

INTRODUCTION

Vitamins and trace elements are known as micronutrients. Vitamins are organic substances not synthesized by the body, and some are cofactors for various enzymes; therefore, they are required for normal metabolism. Trace elements are metals present in very small quantities in the body. They have various biological functions. Trace elements include: selenium (Se), zinc (Zn), iron (Fe), manganese (Mn), copper (Cu). There are 13 essential vitamins include 4 fat-soluble vitamins (A,D,E,K) and nine water-soluble vitamins (ascorbic acid, folate, niacin, riboflavin, thiamine, pyridoxine, cobalamine, pantothenic acid, biotin) are essential for catalyzing homeostatic reaction in human body (*Ozmen, 2010*).

Micronutrient deficiencies are often present in critically ill patients and may occur as a result of the underlying disease, inadequate or inappropriate administration during therapy, or increased losses or increased requirements due to the severe illness (*Taylor, 2010*).

Critically ill patients often develop systemic inflammatory response syndrome (SIRS) with the production

of various mediators, including cytokines which modulate the inflammatory response. SIRS is associated with marked increase in reactive oxygen species (ROS) levels in blood. Antioxidants enzymes such as superoxide dismutase, catalase and glutathione peroxidase that catalyze the breakdown of ROS need co-factors such as selenium, zinc, iron, vitamin E and Vitamin C (*Visser, 2010*).

Whatever the cause is, when the deficiencies occur, they affect various biochemical processes and enzymatic function, resulting in organ dysfunction, muscle weakness, poor wound healing, and altered immune functions, all of which carry deleterious patient outcomes (*Buchman et al., 2009*).

AIM OF THE WORK

This review aims to highlight the clinical significance of micronutrients and the detrimental effects of their imbalance in the critically ill patients.

Chapter 1

PHARMACOLOGY OF MICRONUTRIENTS

What are the micronutrients?

Micronutrients are nutrients required by humans and other organisms throughout life in small quantities to orchestrate a range of physiological functions. For people, they include dietary trace minerals in amounts generally less than 100 milligrams/day - as opposed to macrominerals which are required in larger quantities. The microminerals or trace elements include iron, copper, manganese, selenium and zinc. Micronutrients also include vitamins, which are organic compounds required as nutrients in tiny amounts by an organism (*Canadian UNICEF committee, 2006*).

1. Trace elements:

1.1. Selenium:

Several forms of selenium enter the body as part of amino acids within proteins. The two most common forms of the element that enter the body are selenomethionine and selenocysteine which are found mainly in plants and animals respectively (*Burk and Levander, 1999*).

- **Absorption:**

The primary sites of absorption are throughout the duodenum. Virtually no absorption occurs in the stomach and very little takes place in the remaining two segments of the small intestine. This variation in absorption reduces total absorption of all forms to somewhere between 50 and 100%. Selenium absorption is not affected by body selenium status. Absorption of selenium is closely related to multiple nutritional factors that inhibit or promote absorption. Vitamins A, C, and E along with reduced glutathione enhance absorption of the element. In contrast, heavy metals (i.e. mercury) decrease absorption via precipitation and chelation (*Groff et al., 1995(b)*).

- **Transport:**

The exact mechanisms of selenium transport are thus far unclear and debatable. Some aspects of selenium transport are better understood than others. For example, selenium has been hypothesized to enter red blood cells via diffusion and carried throughout the body. Within the blood, free selenium binds to lipoproteins such as VLDL or LDL. The transport properties of a second protein, identified as selenoprotein P, have been met with opposing viewpoints. The protein is found in the plasma and is believed to be a carrier by some. Others believe that the presence of selenocysteine within the structure inhibits the transport abilities of the protein (*Burk et al., 1999*).

- **Storage:**

Selenium that is absorbed becomes a part of both transport and storage proteins. Selenium is believed to influence the formation of the proteins. The uptake of selenium is a complex process that involves numerous factors. The heart, kidney, lung, liver, pancreas, and muscle contain very high levels of selenium as a component of glutathione. In addition, type I (slow twitch) muscle likely contains greater amounts of reduced glutathione than Type IIb (fast twitch) because of their oxidative capacity. The liver is a major supplier of circulating reduced glutathione, which is reflected in the amount of its reserves (*Powers and Ji, 1999*).

- **Excretion:**

Selenium homeostasis is regulated primarily through excretion. Selenium is excreted via two main paths: urinary (50-67%) and fecal (40-50%). Extremely high intakes of selenium can lead to ventilatory elimination of the mineral in the form of dimethylselenide. Excretion via the lungs is characterized by a garlic smell odor to the volatile selenium compound. Fecal excretion does not appear to be a major pathway in regulation. Instead, urinary excretion is the primary route of regulation under normal physiological conditions. Common to all of the excretory pathways is the lack of knowledge regarding metabolite formation (*Powers and Ji, 1999*).

- **Physiological Role:**

1-Selenium is incorporated into the amino acid selenocysteine. It is an important cofactor in at least 25 selenoproteins, including important immune, endocrine, and antioxidant enzymes. Selenium is most readily bioavailable in the form of inorganic salts, such as selenate and selenite, and recent advances have been made in identifying novel biomarkers of selenium status. The precise role of selenium in humoral immunity remains unclear. Macrophages and neutrophils rely on selenoprotein-dependent generation of reactive oxygen species (ROS), and reduced selenium availability decreases neutrophil function (*Pierre et al., 2013*).

2-Selenium activates glutathione peroxidase which protects against the formation of free radicals. There appear to be at least two distinct families of selenium-containing enzymes. The first includes glutathione peroxidases and thioredoxin reductase, which are involved in controlling tissue concentrations of highly reactive oxygen-containing metabolites. These metabolites are essential at low concentrations for maintaining cell-mediated immunity against infections but highly toxic if produced in excess. The role of selenium in the cytosolic enzyme glutathione peroxidase (GPx) was first illustrated. During stress, infection, or tissue injury, selenoenzymes may protect against the damaging effects of hydrogen peroxide or oxygen-rich free radicals. This family of enzymes catalyses the destruction of hydrogen peroxide or lipid

hydroperoxides. Selenium-containing glutathione peroxidases (GPx) constitute a family of anti-oxidative enzymes that are capable of reducing organic and inorganic hydroperoxides to the corresponding hydroxy compounds utilizing glutathione or other hydrogen donors as reducing equivalents (see **figure 1** (Westermarck *et al.*, 2014)).

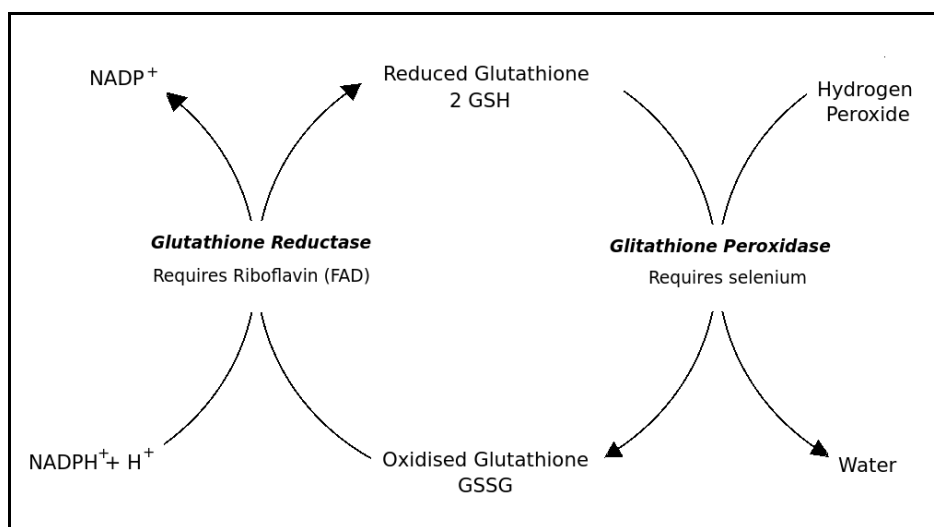


Figure (1): Glutathione peroxidase role as antioxidant (Westermarck *et al.*, 2014).

- **Pharmacology and Dosing:**

Selenium is available alone or in combination with other TEs. Parenterally, it can be given as a bolus dose or continuous infusion. Most intervention trials in the ICU have been performed using parenteral selenium, although no comparative data are available between EN and PN supplementation (Rech *et al.*, 2014).

- **Adverse Effects:**

Oral selenium supplements are generally not associated with side effects if taken at recommended doses. There is a relatively narrow margin between selenium intakes that result in deficiency or toxicity. Selenosis is a result of acute or chronic selenium intoxication secondary to high concentrations in food or drinking water, environmental exposure, or oral supplementation. Signs and symptoms include GI upset, changes in nails and hair, fatigue, irritability, and garlicky breath. More severe manifestations, such as neurotoxicity, anemia, and liver dysfunction, have also been observed. Short-term parenteral selenite as a high-dose bolus injection followed by continuous infusion is well tolerated (*Rech et al., 2014*).

1.2. Zinc:

It is an essential trace element, necessary for plants, animals, and microorganisms. It is "typically the second most abundant transition metal in organisms" after iron and it is the only metal which appears in all enzyme classes. There are 2-4 grams of zinc distributed throughout the human body. Most zinc is in the brain, muscle, bones, kidney, and liver, with the highest concentrations in the prostate and parts of the eye. Semen is particularly rich in zinc, which is a key factor in prostate gland function and reproductive organ growth.

In the brain, zinc is stored in specific synaptic vesicles by glutamatergic neurons and can "modulate brain excitability". It plays a key role in synaptic plasticity and so in learning. However it has been called "the brain's dark horse" since it also can be a neurotoxin, suggesting zinc homeostasis plays a critical role in normal functioning of the brain and central nervous system (*Broadley et al., 2007*).

- **Absorption:**

The primary site of absorption of exogenous zinc in the human is thought to be in the proximal small bowel, either the distal duodenum or proximal jejunum. Factors known to influence absorption include the amount of zinc present in the intestinal lumen; the presence of dietary promoters (e.g., human milk, animal proteins) or inhibitors (e.g., phytate, other minerals); zinc "status," especially in relation to chronic zinc intake; and physiologic state (*Krebs et al., 1998*).

- **Excretion:**

Zinc is lost from the body through the kidneys, skin, and intestine. The endogenous intestinal losses can vary from 7mmol/day (0.5 mg/day) to more than 45 mmol/day (3 mg/day) depending on zinc intake. Urinary and skin losses are of the order of 7-10 mmol/day (0.5-0.7 mg/day) each and depend less on normal variations in zinc intake. Starvation and muscle catabolism increase zinc losses in urine. Strenuous exercise and

elevated ambient temperatures could lead to losses by perspiration. The body has no zinc stores in the conventional sense. In conditions of bone resorption and tissue catabolism, zinc is released and may be re-utilized to some extent, figure 2, (Sandström et al., 1997).

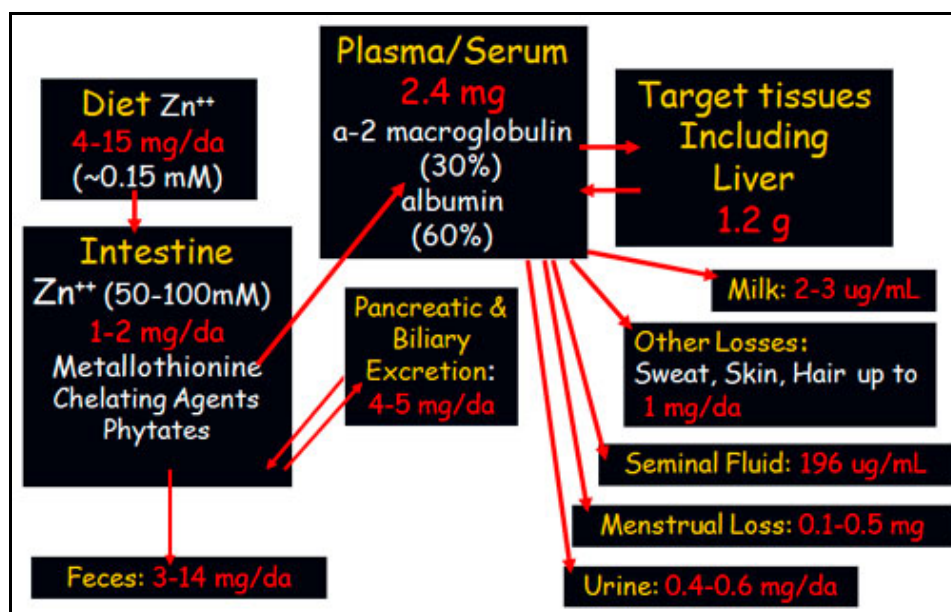


Figure (2): Zinc Distribution in human body (Sandström et al., 1997)

- **Physiological role:**

It is involved in many biochemical processes that support life and required for a host of physiological functions including normal immune function, sexual function, neurosensory function such as cognition and vision. Numerous proteins, enzymes and transcription factors depend on zinc for their function. Zinc is an essential component of hundreds of proteins and metalloenzymes including alkaline phosphatase, lactate

dehydrogenase, carbonic anhydrase and DNA and RNA polymerases found in most body tissues. Zinc plays specific and important catalytic, co-catalytic and structural roles in enzyme molecules and in many other proteins and biomembranes (*Broadley et al., 2007*).

- **Pharmacology and Dosing:**

Zinc supplementation may be administered parenterally or orally. Zinc sulfate and zinc chloride are the most common formulations used for supplementation in PN. Absorption of oral zinc occurs through active transport in the duodenum and the proximal small intestine. Bioavailability ranges from 20%–40%. Once absorbed, zinc is distributed mainly to the liver, pancreas, kidney, bone, and muscles and is excreted in the Feces (*Rech et al., 2014*).

1.3. Copper:

Copper is incorporated into a variety of proteins and metalloenzymes which perform essential metabolic functions; this micronutrient is necessary for the proper growth, development, and maintenance of bone, connective tissue, brain, heart, and many other body organs. Copper is involved in the formation of red blood cells, the absorption and utilization of iron, the metabolism of cholesterol and glucose, and the synthesis and release of life-sustaining proteins and enzymes. These enzymes in turn produce cellular energy and regulate nerve transmission, blood clotting, and oxygen transport. Copper stimulates the immune

system to fight infections, to repair injured tissues, and to promote healing. Copper also helps to neutralize "free-radicals", which can cause severe damage to cells(**Schreiber et al., 2013**).

- **Absorption:**

The site of maximal copper absorption is not known for humans, but is assumed to be the stomach and upper intestine because of the rapid appearance of Cu64 in the plasma after oral administration. Absorption of copper ranges from 15–97%, depending on copper content, form of the copper, and composition of the diet. Various factors influence copper absorption. For example, copper absorption is enhanced by ingestion of animal protein, citrate, and phosphate. Elevated levels of dietary zinc, as well as cadmium, high intakes of phytate and simple sugars (fructose, sucrose) inhibit dietary absorption of copper, **figure 3 (Stern et al., 2007)**.

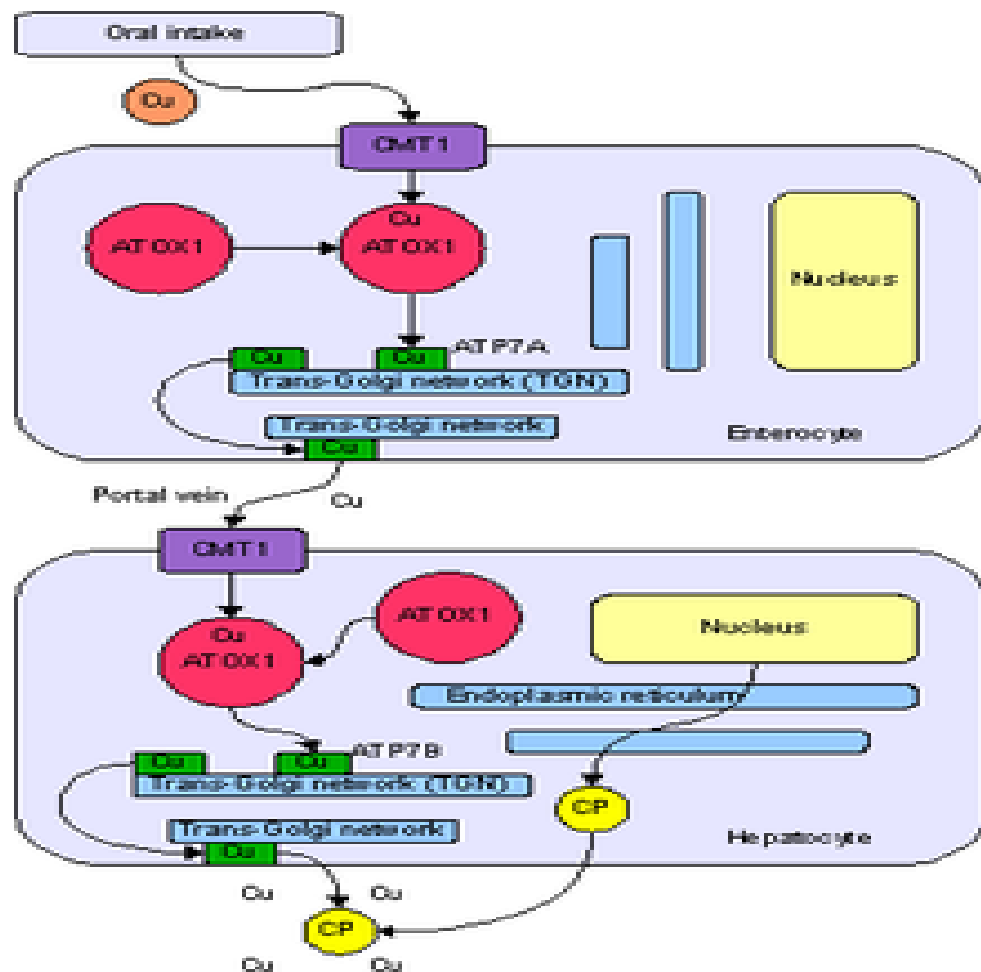


Figure (3): Absorption and distribution of copper (*Stern et al., 2007*)

- **Transport:**

Copper released from intestinal cells moves to the serosal capillaries where it binds to albumin, glutathione, and amino acids in the portal blood. Copper from portal circulation is primarily taken up by the liver. Once in the liver, copper is either incorporated into copper-requiring proteins, which are subsequently secreted into the blood. Most of the copper

(70 – 95%) excreted by the liver is incorporated into ceruloplasmin, the main copper carrier in blood. Copper is transported to extra-hepatic tissues by ceruloplasmin, albumin and amino acids, or excreted into the bile. By regulating copper release, the liver exerts homeostatic control over extrahepatic copper (**Ralph and Mc Ardle, 2001**).

- **Excretion:**

Bile is the major pathway for the excretion of copper and is vitally important in the control of liver copper levels. Most fecal copper results from biliary excretion; the remainder is derived from unabsorbed copper and copper from desquamated mucosal cells (**Turnlund, 1998**).

1.4. Iron:

- **Absorption:**

The body has no effective means of excreting iron and thus the regulation of absorption of dietary iron from the duodenum plays a critical role in iron homeostasis in the body. The body absorbs 1 to 2 mg of dietary iron a day and this is balanced with losses via sloughed intestinal mucosal cells, menstruation. Most of the iron in the body is distributed between red blood cell hemoglobin, the liver, muscle and macrophages of the reticuloendothelial system. Whilst iron is essential for cellular metabolism and aerobic respiration, cellular iron overload leads to toxicity and cell death via free