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FULL PAPER

Mineral and trace elements, dietary sources, biological effects, deficiency, and toxicity: a review

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Minerals are inorganic substances present in the tissues and fluids of our bodies. They are divided into macro minerals (Ca, Mg, K, Na, Cl, P, and S) and microminerals (I, Zn, Si, Fe, Mn, Cu, Co, Mo, F, Cr, and B), which are important for health and should be consumed according to the needs of the organism. Essential minerals have well-characterized physiological functions within the body. The ability of the body to maintain the minerals content within a certain range despite varying intakes, involves the processes of absorption, storage, and excretion. Inappropriate intakes and/or elevated requirements result from a range of conditions, including disease, malabsorption, pregnancy, and excessive losses, lead to deficiency. A severe deficiency of an essential mineral can only be corrected by supplementation. This review provides some detailed information about dietary sources, biological effects, deficiency, and toxicity of minerals and trace elements.

KEYWORDS

Substances; trace elements; absorption; excretion; toxicity.

Introduction

Minerals are inorganic substances that, along with vitamins and other micronutrients, belong to those constituents in the human diet [1]. Trace elements are dietary minerals required in minute quantities for normal physiological function. They are mostly structural components of enzymes or cofactors whose roles include the prevention of nutritional deficiencies, immune functions, regulation of gene expression, antioxidant defense, and prevention of chronic diseases [2]. Deficiency of mineral elements can causes

impaired growth, development, or maturation such that procreation is prevented, the element is not generally considered essential unless it has a defined biochemical function [3].

Mineral

Minerals are the soil's main source. These minerals in soil are absorbed selectively by plants and the food chain is transferred to people. Minerals have functional properties in food, which provide biological requirements, so these minerals are added to food to accomplish desires functional. Minerals have biologically important for biochemical processes and physiological processes. Approximately 25 metals are recognized as needed in the human diet [4]. The dietary minerals are categorized into two groups depending on the total amount of diet required. The first group is called macro minerals including magnesium, calcium, chloride, sodium, phosphorus, and potassium. The second group is called trace minerals include zinc, manganese, copper, selenium, iron, molybdenum, chromium, fluorine, iodine, and cobalt [4, 5].

Calcium

Calcium (Ca^{2+}) is considered as the most common mineral in the human body. Ca^{2+} as a mineral has been most commonly related to bone formation and metabolism. Approximately 99% of the Ca^{2+} was presented as hydroxyapatite calcium in the bones and teeth, while approximately 1% of Ca^{2+} was presented in extracellular and intracellular space [7]. Calcium is found in blood circulation, muscle, extracellular fluid, and other tissues and it is essential for the regulation of vasodilatation and vascular contraction, nerve transmission, muscle function, hormonal secretion, and intracellular signaling. Bone tissue acts as a reservoir and calcium source for these vital metabolic functions via the bone remodeling process [8]. Calcium was found in the blood in three forms (~50%) as ionized Ca^{2+}, (~40%) as Ca^{2+} bound protein and less little of Ca^{2+} is linked with other molecules such as phosphate and citrate [7]. The mitochondria or endoplasmic reticulum (ER) and the lysosomes were the main organs that regulate cell death and survival. In fact, Ca^{2+} microdomains occur between them due to the activity of the numerous Ca^{2+} transporters located within these organelles, so intracellular Ca^{2+} signals in ER may control cell death and survival dichotomously because of these Ca^{2+} microdomains [9].

Dietary sources and absorption of calcium

The main source of calcium intake is commonly correlated with dairy products (milk, cheese, and yogurt), it considered rich sources of Ca^{2+}, cereals, are also typically approximately 30 mg per 100 g but can exceed 180 mg per 100 g if they are fortified. Calcium is found particularly almonds, sesame, and chia, and also rich in nuts and seeds. The vegetables (broccoli, watercress, and kale) are also rich in calcium [10].

Intestinal Ca^{2+} absorption reflects the difference between absorption of the solutes and their secretion in the intestine lumen. Calcium intestinal absorption in humans, under normal conditions, accounts for around 20% of calcium ingested; during growth this percentage is higher. Calcium absorption in the intestines relies on dietary intake, calcium transportation capability of the intestine wall, calcium bioavailability present in the intestinal lumen and secretory flow. Calcitriol mainly regulates intestinal calcium-active absorptive ability [11].

The Ca^{2+} absorption is the strongest in the proximal small intestine (duodenum), regulated by TRPV6 (Transient Receptor Potential Vanilloid Subtype 6). Two elements of intestinal Ca^{2+} are absorption. Firstly, the active transport, transcellular and saturated

form, mainly based on the active form of vitamin D. The second, passive diffusion, paracellular and unsaturated form linearly linked to the diet Ca^{2+} charge, as depicted in Figure 1 [12]. Calcium preservation in the bone relies on the balance between bone mineralization and resorption. Calcium homeostasis in bones includes multiple Transient receptor potential (TRP) channels, such as 4, 5, or 6 of TRPV [13].

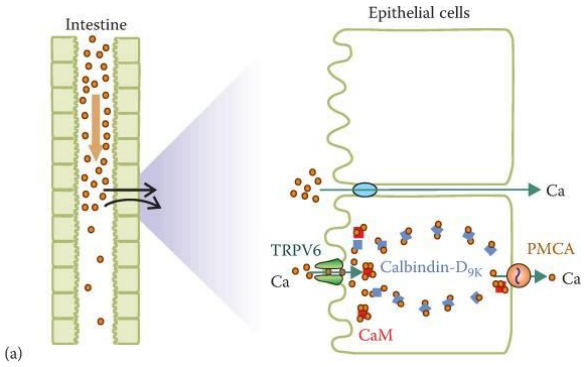

FIGURE 1 Intestinal Ca^{2+} absorption [14]

Excretion and loss of calcium

The activity of many hormones, especially the calcitonin, parathyroid hormone (PTH) and vitamin D, which are regulated of Ca^{2+} homeostasis in the blood. The Ca^{2+} homeostatic blood is control mainly by deposition in or out of the bone, also filtered of Ca^{2+} in kidney was according to Ca^{2+} requirements, Ca^{2+} plasma concentration, renal tubular function, and the availability of phosphorous to form microcrystalline appetite for infants growing [7]. In healthy individuals with a standard Ca^{2+} intake, the urinary calcium excretion is 0.1 to 0.4 grams per day. The renal calcium is filtered, reabsorbed, and excreted at various amounts and reabsorption is greater than 95% of the filtered load in all situations [15].

Deficiency and toxicity of calcium

Causes of calcium deficiency are various, may be due to vitamin D deficiency or resistance, hypoparathyroidism, PTH resistance (pseudohypoparathyroidism), hyperphosphatemia, medications, kidney disease, hypomagnesemia, human immunodeficiency virus, hungry bone syndrome, sepsis, critical illness, and acute pancreatitis [16]. Calcium is also deficiency in sickle cell anemia patients and thalassemia major patients when compared with the controls, in these cases, hypoparathyroidism and vitamin D deficiency are obviously significant causes of hypocalcaemia [17-20].
The main causes of calcium toxicity are malignancy and hyperparathyroidism nearly 90% of all cases of hypercalcemia, other causes of hypercalcemia which involve granulomatous infections, drugs (excess vitamin A and vitamin D intake), immobilization, endocrine (thyrotoxicosis), and milk alkali (or called calcium alkali) [16].

Phosphorus

Phosphorous (P) is also a necessary mineral and cell membrane portion in the formation of a phospholipid matrix. Phosphorous is an essential component of the composition of RNA and DNA nucleic acids. Therefore, the combined unit of nucleic acids is composed of a sugar and phosphate molecule with nitrogenous bases. In addition to phosphorous function in the formation of nucleic acids and cell membranes, phosphorous is an important component of Adenosine Tri-Phosphate (ATP), it is responsible for energy of life. ATP is biochemically transformed to ADP

(Adenosine Di Phosphate) to produce phosphate component with sufficient energy for all cells, tissues and humans [5],[20]. Furthermore, phosphates responsible for pH changes or control, phosphates switch through extracellular, intracellular, and skeletal compartments to regulated acid-based buffer to help preserve plasma and urine pH with a narrow range [21]. The third-most common anion in the body is inorganic phosphate (Pi), representing around 1% of the overall body mass. About 85% of the total Pi is contained in the bone in apatite form to share architecture of the bone. Approximately 15% are contained in soft tissues, while in the blood stream pool just 1% is quick exchangeable [12].

Dietary sources and absorption of phosphorus

The most significant known dietary sources of P are milk or milk product and cereal (grains) as well as cereal products and meat or meat products. There are two forms of P were available (organic and inorganic), the inorganic phosphates may be added through food processing to increase P intake [22]. Nutritional phosphate in the small intestine is absorbed by two methods active and passive mechanisms, the passive component's still unknown in molecular identification. The active mechanisms of phosphate primarily depends on expression and activity NaPi-IIb (sodium-dependent phosphate cotransporter), as illustrated in Figure 2 [23], the P absorption that is largely regulated by varies factors such as vitamin D3, fibroblast growth factor, parathyroid hormone, and dietary phosphate [24].

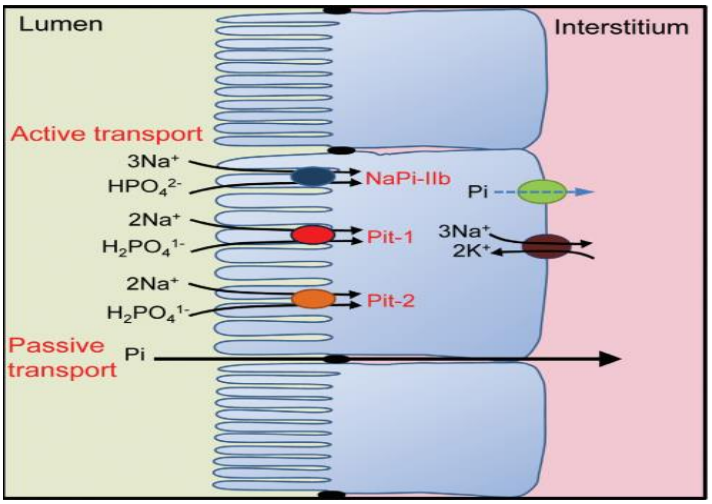

FIGURE 2 Transport of phosphate across enterocytes [23]

Excretion and losses of phosphorus

The excretion of phosphorus in the kidney relies on the balance between reabsorption and filtration. P reabsorption by filtration tubular occurs predominantly in the proximal tubule (PT) in which at least 3 different Na-driven Pi transporters (NaPi-IIa, NaPi-IIc, and PiT2) which facilitate the reabsorption of P in the kidney [25]. There are three hormones which regulate the Pi serum are PTH, FGF-23 with its a-Klotho coreceptor, and Calcitriol [12].

Deficiency and toxicity of phosphorus

The most popular causes of hypophosphatemia are poor intakes of phosphate, elevated excretion of phosphate, and the change from extracellular phosphate to intracellular space with a broad variety of genetic deformities, that lead to defect in cotransporters of sodium phosphate such as

Fanconi's syndrome, disease that induces hypophosphatemia, proximal tubules acidosis, and renal lack of glucose, bicarbonate, phosphate, and amino acids that occurs due to effect in proximal renal tubule which is hereditary or secondary reasons [26]. X-linked hypophosphatemic rickets (XLHR), also called vitamin D rickets, are autosomal dominant hypophosphatemic rickets. XLHR is characterized by loss of phosphate by renal causing developmental disorder, osteomalacia, and rickets [27].

Chronic kidney disease (CKD) is typical with hyperphosphatemia. Hyperphosphatemia is often considered the "silent killer" because of its dramatic effect on blood vessel calcifications, and hyperphosphatemia explains the complex occurrence with mineral and bone disorders, together with a low levels of Ca^{2+}, decreased of vitamin D levels and calcitriol [28]. Moreover, there are other causes of a high levels of phosphate are enemas that contain P and vitamin D, renal excretion decrease (due to hypoparathyroidism, kidney disease, renal resistance to PTH), immobilization (excess bone resorption), sieving extracellular (tumor degeneration syndrome, acidosis, and rhabdomyolysis) [29]. Hyperphosphatemia is also common in haemoglobinopathy patients (thalassemia and sickle cell anaemia). Hyperphosphatemia occurs due to hypoparathyroidism which causes higher phosphorus and lower calcium levels, this state is considered as one of the complications that occur in the second decade [18, 20, 30-32].

Magnesium

Magnesium (Mg) is the third abundant amount of minerals in human body. Approximately 1/3 of Mg is linked to plasma proteins in the blood and the remaining 2/3 is filtered by the renal. Magnesium concentration in serum does not reflect the amount of biologically active fraction of ionized Mg, so the concentration of magnesium in RBCs is considered as a better indicator of Mg amount in the tissues [7].

Magnesium is essential in protein synthesis, release of muscle storage energy, and body temperature regulation. Likewise, Mg is important for bone formation and proper heart function. Mg stimulates over 100 enzymes [33].

Magnesium is an important mineral in many physiological processes including the metabolism of fat and carbohydrates for energy production. Metabolic energy is contained in an adenosine triphosphate (ATP) compound. Many cell functions use ATP-compound magnesium ion that called Mg-ATP. The energy source for metabolic processes that trigger muscle contraction is often Mg-ATP. Each function, from eye blink to heartbeat, uses chemical energy such as Mg-ATP for electric contraction. Mg-ATP further acts in cell signalling, which controls the activation and inhibition of biochemical pathways. Mg-ATP is converted into the second messenger of the cell cyclic AMP (cAMP). The second messengers induce development, proliferation, and decay in cells [5].

Dietary sources and absorption of magnesium

Magnesium is widely distributed in plant and animal foods and in beverages. Green leafy vegetables, such as spinach, legumes, nuts, seeds, and whole grains are good sources, depending on the medication, dietary matrix, enhancing, and inhibiting factors, the bioavailability of Mg^{2+} is differs. Dietary influences that inhibit Mg^{2+} uptake include large concentrations of other nutrients, partially oxalate, phytate, fermentable fibers (hemicellulose) and no fermentable fibers (lignin or cellulose), while magnesium uptake is improved by medium-chain triglycerides or by proteins or by small- or indigestible carbohydrates (inulin, lactulose oligosaccharides, and mannitol) [34].

Mg^{2+} is absorbed in the small bowel. In colon, it is absorbed in lesser amounts. Absorption of intestinal magnesium occurs through two separate transport pathways, as demonstrated in Figure 3. The first transport pathway is mediated by TRPM6 (Transient Receptor Potential, Subfamily M, 6), which is active transporter saturated transcellular pathway. The second transport pathways are an unsaturated paracellular channel, linearly increasing with increasing concentrations of intraluminal magnesium. Hypomagnesemia may be accompanied by secondary low levels of calcium patients, which can correct for the TRPM6 impairment by enhancing the passive paracellular absorption of sufficient oral magnesium consumption [35].

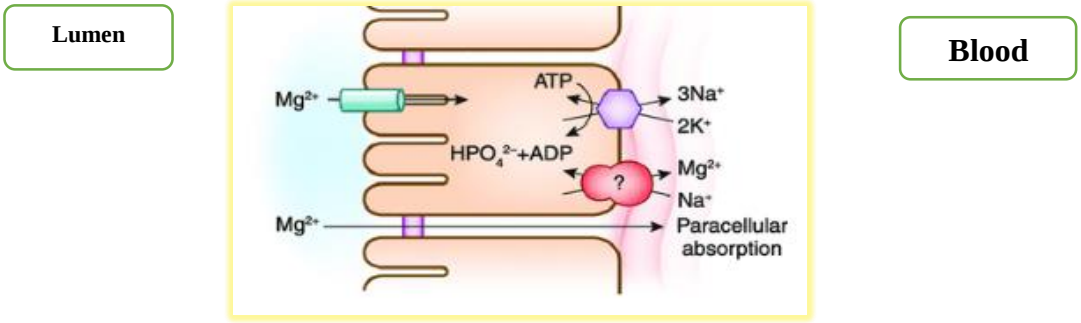

FIGURE 3 Intestinal magnesium absorption [35]

Excretion and losses of magnesium

Management of homeostasis of magnesium body resides mainly in the kidney. In the glomeruli, about 80 percent of total serum magnesium is removed. Then, 95%-97% of filtering magnesium is reabsorbed along the kidney tubule, so that three to five percent of filtered magnesium is eventually excreted in the urine under physiological, normomagnesemia conditions. The proximal tubule also absorbs 15-20 per cent of filtered Mg^{2+}. Most of the extracted Mg^{2+} (~70 percent) is reabsorbed in Henle's loop's thick ascending limb (TAL) [35].

Deficiency and toxicity of magnesium

Deficiency of magnesium is rare in people who eat a balanced diet. Individuals with diseases like alcoholism or diabetes can therefore be at risk for Mg^{2+} deficiency. High blood magnesium conditions can impact blood pressure. The Institute of Medicine's Food and Nutrition Board sets the upper limit for Mg^{2+} supplementation at 350 mg per day[5]. Gitelman syndrome, a main renal salt wasting disease with an average incidence of around 1:40,000, is the most severe hereditary condition involving magnesium retention. SLC12A3 recessive mutations encoding NaCl cotransporter NCCT are the causes of Gitelman syndrome. Patients that used cisplatin drug in regularly show lower Mg^{2+} levels [35]. Magnesium deficiency is shown in the haemoglobinopathies in sickle cell anemia patients and thalassemia major patients when compared with the controls may be due to the low level of magnesium caused by hypoparathyroidism [17],[18],[20],[32].

Trace elements

Trace elements are inorganic substances found along with vitamins and other micronutrients that belong to those constituents in the human diet, human body needed in very small account [1]. Trace elements play a significant role as primary co-factors for enzymes in cellular metabolism and maintenance of homeostasis; some trace elements are essential components of enzymes and other proteins. Concentrations of trace elements within cells and plasma are

regulated by absorption of element by the gastrointestinal tract (GIT) and excretion of element by the renal and the gastrointestinal tract (GIT) [36]. Many diseases, including breast cancer, thalassemia, sickle cell anemia acute leukemia, and diabetes have shown significant differences in trace elements levels. Various biological samples such as hair, nails, tissue, and body fluids (saliva, urine and blood) have been evaluated for the levels of trace elements [37].

Iron

Iron (Fe) is an essential component needed to develop antioxidants to fight reactive oxygen species (R0S). Catalase is an enzyme based on the iron, which is located in the cell peroxisome that catalyzes Hydrogen peroxide (H_2O_2) into oxygen (O_2), and water (H_2O). Iron is also needed to generate the microbiocidal hypochlorite acids, where iron deficiency has been observed to reduce average concentrations of blood T cells in blood stream [38].

There are two forms that iron found in the body the first is primarily found as heme iron, which is responsible for transport of O_2 in hemoglobin, the second is found as non-heme iron, is primarily a part of several mineral proteins with specific functions in metabolic, such as the electron transfer, regulate of transcription, catalytic enzymes, and so forth [39].

Dietary source and absorption of iron

There are two different sources that give the two main forms of iron (heme iron and non heme iron); one animal source, the hemoglobin and myoglobin of meat give heme iron form. Other plant source give Non-heme iron, mainly in ferric form (Fe^{+3}), which comes from vegetable foods [40]. The duodenum and upper jejunum specialize in the rapid transportation both of iron (heme or non heme), and quick movement to bloodstream through the lumen. Absorption of heme iron is mediated by the Heme Carrier Protein 1(HCP1), which is relevant to intracellular breakdown by Heme Oxygenase (HO1) to release iron into bowel cells. Within the duodenum, the non-heme iron is converted by compounds such as ascorbic acid into the ferrous form. Soluble ferric iron is also first reduced by Duodenal Cytochrome B (Dcyt B) before being taken up by intestinal cells through the Divalet-Metal Transporter-1(DMT-1) and is likely connected to peptides, organic acids, or amino acids. The ferrous iron is transported through ferroportin 1 (FPN1) and its hephaestine oxidation (HEPH), and then reach blood circulation at the basolateral membrane. Old erythrocytes are phagocyted via CD91/CD163 by macrophages, which are degraded to release iron in lysosomal compartments, which are then excreted via DMT1 into the cytosol. The iron is transported from the macrophage to the bloodstream through ferroportin 1 [41]. In the bloodstream, ferric iron is bonded to transferrin (Tf) and transferred to the target tissues, the bone marrow, muscle, and hepatic through transferrin receptor (TfR) as shown in Figure 4. When iron stores are sufficient, hepcidin released from the liver into the blood to inhibit ferroportin facilitated iron transfer from small intestine cells and other tissues associated in iron mobilization [42].

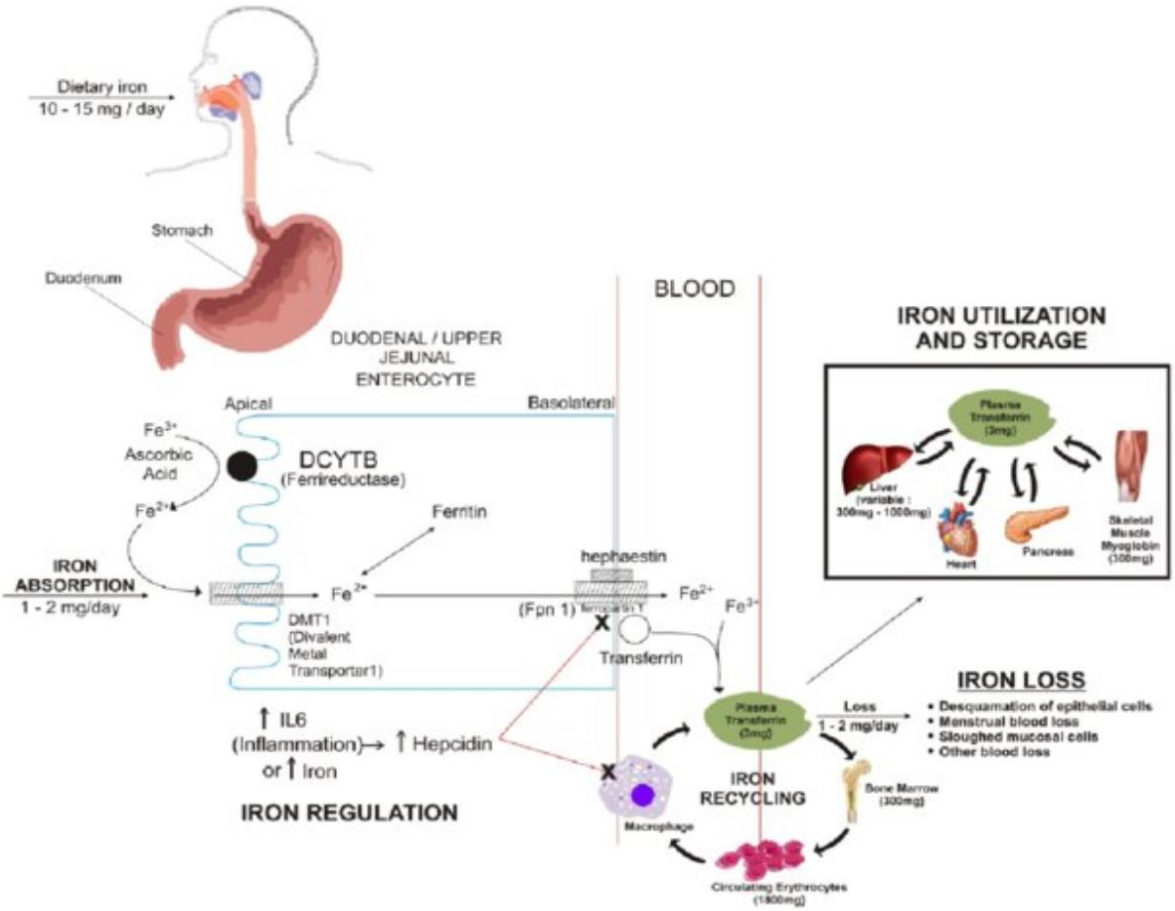

FIGURE 4 Iron absorption and homeostasis [43]

Presence of ascorbic acid in the intestinal, amino acids, and succinate lead to increase absorption of iron whereas the substance oxalates, phytates, and tannates lead to decrease absorption of iron [39,44].

The excretion and loss of iron

There is really no iron excretion mechanism, iron loss through bleeding, exfoliation mucosal cells, skin, urine, and sweat. Iron imbalances occur if the intakes are not matched with losses. Iron deficiency happens if there is insufficient dietary iron or when increased demand due to newborns and young adult growth spurts and pregnancy is compensated by simultaneous amplification of intestinal iron absorption [42,45].

Deficiency and toxicity of iron

If mild Iron deficiency is asymptomatic due to the mechanisms besides compensating are established (increase heart rate and hemoglobin efficiency are needed to keep oxygen supply adequate for tissue demands). While severe iron deficiency causes anemia called Iron deficiency anemia, in the iron deficiency anemia showed ferritin level < 30 ng/mL, saturation of transferrin < 20%, and low of MCV and MCH. The most common Iron deficiency anemia is caused by nutritional disorder, another causes that lead to iron deficiency are pregnancy, parturition, menstruation, lactation, chronic bleeding from GIT, peptic ulceration, hemorrhoids, and gastric ulceration [44].

Primary Hemochromatosis, either inherited or acquired, represents the iron toxicity in human. Hemochromatosis is causes that exceed ferritin and transferrin ability, demonstrates its redox toxicity and causes oxidative damage primarily to organs storage of Fe such as the liver and organs with high mitochondrial activity. Chronic hepatotoxicity

occasionally progresses to fibrosis and cirrhosis, and also may be cause Heart failure and various endocrinopathies, arthritis, skin pigmentation and arthralgia. Hereditary hemochromatosis (HH) is a genetic disease of autosomal recessive disorder that causes increased absorption of iron, mainly through suppression of the pathway of hepcidin. Secondary hemochromatosis generally caused by blood transfusion such as thalassemia disease, sickle cell disease, and myelodysplastic syndrome, which cause iron increase due to the repeated red blood cell transfusion [39], also show that Iron status in thalassemia major patients are show increase due to the patient needing blood transfusion as therapy to keep their level of Hb sufficient. Patients lack an active mechanism for excreting iron excess and repeated blood transfusions lead to an iron overload. Excess transfusional iron is accumulated as free iron in the liver, heart, and other organs, that can contribute to organ failure and damage over time [32],[46],[47].

Zinc

Zinc (Zn) is after iron the second most common nutrient in human body. The free form of zinc is present in the body as Zn^{+2}. Zinc is a critical component in the development of more than 2700 human body enzymes[48]. Serum zinc represents approximately 0.1 percent of the entire body zinc, so it does not really reflect body zinc status. Even so, it demonstrated excellent association with total body zinc shift and was commonly used in medical care after evaluate the zinc status [39]. Nearly 95 percent of zinc in the body resides in intracellular compartments. Zinc is firmly bound in cells with metalloprotein as a structure component or with metal enzymes as cofactor. Homeostasis of zinc cellular is controlled by metallothionein's (MT). Zinc has an essential role in (bone, cartilage, and muscle) development, immune cell proliferation and maturation, wound repair, hair growth, signal transductor activation in postsynaptic neurons, regulation of oxidative stress, and regulate gene expression [48,49].

Zinc has a significant function in the field of cellular immunity. Inflammatory cytokines formed by activated monocytes and macrophages that release ROS are tumor necrosis factor- alpha **(**TNF-alpha) and IL-1ß. An impact of zinc supplementation in health adult is a decrease in the generation of oxidative stress associated with products 4-hydroxyalkenals, malondialdehyde, and 8-hydroxydeoxyguanine, also IL-1β and TNF-alpha [38].

Dietary source and absorption of zinc

The good animal source of zinc is found seafood, especially red meats, oysters, pork, molluscs, poultry, and dairy products. Plants are insufficient sources of zinc. Zinc is linked with nucleic acid and amino acids in diet. Before Zn absorption in small intestine and the main site is Jejunum required Hydrochloric acid, nuclease, and protease to release zinc from food [50].

Factors known to influence zinc absorption include the quantity and type of zinc eaten; dietary promoters such as animal protein and organic compounds with low molecular weight; dietary inhibitors such as alcohol intake, phytate, and probably iron and calcium when ingested as supplements; physiological conditions such as breastfeeding, gestation, early infancy, and tissue repair, so all of which raise the demand for absorbed zinc [51]. In the human body no storage system for Zn [52].

Excretion and loss of zinc

The digestive tract, particularly small intestine and the pancreas, plays an important role in keeping zinc homeostasis in the whole body. Expression of Zn transporter is an essential component of homeostatic control, involving control of zinc absorption by the small bowel

and zinc excretion by both the pancreas and the small bowel. There are 16 Zn transporters have been identified in pancreas and the small bowel. There are two families of Zn transporters (ZIP and ZnT proteins), ZIP proteins carry zinc from the extracellular space and intracellular organs to the cytoplasm while ZnT proteins carry zinc from the intracellular zinc to the extracellular space [51]. Zinc, which is excreted by pancreatic secretions and Dietary zinc, is absorbed by ZIP 4 on the apical surface of the enterocyte and transferred by ZnT1 to blood stream. Plasma zinc link to albumin or in free form is absorbed by the hepatic, bone marrow, testis, heart, renal, skeletal, and skin tissues, as displayed in Figure 5.

Zinc is lost by urine, feces, sweat, and semen, the amount of znic in fecal excretion to which the body's zinc level is responsive [42].

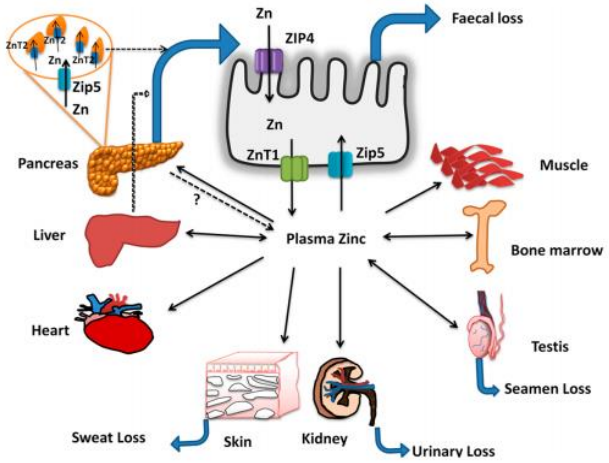

FIGURE 5 Zinc absorption and homeostasis [53]

Deficiency and toxicity of zinc

Zinc deficiency is becoming a public health problem which can be caused by inadequate food intake, increased requirements, decreased of absorption, increased loss, decreased utilization, and genetic disorder [51].

There are two forms of zinc deficiency occur, the first is acquired zinc deficiency caused by inadequate food intake or other causes mention up, the second genetic disorder Zinc deficiency such as acrodermatitis enteropathy. Acrodermatitis enteropathy disease is an autosomal recessive result from defect in the gene responsible for absorption of zinc in intestinal. Zinc deficiency affects the immune system, development of neurobehavioral, reproductive function, and physical growth. Signs and symptoms of znic deficiency are diarrhea, hypogonadism, short stature with defect in development, skin disorders, cognitive dysfunction, anorexia, impaired smell and taste, change of bacterial infections, and wound healing [54].

In Previous study on the haemoglobinopathies, it was found that zinc status is decease in haemoglobinopathy patients thalassemia major and sickle cell disease, zinc deficiency may cause by food insufficiency of zinc or caused by that patients take up deferoxamine dose without adjustment for each patient [20,47]. During childhood, zinc toxicity was rarely recorded. Signs and symptoms of zinc toxicity are diarrhea, vomiting, nausea, headaches, and poor appetite. The increase in the zinc availability fortified foods and increased zinc supplementation may cause zinc toxicity [54].

Copper

Copper (Cu) is essential trace element in human body. Human requires only trace amounts, and contains about 100 mg of Cu [55]. Copper will now be essential for energy production processes such as Cytochrome oxidase operation that improves ATP produce in the mitochondrial. Cu plays a major role, as well as iron and selenium, in the protection of cells against reactive oxygen species, like the superoxide dismutase which converts the superoxide radical (O_2-) into water and hydrogen peroxide [38]. Cu has important role as Co-factor for enzymes involved in various fundamental processes including angiogenesis, neuropeptide signaling, oxygen transport, iron metabolism, antioxidant defense, immune function, and energy production [3].

Dietary source and absorption of copper

Copper-rich animal sources include the liver, shellfish, and nuts. Copper plant sources include bread, nuts, cereals, dried fruits, and legumes. Copper amounts in the foods are largely dependent on soil copper levels, local use of copper-compounding pesticides / feticides, and industrial process release of copper [55,56].

Gastric acidity was thought to improve solubility of copper because the copper is interaction with some ions for uptake in stomach. The factor that effect on absorption of copper by enterocytes are dietary protein, phytate, ascorbic acid, fiber, and L-amino acids [57].

The absorption of copper commonly occurs in the proximal part of the small intestine, in which it is transferred through the portal vein to the liver [55]. The copper absorption by the intestine is saturable. Luminal copper is reduced to the cuprous (Cu^+) form by a cytochrome B reductase1 enzymes before to transport [57]. In blood stream, approximately 75% of Cu is absorbed by the liver in the portal vein, where it is incorporated into the ceruloplasmin and resecreted again to blood circulation, while other amount of Cu about 25% which do not undergo a hepatic cycle is reached directly into circulation when linked to albumin and α_2-macroglobulin [36,39].

Excretion and loss of copper

The main excretion route for copper is the bile duct. The copper production in hepatocytes occurs via the copper transfer of hepatocyte to the bile, P1B type ATPase (ATP7B). Copper in feces contains products not consumed from the beginning, excreted by the liver and other intestinal secretions. ATP7B disorder induces harmful hepatic copping and certain tissues in which elevated ATP7B, for example, are generally expressed in the brain [39].

Deficiency and toxicity of copper

There are two forms of copper deficiency occur, the first is acquired copper deficiency caused by insufficient stores (preterm and infants), insufficient intakes, physiological condition (pregnancy or lactation), malabsorption, diabetes, and alcoholism. The second form caused by genetic disease such as Menkes' Disease (MS), aceruloplasminemia, and zinc-induced myeloneuropathy. [56], [58].

Menkes disease, also named "kinky" hair syndrome, occurs approximately in 1/100,000 live births, MS is inherited X-linked condition that caused by mutations in Cu transporter ATP7A gene that lead to the low serum copper concentration, effect of copper dependent enzymes, premature mortality, and infantile neurodegeneration [59].

Wilson's disease is an autosomal recessive condition triggered by ATP7B gene mutations. This gene primarily codes a copper transporter from liver to bile also copper transporter to the Golgi network in the cell. Approximately, there are 500 mutations have been identified in ATP7B gene. The effected of

Wilson disease range from moderate serum aminotransferase defects to chronic or acute hepatitis, liver failure, and cirrhosis, also copper accumulation in the brain, which triggered other neurological problems primarily because of mitochondrial damage correlated with oxidative stress [60].

Copper status of sickle cell disease (SCD) and thalassemia patients were significantly increased [20,32,61].

Selenium

Selenium (Se) is an important trace element with global human health significance. Diet is the main source of Se and its intake depends on its concentration in sources of food and the quantity of those sources consumed. The sufficient Se intake for adult females and males has been calculated to be 55 and 70 mg/day, respectively [62]. Selenium is an important product of ~25 selenoproteins in humans where it is an integral part. It has functions in the immune system, oxidative stress responses, DNA synthesis, cell signaling, and regulation of thyroid hormone metabolism [39,63].

There are 25 genes associated with selenoproteins in the human genome. Glutathione peroxidases (GPxs) is enzyme selenoprotein present in several cells that can catalyze hydroperoxides and defend the cells from ROS [39]. Selenocysteine is an amino acid at the active site for GPxs, GPx stopping H_2O_2 mediated hemoglobin oxidation which is dependent on the Se presence [38].

Dietary source and absorption of selenium

The animal source of selenium is found as selenocysteine and selenomethionine particular, Selenocysteine is the most dominates in origin animal. The plant source of selenium is found as inorganic compounds selenates that are converted into organic forms later. The diet contains varying levels of selenium which relies on the position of plants and animals [64].

When consumed selenium compounds are primary absorbed in duodenum and little amounts are absorbed by jejunum and ileum, also stomach and rumen may be absorption of selenium compounds. The absorption of selenium compounds are greatly affected by chemical form so the absorption was not under homeostatic regulation of selenium such as selenite is absorbed through the brush-bound membranes by passive diffusion whereas selenate is less affinity to the brush-bound membranes. Selenate is absorption by a sodium cotransport system which is often associated for sulfate. Selenium, in the form of selenomethionine, selenoamino acids, and selenocysteine, is transported by effective amino acid transport pathways and is more bioactive than selenite or selenate [65].

Excretion and loss of selenium

The hepatic and renal and kidney are produced selenium metabolites, but the major pathway of excretion is by urine in the form of methylated selenosugars. Selenium is often exhaled in the form of dimethydselenide in high selenium intake subjects [39].

Deficiency and toxicity of selenium

Excess selenium and deficiency is associated with the human health risks [66]. The low levels of selenium were possibly caused in the affected area by low soil selenium level, causing poor selenium content in regional maize and rice. The Keshan disease (deficiency selenium) is named after the endemic area, Heilongjiang province's Keshan County. Keshan disease has been described by cardiac arrhythmia, cardiogenic shock, cardiomegaly, and heart failure; other complication may be cartilage abnormalities, young joint deformity and osteoarthritis. In addition, the Keshan disease was caused by selenium deficiency. Other possible hypothesis showed that

coetiologic Keshan disease were viral infection and vitamin E deficiency [39].

Toxicity to selenium in livestock digesting food and water was recognized in elevated-selenium soil regions. Chronic poisoning is characterized by hair loss, emaciation, joint erosion, loss of hoofs, cirrhosis, and cardiac atrophyand anemia. Selenium toxicity or called selenosis in humans has been noted in areas of the world with elevated selenium with in soil, resulting in increased of selenium in plants, and food [3].

In Previous study on the hemoglobinopathies, it was found that selenium status is deceased in haemoglobinopathy patients of thalassemia major and sickle cell disease, selenium deficiency may be caused by food insufficiency of selenium or by oxidant damage due to increased resting oxygen consumption and circulating pro-oxidative free hemoglobin [67,69].

Manganese

The fifth most abundant element on earth is manganese (Mn). It is ubiquity in the environment, and is found in water, air, food, and soil. It is an essential trace element which is well established for humans and domestic animals [70]. Mn is a mineral which is used by the body as an enzyme cofactor in glucose metabolism [5]. It is also one of the important heavy metals essential for normal growth and metabolism. Mn is involved in a variety of biological processes that act as a cofactor for numerous enzymes including hydrolyses (superoxide dismutase), pyruvate carboxylase, arginase, transfers (sugar transferases), isomerases, ligases, lyases, and oxidoreductases [71,72]. When exposed to hydrogen peroxide, manganese is much less sensitive than iron for the toxic chemistry of Fenton, Manganese can function as an antioxidant, rather than promoting reactive oxygen toxicity. Therefore, manganese is essential for formation of bone, carbohydrate and lipid metabolism, as well as in controlling blood sugar [72].

Dietary source and absorption of manganese

The plant is good sources for manganese such as grain cereals and all types of nuts, tea, legumes, beans, almonds, chickpeas, and coffee (Filippini et al., 2018). The animal source is food content minimal. The material such as phytic acid, oxalic acid, and tannins abundant in plant source foods can prevent Mn's absorption. Those dietary factors should be taken into consideration when analyzing Mn consumption [74].

Manganese is absorbed through diffusion in small bowel mucous cells, but the rate of absorption is very poor at 1–5 % of Mn consumption [74].

Absorption of Mn happens primarily in the small intestine (duodenum). Mn is absorbed through divalent metal-ion transporter-1 (DMT-1) through enterocytes; following absorption manganese is then transferred to the liver, where it reaches the bloodstream for serum transfer to the other tissues. Some plasma manganese is in the β1-microglobulin and albumin complexes, whereas a small amount of manganese plasma is oxidized to Mn^{3+} and bound to transferrin [72].

Excretion and loss of manganese

Manganese levels in the body are strictly regulated by intestinal absorption and hepatobiliary metal secretion throughout the gastrointestinal tract, so the organs that control the level of manganese are intestinal and liver [71]. The amount of Mn consumption and its interactions with other nutrients can effect on absorption and excretion process [74].

Deficiency and toxicity of manganese

The human deficiency of manganese is very rare, since the demands are very limited, and

the dietary manganese deficiency has not been reported because of its ubiquity [75,76].
Human toxicity of manganese has been reported in the welders, ferroalloy workers, battery manufacturers, and occupational exposure in miners. In the basal ganglia, excess Mn mostly accrues, particularly the global pallidus which causes a distinctive extrapyramidal syndrome known as manganism. The symptoms of toxicity of manganese are cognitive and psychological disorders accompanied by motion disability similar to Parkinson's disease with limb rigidity, dystonia and a wide-stepping gait feature [71]. The serum manganese concentration was significantly elevated in the sickle cell patients and thalassemia major, this elevation of Mn may be associated with iron overload [20,52,67].

Chromium

Chromium (Cr) is an important mineral which show to have beneficial effects in the control of insulin action and enhancing lipid and carbohydrate metabolism. Previous studies appear lower levels of chromium of individual with type 2 diabetes than individual without type 2 diabetes. Insulin resistance is a common factor within a cluster of risk factors for cardiovascular disease. Chromium picolinate (CrPic) was shown to minimize resistance to insulin and reduce the risk for type 2 diabetes and cardiovascular disease [77].

Dietary source and absorption of chromium

In food sources, chromium is mainly determined by its quantity in regional water and soil. The primary source of human chromium intake comes from pollution throughout food preparation, using cookware and machinery made from stainless steel. Just a small proportion of chromium is absorbed, and the rest is excreted with in feces [78]. A sufficient intake of chromium for males and females is established at 35 and 25 mg/day, respectively. The chromium absorbed is transferred by protein transferrin to the tissue in which it binds to chromodulin (oligopeptide) made up of glutamine, glycine, aspartate, and cysteine. *In vitro*, chromodulin helps to stimulate tyrosine kinase activity of the insulin receptor by enhancing insulin signaling, and consequently increase cell glucose inflow. It is not known if that same mechanism exists *in vivo* [39].

Excretion and loss of chromium

Chromium excreted by the kidneys in the form of chromodulin. Chromodulin is the major form of chromium. The loss of urinary chromium under the influence of insulin has been found, it was suggested to raise the risk of chromium deficiency in diseases with the persistent high level of insulin. However, some research has found no variance in urinary chromium excretion between patients with diabetes mellitus and individual healthy controls to support the theory [39].

Deficiency and toxicity

Chromium deficiency may lead to causes reversible insulin resistance, diabetes, elevated blood triglycerides, and cholesterol. Chromium deficiency can be seen in individuals with very limited diets or those with severe malnutrition [79]. In the sickle cell, anemia patients have chromium deficiency [32,67]. As with other minerals, chromium toxicity may result from the over-supplementation [80].

Cobalt

Cobalt (Co) metal ions are generally spread trace elements in nature [81]. Cobalt is a key constituent of vitamin B12 and is essential for hemoglobin synthesis. Cobalt is a silvery gray, rigid, and metal element ductile. The chemical properties of cobalt are largely similar to nickel (Ni) and iron (Fe). Cobalt compounds

mainly occur in two valence states [cobaltous (Co^{2+}) and cobaltic (Co^{3+})], the Co^{2+} was the most environmentally and commercially available[36].

Dietary source and absorption of cobalt

The main source of food that rich in cobalt include nuts, fish, leafy green vegetables (spinach and broccoli), and cereals (oats) [36]. The consumption of cobalt in humans is highly variable and has been noted to be between 5 and 50 μg/day. Most of the Co that humans consume is inorganic. The GI absorption of Co compounds in different individuals has been reported to be between 5 and 45%. The amount of cobalt administered and the nutritional factors affect absorption and/or excretion of Co. There is limited information on the respiratory tract absorption in humans of inhaled cobalt materials [82].

Excretion and losses of cobalt

Cobalt is closely linked to albumin and excreted easily and quickly in the urine. The amount of cobalt excretion is determined by the amount of Co given [80].

Deficiency and toxicity of cobalt

Nutritional deficiency is rare, but more recently, cobalt toxicity has occurred from metal emissions such as artificial hips that lead to neurological symptoms (incoordination, hand tremor, cognitive decline, vertigo, depression, visual changes, and hearing loss). Likewise, another symptoms that show in cobalt toxicity are endocrine (hypothyroidism) symptoms, cardiac (cardiomyopathy and arrhythmias), and polycythemia [36].

Conclusion

Minerals and trace elements are naturally occurred in minute concentrations in soil, plant, and animals. The optimal concentrations of minerals and trace elements are essential for normal functioning of our systems. However, deficiency of any minerals and trace elements can cause wide range of functions disorders, while excess levels of minerals or elements result in damage to certain organs. The current review highlighted the absorption, the basic biology, function and health effect, deficiency and toxicity of minerals, and trace elements.

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Conflict of Interest

The authors have no conflict of interest.

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References

[1] P.A. Tsuji, J.A. Canter, L.E. Rosso, Trace minerals and trace elements, *Encyclopedia of Food and Health*, **2016**, 331–338. [Crossref], [Google Scholar], [Publisher]

[2] S. Strachan, Trace elements, *Curr. Anaesth. Crit. Care*, **2010**, *21*, 44–48. [Crossref], [Google Scholar], [Publisher]

[3] F.H. Nielsen, Trace and ultratrace elements, *Reference Module in Biomedical Science*.٢٠١٤ ,s [Crossref] [Publisher]

[4] W. Maret, Vitamins and minerals, *Int. J. Mol. Sci.*, **2016**, *17*, 1–8, [Crossref], [Google Scholar], [Publisher]

[5] M. Zeece, Vitamins and minerals, *Introduction to the Chemistry of Food*, **2020**, 163–212. [Crossref], [Publisher]

[6] J. Briffa, E. Sinagra, R. Blundell, Heavy metal pollution in the environment and

their toxicological effects on humans, *Heliyon*, **2020**, *6*, e04691. [Crossref], [Google Scholar], [Publisher]

[7] W. Mihatsch, M. Fewtrell, O. Goulet, C. Molgaard, J.C. Picaud, T. Senterre, ... W. Yan, ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Calcium, phosphorus and magnesium, *Clin. Nutr.*, **2018**, *37*, 2360–2365. [Crossref], [Google Scholar], [Publisher]

[8] H.B.D.V. Catharine Ross, Christine L. Taylor, Ann L. Yaktine, Dietary reference intakes for vitamin D and calcium, *Food Nutr. Board*, **2018**, *356*, 1053–1061. [Crossref], [Google Scholar], [Publisher]

[9] R.M.L. La Rovere, G. Roest, G. Bultynck, J.B. Parys, Intracellular Ca 2+ signaling and Ca 2+ microdomains in the control of cell survival, apoptosis and autophagy, *Cell Calcium*, **2016**, *60*, 74–87. [Crossref], [Google Scholar], [Publisher]

[10] G. Cormick, J. M. Belizán, Calcium intake and health, *Nutrients*, **2019**, *11*, 1606. [Crossref], [Google Scholar], [Publisher]

[11] R. Rizzoli, Hypercalcemia: Other causes than primary hyperparathyroidism, *Encyclopedia of Endocrine Diseases*, **2018**, *4*, 160–167. [Crossref], [Google Scholar], [Publisher]

[12] S. Ferrè, J.A. Neyra, O.W. Moe, Calcium, phosphate, and magnesium metabolism in chronic kidney disease, *Chronic Renal Disease*, **2020**, 661–679. [Crossref], [Google Scholar], [Publisher]

[13] M.K.C. van Goor, J.G.J. Hoenderop, J. van der Wijst, TRP channels in calcium homeostasis: from hormonal control to structure-function relationship of TRPV5 and TRPV6, *Biochim. Biophys. Acta - Mol. Cell Res.*, **2017**, *1864*, 883–893. [Crossref], [Google Scholar], [Publisher]

[14] J.B. Peng, Y. Suzuki, G. Gyimesi, M.A. Hediger, TRPV5 and TRPV6 calcium-selective channels, *Calcium Entry Channels in Non-Excitable Cells, CRC Press/Taylor & Francis*, **2018**. [Google Scholar], [Publisher]

[15] M. Cozzolino, F. Elli, P. Ciceri, E. Ottaviano, F. Conte, Calcium and phosphate physiology, *Critical Care Nephrology: Third Edition*, **2017**, 345–349. [Crossref], [Publisher]

[16] L.A. Negrea, Hypocalcemia and hypercalcemia, *Nephrology Secrets*, **2019**, 526–531. [Crossref]

[17] C. Antwi-Boasiako, Y.A. Kusi-Mensah, C. Hayfron-Benjamin, R. Aryee, G.B. Dankwah, L.A. Kwawukume, E.O. Darkwa, Total serum magnesium levels and calcium-to-magnesium ratio in sickle cell disease, *Med.*, **2019**, *55*, 1–8. [Crossref], [Google Scholar], [Publisher]

[18] I. Aslan, D. Canatan, N. Balta, G. Kacar, C. Dorak, A. Ozsancak, N. Oguz, R. Cosan, Bone mineral density in thalassemia major patients from Antalya, Turkey, *Int. J. Endocrinol.*, **2012**, *2012*, 1–4. [Crossref], [Google Scholar], [Publisher]

[19] I. Aslan, D. Canatan, N. Balta, G. Kacar, C. Dorak, A. Ozsancak, N. Oguz, R. Cosan, Bone mineral density in thalassemia major patients from Antalya, Turkey, *Int. J. Endocrinol.*, **2012**, *2012*, Article ID 573298. [Crossref], [Google Scholar], [Publisher]

[20] Q.R. Lahhob, N.Y. Mohammed, H.J. Abbas, Study of some minerals and trace elements levels in patients with sickle cell anemia and sickle cell anemiathalassemia in South of Iraq, *Biochem. Cell. Arch.*, **2021**, *21*, 1091–1095. [Google Scholar], [Publisher]

[21] L.A. DiMeglio, E.A. Imel, Calcium and Phosphate, *Basic and Applied Bone Biology*, **2019**, 257–282. [Crossref], [Google Scholar], [Publisher]

[22] L. McAlister, P. Pugh, L. Greenbaum, D. Haffner, L. Rees, C. Anderson, A. Desloovere, C. Nelms, M. Oosterveld, F. Paglialonga, N. Polderman, L. Qizalbash, J. Renken-Terhaerdt, J. Tuokkola, B. Warady, J.V. Walle, V. Shaw, R.

Shroff, The dietary management of calcium and phosphate in children with CKD stages 2-5 and on dialysis—clinical practice recommendation from the pediatric renal nutrition taskforce. *Pediatr. Nephrol.*, **2020**, *35*, 501–518. [Crossref], [Google Scholar], [Publisher]

[23] C.A. Wagner, N. Hernando, I.C. Forster, J. Biber, The SLC34 family of sodium-dependent phosphate transporters, *Pflugers Arch. Eur. J. Physiol.*, **2014**, *466*, 139–153. [Crossref], [Google Scholar], [Publisher]

[24] N. Hernando, C.A. Renal, Mechanisms and regulation of intestinal phosphate absorption, *Comprehensive Physiology*, **2018**, *8*, 1065–1090. [Crossref], [Google Scholar], [Publisher]

[25] J. Blaine, M. Chonchol, M. Levi, Renal control of calcium, phosphate, and magnesium homeostasis, *Clin. J. Am. Soc. Nephrol.*, **2015**, *10*, 1257–1272. [Crossref], [Google Scholar], [Publisher]

[26] M. Christov, H. Jüppner, Phosphate homeostasis disorders, *Best Pract. Res. Clin. Endocrinol. Metab.*, **2018**, *32*, 685–706. [Crossref], [Google Scholar], [Publisher]

[27] J.M. Forero-Delgadillo, D. Cleves, V. Ochoa, H. Londoño-Correa, J.M. Restrepo, J.A. Nastasi-Catanese, H. Pachajoa, PHEX gene mutation in a patient with X-linked hypophosphatemic rickets in a developing country, *Appl. Clin. Genet.*, **2020**, *13*, 57–62. [Crossref], [Google Scholar], [Publisher

[28] J. Bacchetta, J. Bernardor, C. Garnier, C. Naud, B. Ranchin, Hyperphosphatemia and chronic kidney disease: A major daily concern both in adults and in children. *Calcif. Tissue Int.*, **2020**, 1–12. [Crossref], [Google Scholar], [Publisher]

[29] H. Komaba, M. Fukagawa, Phosphate—a poison for humans, *Kidney Int.*, **2016**, *90*, 753–763. [Crossref], [Google Scholar], [Publisher]

[30] S. Shah, Assessment of serum calcium and phosphorus levels among transfusion-dependent beta thalassemia major patients on chelation therapy, *J. Postgrad. Med. Inst.*, **2015**, *29*, 168–171. [Google Scholar], [Publisher]

[31] O. Oladipo, E. Temiye, V. Ezeaka, P. Obomanu, Serum magnesium, phosphate and calcium in Nigerian children with sickle cell disease, *West Afr. J. Med.*, **2005**, *24*, 120–123. [Crossref], [Google Scholar], [Publisher]

[32] Q.R. Lahhob, N.Y. Mohammed, H.J. Abbas, Investigation of some trace elements levels & antioxidants in patients with thalassemia major and sickle cell anemia thalassemia in South of Iraq, *Indian J. Forensic Med. Toxicol.*, **2021**, *21*, 1091–1095. [Crossref], [Google Scholar], [Publisher]

[33] A.R. Vincente, G.A. Manganaris, C.M. Ortiz, G.O. Sozzi, C.H. Crisosto, Nutritional quality of fruits and vegetables, *Postharvest Handling: A Systems Approach*, **2014**, 69–122. [Crossref], [Google Scholar], [Publisher]

[34] J.P. Schuchardt, A. Hahn, Intestinal absorption and factors influencing bioavailability of magnesium- An update. *Curr. Nutr. Food Sci.*, **2017**, *13*, 260–278. [Crossref], [Google Scholar], [Publisher]

[35] K.P.S.M. Konrad, Magnesium Homeostasis. *Principles of Bone Biology*, **2020**, 487–513. [Crossref]

[36] A. Davenport, Trace elements in chronic kidney disease, *Chronic Renal Disease*, **2020**, 703–717. [Crossref], [Google Scholar], [Publisher]

[37] A. Mohammed Nawi, S.F. Chin, R. Jamal, Simultaneous analysis of 25 trace elements in micro volume of human serum by inductively coupled plasma mass spectrometry (ICP-MS), *Pract. Lab. Med.*, **2020**, *18*, e00142. [Crossref], [Google Scholar], [Publisher]

[38] Shah, R. Verma, J. M. Oleske, A. Scolpino, J.D. Bogden, Essential trace elements and

progression and management of HIV infection. *Nutr. Res.*, **2019**, *71*, 21–29. [Crossref], [Google Scholar], [Publisher]
[39] S. Rattanachaiwong, P. Singer, *Diets and Diet Therapy : Trace Elements.*, *Elsevier*, **2018**. [Crossref], [Google Scholar], [Publisher]
[40] R. Collings, L.J. Harvey, L. Hooper, R. Hurst, T.J. Brown, J. Ansett, M. King, S.J. Fairweather-Tait, The absorption of iron from whole diets: a systematic review, *Am. J. Clin. Nutr.*, **2013**, *98*, 65–81. [Crossref], [Google Scholar], [Publisher]
[41] H. Drakesmith, E. Nemeth, T. Ganz, Ironing out ferroportin, *Cell Metab.*, **2015**, *22*, 777–787. [Crossref], [Google Scholar], [Publisher]
[42] P. Kondaiah, P.S. Yaduvanshi, P.A. Sharp, R. Pullakhandam, Iron and zinc homeostasis and interactions: does enteric zinc excretion cross-talk with intestinal iron absorption, *Nutrients*, **2019**, *11*, 1885. [Crossref], [Google Scholar], [Publisher]
[43] J.P. Kothadia, R. Arju, M. Kaminski, A. Mahmud, J. Chow, S. Giashuddin, Gastric siderosis: An under-recognized and rare clinical entity, *SAGE Open Med.*, **2016**, 1–8. [Crossref], [Google Scholar], [Publisher]
[44] N. V. Bhagavan, C.-E. Ha, Metabolism of iron and heme, *J. Med. Biochem.*, **2015**, 511–529. [Crossref], [Google Scholar], [Publisher]
[45] N.C. Andrews, T. Ganz, The molecular basis of iron metabolism, *Molecular Hematology 4e*, **2019**, *92*, 161–172. [Crossref], [Google Scholar], [Publisher]
[46] V. Jeney, Clinical Impact and Cellular Mechanisms of Iron Overload-Associated Bone Loss, *Front. Pharmacol.*, **2017**, 8, 1–11. [Crossref], [Google Scholar], [Publisher]
[47] A. Teli, S. Nibedita, B. Adit, Zinc and ferritin in haemoglobinopathies: an observational study, *Int. J. Heal. Res. Med. Leg. Pract.*, **2019**, 5, 14. [Crossref], [Google Scholar], [Publisher]
[48] A.K. Baltaci, K. Yuce, R. Mogulkoc, Zinc Metabolism and Metallothioneins, *Biol. Trace Elem. Res.*, **2018**, *183*, 22–31. [Crossref], [Google Scholar], [Publisher]
[49] T. Kimura, T. Kambe, The Functions of metallothionein and ZIP and ZnT transporters: an overview and perspective, *Int. J. Mol. Sci.*, **2016**, *17*, 336. [Crossref], [Google Scholar], [Publisher]
[50] W. Zhong, Q. Sun, Z. Zhou, Role of zinc in alcoholic liver disease, *Molecular Aspects of Alcohol and Nutrition*, **2016**, 143–156. [Crossref], [Google Scholar], [Publisher]
[51] D. Kumari, N. Nair, R.S. Bedwal, Dietary zinc deficiency and testicular apoptosis, Handbook of Fertility, **2015**, 341–353. [Crossref], [Google Scholar], [Publisher]
[52] A. Şahin, E.Ö. Er, E. Öz, Z.Y. Yıldırmak, S. Bakırdere, Sodium, magnesium, calcium, manganese, iron, copper, and zinc in serums of beta thalassemia major patients, *Biol. Trace Elem. Res.*, **2020**. [Crossref], [Google Scholar], [Publisher]
[53] P. Kondaiah, P.S. Yaduvanshi, P.A. Sharp, R. Pullakhandam, Iron and zinc homeostasis and interactions: does enteric zinc excretion cross-talk with intestinal iron absorption? *Nutrients*, **2019**, *11*, 1885. [Crossref], [Google Scholar], [Publisher]
[54] J.L. Willoughby, C.N. Bowen, Zinc deficiency and toxicity in pediatric practice ,*Curr. Opin. Pediatr.*, **2014**, *26*, 579–584. [Crossref], [Google Scholar], [Publisher]
[55] M. Bost, S. Houdart, M. Oberli, E. Kalonji, J.-F. Huneau, I. Margaritis, Dietary copper and human health: Current evidence and unresolved issues, *J. Trace Elem. Med. Biol.*, **2016**, *35*, 107–115. [Crossref], [Google Scholar], [Publisher]
[56] M. Altarelli, N. Ben-Hamouda, A. Schneider, M.M. Berger, Copper deficiency: causes, manifestations, and treatment. *Nutrition in Clinical Practice*, **2019**, *34*, 504–513. [Crossref], [Google Scholar], [Publisher]
[57] R.J. Cousins, J.P. Liuzzi, Trace metal absorption and transport, *Physiology of the*

Gastrointestinal Tract, **2018**, 1485–1498. [Crossref], [Google Scholar], [Publisher]
[58] A.P. Ingle, P. Paralikar, S. Shende, I. Gupta, J.K. Biswas, L.H. da Silva Martins, M. Rai, Copper in medicine: perspectives and toxicity, *Biomedical Applications of Metals*, **2018**, 95–112. [Crossref], [Google Scholar], [Publisher]
[59] C.A. Zeid, L. Yi, S.G. Kaler, Menkes disease and other disorders related to ATP7A, Clinical and *Translational Perspectives on WILSON DISEASE*, **2019**, 439–447. [Crossref], [Google Scholar], [Publisher]
[60] M. Latorre, R. Troncoso, R. Uauy, Biological aspects of copper, *Clinical and Translational Perspectives on WILSON DISEASE*, **2019**, 25–31. [Crossref], [Google Scholar], [Publisher]
[61] C.B.S. Dangi, M. Kaur, M. Singh, Copper and zinc quotient in haemoglobinopathies, *Biomed. Pharmacol. J.*, **2011**, *4*, 165–173. [Crossref], [Google Scholar], [Publisher]
[62] B.A. Zachara, Selenium in complicated pregnancy, *A Review. Adv. Clin. Chem.*, **2018**, *86*, 157–178. [Crossref], [Google Scholar], [Publisher]
[63] F.P. Phiri, E.L. Ander, R.M. Lark, E.H. Bailey, B. Chilima, J. Gondwe , E.J.M. Joy, A.A. Kalimbira, J.C. Phuka, P.S. Suchdev, D.R.S. Middleton, E.M. Hamilton, M.J. Watts, S.D. Young, M.R. Broadley, Urine selenium concentration is a useful biomarker for assessing population level selenium status, *Environ. Int.*, **2020**, *134*, 105218. [Crossref], [Google Scholar], [Publisher]
[64] M. Kieliszek, Selenium–fascinating microelement, properties and sources in Food ,Molecules, **2019**, *24*, 1298. [Crossref], [Google Scholar], [Publisher]
[65] J.O. Hall, Selenium. *Veterinary Toxicology*, **2018**, *2*, 469–477. [Crossref], [Publisher]
[66] S.H. Yim, C.B. Clish, V.N. Gladyshev, Selenium deficiency is associated with pro-longevity mechanisms, *Cell Rep.*, **2019**, *27*, 2785-2797.e3. [Crossref], [Google Scholar], [Publisher]
[67] B.O. Idonije, O.I. Iribhogbe, G.R.A. Okogun, Serum trace element levels in sickle cell disease patients in an urban city in Nigeria, *Nat. Sci.*, **2011**, *9*, 67–71. [Pdf], [Google Scholar], [Publisher]
[68] M.M. Hamdy, D.S. Mosallam, A.M. Jamal, W. A. Rabie, Selenium and Vitamin E as antioxidants in chronic hemolytic anemia: Are they deficient? A case-control study in a group of Egyptian children, *J. Adv. Res.*, **2015**, *6*, 1071–1077. [Crossref], [Google Scholar], [Publisher]
[69] Z. Ozturk, G.E. Genc, S. Gumuslu, Minerals in thalassaemia major patients: An overview, *J. Trace Elem. Med. Biol.*, **2017**, *41*, 1–9. [Crossref], [Google Scholar], [Publisher]
[70] G. Bjørklund, M.S. Chartrand, J. Aaseth, Manganese exposure and neurotoxic effects in children, *Environ. Res.*, **2017**, *155*, 380–384. [Crossref], [Google Scholar], [Publisher]
[71] S. Anagianni, K. Tuschl, Genetic Disorders of Manganese Metabolism, *Curr. Neurol. Neurosci. Rep.*, **2019**, *19*, 33. [Crossref], [Google Scholar], [Publisher]
[72] L.J. Juttukonda, E.P. Skaar, Manganese and Nutritional Immunity, *Molecular, Genetic, and Nutritional Aspects of Major and Trace Minerals*, **2017**, 377–387. [Crossref], [Google Scholar], [Publisher]
[73] T. Filippini, S. Cilloni, M. Malavolti, F. Violi, C. Malagoli, M. Tesauro, I. Bottecchi, A. Ferrari, L. Vescovi, M. Vinceti, Dietary intake of cadmium, chromium, copper, manganese, selenium and zinc in a Northern Italy community, *J. Trace Elem. Med. Biol.*, **2018**, *50*, 508–517. [Crossref], [Google Scholar], [Publisher]
[74] M.K. Choi, Y.J. Bae, Dietary intake and urinary excretion of manganese in Korean healthy adults, *Biol. Trace Elem. Res.*, **2019**, 1–9. [Crossref], [Google Scholar], [Publisher]
[75] J.P. Gray, N. Suhali-Amacher, S.D. Ray, Metals and metal antagonists, *Side Effects of*

Drugs Annual,. **2017**, *39*, 197–208. [Crossref], [Google Scholar], [Publisher]

[76] S. Anagianni, K. Tuschl, Genetic Disorders of Manganese Metabolism, *Curr. Neurol. Neurosci. Rep.*, **2019**, *19*, 33. [Crossref], [Google Scholar], [Publisher]

[77] Z.Q. Wang, Y. Yu, X.H. Zhang, J. Komorowski, Chromium-insulin reduces insulin clearance and enhances insulin signaling by suppressing hepatic insulin-degrading enzyme and proteasome protein expression in KKAy mice, *Front. Endocrinol.*, **2014**, *5*, 1–6. [Crossref], [Google Scholar], [Publisher]

[78] J.B. Vincent, New evidence against chromium as an essential trace element, *J. Nutr.*, **2017**, *147*, 2212–2219. [Crossref], [Google Scholar], [Publisher]

[79] P. Chaubey, V. Suvarna, P. C. Sangave, A.K. Singh, Nutritional management of diabetes—a critical review, *Bioactive Food as Dietary Interventions for Diabetes*, **2019**, 289–308. [Crossref], [Google Scholar], [Publisher]

[80] J.B. Marcus, Vitamin and mineral basics: the ABCs of healthy foods and beverages, including phytonutrients and functional foods, *Culinary Nutrition*, **2013**, 279–331. [Crossref], [Google Scholar], [Publisher]

[81] L. Leyssens, B. Vinck, C. Van Der Straeten, F. Wuyts, L. Maes, Cobalt toxicity in humans—a review of the potential sources and systemic health effects, *Toxicology*, **2017**, *387*, 43–56. [Crossref], [Google Scholar], [Publisher]

[82] D. Lison, Cobalt, *Handbook on the Toxicology of Metals*, **2015**, *1*, 743–763. [Crossref], [Google Scholar], [Publisher]

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