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THE ROLE OF MINERALS IN THE HUMAN METABOLISM AND THEIR INTERACTIONS IN MITOCHONDRIAL ENZYMES

Ferro M., Ratleff G.
FG Scientifica and Science Department at Nutrition Formulators Inc., Miramar, Fl, USA

Abstract: *Minerals are inorganic substances present in all tissues and body fluids. As the human body cannot synthesize minerals, their concentrations depend exclusively on the diet. Most minerals work as coenzymes in human metabolism, that is, they are enzymatic activators for cells to perform work. A cell with a low energy production capacity is a cell that is vulnerable to developing neurological diseases as well as metabolic syndrome. In this review, we detail the specific functions of minerals in mitochondrial metabolism, their action on the respiratory chain in electron transfer as well as their actions on enzymes for the removal of reactive oxygen species (ROS). As the action of minerals as enzymatic cofactors is essential not only for human metabolism in the generation of chemical energy but also in the balance of the electrochemical potential, the lack of these micronutrients present in diet can trigger innumerable diseases in the human body. In this way, paying special attention to adequate mineral intake in the diet is a crucial factor to keep cellular metabolism balanced and the vital functions of the human body preserved.*
Keywords: *Minerals, Mitochondria, ATPase, Superoxide dismutase, Glutathione peroxidase.*

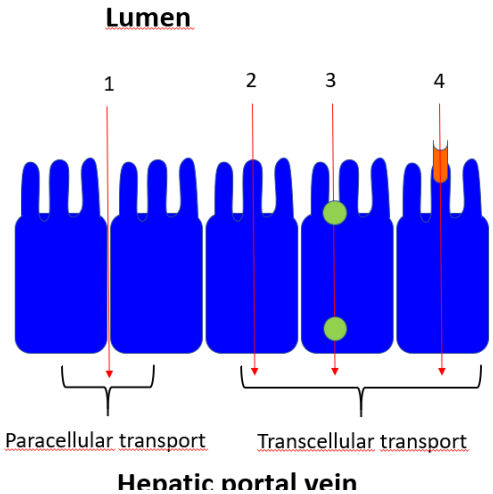
INTRODUCTION

Minerals are inorganic substances present in all tissues and body fluids. The presence of minerals is indispensable to any living organism since minerals are responsible for maintaining important physical-chemical processes that allow the organism to stay alive [1]. Minerals are used by the metabolism in several ways. Although they do not produce energy, they have a key role as enzymatic cofactors in many metabolic activities in the human body [2]. Not only in humans but each form of living matter requires these inorganic or mineral elements for their physiological processes and maintenance of life

Mineral concentrations in mammalian muscles basically depend on the imbalance of the animal's intake/absorption, type of muscle, age, environment, breed, and genetic factors [4]. Studies suggest that minerals can only perform their biological function in muscle cells if they are available in the right amount, and their concentration is under strict control for homeostasis maintenance [4]. Therefore, processed, and ultra-processed food due to mineral deficiency in the soil is associated with a high prevalence of inadequate mineral intake and deficiency of minerals in human metabolism [5].

Interestingly, in a study on the characteristics of the metabolic syndrome, Costa-Vieira et al (2019) evaluated the benefits of the mineral-rich water. These natural mineral waters originate from underground sources, which allow their physical-chemical composition and organoleptic characteristics to remain practically constant and intact, protecting them from any risk of contamination [6].In fact, the consumption of water can make important contributions to mineral nutritional needs depending on its composition, and the need to promote the consumption of highly mineralized water has been supported [7, 8, 9, 10]. According to Schneider et al (2017), mineral water elements are well-absorbed and highly bio available [11].Some studies suggest because of their chemical forms of presentation in water, minerals can be more quickly absorbed when administered in this way [12, 13], and their bioavailability in water is greater than in food [11]. This is also due to the passage of water through the par cellular pathways between the enterocytes, reaching the bloodstream more quickly (Fig. 1) [14]. On the other hand, in a study of healthy young women, it was shown that approximately 50% of the magnesium in the magnesium-rich mineral water was absorbed when consumed alone [15]. The bioavailability of magnesium in mineral water was increased when the water was consumed with a meal. The authors suggest that perhaps because of a slower gastrointestinal transit time and the presence of digestion products from the meal was the reason [15].

Figure 1



The figure shows the different forms of absorption and transport by enterocytes: (1) Paracellular transport; (2) Passive diffusion from the apical (brush border) to basolateral membrane; (3) vesicle mediatetranscytosis; (4) carrier mediated transport (active transport).

MINERALS AS AN ENZYMATIC COFACTOR

Most minerals work as coenzymes in human metabolism, that is, they are enzymatic activators for cells to perform work[16, 17]. Minerals such as calcium, magnesium, copper, iron, zinc,selenium, and manganese are responsible not only to produce energy in the cells, but also for the synthesis of neurotransmitters, proteins, and DNA [18]. A cell with a low energy production capacity is a cell that is vulnerable to developing neurological diseases as well as metabolic syndrome [19, 20]. While some minerals interact as an energy enzymatic cofactor, other minerals such as sodium, potassium, calcium, and chlorine act as regulators of electrical potentials between neurons and muscles [21]. The lack of these minerals in the tissue can develop serious changes in behavioral disorders.

Several studies have demonstrated the importance of mineral balance in several pathologies, including type 2 diabetes [22], depressive disorder [18, 23], osteoporosis [24], periodontal disease [25],and several others. As minerals participate in tens of hundreds of metabolic reactions so that the enzymes can perform work, if there is a lack of minerals in the system, the enzymes cannot be activated to perform the metabolic actions, and this ends up triggering associated pathologies [26].Magnesium considered the master mineral,plays a fundamental role both in the production of energy in cells and in protein synthesis [27]. In the hydrolysis of adenosine triphosphate (ATP), magnesium is the cofactor of the ATPase enzyme, and it assists in the potassium/sodium pump in the cell membrane[28]. Magnesium also has a great influence on protein synthesis, acting mainly on the enzyme RNA polymerase in the transcription process [29], and the translation process through ribosomes [30]. However, the action of the ATPase cofactor does not limit only to magnesium, calcium also interactswith ATPase in the generation of cellular energy [31].

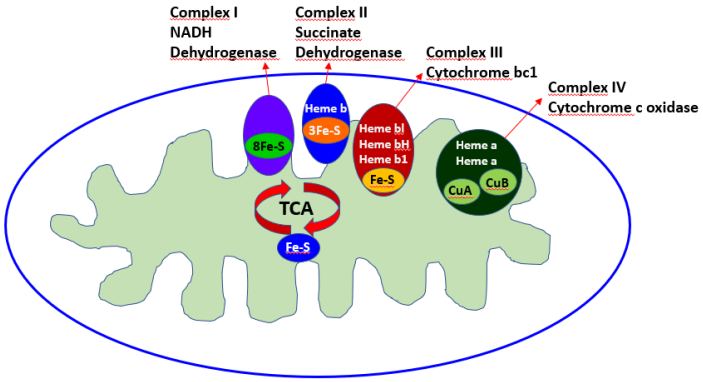
Calcium plays a well-known and important regulatory role in mitochondria, where it can accumulate at much higher concentrations than in the cytoplasm [32]. Studies have found that calcium can replace magnesium to support the mitochondrial TNF receptor–associated protein 1 (TRAP1) ATPase activity [33]. This process is extremely complex, but it demonstrated that in the presence of calcium, ATPase activity was greater when there are large amounts of ATP available for hydrolysis [33]

As cell respiration in mitochondria is the determining factor in life, this process is also directly linked to aging [34]. The lower the capacity of mitochondria to manage reactive oxygen species (ROS) formed in the respiratory chain, the more damage to protein structures, DNA, and especially mitochondrial DNA will occur [35]. Concentrations of iron and copper are crucial for the transport of electrons in the respiratory chain [36] (Fig. 2).Without these minerals, it would be impossible to transfer electrons from hydrogen to oxygen for the generation of ATP [36]. In the case of iron (Fe^{++}), in iron-sulfur (Fe/S)protein specifically, their participation in electron transfer occurs in practically all multi-enzymatic complexes in the respiratory

chain [37].Succinate dehydrogenase is a key enzyme in complex II of the respiratory chain in the tricarboxylic acid cycle that usesa reduced form of flavine dinucleotide($FADH_2$) to convert succinate to fumarateand to initiate electron transfer [38]. In this biochemical pathway, in complex II electron transfer continues through three Fe-S protein centers to ubiquinone [39].In the same way, in complex I the electrons move until the Fe-S proteinthrough NADH,not $FADH_2$, which is a complex II specific coenzyme (Fig. 2)[40]. Dehydrogenase enzymes in complex I, such as pyruvate dehydrogenase, isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, and malate dehydrogenase trigger the four respiratory chains in the electron transfer present in mitochondria using the same Fe-S protein to transfer an electron to ubiquinone, while complex II the process occurs only through the succinate dehydrogenase[41]. Unlike the Fe-S protein, where iron is bound to a sulfur atom of the cysteine, in cytochromes iron transfers electrons directly by reducing $Fe3^+$ (ferrous) to $Fe2^+$ (ferrous) in the heme group[42].

The synthesis of heme is totally dependent on mitochondria [43]. This protein is a complex of ferrous iron and protoporphyrin IX [44]. Heme is an important prosthetic group for numerous proteins, mainly cytochrome c present in complex III of the mitochondrial respiratory chain [45]. In the respiratory chain, heme is involved in the transfer of electrons for enzymatic redox reactions [46]. In mammals, heme synthesis involves the sequential action of eight different enzymes, one of which is the insertion of Fe ++ itself in the pyrrole ring during its synthesis [42]. This process is initiated in the mitochondrial matrix by the formation of 5-aminolevulinic acid (ALA) through glycine and succinyl CoA by ALA synthase (Fig.3)[42, 45].

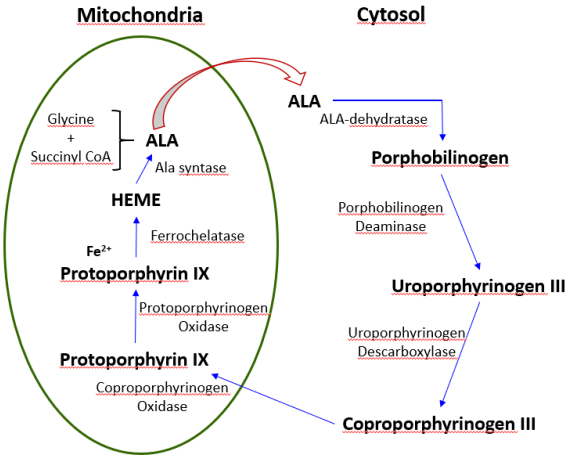
Figure 2



The figure shows the presence of the iron-sulfur protein in complexes I to IV of the mitochondrial respiratory chain, as well as the presence of copper in the cytochrome c oxidase.**TCA** - Tricarboxylic acid cycle; **Fe-S -** iron-sulfur protein; **CuA and CuB**- Copper ions.

Another essential mineral for the metabolism of the respiratory chain in electron transfer is copper [47]. Copper ions undergo differentiated chemistry due to their ability to adopt different redox states, oxidized [Cu (II)] or reduced [Cu (I)] [48]. Its function as a catalytic cofactor in redox chemistry for proteins and enzymes that perform biologicalfunctions is fundamental [47]. In complex IV of the mitochondrial respiratory chain, the metalloenzyme cytochrome c oxidase (COX) contains copper as a cofactor, which participates as the final acceptor in electron transport to oxygen in the aerobic production of ATP [49]. Copper can be extremely toxic to cells due to its high redox reactivity, triggering the high production of ROS [50]. Therefore, a network of copper transporters strictly controls the traffic of this mineral in living systems [48]. Once inside the cell, copper is sequestered by metallothionein, among them Cup1p and Crs5p, directed to the vacuole, which is important for copper detoxification [51]. On the other hand, Elsawi et al (2019) conducted a study to cancel acrylamide-induced hepatotoxicity in male rats by the administration of a copper (i) nicotinic acid complex. The biochemical and histological study proved the drastic effect of acrylamide on the functions and structure of the liver of rats, which were notably improved by the administration of a copper (i) nicotinic complex [52].In fact, the copper (i) nicotinic acid complex has a remarkable antioxidant and anti-inflammatory action. This is due to the ability to mimic the superoxide dismutase (SOD) mechanisms in removing the reactive oxygen species (ROS)[53].

Figure 3



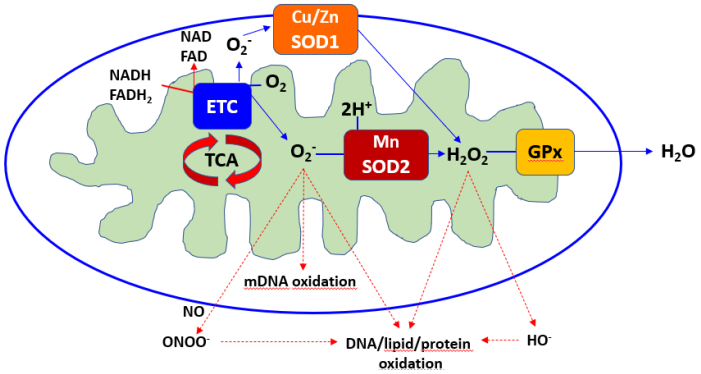
The figure shows the metabolism of the Heme protein as well as the synthesis of aminolevulinic acid (ALA) through the mitochondria

Minerals as a cofactor in removing reactive oxygen species through SOD and GPx

The determining factor for the removal of ROS is the activation of SOD[54]. This enzyme removes the excess superoxide($O2^-$) produced through cellular respiration [55]. SOD converts $O2^-$ into hydrogen peroxide (H_2O_2) which will be converted to water (H_2O) by glutathione peroxidase [56]. Superoxide radicals can also react with other species of ROS, such as nitric oxide, forming highly toxic species, including peroxynitrite[57].Peroxynitrite reacts with tyrosine residues in proteins triggering high production of nitrotyrosine in plasma proteins [58]. This reaction is direct evidence of peroxynitrite production with consequences in increasing cellular oxidative stress [58]. Interestingly, a significant correlation was found between plasma nitrotyrosine values and plasma glucose concentrations, mainly in individuals with type 2 diabetes [59] and SOD is fundamental to removing ROS in the beginning process [55].

There are two forms of SOD that contain copper. The first is Cu / Zinc (Zn) -SOD found in most cells in the body [60]. The second is extracellular SOD, which is found in high levels in the lungs and low levels in blood plasma [61]. Almost all the copper in our bodies is linked to transport proteins. Ceruloplasmin and Cu-albumin, as well as storage proteins (metallothionein's) or even enzymes containing copper, are fundamentals to the transport of this mineral[56]. Ceruloplasmin works as an antioxidant by binding to Cu reducing the oxidative damage of this mineral in its free form [62]. Ceruloplasmin also prevents free copper ions from catalyzing oxidative damage [63]. Another way for this enzyme to act is through the oxidation of ferrous iron, facilitating the loading of iron in its transport protein (transferrin), and preventing free ferrous ions from participating in reactions that generate free radicals [64]. In the SOD metabolism, Cu/Zn act as cofactors for SOD1 in the mitochondrial intermembrane space and cytoplasm [65], and manganese acts on SOD2 in the mitochondrial matrix by removing the large amounts of O_2^- produced through cellular respiration (Fig. 4)[66]. Both SOD1 and SOD2 convert O_2^- to H_2O_2, a less toxic form of ROS[65, 66].

Figura 4



The figure shows the metabolism of superoxide dismutase in the removal of superoxide formations: **SOD1/2** - Superoxide dismutase 1 and 2; **ETC** - Electron transport chain; **TCA** - tricarboxylic acid cycle; **NADH** - Nicotinamide adenine dinucleotide reduced; **NAD** - Nicotinamide adenine dinucleotide; **$FADH_2$** - Flavine adenine dinucleotide reduced; **FAD** - Flavine adenine dinucleotide; **GPx** - Glutathione peroxidase.**NO** - nitric oxide; **$ONOO^-$** - Peroxynitrite. **HO^-**- hydroxyl radical.

The removal of H_2O_2 occurs by another family of enzymes, also known as glutathione peroxidase(1-8) andthe availability of selenium regulates its activity of it[67]. Glutathione peroxidase 4, for example, has the ability not only to convert H_2O_2 to H_2O, but also to convert the lipid hydroperoxide into respective alcohols [68]. In human metabolism we find eight types of glutathione peroxidase, depending on the tissue, the most common being glutathione peroxidase 1, which is present in all cytoplasm of mammalian cellsand is also expressed in the liver [69]. These enzymes convert reduced glutathione (GSH) into oxidized glutathione (GSSG) or glutathione disulfide [70]. Over the years, it has been discovered that the trace mineral, selenium, in the form of the amino acid selenocysteine, is essential for the activity of GPx-1 [71]. This mechanism involves the oxidation of selenol (RSeH), a part of selenocysteine that allows the removal of hydrogen peroxide, forming a derivative of selenic acid (RSeOH) [71. 72]. In a second step, another GSH again reduces selenic acid to selenol, again forming GSSG (The reaction can be seen below) [72]. The lack of these minerals can cause serious damage to the structures of both the mitochondria themselves and the molecular structures of the entire cell.

$$RSeH + H_2O_2 \rightarrow RSeOH + H_2O$$
$$RSeOH + GSH \rightarrow GS\text{-}SeR + H_2O$$
$$GS\text{-}SeR + GSH \rightarrow GS\text{-}SG + RSeH$$

Table 1

S.no.	Mineral	Diseases related to deficiency	Reference
1	Calcium	Osteoporosis, periodontal disease, several types of cancer, hypertension, and cardiovascular disease.	Peterlik et al (2013)
2	Magnesium	Atherosclerosis, myocardial infarction, hypertension, cancer, kidney stones, and psychiatric disorders.	Elin (1988)
3	Zinc	Acrodermatitis enteropathica, impairment of the immune system, neurological and psychological changes	Roohani et al (2013)
4	Copper	Myelopathy, peripheral neuropathy, and optic neuropathy.	Jaser & Wiston (2010)
5	Sodium	Hyponatremia: Brain swelling, coma and death	Dineen et al (2017)
6	Potassium	Hypokalemia: Cardiac arrhythmia, paralysis and death	Asmar et al (2012)

DISCUSSION

In fact, minerals play a crucial role in cellular metabolism in general. Adequate intake of vitamins and minerals is of concern to the American population today. Many Americans have an inadequate intake of several essential nutrients [73]. The recent 2015-2020 Dietary Guidelines for Americans (DGA) [74] identified some vitamins and minerals on an under-consumed scale, such as vitamins A, D, E, and C, and choline, calcium, magnesium, iron (for certain age groups and gender), potassium and fiber, to the point of leading to adverse health outcomes and, as such, have been designated as "nutrients of concern for public health". Therefore, the DGA recommends the consumption of nutrient-rich foods for healthy eating and, in some cases, enriched foods and dietary supplements, especially for specific population groups [74]. This coupled with the high supply of processed foods is leading the human body to trigger numerous pathologies [5]. Therefore, the replacement of minerals has been an alternative.

Seeking to maintain the balance of minerals in cellular metabolism can be a good alternative in preserving health. As we saw in this present review, most minerals function as coenzymes, and a small deficiency of these micronutrients can trigger many problems in cell metabolism [26]. A balanced nutritional intake of minerals can serve as disease prevention and to alleviate idiopathic symptoms, especially in relation to magnesium, considered by nutrition as a master mineral [27]. However, despite the synergism of some minerals in human metabolisms, such as copper and iron, calcium and magnesium, and zinc and copper, some minerals should not be administered concurrently because of their absorptive antagonism, among calcium and magnesium itself, zinc and copper, and iron and calcium [75].

Notably, while some minerals are synergistic in metabolism, those same minerals are completely antagonistic in the absorptive process. The example of calcium, absorption occurs by two distinct mechanisms, including transcellular absorption in the duodenum, and passive paracellular absorption in the jejunum and ileum, and there may be a much smaller absorption in the colon [76]. In this way, ionized calcium diffuses through the narrow junctions to the basolateral spaces around the enterocytes and, consequently, to the blood [77]. When calcium availability is high, this route is responsible for most of the mineral's absorption, due to the short time available for active transport in the duodenum. [76]. This can show us how these absorption pathways can vary the bioavailability and the difference of opinion of some studies on the best way to absorb minerals.

In the case of iron, this mineral is absorbed through enterocytes in the villi of the proximal duodenum [78]. Since efficient absorption of iron requires an acidic environment, antacids or other conditions that interfere with the secretion of gastric acid can interfere with the absorption of this mineral [79]. The iron absorptive process occurs when ferric iron (Fe^{+++}) in the duodenal lumen is reduced to its ferrous form (Fe^{++}) by the action of a ferrireductase enzyme present in the brush border [76]. Iron is co-transported with a proton (H^{+}) to the enterocyte via a specific DMT-1 divalent metal transporter [80]. As this carrier is not specific for iron, it also carries many divalent metal ions which can lead to saturation leading to the antagonism of the absorption of other metals [75].Therefore, the interaction between calcium and iron in the most plausible luminal absorption is associated with the uptake of iron through DMT1 (divalent metal transporter 1) in the apical membrane and also in ferroportin, a transmembrane protein that transports iron from the inside of the cell to the outside of the cell [76]. However, this inhibition does not occur at the transmembrane protein that transports iron from the inside of a cell to the outside of the cell [81]. The studies by Mónica et al (2018) demonstrated that the expression of the DMT1 mRNA decreased when the intracellular iron increased. On the other hand, the mixture of calcium, zinc and iron increased the expression of DMT1 and ferroportin mainly under high concentrations of zinc. The findings of this study suggest that calcium and zinc interfere with iron metabolism. This interference occurs due to an increase in ferroportin activity, which results in decreased iron absorption [82].

As we have seen in this present review, once in cell metabolism, minerals are highly synergistic in relation to enzyme activity. The mitochondrial respiratory chain, for example, cannot perform work without iron and copper [36], as well as the synthesis and hydrolysis of ATP without calcium and magnesium [28, 31]. This is also the case with enzymes that remove ROS. SOD1 cannot remove O2- unless it has zinc and copper in

synergy [60]. No less important in the subsequent stages of ROS removal, it is still necessary to have manganese in SOD 2 (mitochondrial) [66] and selenium in GPx to remove H_2O_2 [71].The synergy of minerals in cellular metabolism is also present in the electrical potential between neurons. Minerals like sodium and potassium play a crucial role in the electrical potential not only in neurons but also in muscle tissue [21]. For this potential to be activated, depolarization in these cells is necessary, basically depending on the electrochemical potential between the inner membrane and the outer membrane [83]. However, this process is only possible with the activation of the ATP-dependent sodium/potassium pump [84]. In other words, a cascade of interactions between the synergy of minerals initiates a chemical action so that the electrical potential can be unleashed.

CONCLUSION

Minerals need to be always in balance in the system for cells to be able to perform work, whether chemical or electrical. Cellular life-sustaining processes depend on a careful balance between minerals. Consequently, this balance depends exclusively on the diet since these micronutrients cannot be synthesized by the body. Due to the excessive unrestrained consumption of industrialized and genetically modified products, the imbalance between minerals in human metabolism today is a fact. A review of the amounts of minerals ingested in the diet becomes essential to maintain an organism in good health. The contemporary lifestyle shows that foods with empty calories are increasingly present on the menus, leading individuals to be vulnerable to certain diseases. Therefore, attention to the intake of minerals to maintain a metabolic balance in cells has become increasingly necessary in nutrition, both in the addition of minerals in food and in replacement as a supplement.

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