Introduction

Selenium (Se) is one of the key elements of proteins, so-called selenoproteins. These proteins with enzymatic activity are necessary for metabolic processes in multiple tissues and systems. Se participates in the metabolism of cells of myocardium, skeletal muscle, thyroid, brain, gastrointestinal tract, liver, kidney, endothelium and others ***(Huang et al., 2011).***

Selenium is a trace mineral with important structural andenzymatic roles, found in minute quantities within the body.The main dietary sources of selenium are from bread, cereals,fish, and meat; Brazil nuts contain the highest quantity ofSelenium per gram***(National Institute of Health: Office of DietarySupplements.Selenium.http://dietarysupplements.info. nih.gov/factsheets/selenium.asp Accessed December 2008).***

Se also plays an important rolein cellular immunity. Se deficiency has beenassociated with a higher incidence of malignant growth and the progression of HIV infection ***(Fainveather et al., 2011).***

Plasma selenium levels appear to be astrong predictor of outcome in HIV disease and seleniumsupplementation appears to inhibit the progression of HIVdisease to AIDS and prevents HIV replication***(Rayman, 2000).***

It is important to know that Critical illness is characterized by hyperinflammation, cellular immune dysfunction, oxidative stress and mitochondrial dysfunction***(Brealey et al., 2002).***

In critically ill patients, plasma selenium levels fall duringperiods of oxidative stress as occurs with severe sepsis and thesystemic inflammatory response syndrome (SIRS) and there isincreasing evidence that selenium may be an importantadjuvant therapy possibly offering a mortality benefit topatients with severe sepsis***(Strachan and Wyncoll, 2009).***

Trace elements, such as copper, manganese, zinc, iron and selenium are required for the activity of superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx), respectively. In addition, the non-enzymatic defense mechanisms include endogenous molecules (that is, glutathione, Albumin) and vitamins (such as E, C and b -carotene) ***(Berger, 2005).***

Low levels of endogenous vitamins and trace elements in SIRS are due to escape to the interstitial compartment by capillary leakage, hemodilution, previous insufficient intake, and continuous renal replacement therapies (CRRT) ***(Berger, 2006).***

In the critically ill, the most severecases of SIRS are associated with the most severe antioxidantdepletion ***(Berger and Chiólero, 2007).***

The antioxidant endogenous defense system in humans consists of a variety of extracellular and intracellular antioxidants

which are able to protect tissues from reactive oxygen species (ROS) and reactive nitrogen species (RNS) induced injury ***(Berger, 2005).***

Evidence suggests that ROS production increases expression of proinflammatorycytokines through upregulation of nuclear factor–kappaB (NF-κB) activity. Lymphocytes, macrophages, and especiallyneutrophils require ROS and proinflammatory moleculesfor activation, differentiation, and phagocytosis. Depressed Selevels are associated with fewer natural killer cells***(Forman and Torres, 2002).***

On theother hand, when incorporated into the various selenoenzymes,Se acts as a crucial antioxidant influencing the inflammatorysignaling pathways that modulate ROS by inhibiting activationof the NF-κB cascade and thus suppressing the production ofinterleukins and tumor necrosis factor–α (TNF-α) ***(Steinbrenner and Sies, 2009).***

Se deficiencylowers antioxidant activity and thereby impairs free radical neutralization**.** Consequently, Se is arguably one ofthe cornerstones of the body's antioxidant defense systems inacute critical illness ***(Heyland et al., 2005).***

Aim of the Work

The aim of the work is to review Selenium in critical illness and its role in affecting morbidity and mortality of the critically ill patient.

The objective of the work is to determine role of Selenium as an anti-inflammatory, immuo-modulator and antioxidant in different clinical situations in critical care and its effect on the outcome of the patient.

Chapter (1):
Selenium Functions and Metabolism

Food sources and selenium species:

The amount of selenium in the diet largely depends on where crops are grown and cultivated, the soil to which animals are exposed, and the actual foods consumed. The main food groups providing selenium in the diet are bread and cereals, meat, fish, eggs, and milk (dairy products). Some Brazil nuts are a particularly rich source, with selenium concentrations ranging from 0.03–512mg/kg fresh weight (Figure 1)***(Rayman et al., 2008).***

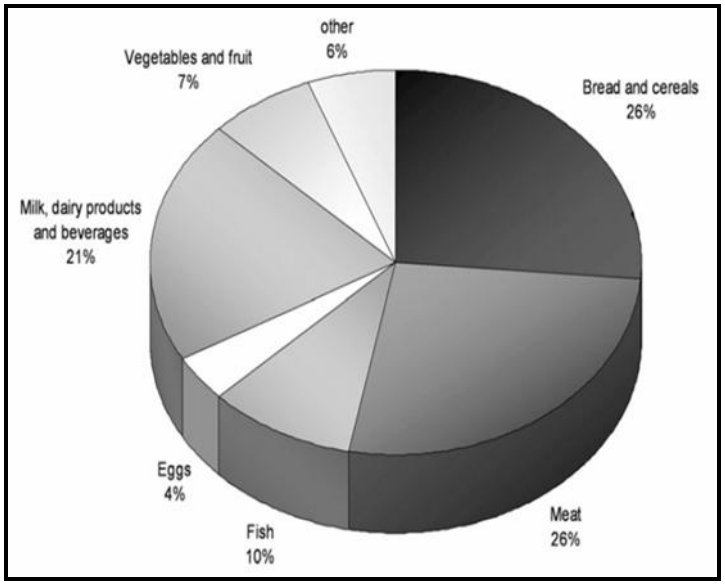

Figure (1): Food sources of Selenium***(Susan et al., 2011)***

1. **Bread and cereals**: The selenium content of bread and cereals can vary widely from 0.01–30mg/kg. On average, bread and cereals provide a quarter of the selenium intake in the UK. The predominant species of selenium in wheat and bread are selenomethionine (usually 55%– 85%), selenocysteine (4%–12%), and selenite (12%–19%) (Figure 2)***(Wolf and Goldschmidt, 2007)***.

2. **Meat, fish, and eggs**: The selenium content of meat depends on many factors. Offal contains relatively high levels of selenium, in particular liver and kidneys; the selenium concentrations of kidney, liver, and heart tissue from beef were 4.5, 0.93, and 0.55mg/kg, respectively, whereas muscle was in the region of 0.2mg/kg ***(Juniper et al., 2008).***

Supplementation of cattle with selenium-enriched yeast increased muscle selenium concentration to 0.6mg/kg ***(Juniper et al., 2008)***.

In the United States, the average selenium content of chicken is 0.2mg/kg and beef 0.25–0.3mg/kg ***(U.S. Department of Agriculture, Agricultural Research Service, 2010).***

Meat generally provides a relatively large proportion of the selenium intake in omnivorous populations, and in the UK, it provides one quarter of the total estimated intake. The predominant species of selenium in edible portions of meat may

be selenomethionine (50%–60% of total extractable selenium species) and selenocysteine (20%–31% and 50% of total extractable selenium species in chicken and lamb, respectively. However, the total content and species depends mainly on the animals' diet (Figure 2)***(Bierla et al., 2008)***.

The selenium content in fish is between 0.1 and5.0mg/kg; some marine fish are relativelyhigh in selenium; for example, the selenium content of cod,shark, and canned tuna is 1.5, 2.0, and 5.6mg/kg, respectively**(Fairweather-Tait, 2010).**

In the UK, the average selenium content offish is 0.42mg/kg ***(Food Standards Agency, 2009).***

The main selenium species in fishare selenomethionine (29%–70%) and selenite/selenate (12%–45%) with the species profile differing betweenfish species and the total selenium content (Figure 2)***(Fairweather-Tait, 2010).***

Hens' eggs contain from 3 to 25 mg selenium per whole egg. Selenium supplementation of the hen's diet mayincrease the selenium content of eggs to 0.34–0.58mg/kg**.**Selenium-enriched eggs are widely produced around the world. The main selenium species in eggs are selenocysteine,selenomethionine, and possibly selenite, withselenomethionine and selenocysteine as the predominantspecies (>50%) in egg white and egg yolk, respectively(Figure 2)**(Lipiecet al., 2010).**

3. Milk, dairy products, and beverages: The selenium

content of milk and dairy products varies widely; in the UK, milk and dairy products contain 0.01–0.03mg/kg selenium. The predominant selenium species in cows' milk are selenocysteine and selenite. Supplementation of dairy cows with selenium-enriched yeast alters the species profile in the milk and the major species after supplementation are selenocysteine, selenomethionine, and selenite ***(Muniz-Naveiro et al., 2007).***

4. **Fruit and vegetables**. Fruit and vegetables typicallycontain relatively small amounts of selenium. In unenrichedvegetables with low levels of selenium, the major speciesmay be, for example, selenate in onions,orselenomethionine(53%), g-glutamyl-Se-methyl-selenocysteine (31%),Se-methylselenocysteine (12%), and selenate (4%) in garlicwith natural selenium content of <0.5mg/kg ***(Kotrebai et al., 2000).***

However,certain vegetables, such as onions, garlic, and broccoli whengrown on selenium-rich soil can accumulate selenium, resulting in selenium-enrichment from <0.5mg/kg up to 140– 300mg/kg. The main selenium species in Se-enriched foodsuch as onions is g-glutamyl-Se-methylselenocysteine, accounting for 63% of the species, with a relatively smaller proportion of 10% selenate and 5% selenomethionine, plusother species ***(Hurstet al., 2010).***

In Se-enriched garlic, similar to Seonions, g-glutamyl-Se-

methylselenocysteine may be the predominant species (73%) with also 13% selenomethionine, 4% g-glutamyl-selenomethionine, 3% Se-methylselenocysteine and 2% selenate (Figure 2)***(Ipet al., 2000).***

Selenium-enriched broccolisprouts may contain predominantly Se-methylselenocysteine (45%) with smaller amounts (12%–20%) of selenate andselenomethionine, plus other species of selenium (e.g., adenosylselenohomocysteine)***(Finleyet al., 2001)***.

In summary, in vegetables such as broccoli, onions and garlic, the selenium species profile is variable depending on the total level of selenium enrichment, the forms of selenium used for enrichment, and the type of vegetable; predominant species in selenium-enriched vegetables analyzed to date are Se-methylselenocysteine or g-glutamyl-Se-methylselenocysteine; these forms of selenium in foods have received attention due to purported protection against cancer in animal models when compared with other forms of selenium ***(Finley, 2005).***

5. **Selenium-enriched foods**: The only permitted speciesof selenium added to foods for particular nutritional use inEurope, including baby formula milk and total parental nutritionfoods, are sodium selenate, sodium selenite, and sodium hydrogen selenite ***(Flynnet al., 2009).***

Whereas the predominantselenium species in most natural and unenriched foods is selenomethionine. Selenium-enrichment through fertilizationor feeding supplements to animals changes the seleniumspecies profile in some foods, for example, eggs,onions, garlic, and broccoli, but wheat andmeat tend to retain the predominant selenium species as selenomethionine***(Bierlaet al., 2008)***.

The selenium speciation of foodsand the effect of processing and cooking on thespecies profileis a priority for future research.

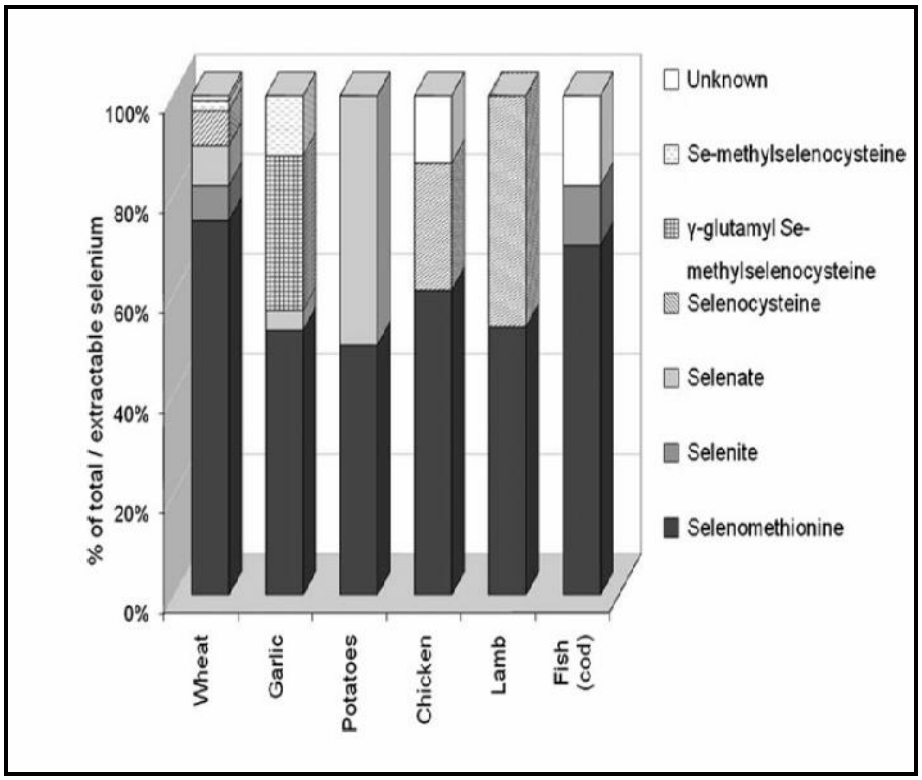

Figure (2): Selenium species in food***(Susan et al., 2011)***

Selenium Absorption and Metabolism

There is limited knowledge about the biochemical interconversionsinvolved in the metabolism of the different seleniumspecies in mammals, and information concerningtissue specificity of pathways remains scant.

The absorptionof selenium for assimilation and excretion through thesepathways potentially involvesmultiplemembrane transportmechanisms, but it is a topic that has received little attention to date ***(Susan et al., 2011).***

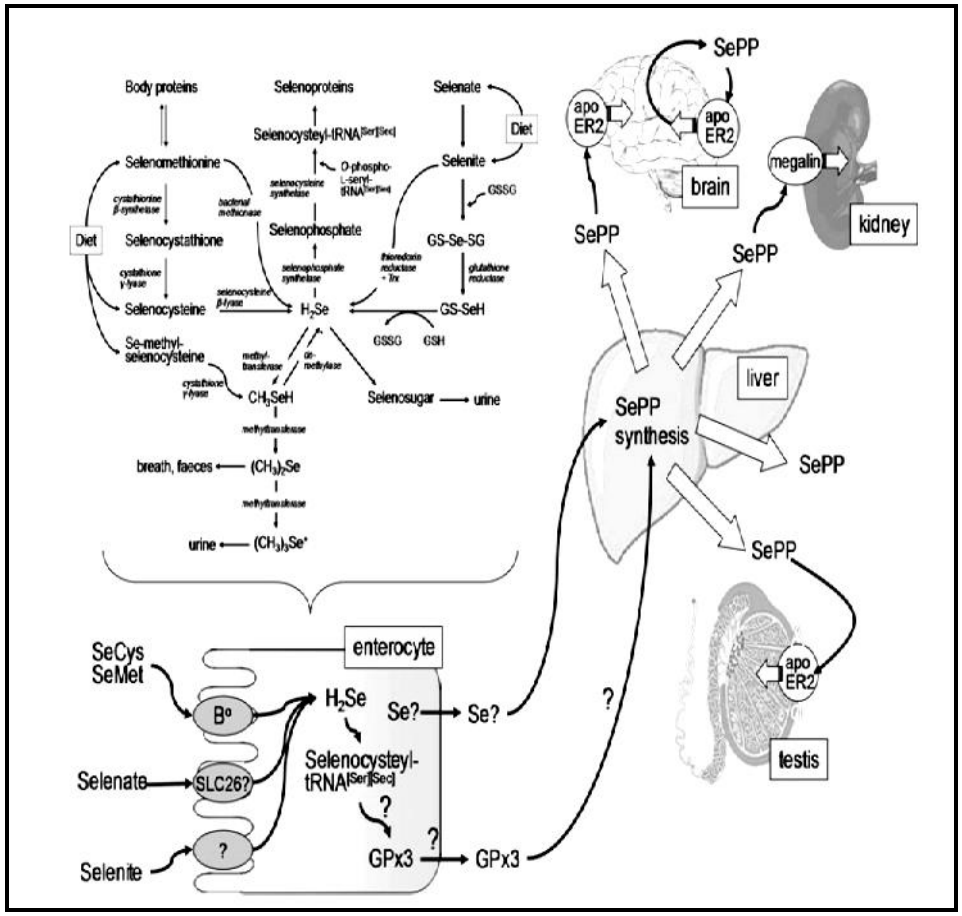

Figure (3): Selenium absorption and metabolism***(Susan et al., 2011)***

A. Absorption of dietary selenium

The identity of the transporter proteins responsible for theabsorption of dietary selenium remains uncertain. Membranetransport proteins with the capacity to mediate uptake oforganic forms of selenium have been identified on the basis ofquantification of the total selenium content of Xenopus laevisoocytes expressing individual transporters (from injectedin vitro-transcribed mRNA) and provided with different test substrates ***(Nickel, 2009)***.

B. The biochemical interconversion of selenium species

Assimilation of dietary selenium into selenoproteins occurs through a series of interconversions about which many details are still lacking. For clarity, selenide (H2Se) is considered as a central point in the metabolic interconversions of both organic and inorganic selenium compounds (Figure 3)***(Susan et al., 2011).***

Dietary selenomethionineis converted to selenocysteine (also obtained directlyfrom the diet, as is Se-methylselenocysteine) via the intermediateselenocystathionine through the action of cystathionineb-synthase and then cystathionine γ-lyase ***(Ohtaand Suzuki, 2008).***

Selenomethioninereleased through protein catabolic processes entersthe process of metabolic interconversion in the same way and unlike selenocysteine, is incorporated nonspecifically inplace of methionine into proteins, depending

on availability.Selenocysteine b-lyase releases selenide (H2Se) from selenocysteine***(Ohta and Suzuki, 2008*).**

Dietary Se-methylselenocysteine can be converted to methylselenol (CH3SeH) in a cystathioneγ -lyase-catalysed reaction**,**which can in turn be demethylated to produce selenide ***(Pinto et al., 2010).***

Selenite can be reduced to selenide directly through the action of thioredoxin reductase (TXNRD, (itself a selenoprotein)) plus thioredoxinor it can react with glutathione to form selenodiglutathione ***(Lu et al., 2009).***

Selenodiglutathione is a substrate for reduction to glutathioselenol by glutathione reductase ; glutathioselenolthen reacts with glutathione to yield selenide . Selenateis, presumably, assimilated into proteins through reduction toselenide via the same pathways; however, the mechanism forreduction of selenate to selenite remains unclear but may involvethe activity of TXNRD in the presence of glutathioneand thioredoxin ***(Lu et al., 2009).***

Further steps in the assimilation ofselenide into selenoproteins involve generation of the highlyreactive selenium donor selenophosphate through the activityof selenophosphate synthetaseand then incorporation ofselenium into selenocysteyl-tRNA through conversionof O-phospho-l-seryl-tRNA***(Ganichkin et al., 2008)***.

Selenide is also theintermediate metabolite for selenium excretion; at lower levelsof intake it is incorporated into selenosugar for excretion inurine, and at higher levels of intake methyltransferases add methyl groups sequentially to convert selenide to methylselenolthen dimethylselenide, which is excreted in the breathand in the feces, then trimethylselonium, which is excreted in the urine ***(Krittapholet al., 2010)***.

C. Systemic transport of Selenium

Plasma selenoprotein P (SePP) is the major circulating transport form of selenium, accounting for the majority of selenium in plasma up to 60, and is responsive tochanges in level ofdietary exposure***(Hurst et al., 2010)***.

SePP synthesis is reduced under conditions of dietaryselenium deficiency and plasma concentrations fall***(Burk and Hill, 2009).***

In humans, full-length SePP is a glycosylated protein of 366 amino acids. Approximately two-thirds of the molecule (amino acid residues 1–244) is folded into an N-terminal domain that includes one selenocysteine residue, whereas the smaller C-terminal domain includes nine selenocysteines, providing the selenium transport capacity ***(Burk and Hill, 2009)***.

Thiol-redox function has been attributedto the N-terminal domain, based on the presence of athioredoxin fold and on measured functional properties ***(Takebe et al., 2002).***

A noteable exception is the thyroid gland, for which mechanisms for prioritization of selenium supply appear to includeSePP-independent supply of selenium***(Schomburget al., 2006).***

Although SePPis expressed in most tissues, the current model is that SePPsynthesis in the liver incorporates selenium into SePP fordistribution to other tissues ***(Renkoet al., 2008)***.

Local SePP biosynthesisappears to be important in protecting the brain against seleniumloss under selenium-deficient conditions ***(Schweizeret al., 2005)***.

Uptake of SePP from the plasma into tissues, includingtestis, kidney, and brain, is emerging as a receptor-mediatedprocess. For example, mouse Sertoli cells were observed byimmunohistochemistry to contain SePP1-positive vesicles,and apolipoprotein E receptor-2 (apoER2) was found to beassociated with SePP in preparations of mouse testis ***(Olsonet al., 2007)***.

Another member of the lipoprotein receptor family—megalin(Lrp2)—is believed to mediate SePP uptake from the glomerular filtrate in the kidney ***(Olsonet al., 2005).***

In summary, the form in which absorbed dietary seleniumenters the portal circulation appears to have received little attention, and is likely to vary depending on the dietarysource (e.g., organic or inorganic).