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# Mineral Deficiencies: A Root Cause for Reduced Longevity in Mammals

*Nyshadham S.N. Chaitanya and Sibani Sahu*

## Abstract

Metals, inorganic compounds and their elements that act as cofactors for enzymes that play an essential role in various biological processes constitute mineral nutrients. Their primary source is soil and enters the climax consumers in food chain through plants as they contain most minerals that are essential for humans. They are required in small and precise amounts according to their requirement they were classified as Major (phosphorous (P), potassium (K)), Secondary (calcium (Ca), magnesium (Mg), sulphur (S)), Minor/trace/rare (Boron (B), chlorine (Cl), chromium (Cr), fluoride(F), iodine (I), iron (Fe), manganese (Mn), molybdenum (Mo), nickel (Ni), selenium (Se), sodium (Na), vanadium (V) and zinc (Zn)). The daily requirement of minerals for individuals for effective biological function inside the cell is known as recommended dietary allowance (RDA) that varies for element. The daily requirement of major element is up to 10 g/d, whereas secondary and micro minerals was 400 - 1500 mg/d and 45 µg/d - 11 mg/d, respectively. Meats, vegetables, fruits, grains contains high amount of minerals that protect humans from mineral deficiencies. Some of the mineral deficiencies include ageing, cancer, hair loss etc. The key for these root problems include supplementation of healthy foods rich in minerals and understanding the importance of food by nutrition education, practice of physical activity, and about food habits. A detailed understanding of each mineral and their biological importance through mechanism of action studied in detail to overcome their deficiencies.

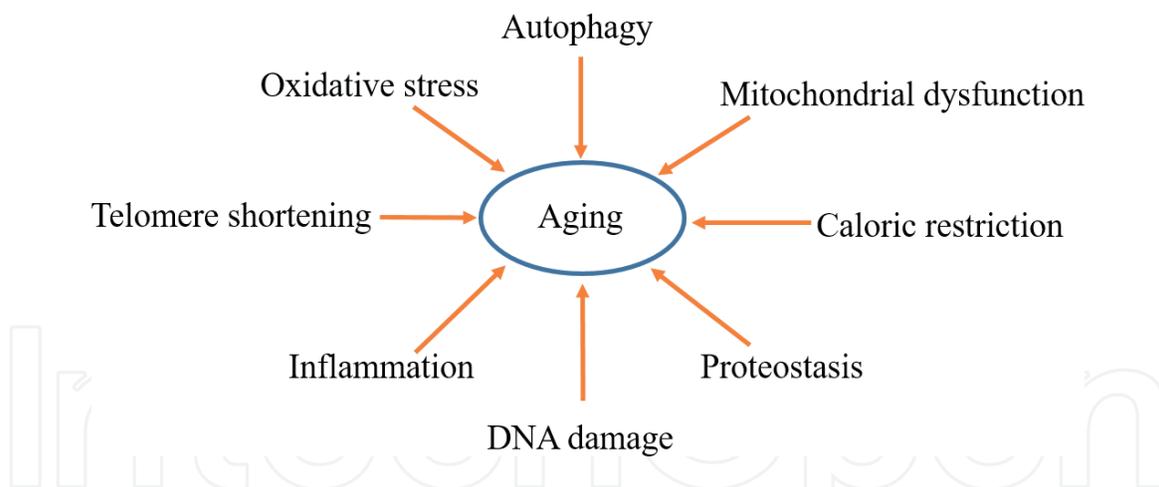
**Keywords:** nutrients, recommended dietary allowance, ageing, food habits, health

## 1. Introduction

A regulated diet with all the constituents consumed in appropriate way maintains cell homeostasis and keeps the body under physiological state that are essential for cellular demands. A number of factor contribute to body function such as biomolecules, vitamins, minerals, and hormones etc....of these minerals gain utmost importance due to availability inside the cell is low but shows a major effects even small change in concentration. Minerals perform wide variety of functions, which are essential for existence of organism. Some of them form integral components, some as cofactors, and some as essential components of enzymes. The existence of these minerals as part of enzymes helps to play a role in metabolism of molecules

consumed through diet and maintain cell homeostasis. Some of the minerals acts in concert with aid of hormones according to their need in specific organelle. Minerals either in part or in combination with vitamins shows major functions required for the cell and their deficiencies shows adverse side effects although not hereditary. Minerals classified according to the need includes major (phosphorous (P), potassium (K), calcium (Ca), magnesium (Mg), sulphur (S)), minor/trace/rare (Boron (B), chlorine (Cl), chromium (Cr), fluoride (F), iodine (I), iron (Fe), manganese (Mn), molybdenum (Mo), nickel (Ni), selenium (Se), sodium (Na), vanadium (V) and zinc (Zn)). In this chapter a detailed explanation of selected minerals about their importance as a source requirement, uptake and transport mechanism, toxicity and tolerance mechanism, taken as means of measurement for determining their beneficial effects to study in detail about the specific role in metabolism their mechanism of action and deficiency diseases associated with reduced life span had described.

Decline of physiological functions leading to senescence of cells with arrest at G1 phase is characteristic feature of ageing [1]. At cellular level senescence was caused due to several factors such as oxidative stress, mitochondrial dysfunction, inflammation, autophagy deregulation, telomere shortening [2, 3]. Cells senesce either due to continuous replication or due to stress induction thereby activating p16, p53 pathways and phosphorylation of Rb protein [4] leading to inflammatory condition with high lysosomal  $\beta$ -galactosidase activity [5–7]. As cells continuously, divide chromosomes containing telomere with repeated nucleotides region gets shortened [8] leads to replicative senescence [9] and result in ageing. In humans, the repeated sequence at telomere region is TTAGGG [10]. Cells capable of replicating continuously express telomerase for replication of telomere ends of chromosome, which had tendency to reverse ageing process and used as targeted approach [2]. Increased ROS production due to stress apart from normal cellular homeostasis as a compensatory mechanism aggravates ageing phenomenon. Free-radical theory proposes ROS leads to oxidative damage and contributes to plays a role in the ageing process [11]. First call to increased ROS levels inside the cells is activation of survival pathways, which further leads to apoptosis due to failure of antioxidant system to defence against ROS that ultimately leads to cell death [12, 13]. Several factors were responsible for production of ROS that disturbs balance between cell survival and cell death through increased redox potential towards pro-inflammatory state and connects oxidative stress, inflammation and ageing [14–16]. The release of pro-inflammatory agents inside the senescent cells include TNF- $\alpha$ , IL-6, IL-1 $\beta$  [17] regulated by transcription factors such as AP-1, NF $\kappa$ B [18]. The activation of AP-1, NF $\kappa$ B requires kinases such as ERK, JNK, p38MAPK, PI3K [19] and leads to expression of target proteins such as MMP9, ICAM-1, iNOS, COX-2 [20–22]. Mitochondria apart from playing a role in oxidative phosphorylation system it also plays a role in apoptosis, metabolism, innate immunity and ageing [23–25]. Mitochondrial regulation occurs through PGC-1 ( $\alpha$  &  $\beta$ ) that responds to NAD<sup>+</sup> levels inside the cell [26, 27] and in response to SIRT1 regulation occurs by HIF-1 $\alpha$  independent of PGC-1 [28]. In ageing NAD<sup>+</sup> levels decreases without loss of SIRT1 but downregulates it [29]. One of the contributing factor for cell survival under stress conditions is autophagy [30]. Autophagy is downregulated under nutrient rich conditions through mTOR protein [31] and stimulated through AMPK by phosphorylating mTOR (inactivation) ultimately activating ULK-1 [32]. Reports reveal autophagy deregulates due to overexpression of mTOR [33, 34] in ageing. Several Genetic events (mTOR, TGF $\beta$ ), Molecular events (oxidative stress, autophagy) also contribute to ageing phenomenon. A summary of factors responsible for cellular ageing were shown in **Figure 1**.



**Figure 1.** Factors responsible for aging: Different factors enhances process of aging includes autophagy, oxidative stress, shortening of telomere, caloric restriction, proteostasis, inflammation, mitochondrial dysfunction and DNA damage.

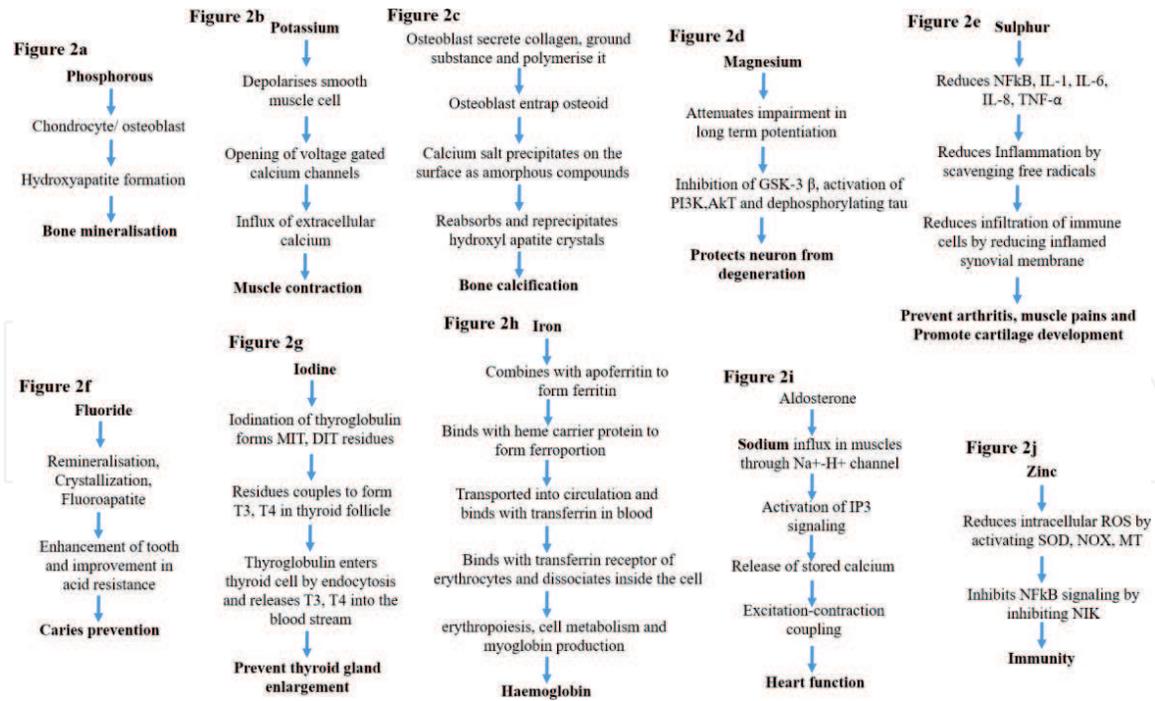
## 2. Deficiency of major mineral elements and lifespan

### 2.1 Phosphorous (P)

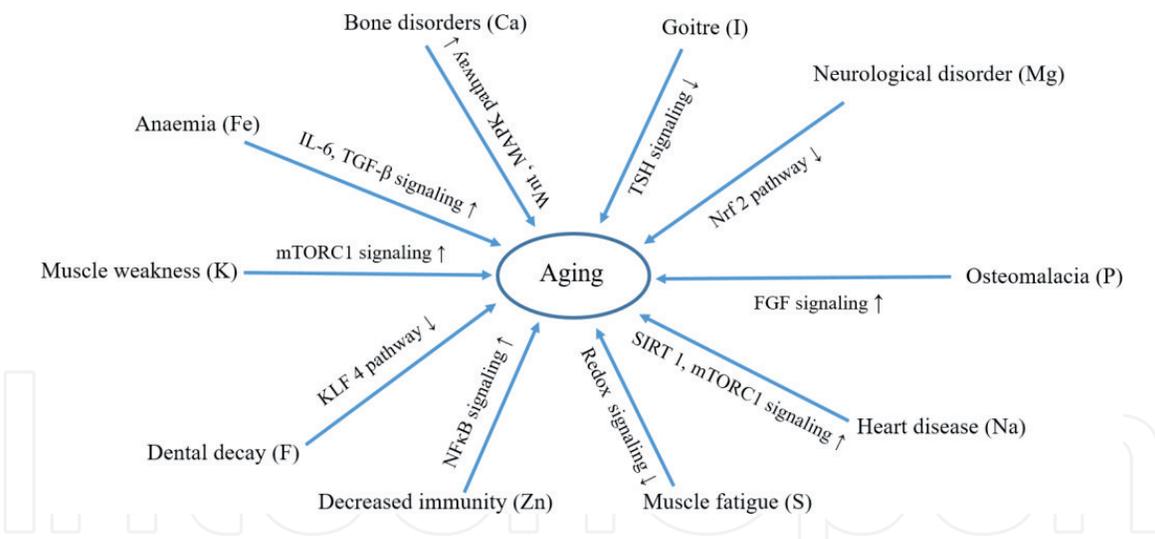
Phosphorous is mostly present in meat, fish, eggs, and milk and dietary intake is 0.8-1.0 g/day. Phosphorous is essential for the formation of healthy bones, part of buffer system and component of DNA and RNA. Functions of phosphorous include formation of high-energy phosphates, nucleic acids, nucleotide coenzymes. Activation of enzymes require phosphate moiety and found in cell walls. Phosphorous deficiency include rickets, osteomalacia observed mostly in cases of malnutrition, anorexic individuals, or alcoholics. Symptoms are poor appetite, anxiety, and irritability. Phosphate absorption occurs in jejunum calcitriol, low pH favours their absorption while phytate reduces its absorption. Serum phosphate level is about 3-4 mg/dl and reduced in renal rickets, vitamin D deficient rickets and in diabetes mellitus. Phosphate excreted by kidney in the form of urine. Phosphate is mainly involved in mineralisation of the bone from chondrocytes and osteoblast. The process of mineralisation begins with hydroxyapatite formation from calcium ( $\text{Ca} + 2$ ) and inorganic phosphate. Calcium incorporated through annexin calcium channel here as inorganic phosphate from type III sodium inorganic phosphate transporter and from PHOSPHO1. Hydroxyapatite penetrate the matrix vesicle and elongate due to tissue non-specific alkaline phosphatase (TNAP) and deposit in collagen fibre spaces [35]. The role of phosphorous in bone mineralisation shown in **Figure 2a**. Osteomalacia resulting from hypophosphatemia occurs through fibroblast growth factor signalling (FGF) [36] that links with ageing process [37]. Reduced phosphate levels inside the cell leads to increased FGF 23 levels in the serum and acts by inhibiting calcitriol, PTH,  $1\alpha$ -hydroxylase and stimulating 24-hydroxylase [38]. The signalling pathway connecting phosphorous deficiency and ageing shown in **Figure 3**.

### 2.2 Potassium (K)

Potassium is principal intracellular cation required daily about 3-4 g that is present majorly in banana, orange, potato, chicken, and liver. It helps regulate fluid balance, nerve signals and muscle contractions and beneficial aspects include reduction in blood pressure, water retention; prevention of kidney stones, osteoporosis, and protection against strokes. It functions to maintain intracellular osmotic



**Figure 2.** Role of mineral elements in disease prevention. a: Role of phosphorous in bone mineralisation, b: Potassium involvement in muscle contraction, c: Calcium in bone calcification, d: Magnesium in protection of neuron degeneration, e: Sulphur in prevention of muscle pains and joint pains, f: Fluorine in prevention of dental caries, g: Iodine in thyroid hormones, h: Iron in haemoglobin synthesis, i: Sodium in heart function, j: Zinc in immunity.



**Figure 3.** Deficiency disease leads to aging through disturbed signalling pathway. Mineral deficiencies were shown in parenthesis. Ca: Calcium, I: Iodine, Mg: Magnesium, P: Phosphorous, Na: Sodium, S: Sulphur, Zn: Zinc, F: Fluorine, K: potassium, Fe: Iron. TSH: Thyroid stimulating hormone, Nrf 2-nucleoid erythroid receptor factor 2. FGF-fibroblast growth factor, SIRT1; Sirtuins 1, mTORC1: mammalian target of rapamycin complex 1, NFκB: Natural factor kappa beta, IL-6: interleukin 6, TGF-tumor growth factor, MAPK-mitogen activated protein kinase, Wnt-Wingless-related integration site.

balance, regulation of acid–base balance, required for transmission of nerve impulse, and necessary for biosynthesis of proteins. Plasma levels are 3.4-5 mEq/L absorbed through intestine excreted in form of urine. Deficiency diseases include muscle weakness, mental confusion. Potassium ion present on the cells as potassium ion channels and various types of potassium ion channels include ATP-sensitive K channels (KATP), voltage-dependent K channels (Kv), Ca<sup>2+</sup> – and voltage-dependent K channels (BKCa), inward rectifier K channels (Kir), and tandem two-pore K channels (K2P) their activity varies in different types of diseases [39]. Potassium as

known to play a role in Na<sup>+</sup>-K<sup>+</sup> ATPase for effective muscle contraction [40] and motor regulation is by ATP driven potassium channels [41]. ATP driven potassium channel deficiency affected resting tension of skeletal muscle [42] deficiency of potassium ions alters sodium potassium pump of skeletal muscle and augments its contraction in ageing [43]. According to previous reports, high potassium levels depolarizes smooth muscle cells that opens up voltage gated calcium channels resulting in entry of calcium ions inside the cells thereby leading to activation of smooth muscle contraction [44] The role of potassium in muscle contraction shown in **Figure 2b**. It had reported that activation of mTORC1 signalling correlated with decline in muscle mass [45, 46] activated mTORC1 induces oxidative stress that leads to protein degradation, autophagy and necrosis showing an aged phenotype [47]. The signalling pathway connecting potassium deficiency and ageing shown in **Figure 3**.

### 2.3 Calcium (Ca)

Biological availability of calcium is green leafy vegetables, nuts, seafood, cereals etc. Cow's milk is rich source of calcium and required daily about 0.8-1.0 g/day. Calcium plays an important role in development of bones, muscle contraction, blood coagulation, nerve transmission, membrane integrity, activation of enzymes, intracellular messenger, contact inhibition, nerve excitability, skeletal muscle integrity and maintenance, and cardiac tone. Factors promoting calcium absorption include low pH, parathyroid hormone, vitamin D, lactose. Most of blood calcium is in plasma and ranges about 9-11 mg/dl. Factors regulating plasma calcium include calcitriol, parathyroid hormone, and calcitonin. Calcium excreted mostly through intestine and partly by kidneys. Deficiency of calcium leads to hypocalcemia and shown signs such as fragility of bone, muscle cramping, and dry skin. Deficiency diseases include rickets osteomalacia, osteoporosis. Evidences reveal that calcium is involved in bone calcification where osteoblasts secrete collagen as ground substance and polymerises it then osteoblast entrap osteoid and calcium salts precipitates as non-crystalline amorphous substance. Reabsorption and reprecipitation of hydroxyapatite crystals makes bone calcified. Existing reports evidence that stimulation of PGC-1 $\alpha$  signalling regulate osteoporosis and ageing [48]. The role of calcium in osteoblast calcification shown in **Figure 2c**. Recent reports reveal that Wnt, MAPK, oestrogen pathways are targets for osteoporosis and ageing, it had shown that Wnt pathway responsible for production of sclerotin is dysregulated and MAPK pathway altered in osteoporosis [49]. The signalling pathway connecting calcium deficiency and ageing shown in **Figure 3**.

### 2.4 Magnesium (Mg)

Sources of this mineral include milk, meat, fruits, and cereals. Biochemical functions include formation of bone, teeth, neuromuscular irritability, and cofactor for enzymes (kinases). Daily intake is 300-350 mg, serum concentration is 2-3 mg/dl and deficiency leads to convulsions, neuromuscular irritation, uraemia, and rickets. Magnesium absorption occurs in intestine alcohol inhibits it whereas parathormone enhances it. Causes of magnesium deficiency include alcohol abuse, poorly controlled diabetes, excessive or chronic vomiting and/or diarrhoea. Research on neurodegenerative diseases reveal magnesium had neuroprotective role by inhibiting influx of amyloid  $\beta$  from blood and promote its clearance [50] furthermore it attenuates impairment in long-term potentiation and impaired recruitment of synaptic proteins through activation of PI3K/Akt and inhibition of GSK3  $\beta$  thereby reducing neuronal damage [51]. To date several reports indicate that Nrf-2

an antioxidant responsive protein plays a role in protection of cells from oxidative stress and essential for optimal activity inside the cell [52]. The role of magnesium in neuro degeneration shown in **Figure 2d**. Dysregulated Nrf-2 activity in neuro-degenerative diseases linked to ageing [53, 54]. The signalling pathway connecting magnesium deficiency and ageing shown in **Figure 3**.

2.5 Sulphur (S): Egg white, chicken, fish, beef are major sources of sulphur. Daily intake is 14 mg for healthy adult and distributed in nails, hair, and skin. Sulphur plays a role as antioxidant, anti-inflammation, metal transport, free radical scavenging, protein stabilisation, xenobiotic detoxification, metabolism of lipids. Sulphur resides inside the body in organic form as methionine, cysteine, and cysteine functions as part of vitamins such as thiamine, biotin, and coenzyme A and excreted through oxidised form as taurine and cholic acid. Deficiency diseases are almost unknown. Although reports revealed that, sulphur containing amino acids in the form of methionine and cysteine forms creatinine, carnitine and coenzyme. Sulphur in the form of methylsulfonylmethane (MSM) acts to prevent muscle pains and joint pains through reduction of pro-inflammatory cytokines (NFkB, IL-1, IL-6, IL-8, TNF- $\alpha$ ) [55–57] and decreased infiltration of immune cells by reducing inflamed synovial membrane [58, 59]. The role of sulphur in muscle pains and joint pains shown in **Figure 2e**. An essential for muscle functioning and deficiency leads to muscle impairment and aged phenotype. Aged muscle has altered Redox signalling [60–62] and exercised individuals in their lifetime had preserved enough muscle fitness comparable to younger ones [63] whereas NAD<sup>+</sup> treatment [28] reverse these effects. Strenuous exercise result in muscle damage [64] and dysregulated redox response within the muscle increase in transient ROS/RNS. This clearly explains redox mechanisms operate with ageing and contraction of skeletal muscle can activate a number of transcription factors thereby affecting gene expression of specific cellular pathways. The signalling pathway connecting sulphur deficiency and ageing shown in **Figure 3**.

### **3. Deficiency of minor mineral elements and lifespan**

#### **3.1 Boron (B)**

It occurs mostly in soil and water; dietary sources include leafy vegetables, pineapple, dry fruits, lemon, nuts, and berries and daily intake is <20 mg. It is ingested through diet and found higher quantities in hair, nails, bone whereas fat tissue being low [65]. It is absorbed into the intestine through boric acid and stored in tissues. The toxic effects of boron include DNA damage and repair and has effect on protein folding and stability. In infants, excess of boron leads to anaemia, seizures, erythema, dermatitis, cardiac problems [66–68]. Chronic exposure leads to disorders of brain, kidney, and testis (88). Boron determination utilises spectrophotometry [69], spectrofluorimetry [70], potentiometry [71], inductive coupled plasma atomic emission spectroscopy [72], and inductive coupled plasma mass spectrometry techniques [73]. Beneficial effects include reduction in sterility, osteoporosis, inflammation, coagulation, and cancer. Its application widely relays on food and medicinal sector.

#### **3.2 Fluoride (F<sup>-</sup>)**

Fluoride levels abundantly found in barley, rice, cassava, canned fruits and least in food grain, breast milk, beverages and daily intake is about 2 ppm. Fluoride levels in the environment is taken up either by food, water or inhaled by air, drugs and

reach the digestive tract for metabolism and distributed inside the body bone, soft tissue, milk, tooth. The factors that influence the fluoride metabolism inside the body include acid–base disorders, hormones, physical activity, cardiac rhythm, and diet. Fluorine functions as prevention of dental caries, necessary for development of bones. The mechanism of action of fluoride inside the body involves inhibition of demineralisation of enamel. A small amount may substantially contribute to health benefits that include dental caries, decreases acid production. High levels leads to alterations in cell architecture, abnormalities in hepatic and renal systems. Fluoride poisoning inside the cells diagnosed by contraction of muscle, stiffness of body, failure of respiratory and cardiac systems. The methods for removing excess of fluorine done using coagulation-precipitation, electro coagulation, adsorption etc. Excreted through faeces, urine. Deficiency diseases include dental caries, osteoporosis. Fluoride helps in remineralisation, crystallisation and Fluoroapatite formation through enhancement of tooth and improves against acid resistance thereby preventing dental caries [74]. The role of fluorine in dental caries shown in **Figure 2f**. Reports reveal that klotho/KLF4 protein is involved in secretion of saliva from salivary gland and attenuation of KLF4 pathway thereby inactivating mTOR, AMPK, cyclin D1 that leads to dental caries [75]. The signalling pathway connecting fluoride deficiency and ageing shown in **Figure 3**.

### 3.3 Iodide ( $I^-$ )

It is abundant in seafood, iodised salt and daily intake is about 150-200 ug. It is component of thyroid hormones stored in the form of thyroglobulin and toxicity symptoms include thyrotoxicosis, goitre. Iodine is mainly absorbed through small intestine but also occurs through skin and lungs. Plasma level is 4-10 mg/dl. Iodine mainly excreted through kidney but also through skin, milk saliva and bile. Deficiency causes cretinism, goitre, and myxoedema. It is evident from existing reports that iodine uptake by thyroid cells occurs with the help of sodium iodine symporter and translocates to apical membrane fuses with thyroglobulin with the help of thyroperoxidase to form monoiododthyronine (MIT), diiodothyronine (DIT) in thyroid follicle cells. Coupling of MIT & DIT results in triiodothyronine (T3) & tetra iodothyronine (T4) which is internalised through endocytosis that releases free T3, T4 into the blood stream. Iodine deficiency leads to uptake of more thyroid-stimulating hormone (TSH) into thyroid cells for production of thyroid hormones (T3 & T4) which results in enlargement of thyroid gland to form goitre [76]. Age associated abnormality of thyroid gland is not consequence of ageing but result of thyroid autoantibodies that leads to age associated diseases [77]. The role of iodine in goitre shown in **Figure 2g**. Disturbed TSH signalling found in ageing individuals due to reduced release of TRH and less production of TSH thereby lowering the thyroid gland response to TSH with concomitant release of T3 and T4 [78] and enhances Ras activity that leads to increase of thyroid gland cell proliferation [79]. The signalling pathway connecting iodine deficiency and ageing shown in **Figure 3**.

### 3.4 Iron (Fe)

Iron (non-heme) abundantly found in cereals, pulses, fruits, vegetables whereas heme is from poultry, fish and daily requirement is about 10-15 mg. Iron present in the form of heme transports oxygen, involved in electron transport chain, required for phagocytosis in form of peroxidase. Iron is absorbed in stomach and duodenum low pH, vitamin C enhances its absorption whereas phytate and oxalate interfere its absorption. Enterocytes absorb iron through metal transporter 1 protein and

gets metabolised (heme) through heme oxygenase-1 [80, 81]. Inhibitors of iron absorption includes phytic acid [82], polyphenols [83], and calcium [84] whereas ascorbic acid is enhancer [85]. Iron is transported inside the body through circulating proteins namely transferrin, lactoferrin, ferritin, heme proteins [86]. Iron regulation inside the cells occurs by 2 mechanisms one is by binding of iron responsive elements (IRE) [87] to iron responsive proteins (IRP) and other by hepcidin. Gene mutations of transferrin receptor 2, haemochromatosis, haemochromatosis type 2, hepcidin antimicrobial peptide (HAMP) [88] for impaired expression had observed. Iron storage inside the body is by ferritin [89] in liver, spleen, bone marrow [90]. Bodily iron is mostly excreted in form of blood through menstrual release and other forms includes skin and gastro intestinal tract [91] but not through urine. Iron deficiency results in depletion of iron and primary cause is low bioavailability of iron. It also occurs through pregnancy, menstruation, and pathologic conditions [92, 93]. Anaemia is the sign of iron deficiency [94]. Iron deficiency overcome by improvement in iron uptake and bioavailability, supplementation of iron with food and its fortification. Deficiency diseases include hypochromic microcytic anaemia. Reports evidence that iron ( $Fe^{+2}$ ) is absorbed by duodenal cells and binds with apoferritin to form ferritin which then binds to heme carrier protein (HCP) to form ferroportin (FPN). Ferroprotein is either stored in liver or transported in the blood, combines with transferrin in blood and reach erythrocytes that then binds to transferrin receptor and internalised into the cell and gets dissociated with the help of divalent metal carrier transporter 1 and performs functions such as erythropoiesis, cell metabolism, myoglobin production in muscles. Heme combines with myoglobin to form haemoglobin [59]. Recent reports reveal that PR domain zinc finger protein 8 (PRDM8) gene had a role in premature ageing of haematopoietic cells through DNA methylation that leads from aplastic anaemia (AA) patients independent of telomere attrition a haemoglobin disorder [95]. The role of iron in haemoglobin synthesis shown in **Figure 2h**. Reports also state that anaemia resulting from erythropoiesis of haematopoietic ageing of intrinsic altered micro-environment had upregulated IL-6, TGF- $\beta$  signalling [96]. The signalling pathway connecting iron deficiency and ageing shown in **Figure 3**.

### **3.5 Molybdenum (Mo)**

The daily intake of molybdenum was 75-250 ug and toxicity characterised by gout and joint pains. Molybdenum is present as cofactor for nitrate reductase, Xanthine oxidase and sulphite oxidase enzymes. Molybdenum cofactor biosynthesis occurs in steps formation of precursor Z from GTP, synthesis of molybdoenzyme from precursor Z, addition of adenyl group to molybdoprotein and its insertion [97]. Molybdenum uptake inside the cells occurs with the help of ATP binding cassette transporters [98]. Molybdenum deficiency results in improper functioning of enzymes responsible for specific metabolic pathways in which they were involved and leads to metabolic diseases such as Xanthinuria, Hyperuricemia, and neuro-degeneration. Deficiency diseases are almost unknown but some reports reveal its deficiency leads to chrons disease.

### **3.6 Sodium (Na)**

Abundantly found in common salt and other sources include leafy vegetables, milk, eggs, and nuts and daily intake is about 5-10 g. Absorbed as sodium ions and circulates inside the body in plasma and plasma levels were 135-145 mEq/L. It is chief extra cellular cation regulates acid-base balance and involved in osmotic pressure. It is involved in activation & transmission of nerve impulse, absorption of biomolecules

and aldosterone. High levels were observed in cushions disease and low levels were observed in addisons disease. Excreted from kidney in the form of sodium chloride through urine or as phosphate and other routes is by sweat. Deficiency diseases are almost unknown but reports reveal that higher risk of cardiovascular disease with low sodium intake [99]. Sodium inside the cells were present as sodium channels as (sodium-potassium ATPase, sodium-proton antiporter) the role of sodium in heart function is mostly presented by stimulation of aldosterone which enhances its influx into the cell and activates inositol 1,4,5 tri phosphate (IP3) [100, 101]. Activated IP3 releases stored calcium from endoplasmic reticulum and makes excitation coupled to contraction for effective heart function [102]. The role of sodium in heart function shown in **Figure 2i**. SIRT1, mTORC1 regulate cell balance between cell growth and survival. Activation of SIRT1 along with PGC-1 $\alpha$ , AMPK and inhibition of mTORC1 along with Akt act to prolong cell longevity and retard cardiac ageing. Autophagy underlies the activation of SIRT1/PGC-1  $\alpha$ /AMPK and inhibition of Akt/mTORC1 responsible for cardiac ageing. Chronic heart failure involves deficient autophagy phenomenon through hyperactivation of Akt/mTORC1 and suppression of SIRT1/PGC-1  $\alpha$ /AMPK pathway that finally leads to cardiac ageing [103, 104]. The signalling pathway connecting sodium deficiency and ageing shown in **Figure 3**.

### 3.7 Zinc (Zn)

Zinc mostly found in meat, cabbage, dates, mushrooms etc. and daily intake is 10-15 mg. Exposure of zinc is mainly by three ways inhalation, dermal exposure, oral exposure [105] and excess zinc shows symptoms such as abdominal pain, nausea, anaemia, gastrointestinal effects. Zinc plays an essential role as structural, catalytic, mild deficiency causes oligospermia, hyperammonemia [106]. Zinc is absorbed in duodenum phytate inhibits absorption whereas amino acids enhances its absorption. Oral uptake of zinc absorbs through small intestine and distributed in serum by binding to albumin,  $\alpha$ -microglobulin, and transferrin [107]. Zinc homeostasis occurs mainly with the help of transport proteins namely Zinc importer (ZIP) and zinc transporter (ZnT) [108] which then binds to metallothionin, and sequester to other cell organelle. Beneficial aspects of zinc were antioxidant [109], antidepressant, antidiabetic [110], delayed wound healing, and anticancer [111]. Toxic effects of zinc observed when it crosses more than 100-300 mg/day typical symptoms include reduction of HDL and cholesterol levels, vomiting, lethargy, and fatigue. Serum zinc levels is about 100 mg/dl. Excretion of zinc occurs mainly by kidney, skin, and intestine. The role of zinc as immune protector well studied as anti-inflammatory and performs its action through reducing intracellular ROS by activating superoxide dismutase (SOD), NADPH oxidoreductase (NOX), metallothionin (MT) thereby suppressing inflammatory pathway (NFkB) and reduces it [112]. The role of zinc in immunity shown in **Figure 2j**. Zinc deficiency induces oxidative stress activates transcription factors NFkB, AP 1 through NFkB signalling in ageing process [113, 114]. The signalling pathway connecting zinc deficiency and ageing shown in **Figure 3**.

## 4. Conclusion

Minerals play an important role in daily life ranging from nuts to leafy vegetables. Minerals mainly function as cofactors along with enzymes to show their metabolic effect. Minerals form holoenzymes in metabolism of biomolecules and help in cellular vital process for cell survival. In their absence, they show some deficient metabolic effects and required in small amounts to function effectively. Intake

Mineral	Physiological function	Mechanism of action	Deficiency disease	Signalling pathway associated with ageing
Phosphorous (P)	Formation of high energy phosphates, nucleic acids, nucleotide coenzymes	Bone mineralisation through hydroxyapatite formation [35]	Osteomalacia	FGF signalling [36, 37]
Potassium (K)	Chief cation of intracellular fluid, osmotic balance, muscle function	Contraction of smooth muscle cell [44]	Muscle weakness, mental retardation	mTORC1 signalling [47]
Calcium (Ca)	Development of bones, muscle contraction, blood coagulation, nerve transmission, intracellular messenger etc.	Bone calcification through formation of hydroxyl apatite crystals	Rickets, Osteoporosis, Osteopetrosis (marble bone disease)	Wnt, MAPK pathway [49]
Magnesium (Mg)	Constituent of bones, cofactor for kinases	Protects neuronal cell death by activating PI3K/Akt signalling [51]	Neuromuscular weakness, muscle irritation	Nrf 2 pathway [53, 54]
Sulphur (S)	Constituent of vitamins, heparin, chondroitin sulphate	Reduces muscle pain and body pain [55–57]	Muscle fatigue, convulsions	Redox signalling [60–62]
Fluorine (F)	Formation of bones and teeth	Prevents dental caries by remineralisation of enamel and improving acid resistance [74]	Dental caries	KLF 4 pathway [75]
Iodine (I)	Constituent of thyroxine, triiodothyronine	Prevents thyroid enlargement through T3 & T4 [76]	Goitre, Myxoedema	TSH signalling [78]
Iron (Fe)	Transports oxygen in constituent of heme	Haemoglobin formation through erythropoiesis [59]	Hypochromic microcytic anaemia	TGF- $\beta$ signalling [96]
Sodium (Na)	Chief cation of extracellular fluid, osmotic balance, acid–base balance, nerve function	Regulates heart function through IP3signaling by aldosterone [100–102]	Heart disease	SIRT1, mTORC1 signalling [103, 104]
Zinc (Zn)	Cofactor for alcohol dehydrogenase, carbonic anhydrase, lactate dehydrogenase	Reduces intracellular ROS by activating SOD, NOX, MT [112]	Growth retardation, hypogonadism, decreased immunity	NFkB signalling [113, 114]

Abbreviations: FGF-fibroblast growth factor, SOD-superoxide dismutase, NOX-NADPH oxidase, MT-metallothionin, T3-tri iodothyronine, T4-tetra iodothyronine, PI3K-Phosphatidyl inositol 3 kinase, MAPK-mitogen activated protein kinase, Wnt-Wingless-related integration site, Nrf 2-nucleoid erythroid receptor factor 2, TSH-thyroid stimulating hormone, TGF-tumour growth factor, SIRT 1-sirutin1, mTORC1-mammalian target of rapamycin complex 1, NFkB-natural factor kappa beta.

**Table 1.** Summary of mineral elements mechanism of action and association with longevity.

varies from infants to adults, gender excess amounts shows hyper forms, and low amounts leads to hypo effects. Mineral deficiencies mostly show aged phenotype and age related diseases have mineral deficiencies. In their absence cell, survival pathways are mostly non-functional and leads to decreased metabolic function that is characterised by aged phenotype. Minerals classified mostly upon their requirement as major (phosphorous (P), potassium (K), calcium (Ca), magnesium (Mg), sulphur (S)), minor/trace/rare (Boron (B), chlorine (Cl), chromium (Cr), fluoride (F), iodine (I), iron (Fe), manganese (Mn), molybdenum (Mo), nickel (Ni), selenium (Se), sodium (Na), vanadium (V) and zinc (Zn)). A selected mineral with their function importance in mammals have been described in detail in which Phosphorous (P), Potassium (K), Calcium (Ca), Magnesium (Mg), Sulphur (S), Fluoride (F<sup>-</sup>), Iodide (I<sup>-</sup>), Iron (Fe), Sodium (Na), Zinc (Zn) along with mechanism of action and its diseased mechanism associated with ageing. Phosphorous is involved in bone mineralisation from osteocyte through hydroxyl apatite formation and deficiency leads to osteomalacia that related to ageing through increased fibroblast growth factor signalling. Potassium is involved in muscle contraction and its deficiency leads to muscle weakness and shows aged phenotype through enhanced mTORC1 signalling. Calcium is involved in bone calcification through hydroxyl apatite crystals its deficiency leads to bone disorders shows aged phenotype through dysregulated Wnt, MAPK pathway. Magnesium is involved in protection of neuron from degeneration through inhibition of GSK3 $\beta$  signalling and hyper activation of PI3K, Akt signalling and shows aged phenotype through dysregulated Nrf 2 pathway. Sulphur is involved in prevention of muscle pains and joint pains by reducing inflammation by scavenging free radicals its deficiency leads to muscle fatigue shows aged phenotype through reduced redox signalling. Fluorine is involved protection of enamel layer by remineralisation, crystallisation of dentine and enhancement in acid resistance its deficiency leads to dental caries which is also an aged phenotype due to disturbed KLF4 pathway. Iodine is necessary for thyroid gland for production of thyroid hormones deficiency of it leads to goitre that is characterised by thyroid gland enlargement seen mostly in aged people or people taking iodine deficient diets that occurs through reduced TSH signalling. Iron is necessary for body for haemoglobin synthesis for oxygen transport and its deficiency leads to anaemia an aged phenotype occurs through enhancement in IL-6, TGF $\beta$  signalling. Sodium shows its effect by action of aldosterone on muscle cells and helps in heart function deficiency leads to heart diseases an aged phenotype occurs through increased SIRT1, mTORC1 signalling. Zinc well known for immune defence through inhibition of NF $\kappa$ B signalling deficiency leads to reduced immunity through enhancement of this signalling. A summary of different minerals and their mechanism of action along with their associated signalling pathway with ageing had described in **Table 1**.

## Appendices

Ca	calcium
I	iodine
Mg	magnesium
P	phosphorous
Na	sodium
S	sulphur
Zn	zinc
F	Fluorine
K	potassium
Fe	iron

TSH	thyroid stimulating hormone
Nrf	nucleoid erythroid receptor factor
FGF	fibroblast growth factor
SIRT	sirtuins
mTORC	mammalian target of rapamycin complex
NFkB	natural factor kappa beta
IL	interleukin
TGF	tumour growth factor
MAPK	mitogen activated protein kinase
Wnt	Wingless-related integration site
FGF	fibroblast growth factor
SOD	superoxide dismutase
NOX	NADPH oxidase
MT	metallothionin
T3	tri iodothyronine
T4	tetra iodothyronine
PI3K	phosphatidyl inositol 3 kinase
ZIP	zinc importer
ZnT	zinc transporter
GSK3β	glycogen synthase kinase 3β
ROS	reactive oxygen species
RNS	reactive nitrogen species
HDL	high density lipoprotein
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator <i>1-alpha</i>
IP3	inositol 1,4,5 tri phosphate
ATPase	adenosine tri phosphatase
GTP	guanosine triphosphate
PRDM8	PR domain zinc finger protein 8
AA	aplastic anaemia
HCP	heme carrier protein
FPN	ferroportin
IRP	iron responsive proteins
IRE	iron responsive elements
HAMP	hepcidin antimicrobial peptide
MIT	monoiododthyronine
DIT	diiodothyronine
TSH	thyroid-stimulating hormone
AMPK	adenosine monophosphate kinase
DNA	deoxyribose nucleic acid
RNA	ribose nucleic acid
NAD	nicotinamide adenosine dinucleotide
TNF	tumour necrosis factor
MSM	methylsulfonylmethane
FGF	fibroblast growth factor signalling
PTH	parathormone
TNAP	tissue non-specific alkaline phosphatase
ULK 1	Unc-51 like autophagy activating kinase (ULK1/2)
MMP	matrix metallo proteinase
ICAM	inter cellular adhesion molecule
iNOS	induced nitric oxide synthase
COX	cyclooxygenase
RDA	recommended dietary allowance

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### **Author details**

Nyshadham S.N. Chaitanya<sup>1\*</sup> and Sibani Sahu<sup>2</sup>

1 Department of Animal Biology, School of Life Sciences, University of Hyderabad, TS, India

2 Department of Human Genetics, Andhra University, Visakhapatnam, AP, India

\*Address all correspondence to: [nsnchaitanya8@uohyd.ac.in](mailto:nsnchaitanya8@uohyd.ac.in)

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## References

- [1] Campisi J, d'Adda di Fagagna F. Cellular senescence: When bad things happen to good cells. *Nature Reviews. Molecular Cell Biology*. 2007;**8**(9):729-740
- [2] López-Otín C et al. The hallmarks of aging. *Cell*. 2013;**153**(6):1194-1217
- [3] Riera CE et al. Signaling networks determining life span. *Annual Review of Biochemistry*. 2016;**85**:35-64
- [4] Lanigan F, Geraghty JG, Bracken AP. Transcriptional regulation of cellular senescence. *Oncogene*. 2011;**30**(26):2901-2911
- [5] Dimri GP et al. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. *Proceedings of the National Academy of Sciences of the United States of America*. 1995;**92**(20):9363-9367
- [6] Burton DG, Krizhanovsky V. Physiological and pathological consequences of cellular senescence. *Cellular and Molecular Life Sciences*. 2014;**71**(22):4373-4386
- [7] Adams PD. Healing and hurting: Molecular mechanisms, functions, and pathologies of cellular senescence. *Molecular Cell*. 2009;**36**(1):2-14
- [8] Harley CB, Futcher AB, Greider CW. Telomeres shorten during ageing of human fibroblasts. *Nature*. 1990;**345**(6274):458-460
- [9] Bernadotte, A., V.M. Mikhelson, and I.M. Spivak, Markers of cellular senescence. Telomere shortening as a marker of cellular senescence. *Aging (Albany NY)*, 2016. **8**(1): p. 3-11.
- [10] Fyhrquist F, Saijonmaa O, Strandberg T. The roles of senescence and telomere shortening in cardiovascular disease. *Nature Reviews. Cardiology*. 2013;**10**(5):274-283
- [11] Harman D. Aging: A theory based on free radical and radiation chemistry. *Journal of Gerontology*. 1956;**11**(3):298-300
- [12] Hekimi S, Lapointe J, Wen Y. Taking a "good" look at free radicals in the aging process. *Trends in Cell Biology*. 2011;**21**(10):569-576
- [13] Hekimi S, Wang Y, Noë A, Mitochondrial ROS. The effectors of the intrinsic apoptotic pathway in aging cells: The discerning killers. *Frontiers in Genetics*. 2016;**7**:161
- [14] Cervantes Gracia K, Llanas-Cornejo D, Husi H. CVD and oxidative stress. *Journal of Clinical Medicine*. 2017;**6**(2)
- [15] Holmström KM, Finkel T. Cellular mechanisms and physiological consequences of redox-dependent signalling. *Nature Reviews. Molecular Cell Biology*. 2014;**15**(6):411-421
- [16] Dai DF et al. Mitochondrial oxidative stress in aging and healthspan. *Longev Healthspan*. 2014;**3**:6
- [17] Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. 2014;**69**(Suppl 1):S4-S9
- [18] Manea SA et al. Regulation of Nox enzymes expression in vascular pathophysiology: Focusing on transcription factors and epigenetic mechanisms. *Redox Biology*. 2015;**5**:358-366
- [19] Sallam N, Laher I. Exercise modulates oxidative stress and inflammation in aging and cardiovascular diseases. *Oxidative Medicine and Cellular Longevity*. 2016;**2016**:7239639

- [20] Lin CC et al. TNF- $\alpha$ -induced cPLA(2) expression via NADPH oxidase/reactive oxygen species-dependent NF- $\kappa$ B Cascade on human pulmonary alveolar epithelial cells. *Frontiers in Pharmacology*. 2016;**7**:447
- [21] Lin CC et al. NADPH oxidase/ROS-dependent VCAM-1 induction on TNF- $\alpha$ -challenged human cardiac fibroblasts enhances monocyte adhesion. *Frontiers in Pharmacology*. 2015;**6**:310
- [22] Matzkin ME et al. Alterations in oxidative, inflammatory and apoptotic events in short-lived and long-lived mice testes. *Aging (Albany NY)*. 2016;**8**(1):95-110
- [23] Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. *Cell*. 2012;**148**(6):1145-1159
- [24] Held NM, Houtkooper RH. Mitochondrial quality control pathways as determinants of metabolic health. *BioEssays*. 2015;**37**(8):867-876
- [25] Gonzalez-Freire M et al. Reconsidering the role of mitochondria in aging. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. 2015;**70**(11):1334-1342
- [26] Friedman JR, Nunnari J. Mitochondrial form and function. *Nature*. 2014;**505**(7483):335-343
- [27] Fang EF et al. Nuclear DNA damage signalling to mitochondria in ageing. *Nature Reviews. Molecular Cell Biology*. 2016;**17**(5):308-321
- [28] Gomes AP et al. Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. *Cell*. 2013;**155**(7):1624-1638
- [29] Imai S, Guarente L. NAD<sup>+</sup> and sirtuins in aging and disease. *Trends in Cell Biology*. 2014;**24**(8):464-471
- [30] Kim KH, Lee MS. Autophagy--a key player in cellular and body metabolism. *Nature Reviews. Endocrinology*. 2014;**10**(6):322-337
- [31] Lee J, Giordano S, Zhang J. Autophagy, mitochondria and oxidative stress: Cross-talk and redox signalling. *The Biochemical Journal*. 2012;**441**(2):523-540
- [32] Russell RC, Yuan HX, Guan KL. Autophagy regulation by nutrient signaling. *Cell Research*. 2014;**24**(1):42-57
- [33] Shirakabe A et al. Aging and autophagy in the heart. *Circulation Research*. 2016;**118**(10):1563-1576
- [34] Xu S, Cai Y, Wei Y. mTOR signaling from cellular senescence to organismal aging. *Aging and Disease*. 2014;**5**(4):263-273
- [35] Orimo H. The mechanism of mineralization and the role of alkaline phosphatase in health and disease. *Journal of Nippon Medical School = Nippon Ika Daigaku zasshi*. 2010;**77**(1):4-12
- [36] Kumar, S. and T. Diamond, Lessons learnt from delayed diagnosis of FGF-23-producing tumour-induced osteomalacia and post-operative hungry bone syndrome. *Bone Rep*, 2020. 12: p. 100276.
- [37] Lanske B, Razzaque MS. Mineral metabolism and aging: The fibroblast growth factor 23 enigma. *Current Opinion in Nephrology and Hypertension*. 2007;**16**(4):311-318
- [38] Beck-Nielsen SS et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity. *Orphanet Journal of Rare Diseases*. 2019;**14**(1):58
- [39] Rajkovic J et al. Potassium channels on smooth muscle as a molecular target for plant-derived resveratrol. *Cellular*

and Molecular Biology (Noisy-le-Grand, France). 2020;**66**(4):133-144

[40] Jannas-Vela S et al. Assessment of Na<sup>+</sup>/K<sup>+</sup> ATPase activity in small rodent and human skeletal muscle samples. *Medicine and Science in Sports and Exercise*. 2019;**51**(11):2403-2409

[41] Horii K et al. ATP-dependent potassium channels contribute to motor regulation of esophageal striated muscle in rats. *The Journal of Veterinary Medical Science*. 2019;**81**(9):1266-1272

[42] Gong B et al. A K(ATP) channel deficiency affects resting tension, not contractile force, during fatigue in skeletal muscle. *American Journal of Physiology. Cell Physiology*. 2000;**279**(5):C1351-C1358

[43] Li J, Sinoway LI, Ng YC. Aging augments interstitial K<sup>+</sup> concentrations in active muscle of rats. *Journal of Applied Physiology (Bethesda, MD: 1985)*. 2006;**100**(4):1158-1163

[44] Karaki H, Urakawa N, Kutsky P. Potassium-induced contraction in smooth muscle. *Nihon Heikatsukin Gakkai Zasshi*. 1984;**20**(6):427-444

[45] Joseph GA et al. Partial inhibition of mTORC1 in aged rats counteracts the decline in muscle mass and reverses molecular signaling associated with sarcopenia. *Molecular and Cellular Biology*. 2019;**39**(19)

[46] Vainshtein A, Sandri M. Signaling pathways that control muscle mass. *International Journal of Molecular Sciences*. 2020;**21**(13)

[47] Tang H et al. mTORC1 underlies age-related muscle fiber damage and loss by inducing oxidative stress and catabolism. *Aging Cell*. 2019;**18**(3):e12943

[48] Li L et al. Celastrol regulates bone marrow mesenchymal stem cell fate

and bone-fat balance in osteoporosis and skeletal aging by inducing PGC-1 $\alpha$  signaling. *Aging (Albany NY)*. 2020;**12**

[49] Carina V et al. Bone's response to mechanical loading in aging and osteoporosis: Molecular mechanisms. *Calcified Tissue International*. 2020

[50] Zhu D et al. Magnesium reduces blood-brain barrier permeability and regulates amyloid- $\beta$  transcytosis. *Molecular Neurobiology*. 2018;**55**(9):7118-7131

[51] Xu, Z.P., et al., Magnesium protects cognitive functions and synaptic plasticity in streptozotocin-induced sporadic Alzheimer's model. *PLoS One*, 2014. 9(9): p. e108645.

[52] Baird L, Dinkova-Kostova AT. The cytoprotective role of the Keap1-Nrf2 pathway. *Archives of Toxicology*. 2011;**85**(4):241-272

[53] Zhang H, Davies KJA, Forman HJ. Oxidative stress response and Nrf2 signaling in aging. *Free Radical Biology & Medicine*. 2015;**88**(Pt B):314-336

[54] Kubben N et al. Repression of the antioxidant NRF2 pathway in premature aging. *Cell*. 2016;**165**(6):1361-1374

[55] Kim YH et al. The anti-inflammatory effects of methylsulfonylmethane on lipopolysaccharide-induced inflammatory responses in murine macrophages. *Biological & Pharmaceutical Bulletin*. 2009;**32**(4):651-656

[56] Ahn H et al. Methylsulfonylmethane inhibits NLRP3 inflammasome activation. *Cytokine*. 2015;**71**(2):223-231

[57] Kloesch B et al. Dimethyl sulphoxide and dimethyl sulphone are potent inhibitors of IL-6 and IL-8 expression in the human chondrocyte cell line C-28/I2. *Life Sciences*. 2011;**89**(13-14):473-478

- [58] Khanna S, Jaiswal KS, Gupta B. Managing rheumatoid arthritis with dietary interventions. *Frontiers in Nutrition*. 2017;**4**:52
- [59] Withee ED et al. Effects of Methylsulfonylmethane (MSM) on exercise-induced oxidative stress, muscle damage, and pain following a half-marathon: A double-blind, randomized, placebo-controlled trial. *Journal of the International Society of Sports Nutrition*. 2017;**14**:24
- [60] Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metabolism*. 2013;**17**(2):162-184
- [61] Labunskyy VM, Gladyshev VN. Role of reactive oxygen species-mediated signaling in aging. *Antioxidants & Redox Signaling*. 2013;**19**(12):1362-1372
- [62] McDonagh B et al. Differential cysteine labeling and global label-free proteomics reveals an altered metabolic state in skeletal muscle aging. *Journal of Proteome Research*. 2014;**13**(11):5008-5021
- [63] Cobley JN et al. PGC-1 $\alpha$  transcriptional response and mitochondrial adaptation to acute exercise is maintained in skeletal muscle of sedentary elderly males. *Biogerontology*. 2012;**13**(6):621-631
- [64] Aoi W, Naito Y, Yoshikawa T. Role of oxidative stress in impaired insulin signaling associated with exercise-induced muscle damage. *Free Radical Biology & Medicine*. 2013;**65**:1265-1272
- [65] Ku, W.W., et al., Tissue disposition of boron in male Fischer rats. *Toxicology and Applied Pharmacology*, 1991. 111(1): p. 145-151.
- [66] Restuccio A, Mortensen ME, Kelley MT. Fatal ingestion of boric acid in an adult. *The American Journal of Emergency Medicine*. 1992;**10**(6):545-547
- [67] Schillinger BM et al. Boric acid poisoning. *Journal of the American Academy of Dermatology*. 1982;**7**(5):667-673
- [68] Ishii Y et al. A fatal case of acute boric acid poisoning. *Journal of Toxicology: Clinical Toxicology*. 1993;**31**(2):345-352
- [69] Khaliq H et al. Boron affects the development of the kidney through modulation of apoptosis, antioxidant capacity, and Nrf2 pathway in the African ostrich chicks. *Biological Trace Element Research*. 2018;**186**(1):226-237
- [70] Peng G et al. Determination of boron in water samples by dispersive liquid-liquid microextraction based on the solidification of a floating organic drop coupled with a fluorimetric method. *Analyst*. 2016;**141**(7):2313-2318
- [71] Durka M et al. Dopamine/2-Phenylethylamine sensitivity of ion-selective electrodes based on bifunctional-symmetrical boron receptors. *Sensors (Basel)*. 2019;**19**(2)
- [72] Kmiecik E et al. Selected problems with boron determination in water treatment processes. Part I: Comparison of the reference methods for ICP-MS and ICP-OES determinations. *Environmental Science and Pollution Research International*. 2016;**23**(12):11658-11667
- [73] Seedeve P et al. Multi-elemental concentration in different body parts of *Sepiella inermis* by inductively coupled plasma mass spectrometry. *Environmental Science and Pollution Research International*. 2020;**27**(3):2797-2804
- [74] Sathe N, Chakradhar Raju RV, Chandrasekhar V. Effect of three different remineralizing agents on

- enamel caries formation--an in vitro study. *Kathmandu Univ Med J (KUMJ)*. 2014;**12**(45):16-20
- [75] Tai NC, Kim SA, Ahn SG. Soluble klotho regulates the function of salivary glands by activating KLF4 pathways. *Aging (Albany NY)*. 2019;**11**(19):8254-8269
- [76] Rohner F et al. Biomarkers of nutrition for development--iodine review. *The Journal of Nutrition*. 2014;**144**(8):1322s-1342s
- [77] Pinchera A et al. Thyroid autoimmunity and ageing. *Hormone Research*. 1995;**43**(1-3):64-68
- [78] Takaoka M et al. Age-related changes in thyroid lesions and function in F344/DuCrj rats. *Experimental Animals*. 1995;**44**(1):57-62
- [79] Leal AL et al. Hypothyroidism and hyperthyroidism modulates Ras-MAPK intracellular pathway in rat thyroids. *Endocrine*. 2007;**31**(2):174-178
- [80] Muir A, Hopfer U. Regional specificity of iron uptake by small intestinal brush-border membranes from normal and iron-deficient mice. *The American Journal of Physiology*. 1985;**248**(3 Pt 1):G376-G379
- [81] Wang J, Pantopoulos K. Regulation of cellular iron metabolism. *The Biochemical Journal*. 2011;**434**(3):365-381
- [82] Hallberg L, Brune M, Rossander L. Iron absorption in man: Ascorbic acid and dose-dependent inhibition by phytate. *The American Journal of Clinical Nutrition*. 1989;**49**(1):140-144
- [83] Siegenberg D et al. Ascorbic acid prevents the dose-dependent inhibitory effects of polyphenols and phytates on nonheme-iron absorption. *The American Journal of Clinical Nutrition*. 1991;**53**(2):537-541
- [84] Hallberg L et al. Inhibition of haem-iron absorption in man by calcium. *The British Journal of Nutrition*. 1993;**69**(2):533-540
- [85] Lynch SR, Cook JD. Interaction of vitamin C and iron. *Annals of the New York Academy of Sciences*. 1980;**355**:32-44
- [86] Ferrali, M., et al., Iron release and membrane damage in erythrocytes exposed to oxidizing agents, phenylhydrazine, divicine and isouramil. *Biochem J*, 1992. 285 ( Pt 1) (Pt 1): p. 295-301.
- [87] Theil, E.C., Iron regulatory elements (IREs): A family of mRNA non-coding sequences. *The Biochemical Journal*, 1994. 304 ( Pt 1) (Pt 1): p. 1-11.
- [88] De Domenico I, Ward DM, Kaplan J. Heparin regulation: Ironing out the details. *The Journal of Clinical Investigation*. 2007;**117**(7):1755-1758
- [89] Nadadur SS, Srirama K, Mudipalli A. Iron transport & homeostasis mechanisms: Their role in health & disease. *The Indian Journal of Medical Research*. 2008;**128**(4):533-544
- [90] Ross C. *Modern Nutrition in Health and Disease*. Philadelphia: Wolters Kluwer, Lippincott Williams & Wilkins; 2014
- [91] Smith D. *Minerals in animal and human nutrition* (2003), 2nd edn. Tropical Animal Health and Production Tropical Animal Health and Production. 2004;**36**(8):774
- [92] Crompton DW, Nesheim MC. Nutritional impact of intestinal helminthiasis during the human life cycle. *Annual Review of Nutrition*. 2002;**22**:35-59
- [93] Larocque R et al. Relationship between intensity of soil-transmitted helminth infections and anemia during

pregnancy. *The American Journal of Tropical Medicine and Hygiene*. 2005;**73**(4):783-789

[94] De Benoist, B., et al., Worldwide prevalence of anaemia 1993-2005 of : WHO Global Database of anaemia. 2008.

[95] Cypris O et al. PRDM8 reveals aberrant DNA methylation in aging syndromes and is relevant for hematopoietic and neuronal differentiation. *Clinical Epigenetics*. 2020;**12**(1):125

[96] Valletta S et al. Micro-environmental sensing by bone marrow stroma identifies IL-6 and TGF $\beta$ 1 as regulators of hematopoietic ageing. *Nature Communications*. 2020;**11**(1):4075

[97] Mendel RR, Bittner F. Cell biology of molybdenum. *Biochimica et Biophysica Acta*. 2006;**1763**(7):621-635

[98] Grunden AM, Shanmugam KT. Molybdate transport and regulation in bacteria. *Archives of Microbiology*. 1997;**168**(5):345-354

[99] Kong YW et al. Sodium and its role in cardiovascular disease - the debate continues. *Front Endocrinol (Lausanne)*. 2016;**7**:164

[100] Christ M et al. Rapid effects of aldosterone on sodium transport in vascular smooth muscle cells. *Hypertension*. 1995;**25**(1):117-123

[101] White PC. Aldosterone: Direct effects on and production by the heart. *The Journal of Clinical Endocrinology and Metabolism*. 2003;**88**(6):2376-2383

[102] Kockskämper J et al. Emerging roles of inositol 1,4,5-trisphosphate signaling in cardiac myocytes. *Journal of Molecular and Cellular Cardiology*. 2008;**45**(2):128-147

[103] Packer M. Longevity genes, cardiac ageing, and the pathogenesis of cardiomyopathy: Implications for understanding the effects of current and future treatments for heart failure. *European Heart Journal*. 2020

[104] Zhu X et al. Fine-tuning of PGC1 $\alpha$  expression regulates cardiac function and longevity. *Circulation Research*. 2019;**125**(7):707-719

[105] Agency for Toxic. S. and R. disease, environmental health and medicine. Education. 2010

[106] Prasad AS. Clinical and biochemical manifestation zinc deficiency in human subjects. *Journal de Pharmacologie*. 1985;**16**(4):344-352

[107] Scott BJ, Bradwell AR. Identification of the serum binding proteins for iron, zinc, cadmium, nickel, and calcium. *Clinical Chemistry*. 1983;**29**(4):629-633

[108] Lichten LA, Cousins RJ. Mammalian zinc transporters: Nutritional and physiologic regulation. *Annual Review of Nutrition*. 2009;**29**:153-176

[109] Lee SH et al. Combined effects of dietary zinc at 3 years of age and obesity at 7 years of age on the serum uric acid levels of Korean children. *Nutrition Research and Practice*. 2020;**14**(4):365-373

[110] Kinlaw WB et al. Abnormal zinc metabolism in type II diabetes mellitus. *The American Journal of Medicine*. 1983;**75**(2):273-277

[111] Dhawan DK, Chadha VD. Zinc: A promising agent in dietary chemoprevention of cancer. *The Indian Journal of Medical Research*. 2010;**132**(6):676-682

[112] Prasad AS. Zinc: Role in immunity, oxidative stress and chronic

inflammation. *Current Opinion in Clinical Nutrition and Metabolic Care*. 2009;12(6):646-652

[113] Moroni F et al. Interrelationship among neutrophil efficiency, inflammation, antioxidant activity and zinc pool in very old age. *Biogerontology*. 2005;6(4):271-281

[114] Herbein G, Varin A, Fulop T. NF-kappa B, AP-1. Zinc-deficiency and aging. *Biogerontology*. 2006;7(5-6):409-419

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