Chapter 4
Micronutrients in Ageing and Longevity

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Abstract Ageing is a biological process that can be described as the accumulation of molecular damage to cells in response to stress. A tendency in modern society is to optimize longevity by trying to minimize a physical and mental decline and to decrease susceptibility to disease. There are some nutritional factors, including micronutrients, which can support this process of successful ageing. Micronutrients are vitamins (e.g., A, B group, C, D, E, folate) and minerals (e.g., copper, iron, magnesium, selenium, zinc), needed in small amounts but essential for healthy living. They have numerous significant functions in the organism as antioxidants, coenzymes, cofactors in metabolism, and genetic control. Therefore, micronutrients contribute to the normal functions of the immune, nervous, and endocrine system, protect the organism from oxidative stress, thus contributing to longevity and successful ageing. The dietary intake of micronutrients is usually insufficient in the elderly due to low income, reduced mobility, oral health problems, intestinal malabsorption, presence of chronic diseases, and changes in cognition. The result is an inadequate status of micronutrients which may contribute to suppressed immunity and consequent predisposition to infections, cognitive decline, neurodegeneration, development of the cardiovascular disease, disturbance of immune response and other health disorders.

Keywords Ageing · Immunosenescence · Inflammaging · Longevity · Micronutrients · Minerals · Neurocognitive disorders · Nutrition · Oxidative stress · Vitamins

4.1 Introduction

Term micronutrients is commonly used for vitamins and minerals needed in small amounts but vital for a healthy living. They have numerous functions in the organism as antioxidants, coenzymes, cofactors in metabolism, and genetic control. Among

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the micronutrients, only vitamin D is produced in the body while the rest must be taken from the diet (Celep et al. 2017). The appropriate intake of the recommended amounts is important since micronutrients deficiency can have severe consequences for health.

The elderly population is particularly at risk of micronutrients deficiencies. They undergo many physiological changes which decrease their energy requirements. At the same time, the requirements for micronutrients are the same as for younger adults (Kehoe et al. 2019). There are also many other limiting factors in access and consummation of nutrient-reach food for the elderly. Some of them are low income, reduced mobility, oral health problems, and changes in taste, smell, and cognition (Marsman et al. 2018). Furthermore, in older age, most people have chronic diseases. The presence of disease can affect the need for calories and micronutrients (Marian and Sacks 2009). Medications used in the treatment of chronic diseases can be nutrient wasting and cause a decrease in the status of micronutrients essential for health (Marsman et al. 2018).

Micronutrient deficiency makes the older individuals a higher risk group in the body's immune response and increased susceptibility to infection (Bourke et al. 2016). Recent researches suggest that micronutrients participate in immune functions through several mechanisms. Those mechanisms are maintenance of physical barriers, production of antimicrobial proteins, and regulation of immune cells activity. Vitamins A, C, E, and the trace element zinc contribute to the enhancement of the skin barrier function. The vitamins A, B6, B12, C, D, E, folic acid, and the trace elements iron, zinc, copper, and selenium synergistically support the protective activities of the immune cells. All these micronutrients, except vitamin C and iron, are essential for antibody production. Therefore, the inadequate status of mentioned vitamins and trace elements may result in suppressed immunity and consequent predisposition to infections (Maggini et al. 2007).

Combined effects of ageing and insufficient intake of micronutrients contribute to cognitive decline, development of cardiovascular disease, disturbance of immune response and other health disorders. Uncontrolled use of dietary supplements can also have detrimental effects on health (Watson et al. 2018). Therefore, it is necessary to maintain an appropriate balance between the need for micronutrients and their intake, as shown in Table 4.1.

There is a tendency in modern society to optimize longevity by trying to minimize a physical and mental decline (Bowling and Dieppe 2005). This process of successful ageing depends on several factors. Some of them, such as genetic background, cannot be modified. In contrast, social, cultural, or lifestyle choices can be influenced (Porter et al. 2016). The ageing process can be described as the accumulation of molecular damage to cells in response to stress. Among other exogenous factors, there are some nutrition components that can modify the rate of damage (Sofi et al. 2008). For instance, the trace elements from the food can modulate the rate at which damage accumulates in the cells. Also, they influence metabolic pathways, such as oxidative and inflammatory processes, which alter during ageing (Meplan 2011). Therefore, we can say that dietary, with pharmacological and lifestyle interventions, may promote health and longevity.

Table 4.1 Estimated average requirements and tolerable upper intake level for selected micronutrients in the elderly (>65 years) (IOM 2006; IOM 2011)

Micronutrient	Estimated average requirements		Tolerable upper intake level
	males	females	
VITAMINS			
Vitamin A	625 μg/day	500 μg/day	3,000 μg/day
Vitamin B_1	1.0 mg/day	0.9 mg/day	ND*
Vitamin B_2	1.1 mg/day	0.9 mg/day	ND*
Vitamin B_6	1.4 mg/day	1.3 mg/day	100 mg/day
Vitamin B_{12}	2.0 μg/day		ND*
Folate	320 μg/day		1,000 μg/day
Vitamin C	75 mg/day	60 mg/day	2,000 mg/day
Vitamin D	10 μg/day (400 IU)		100 μg/day (4,000 IU)
Vitamin E	12 mg/day		1,000 mg/day
MINERALS			
Copper	700 μg/day		10,000 μg/day
Iron	6.0 mg/day	5.0 mg/day	45 mg/day
Magnesium	350 mg/day	265 mg/day	350 mg/day
Selenium	45 μg/day		400 μg/day
Zinc	9.4 mg/day	6.8 mg/day	40 mg/day

*ND = not determinable

4.2 Vitamins

Vitamins are organic substances that function as regulators in the body. They are divided into two groups: fat-soluble vitamins (vitamin A, D, E and K) and water-soluble vitamins (vitamin B1, B2, B6, B12, C, folic acid, etc.) (Celep et al. 2017).

4.2.1 Vitamin A

Vitamin A includes several fat-soluble substances like retinol, retinyl palmitate, and beta-carotene. There are two forms of vitamin A obtained through diet. From the animal sources, preformed vitamin A (retinol, retinyl ester) is derived while provitamin A (beta-carotenoid) is derived from plants. For the use in biologic processes, retinol and beta-carotenoid must be converted to biologically active forms, retinal and retinoic acid (Moise et al. 2007).

Vitamin A has a great impact on the ageing process due to its role in immune function and oxidative processes. Therefore, vitamin A deficiency is associated

with a defective immune response to infection. The active form of vitamin A regulates immune cell differentiation and activates T cell responses. Recent researches are trying to enlighten the role of vitamin A in the enhanced T cell response in some diseases associated with ageing, such as cancer, infection, inflammation, and immune-mediated diseases (Raverdeau and Mills 2014).

The organ particularly susceptible to oxidative damage is an eye due to its exposure to light and high metabolism (Rasmussen and Johnson 2013). Age-related macular degeneration is one of the age-related degenerative diseases caused, among other factors, by high oxidative stress (Gorusupudi et al. 2017). It is the second most common cause of blindness after cataract in Europe (Bourne et al. 2018). Vitamin A is one of the most effective vitamins (together with vitamins C and E) for reducing the risk of macular degeneration. It plays an essential role in the human retinal pigment epithelial cells. Carotenoids lutein and zeaxanthin are concentrated in the macula and therefore known as macular pigments. They are the most potent antioxidants for the prevention and reduction of the risk of age-related macular degeneration. The human body is not able to synthesize lutein and zeaxanthin. Therefore, they must be obtained from the diet (Khoo et al. 2019).

The role of vitamin A in skin changes is also well studied. The ageing process promotes imbalance of collagen homeostasis resulting in the wrinkled appearance and atrophy of aged skin (Cole et al. 2018). The basis of this process is down-regulation of type I collagen accumulation and promotion of collagen degradation. Type I collagen is the major structural protein in the skin (Quan et al. 2011). Vitamin A and its metabolites promote new deposition of collagen and prevent its degradation by increasing type I procollagen and reducing matrix metalloproteinase-1 activity (Bielli et al. 2019).

Retinoids play a significant role in the development and normal functions of the human brain. Therefore, there is a great interest in potential therapeutic applications, especially for Alzheimer's disease (Das et al 2019). Alzheimer's disease is the most common neurodegenerative disease and the most common cause of dementia and loss of memory in old adults (Andreeva et al. 2017). Retinoids inhibit the expression of chemokines and neuroinflammatory cytokines in microglia and astrocytes, which are activated in Alzheimer's disease. Stimulation of retinoic acid receptors and retinoid X receptors slows down the accumulation of amyloids, reduces neurodegeneration, and thereby prevents pathogenesis of Alzheimer's disease (Das et al. 2019).

It is important to maintain the balance between the vitamin A intake and clearance from the organism since the elderly may have difficulty clearing it (Bolzetta et al. 2015). Some of the manifestations of chronic vitamin A excess are fatigue, hair loss, dry mucous membranes and skin, bone fractures, and abnormal liver function (Marian and Sacks 2009).

4.2.2 Vitamin B

B vitamins are a group of essential water-soluble vitamins which contribute to normal physiological and biochemical functioning of the body. B vitamins include B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxamine), B7 (biotin), B9 (folate) and B12 (cobalamin). Vitamin B4 (choline) is not considered as part of the B vitamins complex (Mikkelsen and Apostolopoulos 2018).

B vitamins have significant roles throughout life, from childhood to old age (McNulty et al. 2019). As coenzymes, they participate in many enzymatic reactions and metabolic processes, play a crucial role in the methylation cycle, synthesis and repair of DNA and RNA, and maintenance of phospholipids. B vitamins are essential for the normal function of the immune and nervous system and for maintaining the cognitive functions (Mikkelsen and Apostolopoulos 2018).

Vitamin B deficiency within the ageing population can be caused by low intake (B2, B9), malabsorption (B12) or increased requirement with ageing (B6) (Porter et al. 2016). The ageing process affects absorption, transport, and metabolism of B vitamins within the body. Some other factors can also contribute to B vitamin deficiency such as interactions between drugs and nutrients, genetic disorders, and some medical conditions (Mikkelsen and Apostolopoulos 2018).

Several diseases are connected to vitamin B deficiency, such as pellagra, beriberi, and pernicious anaemia. Furthermore, vitamin B deficiency contributes to neurocognitive disorders (Mitchell et al. 2014), immune dysfunction, inflammation (Mikkelsen et al. 2017), liver damage, peripheral neuropathy, and anaemia (Mikkelsen et al 2016). In the older population, vitamin B deficiency is linked to cardiovascular disorders, cognitive dysfunction, osteoporosis, and methylation disorders (Porter et al. 2016).

4.2.3 Vitamin B1 (Thiamine)

Vitamin B1 is part of the coenzyme thiamine pyrophosphate (Mikkelsen and Apostolopoulos 2018). It has a crucial role in the normal function of the nervous system because it participates in the generation of nerve impulses and synthesis of neurotransmitters (Nemazannikova et al. 2017).

Deficiency of the vitamin B1 can cause neurological damage by the production of free radicals and increased oxidative stress in the brain and neuronal tissue (Liu et al. 2017). The result is axonal damage, inadequate myelin production, and glutamate-mediated excitotoxicity (Abdou and Hazell 2014). B1 deficiency also causes immune effects through the T-cell infiltration and increased production of pro-inflammatory cytokines, leading to neuroinflammation. Neuroinflammation affects mitochondrial function and increases oxidative stress which leads to endoplasmic reticulum stress

(Wang et al. 2017). All these factors are included in the pathogenesis of ageing-related diseases such as dementia, Alzheimer's disease, Parkinson's disease, and Huntington's disease (Mikkelsen and Apostolopoulos 2018).

4.2.4 Vitamin B2 (Riboflavin)

Vitamin B2 is a powerful antioxidant involved in numerous oxidation/reduction reactions in two coenzymatic forms, flavin mononucleotide and flavin adenine dinucleotide (Moore et al. 2018).

The free radical theory of ageing proposes aerobic metabolism as a cause of oxidative damage that accumulates in body cells and contributes to the ageing process (Wickens 2001). Vitamin B2 acts as an antioxidant by preventing the lipid peroxidation and attenuating reperfusion oxidative injury (Ashoori and Saedisomeolia 2014). Accordingly, riboflavin could be involved in prolonging the life span, but so far, scientific research did not establish a strong link between riboflavin and slowing the human ageing process.

Along with other B vitamins, riboflavin plays a role in slowing cognitive decline and possibly reducing the risk of depression in ageing (Moore et al. 2018). Therefore, B2 deficiency in older adults is linked to reduced cognitive outcome, depression, personality changes and distinct alterations within the central nervous system (Mikkelsen et al. 2016, 2016a).

4.2.5 Vitamin B6 (Pyridoxamine)

Vitamin B6 can be found in three forms: pyridoxine, pyridoxal and pyridoxamine. It has many essential functions within the endocrine, neurological and immune systems. A biologically active form of B6 is coenzyme pyridoxal-5 phosphate which, as a cofactor, aids the synthesis of the neurotransmitters serotonin, dopamine, epinephrine and GABA (Mikkelsen and Apostolopoulos 2018).

Pyridoxamine is an effective inhibitor of the formation of advanced glycation end-products. The pathological complications of diabetes are directly related to the effects of these nonenzymatic reactions between proteins and sugars (Ramis et al. 2019). The prevalence of diabetes is more than two times higher among elderly adults compared to middle age or young adults (Cowie et al. 2009), and the incidence in the older population is constantly growing (Narayan et al. 2006). A large portion of the diabetes-related cost involves treating diabetes-related complications (ADA 2013). Several studies (Degenhardt et al. 2002; Murakoshi et al. 2009; Stitt et al. 2002) have shown that pyridoxamine has therapeutic effects on various complications of diabetes. Vitamin B6 forms stable complexes with metal ions that catalyze the oxidative reactions taking place in the advanced stages of the protein glycation

cascade (Adrover et al. 2008). It also reacts with reactive carbonyl compounds generated as by-products of protein glycation, thereby preventing further protein damage (Voziyan et al. 2002).

Since the advanced glycation end-products have been linked to the increased production of free radicals, they are implicated in causing tissue damage associated with ageing. Advanced glycation end-products can be deposited anywhere within the body and cause abnormal function of the organ or tissue, for example, cataract, arthritis, nephrosis and plaque formation within the vessel wall (Voziyan and Hudson 2005).

4.2.6 Vitamin B9 (Folate)

The term folates is commonly used for the entire family of compounds, naturally occurring and synthetic variants. Vitamin B9 (folate, folic acid) has a vital role in the normal functioning of the body. It is involved in immune response, brain function, DNA synthesis, and it is inevitable for cell division. Without folate, cells cannot divide and function (Craenen et al. 2020).

Folates play a key role in methylation reactions and DNA synthesis as one-carbon carrier/donor (Imbard et al. 2013). It has been known for years that folic acid food fortification and supplementation can reduce the prevalence of birth defects (Blom et al. 2006). Furthermore, it has been noticed that in healthy individuals plasma folate levels decrease while homocysteine levels increase with age, especially between the age of 40 and 90 years (Magnus et al. 2009). Increased homocysteine cytotoxicity has been conferred to have a role in ageing, neuronal plasticity, and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (Obeid and Herrmann 2006; Kalani et al. 2014).

Dementia and depression are considered to be major disorders of ageing (WHO 2016). Folate deficiency has been connected to cognitive decline and memory deficits. Apart from that, folate deficiency can affect the duration and clinical severity of depression. Also, it is associated with a weaker response to antidepressant medication (Reynolds 2006).

4.2.7 Vitamin B12 (Cobalamin)

Vitamin B12 is necessary for the normal function of the nervous system, nerve cell maintenance, cell proliferation and survival, and breakdown of fatty acids and amino acids (Mikkelsen et al 2016a).

Vitamin B12 (together with folate) is involved in the prevention of chronic diseases associated with ageing through the methylation of homocysteine. This process has a vital role in the prevention of amyloid and tau protein accumulation, which lead to cognitive decline (Watson et al. 2018).

An optimal vitamin B12 status does not depend only on adequate dietary intake, and deficiency of the vitamin B12 is not rare. An effective absorption is crucial, but it diminishes with age (Hughes et al. 2013). The absorption of food-bound B12 is difficult because of the decline in gastric acid secretion and the lack of intrinsic factor production in old age (Sawaengsri et al. 2016; Marsman et al. 2018). Deficiency leads to megaloblastic anaemia, demyelinating neurological symptoms, irreversible nerve damage and neuropathy (Sawaengsri et al. 2016). Furthermore, depression, mania, psychosis, and suicidal behaviours can develop (Petridou et al. 2016).

The risk of low B12 levels in elderly is increased by use of proton pump inhibitors and histamine H2 blockers. They inhibit gastric acid secretion (Maes et al. 2017) and interfere with the release of B12 from binding protein, thus reducing the absorption of vitamin B12 (Wong 2015). Since type-2 diabetes is frequent in the elderly, it should be kept in mind that Metformin (a medication used for the treatment of type-2 diabetes) reduces serum B12 levels and could worsen diabetes-associated neuropathy (Out et al. 2018).

Low vitamin B12 levels were found to increase blood pressure, contributing to cardiovascular diseases. Additionally, a decrease in vitamin B12 concentration can result in hyperhomocysteinemia, which could quadruplicate risk of stroke due to atrial fibrillation in elderly patients (Spence 2017). A recent study (Ao et al. 2019) reported that insufficiency of vitamin B12 and folate is a risk for decreased muscle strength, which increases the risk of falling and fractures.

Subclinical deficiency of vitamin B12 seems to be implicated in the development of several chronic age-related diseases. Evidence suggests that suboptimal levels of B12 can raise homocysteine which is associated with the risk of bone fractures (van Wijngaarden et al. 2013) and risk of cardiovascular diseases (Kehoe et al. 2019).

4.2.8 Vitamin C (Ascorbic Acid)

Vitamin C is involved in biological functions as a potent antioxidant and radical scavenger. It protects the cell against oxidative stress-mediated by reactive oxygen species (ROS) and free radicals. Vitamin C is considered the most effective antioxidant in the plasma because of its water solubility and the wide range of ROS that it can scavenge (Harrison 2012).

Since vitamin C acts as a cofactor of the monooxygenase and dioxygenase enzymes, it is required for the synthesis of several crucial biomolecules (Morelli et al. 2020). Vitamin C-dependent enzymatic reactions are involved in the biosynthesis of collagen and cellular procollagen secretion (Kehoe et al. 2019). Also, they participate in the biosynthesis of L-carnitine, norepinephrine, epinephrine, and other molecules. Vitamin C improves the absorption of the non-heme iron, thus increasing the bioavailability of iron (Sourabh et al. 2019).

The ability to transport ingested vitamin C from the intestines into the blood is limited by the saturable sodium-dependent vitamin C transporter (SVCT1) in the gut and thus very high intakes and the use of supplements are often erroneously

considered to be of greater benefit than they really are (Harrison 2012). It has been reported that ageing, oxidative stress, and inflammatory factors cause changes in the expression of SVCT 1 and SVCT2, transporters expressed in liver, brain, heart, chondrocytes, and osteoblast (Patterson et al. 2021).

Experimental studies on animals and human pointed to the important role of vitamin C in the synthesis, remodelling, and maintenance of the dermal extracellular matrix. Environmental and intrinsic oxidative stress decreases the natural cutaneous antioxidative mechanisms and induces pro-ageing signalling pathways and the accumulation of structural and functional changes, thus inducing intrinsic ageing and photoageing. The hallmarks of ROS-induced skin ageing are wrinkle formation, decreased resilience, pigmentation changes, telangiectasia, dehydration of the skin (Crisan et al. 2015). Vitamin C, as a natural antioxidant, is effective in preventing and treating skin ageing. It stimulates the barrier function of the endothelial cells, protects keratinocytes from UV radiation, and shows photoprotective effects (Barbosa and Kalaaji 2014). Topically applied vitamin C contributes to the maintenance of the collagen quantity and density at the dermal level and is also involved in strengthening the collagen fibres (Crisan et al. 2015).

Vitamin C is essential for wound healing. It decreases the expression of pro-inflammatory mediators and enhances the expression of various wound healing mediators. Leukocytes, which are the major players in wound healing, actively accumulate vitamin C (Mohammed et al. 2016).

Severe vitamin C deficiency which leads to scurvy has become rare in most countries. Low levels of vitamin C are much more common. They have been associated with high blood pressure, endothelial dysfunction, heart disease, atherosclerosis, and stroke (Morelli et al. 2020). Long-term vitamin C deprivation, evidenced by low plasma levels in men with normal diets, was linked to nervousness, depression, and emotional lability (Harrison 2012). Furthermore, studies have shown that patients with conditions, such as diabetes, COPD, chronic hypertension, and viral-induced sepsis, have decreased levels of serum and plasma vitamin C (Patterson et al. 2021).

4.2.9 Vitamin D

Vitamin D is a nutrient, a pro-hormone and steroid hormone with an important role in calcium and bone metabolism. The biologically inactive form of vitamin D, vitamin D3, can be obtained from dietary sources or dermal synthesis. D3 is converted in the liver and kidneys to the active metabolite calcitriol (Hill et al. 2018).

Optimal vitamin D status is necessary for mineral homeostasis, bone health, and function of skeletal muscles (Cianferotti et al. 2017). Vitamin D is important for immune response because it stimulates phagocytosis by macrophages and protects immune cells against apoptosis (Watson et al. 2018). As for the current Covid-19 pandemic, some studies offer evidence that vitamin D status may influence the severity of response to Covid-19 and that the prevalence of vitamin D deficiency

in Europe coincides with Covid-19 mortality (Laird et al. 2020). Through its interactions with different types of cells, vitamin D may have several ways to reduce the risk of acute respiratory tract infections and COVID-19: reducing the survival and replication of viruses, reducing the risk of inflammatory cytokine production, increasing angiotensin-converting enzyme-2 concentrations, and maintaining endothelial integrity (Mercola et al. 2020).

Vitamin D intake and absorption drastically decreases with age due to various environmental and biological factors (Boucher 2012). Reduced sunlight exposure, nutrient intake, fat absorption, and conversion to its active form (Watson et al. 2018) contribute to more common and severe hypovitaminosis D in older people (Boucher 2012). It has been reported that over 90% of older adults in most European countries have intakes below 10 μg/day, which is an average daily requirement for vitamin D (Kehoe et al. 2019). Impaired mobility and residential care often limit sun exposure and cause a decrease in the synthesis of vitamin D in the skin while a decline in renal function reduces vitamin D activation (de Jongh et al. 2017).

Regarding the ageing, vitamin D deficiency can be associated with impaired cognition, depression, cancer, and cardiovascular disease (Watson et al. 2018). For sure, the most significant impact of deficiency is on bone metabolism. For people over 70 years of age, the predominant bone health concerns are bone loss and the resulting osteoporotic fractures (Pfortmueller et al. 2014). Osteoporosis is a silent disease, and it is responsible for about 9 million fractures annually worldwide (Johnell and Kanis 2006). A meta-analysis conducted by the National Osteoporosis Foundation found that calcium plus vitamin D supplementation resulted in a statistically significant 15% reduced risk of total fractures and 30% reduced risk of hip fractures (Weaver et al. 2016). Supplementation may reduce the number of subsequent fractures, enhance muscular strength, and improve balance (Childs et al. 2016).

When taking vitamin D supplements, it must be careful not to cause an excess of the vitamin. Consequences of vitamin D overuse are acute kidney injury and pancreatitis, secondary to hypercalcemia and hypercalciuria (Razzaque 2018).

4.2.10 Vitamin E (Alpha-Tocopherol)

Vitamin E includes a group of eight structurally related antioxidants: four tocopherols and four tocotrienols, each designated as α, β, γ and δ. Among them, α-tocopherol is the most abundant and bioavailable antioxidant form of vitamin E in human tissues (Rigotti 2007).

Vitamin E has an important function as an antioxidant, protects cells from oxidative stress caused by ROS (La Fata et al. 2014). ROS are mainly produced in mitochondria and represent important regulators of cell signalling. At high concentrations, they are harmful and cause cellular damage contributing to the ageing process (Bratic and Larsson 2013). It is known that older adults, over 65 years of age, have

less effective enzymatic antioxidant defence and compromised immune and inflammatory responses. This result in an increased risk of infectious and non-infectious chronic diseases in the elderly (Meydani et al. 2018).

The brain is highly susceptible to oxidative stress. For this reason, oxidative stress which increases during ageing is considered a major contributor to neurodegeneration. It is involved in the onset of pathological conditions typical of old age, such as Alzheimer's disease and dementia. Vitamin E could help in these conditions since its high plasma levels were repeatedly associated with better cognitive performance (La Fata et al. 2014). Due to the lack of appropriate treatment for Alzheimer's disease, vitamin E, because of its relative safety and low cost, could be a nutritional compound to promote healthy brain ageing and delay Alzheimer's disease-related functional decline (La Fata et al. 2014).

Vitamin E also has important non-antioxidant functions. The immunomodulatory role of vitamin E includes lymphocyte proliferation, prostaglandin E2 production, gene transcription, translation, cell membrane, and signal transduction (Zingg and Azzi 2004). Therefore, some of the age-related dysregulations of the immune and inflammatory responses have shown improvement due to vitamin E supplementation (Wu and Meydani 2008).

4.3 Minerals

Minerals are essential nutrients divided into two major groups. Major or macro-minerals (calcium, phosphorus, sodium, potassium, magnesium, and chloride) are present in the body at levels greater than 0.01% and required in amounts greater than 100 mg/day. Therefore, their function is both structural and regulatory. Trace or micro-minerals (iron, cobalt, chromium, copper, fluoride, iodine, manganese, selenium, zinc, and molybdenum) are present in the body at levels less than 0.01% and required in amounts less than 50 mg/day. Trace minerals have primarily regulatory role in metabolic and immune functions (Celep et al. 2017).

Trace elements are involved in numerous important processes altered during ageing, such as immune function, oxidative stress, insulin sensitivity, and cognitive function. These elements are vital to enzymatic activity, free radical scavenging, modulation of oxidative damage, DNA repair capacity, and protein functions (Meplan 2011). As with other nutrients, conditions that are common in the elderly, such as malnutrition, interaction with medications, and reduced digestion and absorption, can contribute to reduced intake of the trace elements. Low or inadequate intake of trace elements can affect the ageing process and has been linked to disease development in the older age (Roussel 2002).

4.3.1 Copper

Copper (Cu) is an essential trace element to human health because of its involvement in a wide range of biological functions, especially in a central nervous system. It is an integral component of various enzymes, such as cytochrome C oxidase, lysyl oxidase, superoxide dismutase, dopamine β-oxidase, catalase (Zheng and Monnot 2012). Reduction in the Cu concentration affects the activity of these enzymes and consequently decreases the capacity of the organism to reduce oxidative damage or enhance repair capacity (Mocchegiani et al. 2014).

Copper deficiency has also been linked to the appearance of osteoporosis. Lysyl oxidase is a copper-dependent enzyme that catalyzes the formation of aldehydes from lysine residues in collagen and elastin precursors. In the case of lower Cu intake, the reduction of lysyl oxidase activity occurs and leads to bone mass loss, called osteopenia of copper deficiency (Arredondo et al. 2018).

As an unbound metal ion, Cu participates in the metabolism of neurotransmitters and nerve myelination (Zheng and Monnot 2012). Free Cu ions are present in an organism in a very low concentration to prevent the possibility of inducing highly reactive free radicals (Zoroddu et al. 2019). Due to its chemical reactivity, both a deficiency and an excess of Cu can be detrimental to the central nervous system (Zheng and Monnot 2012). An increase of the circulating Cu which is not bound to ceruloplasmin can contribute to the development of neurodegenerative diseases in the ageing population, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, dementia with a vascular origin, spongiform encephalitis (Creutzfeld-Jakob disease), and Huntington's disease (Squitti et al. 2014; Cerpa et al. 2005).

4.3.2 Iron

Iron (Fe) is an essential trace element inevitable for many biological functions such as oxygen transport, DNA synthesis, and mitochondrial oxidation (Ćurko-Cofek et al. 2017). Therefore, it has an important role during ageing maintaining the immune and antioxidant function and cognitive abilities (Mocchegiani et al. 2012). However, iron homeostatic mechanisms change during physiological ageing and create the basis for iron deficiency or increased body iron stores (Fairweather-Tait et al. 2014).

Anaemia and iron deficiency are two of the most prevalent disorders worldwide. According to the WHO, anaemia affects more than 25% of the population, while iron deficiency is even more prevalent. Chronic inflammation has an important role in the impairment of iron status (Dao and Meydani 2013) and its effects can be further enhanced by malnutrition (Fairweather-Tait et al. 2014). Both, chronic inflammation and malnutrition, are often present in the elderly, making this population susceptible to the development of iron deficiency. Iron deficiency in older adults has been associated with a decline in physical performance, cognitive impairment, increased

susceptibility to falling and frailty, and mortality (Price et al. 2011). In contrast, iron overload is mainly associated with pathological conditions, but it could also be relevant during ageing (Grubić Kezele and Ćurko-Cofek 2020). In older adults, body iron levels can be elevated due to consumption of iron supplements or vitamin C, which enhances non-heme iron absorption (Fleming et al. 2002). Previous researches associate high body iron with coronary heart disease (Hunnicutt et al. 2013), type 2 diabetes (Bao et al. 2012), and risk of cognitive impairment (Penke et al 2012).

During ageing, iron accumulates in different brain regions, creating an imbalance between ROS production and antioxidant defence. Oxidative damage caused by the accumulation of iron in the brain increases the susceptibility of the aged brain to disease and could be the reason why ageing is the major risk factor for neurodegenerative diseases (Ashraf et al. 2018).

4.3.3 Magnesium

Magnesium (Mg) has great physiological importance as a cofactor for numerous biological processes. It participates in oxidative phosphorylation, energy production, protein synthesis, glycolysis, nucleic acid synthesis and stability (Dominguez et al. 2021). Through its role in the active transport of ions across cell membranes, Mg modulates neuron excitability, muscle contraction, and normal heart rhythm (Barbagallo and Dominguez 2013). Furthermore, Mg is involved in immune response participating in signalling pathways that regulate the development, homeostasis, and activation of immune cells (Tam et al. 2003).

Total body Mg and Mg in the intracellular compartment tend to decrease with age (Barbagallo et al. 2009). According to the published data, 73% of older men and 41% of older women in the Western world have inadequate Mg intake (ter Borg et al. 2015). Other frequent causes of Mg deficits in the elderly are reduced Mg intestinal absorption and bone stores, and the excess urinary loss (Barbagallo et al. 2009). Low Mg intake and low Mg body levels are associated with chronic conditions usual in the elderly, such as high blood pressure, type-2 diabetes, osteoporosis (Marsman et al. 2018), and low-grade chronic inflammation. This type of chronic inflammation involves several tissues and organs, which are frequently associated with multiple chronic diseases, and that has been named "inflammaging" (Franceschi and Campisi 2014). The fact that chronic Mg deficiency is frequent in old age (Barbagallo and Dominguez 2013) could be significant in a time of COVID-19 pandemic. Namely, Mg deficiency creates an appropriate microenvironment for the virus to promote thromboembolism (Iotti et al 2020), the main feature of COVID-19.

In contrast, use of Mg supplementation reduces plasma C-reactive protein concentrations (Simental-Mendia et al 2017) and significantly lower blood pressure in those with insulin resistance, prediabetes, and other chronic diseases (Dibaba et al 2017). Also, it has been shown that Mg supplementation improves glucose metabolism and insulin sensitivity in type-2 diabetes (Gommers et al 2016).

The consequences of Mg imbalance in the elderly may contribute to the ageing process itself. Namely, Mg is required to maintain intracellular genomic stability, and it is an essential cofactor in almost all enzymatic systems involved in DNA processing (Hartwig 2001). DNA is continuously damaged either by environmental mutagens or by endogenous processes. Mg has a significant role in removing DNA damage caused by any of these causes (Barbagallo and Dominguez 2010). The data from research (Killilea and Maier 2008) have shown that Mg deficiency may accelerate cellular senescence in the cultured human fibroblasts with a loss of replicative capacity and accelerated expression of senescence-associated biomarkers.

4.3.4 Zinc

Zinc (Zn) is involved in many homeostatic mechanisms as a structural and regulatory catalyst ion for many enzymes, proteins, and signal transcription factors, including cell proliferation, genome stability, and the immune system efficiency (Cabrera 2015). The immune system is specially affected by the ageing process, and therefore the term immunosenescence is often used in this context. Immunosenescence is characterized by a progressive abnormal regulation of immune responses, both innate and adaptive. The result is low-grade inflammation, susceptibility to infections (Alonso and De la Fuente 2011), and lower efficacy of vaccines (Lang et al 2011). There are remarkable similarities in the immunological changes during ageing and Zn deficiency. In the case of Zn content decrease, immune cells show a decline in function. There is a decrease in monocyte cytotoxicity, reduced phagocytosis in neutrophils, increased apoptosis in B cells, deterioration of T cells functions, but also an increase in autoreactivity (Ibs and Rink 2003). Zn deficiency shows the closest link to ageing and immunosenescence through the oxidative inflammatory ageing (oxi-inflamm-ageing) process. The oxi-inflamm-ageing theory associates oxidative stress with ageing effects, particularly on the nervous, endocrine, and immune cells, which have a regulatory systems function (De la Fuente and Miguel 2009). Zn deficiency increases oxidative stress and causes the generation of inflammatory cytokines, such as IL-1β, IL-2, IL-6 and TNF-α (Cabrera 2015). Together, immunosenescence and inflamm-ageing contribute to most of the diseases of the elderly, such as infections, cancer, autoimmune disorders, and chronic inflammatory diseases. However, recent data suggest that these two processes are not only detrimental but also adaptive and remodelling, and therefore may be needed for extended survival/longevity (Fulop et al 2018). Since many studies confirm a decline of Zn levels with age, bearing in mind the important role of Zn in immunity, oral Zn supplementation has the potential to improve immunity and downregulate chronic inflammatory responses in the elderly (Haase and Rink 2009).

4.3.5 Selenium

Selenium (Se) is a trace element essential for human health. However, the safe range of exposure to Se is generally narrow, and both Se deficiency and excess can be harmful to human health (Garcia-Esquinas et al 2021). Se is an essential component of several major metabolic pathways, including thyroid hormone metabolism, antioxidant defence systems, and immune function. The biological functions of Se are exerted by selenoproteins in which Se is incorporated in the form of the amino acid selenocysteine (Kryukov et al 2003). Selenoproteins have antioxidant effects and are involved in regulating antioxidant activities. Reactive oxygen species are initial factors in ageing and ageing-related diseases. Therefore, Se alleviates ROS-mediated processes, such as inflammation or DNA damage (Cai et al 2019). Skeletal muscle is one of the major sites of Se storage (30–45% of the total pool), and several selenoproteins are involved in muscular function. Other potential health benefits of Se status in older populations are reduced risk of immune dysfunction, cognitive decline, cardiovascular disease, certain tumours, and overall mortality (Garcia-Esquinas et al 2021). However, there are still many contradictions regarding the role of Se in longevity and ageing-related diseases, as well as about Se supplementation. In the case of Se excess, Se is non-specifically incorporated into proteins other than selenoproteins, changing protein structures and thereby affecting their function (Cai et al 2019).

4.4 Conclusion

Micronutrients are vital for human health, especially in the ageing process. They support the function of immune, nervous, and cardiovascular system, protect cells from oxidative stress and enable call division, reduce cognitive decline. The best way for the elderly to maintain the quality of life and prevent disease is a healthy diet and a healthy lifestyle. Diet should be rich in fruits, vegetables, whole grains, and lean proteins and within micronutrients DRI values recommended by IOM. However, many factors in the older population influence dietary intake and cause undernutrition. In that case, oral supplements are needed but should be used with caution. Potential drug-nutrient interaction and excess intake should be avoided. Therefore, the best way is to adjust the intake to the actual needs of the organism determined by nutrition assessment.

Compliance with Ethical Standards

Conflict of Interest The author declares no conflict of interest.

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