to exhibit anti-diabetic and insulin-mimetic properties, but recent epidemiological studies indicated supranutritional Seintake and high plasma Se levels as possible

risk factors for development of T2DM, pointing to adverse effects of Se on carbohydrate metabolism in humans. However, increased plasma Se levels might be both a consequence and a cause of diabetes. Dysregulated pathways in carbohydrate metabolism and a disturbance of Se homeostasis are linked via proliferator-activated receptor gamma coactivator1α[4].DM, a common complication of chronic pancreatitis, can disturb the metabolism of zinc (Zn), copper (Cu) and Se. Diabetes due to chronic pancreatitis was associated with decreased plasma Zn and Se concentrations and with increased urinary copper excretion. Of the chronic pancreatitis patients, 17% had low plasma Zn, and 41% of them had low plasma Se. The perturbations of the Cu, Se and Zn metabolism were particularly pronounced in subjects with chronic pancreatitis plus DM[5].

Se, Zn and Cu levels in diabetic patients have led to contradictory findings as the possible relationship between the degree of diabetic control and the changes in mineral contents. The mean plasma Se content in diabetic patients was found to be significantly lower than in controls and a negative correlation between the plasma contents of Se and HbA1c was found. No statistically significant differences in plasma Zn contents, either between patients with T1DM and control, were found. A statistically significant sex difference in plasma Cu contents was observed in the control population. In females, statistically significant differences were found in plasma Cu contents between the control subjects and the diabetic patients with medium or poor metabolic control, as well as between diabetic patients with good and poor metabolic control. In males, the only statistically significant differences were between the control subjects and diabetic patients with poor metabolic control. The correlation between plasma contents of Cu and HbA1c is not significant[6].

There was no statistically significant difference in the serum levels of Se between the groups of patients with T1DM & T2DM. The levels of erythrocyte glycogen were more or less the same in the control T1DM with no statistically significant between-group difference. The decreased levels of Se in serum and erythrocytes of diabetic patients suggest the possible role of glutathione peroxidase activity[7].

3. SELENIUM AND OBESITY

At rest, compared to placebo, Se supplementation had no significant effect on LH, SOD, GSH, and TAS levels. However, Se supplementation decreased LH levels in the OW group, immediately postexercise compared to placebo treatment. Postexercise, with or without Se supplementation, no changes in TAS, SOD, and GSH levels were observed in both the NW and OW group. This study has highlighted a potential benefit of Se in reducing LH levels postexercise in OW individuals. Given that oxidant stress is a predictor of coronary events, it is imperative to better understand oxidant stress-related responses to lifestyle factors (in particular "high-risk" population groups) and potential antioxidant therapy[8].Se treatment led to reduced levels of cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol; fat tissue in Se-treated rats displayed significantly lower expression of adipocyte marker genes along with increased expression of VLCAD and MCAD; and fatty liver formation and β-oxidation gene expression were both significantly reduced in liver tissue of Se-treated rats. She may induce inhibition of adipocyte hypertrophy and abdominal fat accumulation along with suppression of fatty liver formation by the differential regulation of the gene expression for fatty acid β-oxidation in the OLETF model[9].

4. SELENIUM AND OXIDATIVE STRESS

Epidemiological findings link a lowered Se status to neurodegenerative and CVD as well as to increased cancer risk. While evidence exists to suggest that additional selenocompounds would be beneficial in some health conditions, results from future intervention trials are needed to substantiate the argument for increasing Se intake. Several pieces of the puzzle concerning the molecular mechanisms underlying the reactive oxygen species (ROS)-triggered disease state and intervention by enzymatic antioxidants have been elucidated. A novel concept of protection of stromal cells against the dominating influence of tumor cells in tumor-stroma interaction by selenocompounds and other antioxidants have been presented, which may translate into therapeutic strategies in chemoprevention of tumor invasion[10].High Se levels increase OS in some biological processes. More studies are needed to disentangle the complexity of Se biology and the relevance of potential gene-selenium interactions in relation to health outcomes in human populations[11].

The use of "Selenaze" in postoperative patients with tumors of the liver increased Se levels by 10-12%, which was accompanied by a decrease in the content of SOD and NOx, and contributed to earlier recovery of detoxic and synthetic liver function. These findings point to an intensification of OS and metabolic disorders in the malignant process, which is the basis for metabolic correction[12].There are signs of Se and selenoprotein deficiency in the pathogenesis of epilepsy. There is convincing evidence for the proposed crucial role of Se and deficiency of GSH-Px enzyme activity in epilepsy pathogenesis. Blood GSH-Px activities could be a reliable indicator of Se deficiency in patients with epilepsy[13].

5. SELENIUM AND INSULIN RESISTANCE

High Se-activated selenoproteins also weaken insulin-stimulated "good" ROS signal generated by NAD(P)H oxidase, leading to attenuation of insulin signaling. Taken together, these data suggest that excessive intake of Se induces hepatic insulin resistance through opposite regulation of ROS[14].Serum Se levels were inversely correlated with the Homeostasis Model for Assessment of Insulin Resistance (HOMA-IR) values. However, serum Se levels were independent of HCV genotype and loads of HCV-RNA. These findings suggest that Se deficiency was associated with the severity of hepatic fibrosis in patients with HCV-related Chronic Liver Disease (CLD) and that Se deficiency was likely to be one of the factors contributing to IR in those patients[15].

Se as a Se-enriched yeast in rats induced gestational diabetes and IR. Expression of six selenoprotein genes, in particular Gpx1, was linked to this metabolic disorder[16].A 200 μg/day Se supplementation among patients with T2DM and CHD resulted in a significant decrease in insulin, HOMA-IR, HOMA-B, serum hs-CRP, and a significant increase in QUICKI score and TAC concentrations[17].It is reassuring that a nutritional dose of Se had no adverse effect on the concentration of adiponectin, a biomarker of IR, in pregnant women of modest Se status[18].Chromium and Se levels in the hair of viscerally obese adults were inversely associated with IR, whereas Cu levels in the hair were positively associated with IR. This suggests that the mineral status of viscerally obese adults might play a role in the development of IR[19].

6. SELENIUM AND RENAL DISEASES

Low serum Se levels are a frequent finding in patients with Acute Kidney Injury (AKI) or chronic kidney disease. The relationship between hyposelenemia and the comorbidities associated with renal disease has not been extensively evaluated. It has been reported that both low serum Se levels and renal insufficiency are associated with an increased risk of coronary heart disease mortality and an increased risk for all-cause mortality in adults older than 35 years. Although there are intriguing relationships between Se physiology and several derangements and comorbidities associated with acute and chronic kidney disease, only a few studies have analyzed the clinical consequences of hyposelenemia in these patients to date. Available data are encouraging and stimulate interest in further studies to clarify the real extent of Se deficiency and the need for Se supplementation in patients with kidney disease[20].

Although prospective studies suggest that low Se is a risk factor for CVD, most clinical trials of Se supplementation have not shown this benefit. Prospective studies of renal insufficiency show that it is associated with low-Selevels and increased CVDrisk[21]. Seand Zn inhibited effects of Sodium Fluoride (NaF) on OS and apoptosis, promoted the cell number of G2/M phase in cell cycle, but failed to increase relative DNA content significantly.NaF administered at the dose of 50 mg/L for six months induced OS and apoptosis and changes the cell cycle in rat renal cells. Seand Zn antagonize OS, apoptosis and cell cycle changes induced by excess fluoride[22].Plasma Se concentration was lower in patients with a severe organ dysfunction syndrome and correlated with the number of organ failures in these patients. T4 and free-T4 values paralleled decreasing Se concentrations. Thyroid hormone levels were reduced in patients with Acute Renal Failure (ARF)without an increase in TSH. An increase in T4 concentrations became apparent during treatment and may be related to a favorable outcome in AKI. Thyroid hormone concentrations paralleled plasma Se levels, indicating a possible influence of Se on thyroid function in AKI [23].

Se treatment has some potential as a therapeutic for AKI as it inhibits oxidative damage and inflammation and decreases proteinuria, albeit histopathological changes to the kidney and some plasma and urinary markers of AKI remain unaffected after RhobdoMyolysis[24]. Abnormalities of trace elements are primarily the result of uremia, and they may be further modified and sometimes greatly exacerbated by the dialysis procedure. The role of trace elements in hemodialysis (HD) patients has not yet been fully characterized. To prevent some complications in chronic HD patients, it is very important to regulate the levels of trace elements by adequate water treatment. Reverse osmosis is able to prevent the accumulation of the majority of trace elements in the patients. Supplementation with a trace element may be indicated when its depletion was unequivocally documented and when there is evidence of the positive effects of this element on the quality of life of the dialyzed patients[25]. Se supplementation promotes the reduction of chemotherapy side effects in cancer patients, especially by improving the conditions of patients with fatigue, nausea, and impaired physical function. Renal and liver functions have also improved[26].

7. SELENIUM AND CARDIAC FUNCTION

Se protects the heart against Ischemia- reperfusion (I/R) injury due to its action on the redox state and deactivation of NF-kappaB in I/R hearts[27].Se supplementation resulted in normalized serum Se levels, partial improvement of ECG

abnormalities, and an increase of cardiac functions on UCG. It is thought that Se has beneficial effects on the myocardium of chronically tube-fed patients. Se supplementation is recommended in this population[28].It is hypothesized that low Se concentrations are associated with an increased risk of CVD and that Se supplements prevent coronary heart disease (CHD).Se concentrations were inversely associated with CHD risk in observational studies,since such studies have provided misleading evidence for other antioxidants, the validity of this association is uncertain. Few randomized trials have addressed the cardiovascular efficacy of Se supplementation, and their findings are still inconclusive. Evidence from large ongoing trials is needed to establish low Se concentrations as CVD risk factor. Currently, Se supplements should not be recommended for cardiovascular disease prevention [29].

Despite severe Se depletion in some patients on long term home parenteral nutrition had normal cardiac function and no clinically significant signs of skeletal myopathy. The only change after Se supplementation was a small but statistically significant increase of the mean diameter of muscle fiber type 1[30].Selenoprotein N (Se N) is the first selenoprotein linked to genetic disorders consisting of different forms of congenital muscular dystrophies. Understanding the muscle disorders associated with Se deficiency or Se N dysfunction is an essential step in defining the causes of the disease and obtaining a better comprehension of the mechanisms involved in muscle formation and maintenance[31].The trace element Se is of high importance for many of the body's regulatory and metabolic functions. Balanced Se levels are essential, whereas dysregulation can cause harm. A rapidly increasing number of studies characterizes the wide range of Se dependent functions in the human body and elucidates the complex and multiple physiological and pathophysiological interactions of Se and selenoproteins. For the majority of Se dependent enzymes, several biological functions have already been identified, like regulation of the inflammatory response, antioxidant properties and the proliferation/differentiation of immune cells. Although the potential role of Se in the development and progression of CVD has been investigated for decades, both observational and interventional studies of Se supplementation remain inconclusive[32].

8. SELENIUM AND REPRODUCTION

The role of Se supplementation on pregnancy outcomes is promising, and ongoing studies and meta-analysis should soon enable proper recommendations to be suggested. How best to assess Se in terms of cut-off value, sample type (serum, semen, other fluids) and the specific outcome of interest remains to be clarified. In the meantime, assessment of serum Se levels followed by low-dose replacement therapy when necessary is a reasonable approach to improve male idiopathic infertility and gestational outcome [33].

Development of male reproductive tissue requires an optimal level of Se in testis, and a small deviation, either deficiency or excess, leads to abnormal development. Se is a constituent of selenoproteins including GPx1, GPx3, mGPx4, cGPx4, and GPx5 that protect against oxidative damage to spermatozoa throughout the process of sperm maturation, whereas selenoproteins, such as mGPx4 and snGPx4, serve as structural components of mature spermatozoa. Thus Se and selenoproteins ensure viability of spermatozoa as well as providing protection against reactive oxygen species. Gene knock-out studies of selenoproteins revealed that their absence during spermatogenesis results in abnormal spermatozoa, which in turn affects semen quality and fertility. Deviation from the optimal quantities of dietary Se, both above or below, may cause multiple abnormalities of spermatozoa and affect motility and fertility. Libido may also be increased by Se. Dietary Se should be in optimal quantity to maintain reproductive function in males and to avoid infertility [34].

Increasing evidence suggests that this mineral plays an important role in normal growth and reproduction in animals and humans and Se supplementation is now recommended as part of public health policy in geographical areas with severe Se deficiency in soil. Numerous reports implicate Se deficiency in several reproductive and obstetric complications including male and female infertility, miscarriage, preeclampsia, fetal growth restriction, preterm labor, gestational diabetes and obstetric cholestasis. Currently, there is inadequate information from the available small intervention studies to inform public health strategies. Larger intervention trials are required to reinforce or refute a beneficial role of Se supplementation in disorders of reproductive health [35].

9. SELENIUM AND NEUROLOGY

Se and its compounds have dual action profiles with direct anti-cancer and chemotherapy-intensifier effects as well as neuroprotective and cytoprotective agents. Current Se trials and supplementation with focus on neuro-oncology shoud be investigated with regard to low-adequate-to-high/toxic Sestatus[36]. The remarkable progress that has been made in understanding the biological function of Se in the brain has opened up new potential possibilities for the treatment of

neurological diseases by using Se as a potential drug. However, further research in the search for optimal Se donors is necessary in order to achieve an effective and safe therapeutic income[37]. Concurrent use of Se significantly inhibited iminodipropionitrile (IDPN)-induced neurobehavioral changes in a dose-dependent manner. Treatment of rats with Se also reduced the TBARS production in blood and different regions of brain. These findings suggest that Se attenuates the IDPN-induced neurotoxicity by inhibiting lipid peroxidation[38].

Existing data indicate that Se supplementation may be beneficial in critically ill patients and in those with ischemic stroke. Some influences of early administration of Se on neurological outcome after cardiopulmonary resuscitation (CPR) have been observed [39].Se will influence compounds with hormonal activity (and neurotransmitters) in the brain, and this is postulated to be the reason thatSe affects moods in humans and behavior in animals. Even though Se counteracts the neurotoxicity of mercury, cadmium, lead and vanadium, it causes them to accumulate in the brain, presumably in a nontoxic complex[40].A strong association exists between plasma Se and timed performance-based assessments.Lower levels of Se were significantly associated with decreased performance in neurological tests of coordination among older adults. Prospective studies are needed to further investigate the effects of Se on SN dysfunction[41].

10. SELENIUM AND PSYCHIATRIC

The change in mood when taking the active Se tablet was correlated with the level of Se in the diet, which was estimated from a food frequency questionnaire. The lower the level of Se in the diet the more reports of anxiety, depression and tiredness, decreased following 5 weeks of Se therapy and the results have been discussed in terms of the low level of Se in the food chain in some parts of the world[42].In a generalized estimating equations longitudinal model, a doubling of the Se level was associated with a 56% higher odds of having depressive symptoms at an exam. Contrary to previously reported findings related to mood, higher level of Se exposure was associated with presence of elevated depressive symptoms. More research is needed to elucidate the role of Se in depressive disorders[43].Recent research opens new avenues for the potential development of Se containing compounds as preventive or therapeutic agents in psychiatric and neurological conditions. Healthy nutrition and possibly mineral supplementations should be a part of the treatment plan of adolescents with alcohol use disorders especially when alcohol misuse is comorbid with depression[44].

Deficiencies of folate, vitamin B12, iron, Zn and Se tend to be more common among depressed than nondepressed persons. Dietary antioxidants have not been studied rigorously in relation to depression. Childbearing-aged women are particularly vulnerable to the adverse effects of poor nutrition on mood because pregnancy and lactation are major nutritional stressors to the body. The depletion of nutrient reserves throughout pregnancy and a lack of recovery postpartum may increase a woman's risk of depression. Prospective research studies are needed to clarify the role of nutrition in the pathophysiology of depression among childbearing-aged women. Greater attention to nutritional factors in mental health is warranted given that nutrition interventions can be inexpensive, safe, easy to administer, and generally acceptable to patients[45].

11. SELENIUM AND PCOS

Decreased plasma concentrations of Se and a negative correlation between Se and LH, tT in women with polycystic ovary syndrome (PCOS) have been observed indicating that Se may play a role in the pathogenesis of PCOS related with hyperandrogenism[46].Se supplementation could be effective on reproductive outcomes, biomarkers of inflammation and OS among women with PCOS. Se supplementation for 8 weeks among PCOS women had beneficial effects on reproductive outcomes, DHEA, hs-CRP and MDA levels[47]. The lipid peroxidation level was lower in the CPZ and Se groups than that in the PCOS group although GSH and GSH-Px values were higher in the treatment with Se and CPZ suggesting the importance of Ca(2+) influx into the neutrophils through TRPV1 channels in the pathogenesis of the patients with PCOS. The Se appeared to provide a protective effect against oxidative stress and Ca(2+) entry through modulation of neutrophil TRPV1 calcium channels[48].Se supplementation in PCOS patients may worsen IR in them. Until the results of larger studies become available, indiscriminate consumption of Se supplements in PCOS patients will warrant caution[49].

12. SELENIUM AND INFERTILITY

Se is incorporated in the sperm mitochondria capsule and may thus affect the behavior and function of the spermazoon. Se seems to be essential for normal spermatozoa development in both experimental animals and in livestock and probably

also in humans. Regarding Se and female fertility only sparse information exists. In experimental animals a low Se level affects fertility in males, but little attention has been devoted to female reproductive performance and the data are insufficient for conclusion. The optimal sperm Se concentration waits to be defined. Some evidence indicates that a metabolic defect in a Seincorporation into sperm cells may be associated with human infertility. No human data relating Se to female infertility are available[50].The semen Se level appears to be a useful indicator of Se status versus reproductive function. Further studies are warranted concerning the general aspects of metabolism and mechanism of action of Se in infertile couples before any therapeutic modification of intake of this element can be contemplated[51].

Supplemental Se and vitamin E may improve semen quality and have beneficial and protective effects, especially on sperm motility. It is important to analyse their use for the treatment of idiopathic male infertility diagnosed with asthenoteratospermia or asthenospermia in semen analysis[52].Clinical data have pointed to a correlation between abnormal PHGPx content in sperm and disturbance of human male fertility. However, additional evidence is still required to draw any definitive conclusions about therapeutical strategies for improving fertility by Seadministration[53].A strong correlations were observed between serum levels of Zn and Se, a negative correlation between serum levels of testosterone and Zn and a strong positive correlation between serum testosterone and Se in the infertile males and hence there is a relationship between the serum levels of Zn, Se and testosterone in infertile males and that these parameters be considered when investigating cases of infertility in males[54].

13. SELENIUM AND LIVER DISEASES

Dietary assessment of patients with primary biliary cirrhosis and low serum Se levels did not show a reduced dietary intake, confirming that Se levels are low in liver disease irrespective of aetiology and suggest that these low levels are more likely to be related to overall nutritional status than to dietary intake[55].Some authors have reported increased hepatic lipoperoxidation and decreased hepatocellular glutathione levels in animals consuming ethanol. It is hypothesized that the low levels of Se and Zn, in combination with the reported glutathione depletion, makes the hepatocytes more vulnerable toward the toxicity of ethanol[56].Serum Se levels differ in male and female populations. In healthy men, the level of Se in the serum is higher. Antioxidative activity measured by serum Se level is low in men with chronic alcoholic liver disease (during the abstinence period). Increased Se level in the hair may indicate the presence of certain antioxidative reserve, which requires further studies[57].

Patients with hepatitis, serum total cholesterol levels showed a significant correlation with serum Se concentrations demonstrating the important role of Se as an antioxidant agent; similarly, Gamma-Glutamic-Transferase (GGT) levels were significantly correlated with the serum Se levels indicating that when the intensity of the hepatic injury increases (enhancement in serum GGT levels) concomitantly the serum Se levels decrease significantly. No significant relationships between serum Se levels and sex or age of patients were observed[58]. A significant loss of Se from spleen was also accompanied by an increase in its weight. Weights of lungs, testis and kidney, however, were not affected by thioacetamide and there was no change in their Se content. Plasma Sewere significantly reduced in the thioacetamide treated group. All these changes were confirmed to be due to selenium deficiency caused by thioacetamide, as supplementation with Se reversed these changes. The mode of action of Se is unknown but may involve anti-oxidant defense[59].

The use of vegetable oil/fat was also associated with higher Se levels and its was associated with the severity of liver injury in people even in patients who did not exhibit signs and symptoms of CLD.Serum Se level is strongly associated with the severity of liver damage in people with CLD from the early stage on[60].Serum Se levels are drastically decreased in alcoholic liver disease patients, showing that this element has a direct correlation with GPx activity, and lipid oxidation, suggesting that the serum Se/MDA ratio could be an indicator of hepatic damage caused by alcohol consumption, and pointing to Se as a possible antioxidant therapy[61].

14. SELENIUM AND IMMUNOLOGY

The notion that Se "boosts" the immune system has been supported by studies involving aging immunity or protection against certain pathogens. However, studies examining the effects of Se status on other types of immunity such as antiparasitic responses or allergic asthma have suggested more Se may not always be beneficial. Overall, determining how Se intake differentially affects various types of immune responses and dissecting the mechanisms by which this occurs will lead to a better utilization of Se-supplementation for human diseases involving the immune system[62].

Se as an essential component of selenocysteine-containing protein is involved in most aspects of cell biochemistry and function. As such, there is much potential for Se to influence the immune system. The antioxidant GPX are likely to protect neutrophils from oxygen-derived radicals that are produced to kill ingested foreign organisms. When the functions of all selenoproteins are described, only then will it be possible to fully understand their role in maintaining optimal immune function[63].Elevated Se intake may be associated with reduced cancer risk and may alleviate other pathological conditions including OS and inflammation. She appears to be a key nutrient in counteracting the development of virulence and inhibiting HIV progression to AIDS. It is required for sperm motility and may reduce the risk of miscarriage. Se deficiency has been linked to adverse mood states and some findings suggest that Se deficiency may be a risk factor in CVD[64].

15. SELENIUM AND INFECTIOUS DISEASES

Se status may affect the function of cells of both adaptive and innate immunity. SupranutritionalSe promotes proliferation and favors differentiation of naive CD4-positive T lymphocytes toward T helper 1 cells, thus supporting the acute cellular immune response, whereas excessive activation of the immune system and ensuing host tissue damage are counteracted through directing macrophages toward the M2 phenotype. Data from epidemiologic studies and intervention trials, with Se alone or in combination with other micronutrients, and animal experiments are needed against the background of dietary Se requirements to alter immune functions[65].

Additional data from large clinical trials that provide the highest level of evidence will be key to determining the benefits accrued at various Se intake levels. When the strength of the evidence becomes sufficient, clinical health professionals will need to use dietary and clinical assessment methods to ensure that people at increased risk for cancer or inflammatory and infectious diseases can be appropriately advised about Seintake[66].Some cohort studies have shown an association between Se deficiency and progression to AIDS or mortality. In several randomized controlled trials, Se supplementation has reduced hospitalizations and diarrheal morbidity, and improved CD4(+) cell counts, but the evidence remains mixed. Additional trials are recommended to study the effect of Se supplementation on opportunistic infections, and other HIV disease-related comorbidities in the context of highly active antiretroviral therapy in both developing and developed countries[67].

16. SELENIUM AND ENDOCRINE SYSTEMS

Micronutrients, mostly iodine and Se, are required for thyroid hormone synthesis and function. Sedeficiency can exacerbate the effects of iodine deficiency and the same is true for vitamin A or iron deficiency. Substances introduced with food, such as thiocyanate and isoflavones or certain herbal preparations, can interfere with micronutrients and influence thyroid function[68].

Several studies have investigated the potential positive effects of Se supplementation in thyroid diseases, characterized by increased levels of hydrogen peroxide and free radicals, like autoimmune chronic thyroiditis. These studies have supplied evidences indicating that Se supplementation, maximizing the antioxidant enzymes activity, may reduce the thyroid inflammatory status. Then, it may be postulated that Se could play a therapeutical role in thyroid autoimmune diseases. Despite the fact that recent studies seem to be concordant about Se beneficial effects in decreasing thyroid peroxidase antibodies (TPOAb) titers and ameliorating the ultrasound echogenicity pattern, several doubts have to be still clarified, before advising Se supplementation in chronic autoimmune thyroiditis[69].No significant correlation was found between iodine and Cu level.Se and Zn deficiency may accompany iodine deficiency and hence. Se and zinc deficiency should be considered in individuals who are found to have iodine deficiency especially in endemic goitre regions[70].

No obvious effect of Se status is found on the development of thyroid dysfunction in these three areas. But Se deficiency can impair thyroid function by means of disturbing thyroid hormone metabolism and decreasing antioxidant ability of the thyroid[71].The effects of Zn and Se supplementation on thyroid function of overweight or obese female hypothyroid patients in a double-blind, randomized controlled trial showed no significant alterations were found in serum Zn or Se concentrations. Mean serum FT3 increased significantly in the ZS and ZP groups but this effect was significant in the ZP group compared to those in SP or PP groups. Mean serum FT4 increased and TSH decreased significantly in the ZS group. TT3 and TT4 decreased significantly in the SP group. Mean FT3:FT4 ratio was augmented significantly in the ZP group. No significant treatment effects were found for TT3, FT4, TT4, or TSH between groups. This study showed some evidence of an effect of Zn alone or in combination with Se on thyroid function of overweight or obese female hypothyroid patients[72].

17. CONCLUSIONS

This review article has brought into a nutshell the various research findings of the clinical usefulness of selenium for human health and diseases. Its beneficial role has been extensively studied in DM, obesity, IR, OS, cardiac, liver, renal, reproductive, psychiatric, neurologic and endocrine disorders. Both beneficial and toxic effects for all the above diseases have been highlighted in all the studies done during the last two decades. Further studies are conducted inthis field and the contents of this review article will be very useful for future researchers to undertake more studies with diverse population to establish solid diagnostic strategies and to include selenium as one of the laboratory tests to evaluate and workout supplementation protocols for each type of diseases.

REFERENCES

[1] Mueller AS, Mueller K, Wolf NM, Pallauf J. Selenium and diabetes: an enigma?Free Radic Res. 2009;43(11):1029-59.

[2] Rayman MP, Stranges S. Epidemiology of selenium and type 2 diabetes: can we make sense of it?Free RadicBiol Med. 2013;65:1557-64.

[3] Mao S, Zhang A, Huang S. Selenium supplementation and the risk of type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Endocrine. 2014;47(3):758-63.

[4] Holger Steinbrenner, BodoSpeckmann, Antonio Pinto and Helmut Sies· High selenium intake and increased diabetes risk: experimental evidence for interplay between selenium and carbohydrate metabolism. J ClinBiochemNutr. 2011; 48(1): 40–45.

[5] Quilliot D, Dousset B, Guerci B, Dubois F, Drouin P, Ziegler O.Evidence that diabetes mellitus favors impaired metabolism of zinc, copper, and selenium in chronic pancreatitis. Pancreas. 2001;22(3):299-306.

[6] Ruíz C, Alegría A, Barberá R, Farré R, Lagarda J. Selenium, zinc and copper in plasma of patients with type 1 diabetes mellitus in different metabolic control states. J Trace Elem Med Biol. 1998;12(2):91-5.

[7] Kljai K, Runje R. Selenium and glycogen levels in diabetic patients. Biol Trace Elem Res. 2001;83(3):223-9.

[8] Savory LA, Kerr CJ, Whiting P, Finer N, McEneny J, Ashton T. Selenium supplementation and exercise: effect on oxidant stress in overweight adults. Obesity (Silver Spring). 2012;20(4):794-801.

[9] Kim JE, Choi SI, Lee HR, Hwang IS, Lee YJ, An BS, Lee SH, Kim HJ, Kang BC, Hwang DY. Selenium significantly inhibits adipocyte hypertrophy and abdominal fat accumulation in OLETF rats via induction of fatty acid β-oxidation. Biol Trace Elem Res. 2012;150(1-3):360-70.

[10] Brenneisen P, Steinbrenner H, Sies H. Selenium, oxidative stress, and health aspects. Mol Aspects Med. 2005;26(4-5):256-67.

[11] Galan-Chilet I, Tellez-Plaza M, Guallar E, De Marco G, Lopez-Izquierdo R, Gonzalez-Manzano I, Carmen Tormos M, Martin-Nuñez GM, Rojo-Martinez G, Saez GT, Martín-Escudero JC, Redon J, Javier Chaves F. Plasma selenium levels and oxidative stress biomarkers: a gene-environment interaction population-based study. Free RadicBiol Med. 2014;74:229-36.

[12] Gorozhanskaia ÉG, Sviridova SP, Dobrovol'skaia MM, Zybrikhina GN, KashniaShR. [Selenium and oxidative stress in cancer patients]. Biomed Khim. 2013;59(5):550-62.

[13] Nazıroglu M. Role of selenium on calcium signaling and oxidative stress-induced molecular pathways in epilepsy. Neurochem Res. 2009;34(12):2181-91.

[14] Wang X, Zhang W, Chen H, Liao N, Wang Z, Zhang X, Hai C. High selenium impairs hepatic insulin sensitivity through opposite regulation of ROS. ToxicolLett. 2014;224(1):16-23.

[15] Himoto T, Yoneyama H, Kurokohchi K, Inukai M, Masugata H, Goda F, Haba R, Watababe S, Kubota S, Senda S, Masaki T. Selenium deficiency is associated with insulin resistance in patients with hepatitis C virus-related chronic liver disease. Nutr Res. 2011;31(11):829-35.

[16] Zeng MS, Li X, Liu Y, Zhao H, Zhou JC, Li K, Huang JQ, Sun LH, Tang JY, Xia XJ, Wang KN, Lei XG.A high-selenium diet induces insulin resistance in gestating rats and their offspring. Free RadicBiol Med. 2012;52(8):1335-42.

[17] Farrokhian A, Bahmani F, Taghizadeh M, Mirhashemi SM, Aarabi MH, Raygan F, Aghadavod E, Asemi Z. Selenium Supplementation Affects Insulin Resistance and Serum hs-CRP in Patients with Type 2 Diabetes and Coronary Heart Disease. HormMetab Res. 2016. [Epub ahead of print]

[18] Mao J, Bath SC, Vanderlelie JJ, Perkins AV, Redman CW, Rayman MP. No effect of modest selenium supplementation on insulin resistance in UK pregnant women, as assessed by plasma adiponectin concentration. Br J Nutr. 2016;115(1):32-8.

[19] Kim HN, Song SW. Concentrations of chromium, selenium, and copper in the hair of viscerally obese adults are associated with insulin resistance. Biol Trace Elem Res. 2014;158(2):152-7.

[20] Iglesias P, Selgas R, Romero S, Díez JJ. Selenium and kidney disease. J Nephrol. 2013;26(2):266-72.

[21] Eaton CB, Abdul Baki AR, Waring ME, Roberts MB, Lu B. The association of low selenium and renal insufficiency with coronary heart disease and all-cause mortality: NHANES III follow-up study. Atherosclerosis. 2010;212(2):689-94.

[22] Yu RA, Xia T, Wang AG, Chen XM. Effects of selenium and zinc on renal oxidative stress and apoptosis induced by fluoride in rats. Biomed Environ Sci. 2006;19(6):439-44.

[23] Makropoulos W, Heintz B, Stefanidis I. Selenium deficiency and thyroid function in acute renal failure. Ren Fail. 1997;19(1):129-36.

[24] Shanu A, Groebler L, Kim HB, Wood S, Weekley CM, Aitken JB, Harris HH, Witting PK. Selenium inhibits renal oxidation and inflammation but not acute kidney injury in an animal model of rhabdomyolysis. Antioxid Redox Signal. 2013;18(7):756-69.

[25] Zima T, Tesar V, Mestek O, Nemecek K. Trace elements in end-stage renal disease. 2. Clinical implication of trace elements. Blood Purif. 1999;17(4):187-98.

[26] Vieira ML, Fonseca FL, Costa LG, Beltrame RL, Chaves CM, Cartum J, Alves SI, Azzalis LA, Junqueira VB, Pereria EC, Rocha KC. Supplementation with selenium can influence nausea, fatigue, physical, renal, and liver function of children and adolescents with cancer. J Med Food. 2015;18(1):109-17.

[27] Turan B, Saini HK, Zhang M, Prajapati D, Elimban V, Dhalla NS. Selenium improves cardiac function by attenuating the activation of NF-kappaB due to ischemia-reperfusion injury. Antioxid Redox Signal. 2005;7(9-10):1388-97.

[28] Saito Y, Hashimoto T, Sasaki M, Hanaoka S, Sugai K. Effect of selenium deficiency on cardiac function of individuals with severe disabilities under long-term tube feeding.Dev Med Child Neurol. 1998;40(11):743-8.

[29] Gemma Flores-Mateo, Ana Navas-Acien, Roberto Pastor-Barriuso and EliseoGuallar.Selenium and coronary heart disease: a meta-analysis. Am J ClinNutr. 2006; 84(4): 762–773.

[30] Rannem T, Ladefoged K, Hylander E, Christiansen J, Laursen H, Kristensen JH, Linstow M, Beyer N, Liguori R, Dige-Petersen H, et al. The effect of selenium supplementation on skeletal and cardiac muscle in selenium-depleted patients. JPEN J Parenter Enteral Nutr. 1995;19(5):351-5.

[31] Rederstorff M, Krol A, Lescure A. Understanding the importance of selenium and selenoproteins in muscle function. Cell Mol Life Sci. 2006;63(1):52-9.

[32] Carina Benstoem, Andreas Goetzenich, Sandra Kraemer, Sebastian Borosch, William Manzanares, Gil Hardy and Christian Stoppe. Selenium and Its Supplementation in Cardiovascular Disease—What do We Know? Nutrients. 2015; 7(5): 3094–3118.

[33] Mirone M, Giannetta E, Isidori AM. Selenium and reproductive function. A systematic review. J Endocrinol Invest. 2013;36(10):28-36.

[34] Ahsan U, Kamran Z, Raza I, Ahmad S, Babar W, Riaz MH, Iqbal Z. Role of selenium in male reproduction - a review. AnimReprod Sci. 2014;146(1-2):55-62.

[35] Mistry HD , Broughton Pipkin F , Redman CW , Poston L .Selenium in reproductive health.American Journal of Obstetrics and Gynecology. 2012; 206(1):21-30.

[36] Yakubov E, Buchfelder M, Eyüpoglu IY, Savaskan NE. Selenium action in neuro-oncology. Biol Trace Elem Res. 2014;161(3):246-54.

[37] Dominiak A, Wilkaniec A, Wroczyński P, Adamczyk A. Selenium in the Therapy of Neurological Diseases. Where is it Going? CurrNeuropharmacol. 2016;14(3):282-99.

[38] S al-Deeb, K al-Moutaery, G W Bruyn, and M Tariq. Neuroprotective effect of selenium on iminodipropionitrile-induced toxicity. J Psychiatry Neurosci. 1995; 20(3): 189–192.

[39] Reisinger J, Höllinger K, Lang W, Steiner C, Winter T, Winter A, Mori M, Lindorfer A, Kiblböck D, SiostrzonekP.Does early administration of selenium improve neurological outcome after cardiac arrest? Am J Emerg Med. 2009;27(2):176-81.

[40] WhangerPD.Selenium and the brain: a review. NutrNeurosci. 2001;4(2):81-97.

[41] A Shahar, KV Patel, RD Semba, S Bandinelli, DR Shahar, L Ferrucci and JM Guralnik.Plasma selenium is positively related to performance in neurological tasks assessing coordination and motor speed. MovDisord. 2010; 25(12): 1909–1915.

[42] Benton D, Cook R. The impact of selenium supplementation on mood. Biol Psychiatry. 1991;29(11):1092-8.

[43] Laura A Colangelo, Ka He, Mary A Whooley, Martha L. Daviglus, Steven Morris and Kiang Liu.Selenium exposure and depressive symptoms: the Coronary Artery Risk Development in Young Adults Trace Element Study. Neurotoxicology. 2014; 41: 167–174.

[44] Sher L. Depression and suicidal behavior in alcohol abusing adolescents: possible role of selenium deficiency. Minerva Pediatr. 2008;60(2):201-9.

[45] Lisa M. Bodnar and Katherine L. WisnerNutrition and Depression: Implications for Improving Mental Health Among Childbearing-Aged Women. Biol Psychiatry. 2005; 58(9): 679–685.

[46] Coskun A, Arikan T, Kilinc M, Arikan DC, Ekerbiçer HÇ. Plasma selenium levels in Turkish women with polycystic ovary syndrome. Eur J ObstetGynecolReprod Biol. 2013;168(2):183-6.

[47] Razavi M, Jamilian M, Kashan ZF, Heidar Z, Mohseni M, Ghandi Y, Bagherian T, Asemi Z. Selenium Supplementation and the Effects on Reproductive Outcomes, Biomarkers of Inflammation and Oxidative Stress in Women with Polycystic Ovary Syndrome. HormMetab Res. 2016;48(3):185-90.

[48] Köse SA, Nazıroğlu M. Selenium reduces oxidative stress and calcium entry through TRPV1 channels in the neutrophils of patients with polycystic ovary syndrome. Biol Trace Elem Res. 2014;158(2):136-42.

[49] Mohammad Hosseinzadeh F, Hosseinzadeh-Attar MJ, Yekaninejad MS, Rashidi B. Effects of selenium supplementation on glucose homeostasis and free androgen index in women with polycystic ovary syndrome: A randomized, double blinded, placebo controlled clinical trial. J Trace Elem Med Biol. 2016;34:56-61.

[50] Hansen JC, Deguchi Y. Selenium and fertility in animals and man--a review. Acta Vet Scand. 1996;37(1):19-30.

[51] Bleau G, Lemarbre J, Faucher G, Roberts KD, Chapdelaine A. Semen selenium and human fertility. FertilSteril. 1984;42(6):890-4.

[52] Moslemi MK, Tavanbakhsh S. Selenium-vitamin E supplementation in infertile men: effects on semen parameters and pregnancy rate. Int J Gen Med. 2011 Jan 23;4:99-104.

[53] Boitani C, Puglisi R. Selenium, a key element in spermatogenesis and male fertility. AdvExp Med Biol. 2008;636:65-73.

[54] Oluboyo AO, Adijeh RU, Onyenekwe CC, Oluboyo BO, Mbaeri TC, Odiegwu CN, Chukwuma GO, Onwuasoanya UF. Relationship between serum levels of testosterone, zinc and selenium in infertile males attending fertility clinic in Nnewi, south east Nigeria. Afr J Med Med Sci. 2012;41:51-4.

[55] Thuluvath PJ, Triger DR. Selenium in chronic liver disease. J Hepatol. 1992;14(2-3):176-82.

[56] Aaseth J, Smith-Kielland A, Thomassen Y. Selenium, alcohol and liver diseases. Ann Clin Res. 1986;18(1):43-7.

[57] Jabłońska-Kaszewska I, Swiatkowska-Stodulska R, Łukasiak J, Dejneka W, Dorosz A, Dabrowska E, FalkiewiczB.Serum selenium levels in alcoholic liver disease. Med SciMonit. 2003;9(3):15-8.

[58] Navarro-Alarcón M, López-Ga de la Serrana H, Pérez-Valero V, López-Martínez MC. Selenium concentrations in serum of individuals with liver diseases (cirrhosis or hepatitis): relationship with some nutritional and biochemical markers. Sci Total Environ. 2002;291(1-3):135-41.

[59] Al-Bader A, Abul H, Hussain T, Al-Moosawi M, Mathew TC, Dashti H. Selenium and liver cirrhosis. Mol Cell Biochem. 1998;185(1-2):1-6.

[60] Petrovski BÉ, Pataki V, Jenei T, Adány R, Vokó Z. Selenium levels in men with liver disease in Hungary. J Trace Elem Med Biol. 2012;26(1):31-5.

[61] Rua RM, Ojeda ML, Nogales F, Rubio JM, Romero-Gómez M, Funuyet J, Murillo ML, Carreras O. Serum selenium levels and oxidative balance as differential markers in hepatic damage caused by alcohol. Life Sci. 2014;94(2):158-63.

[62] Hoffmann PR, Berry MJ. The influence of selenium on immune responses. MolNutr Food Res. 2008;52(11):1273-80.

[63] Arthur JR, McKenzie RC, Beckett GJ. Selenium in the immune system. J Nutr. 2003;133(5 -1):1457S-9S.

[64] Ferencík M, Ebringer L. Modulatory effects of selenium and zinc on the immune system. Folia Microbiol (Praha). 2003;48(3):417-26.

[65] Steinbrenner H, Al-Quraishy S, Dkhil MA, Wunderlich F, Sies H. Dietary selenium in adjuvant therapy of viral and bacterial infections. AdvNutr. 2015;6(1):73-82.

[66] Ryan-Harshman M, Aldoori W. The relevance of selenium to immunity, cancer, and infectious/inflammatory diseases. Can J Diet Pract Res. 2005;66(2):98-102.

[67] Stone CA, Kawai K, Kupka R, Fawzi WW. Role of selenium in HIV infection. Nutr Rev. 2010;68(11):671-81.

[68] Triggiani V, Tafaro E, Giagulli VA, Sabbà C, Resta F, Licchelli B, Guastamacchia E. Role of iodine, selenium and other micronutrients in thyroid function and disorders. EndocrMetab Immune Disord Drug Targets. 2009;9(3):277-94.

[69] Roberto Negro.Selenium and thyroid autoimmunity. Biologics. 2008; 2(2): 265–273.

[70] TanjuÇelik, NazanSavaş, SelimKurtoğlu, ÖzlemSangün, ZekiAydın, Didin Mustafa, OktayHasanÖztürk,SeherMısırlıoğlu and Murat Öktem. Iodine, copper, zinc, selenium and molybdenum levels in children aged between 6 and 12 years in the rural area with iodine deficiency and in the city center without iodine deficiency in Hatay. Turk PediatriArs. 2014; 49(2): 111–116.

[71] Tong YJ, Teng WP, Jin Y, Li YS, Guan HX, Wang WB, Gao TS, Teng XC, Yang F, Shi XG, Chen W, Man N, Li Z, Guo XJ. An epidemiological study on the relationship between selenium and thyroid function in areas with different iodine intake. Zhonghua Yi XueZaZhi. 2003;83(23):2036-9.

[72] Mahmoodianfard S, Vafa M, Golgiri F, Khoshniat M, Gohari M, Solati Z, Djalali M. Effects of Zinc and Selenium Supplementation on Thyroid Function in Overweight and Obese Hypothyroid Female Patients: A Randomized Double-Blind Controlled Trial. J Am CollNutr. 2015;34(5):391-9.