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Aging and Nutrition: Theories, Consequences, and Impact of Nutrients

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Abstract

Purpose of Review This review tries to provide a comprehension of the relation existing between aging and nutrition.

Recent Findings Macronutrients and micronutrients obtained from food intake support biological and physiological activities required for optimal health. The past decade has witnessed studies demonstrating a link between malnutrition and accelerated aging or age-related disorders. Aging causes loss of function in tissues and organs and is explained by different theories such as free radical or reactive oxygen species (ROS), nutritional intervention in the name of caloric or dietary restriction (CR/DR), or endocrine theories. These theories confirm the bridge between nutrition and aging, and give the clues on how aging and age-related diseases can be mitigated by macronutrients like proteins and carbohydrates, and by micronutrients, including vitamins and essential minerals.

Summary This review, besides giving insight into the precedent theories and findings, answers the following questions: Which nutrients are essential or need to be considered in the elderly? Do elderly feed themselves without difficulties? What are the basic causes and consequences of aging that link it to nutrition? Through this insight and those answers, the article lays the path down for further studies on the interaction between the aging process and different types of nutrients.

Keywords Aging · Nutrition · Minerals · Vitamins · Food intake

Introduction

The term "healthy aging" is employed many times to refer to the malfunctioning of the body associated with aging but also to point out the effort or the need to give a clearer and focus strategy to help elderly people live a better life [1]. Healthy aging could be defined as strategies put into practice by the public health authorities to provide appropriate care and support, and to maintain the highest standard of life possible to people who have reached their 60's and beyond. The World Health Organization has defined the term as: "the process of developing and maintaining the functional ability that enables wellbeing in older age. Functional ability is about having the capabilities that enable all people to be and do what they have reason to value. This includes a person's ability to: meet their basic needs; to learn, grow and make decisions; to be mobile; to build and maintain relationships; and to contribute to society" [1]. One of the main factors that influence well-being is nutrition, especially at later ages. Indeed, nutrition has been scientifically proved by various studies to be one of the main factors influencing healthy aging.

Nutrition is the set of processes by which foods are processed to ensure the healthy functioning of the body. It includes food intake, absorption, assimilation, biosynthesis, catabolism, and excretion. Human nutrition is composed of macronutrients and micronutrients. Macronutrients are proteins, carbohydrates, and lipids; they provide our calorie needs. Micronutrients, including vitamins and essential minerals, support biochemical and metabolic activities required for optimal health [2]. An imbalanced diet can cause deficiency-related diseases such as

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blindness, anemia, or frailty and common chronic systemic diseases associated with aging such as cardiovascular disease, diabetes, and osteoporosis. In recent years, malnutrition or poor nutritional state has been shown to be a main reason for older patients' hospitalization [3], underpinning the link between malnutrition and accelerated aging or age-related diseases. For instance, in 1935, McCay [4] through the caloric restriction theory of aging has paved the way on the mechanisms by which nutritional deficiency or excess contributes to the aging process. Ample evidence generated over the past decade go into that direction; caloric and dietary restrictions have shown to be the most effective longevity intervention range [2, 5].

This review, after presenting the theories behind aging, outlines the physiological consequences of aging which involve nutrition and why it is important to adjust the nutritional needs during this biological state of the human body.

Nutritional Process Underlying Aging

Aging can be defined as the time-related progressive physiological changes in an organism that lead to a deterioration or decline of the biological functions and of the organism's ability to adapt to metabolic stress. It takes place in a cell, a tissue, an organ, and ultimately the total organism, and is characterized by a variety of changes in the body, including muscle loss, thinner skin, and less stomach acid. These manifestations of aging observed at the organism level are sustained by multicausal, progressive, and irreversible modifications that occur at molecular and cellular levels [6]. Scientific studies in the last decades have investigated the process underlying aging at this level and come up with a number of theories [7]. Currently, there is a multitude of aging theories [8–11, 12••], but these taken individually cannot explain all the phenomena of aging. However, some of these theories such as complementary free radical, caloric or dietary restriction, and endocrine theory seem to be more representative of the causes of aging. Food intake or nutrition status plays a central role in these theories since they mediate free radical, dietary, or hormonal production.

The free radical or reactive oxygen species (ROS) are formed from oxygen and biomolecules brought by food absorption. The ROS are mainly produced by mitochondria during mitochondrial metabolism. This notion is at the basis of Mitochondrial Free Radical Theory of Aging proposed by Harman and Gerschman to explain the aging process [12••, 13]. But an imbalance between the production of ROS and the antioxidant defenses of the body will lead to oxidative stress production which is partly responsible for cellular damages in the organismal tissues. Various cellular biomolecule components such as, lipids, proteins, or DNA are the particular targets of the ROS. And, the accumulation of damages linked to ROS actions would be largely responsible for the lesions observed during aging and the progression of some age-related diseases such as cardiovascular and neurodegenerative diseases. Apart from the mitochondria, organelles such as the endoplasmic reticulum, cytochrome P450, and enzymes such as NAPDH oxidase, lipoxygenase, and peroxisomes are also primary sites of ROS production [14]. Besides the intrinsic and cellular factors, in general, malnutrition and lifestyle are non-negligible sources of ROS. Smoking, low consumption of fruits and vegetables, alcoholism, and exposure to certain environmental factors such as carcinogens would lead to endogenous biochemical reactions including the oxidation of hypoxanthine and xanthine, inflammation, alteration of endothelial function, iron overload, oxidation of hemoglobin, and mitochondrial alterations which are also potential sources for oxidative stress [15]. In alignment with Mitochondrial Free Radical Theory of Aging, several studies suggest that supplementation of antioxidants including vitamins (E and C) can also interact with free radicals and prevent their accumulation [16, 17]. Although this free radical theory of aging was proposed since 1954, it is yet to be proven or disproven.

The second aging theory, the nutritional intervention known as caloric or dietary restriction (CR/DR), has been showed to regulate ROS production [4, 18]. CR is referring to a dietary intervention with an overall 20–40% reduction of total caloric intake, and DR represents a broader range of dietary interventions including those with specific restrictions on macronutrients and dietary patterns [19]. But they both have an impact on aging and retard age-related chronic diseases by decreasing ROS generation and oxidative damage [18, 19]. Mechanistically, they are mainly based on the reduction of metabolic rate and oxidative stress: two components related to the nutrition state which have beneficial impacts on body composition, ROS damages, insulin sensitivity, and neuroendocrine function [19]. However, the mechanisms remain elusive; CR or DR continues to be the most robust metabolic intervention capable of extending longevity and improving health span in diverse organisms including yeast, drosophila, nematodes, fish, and mice, and in rhesus monkeys and humans [4, 19, 20]. Experiments performed on mammalian cells or models showed that both of them can mitigate the incidence, time of onset, and progression of many age-related pathologies including cardiomyopathy, nephropathy, type II diabetes, muscle atrophy, hypertension-related diseases, autoimmune diseases, and several neurodegenerative disorders like Parkinson's or Alzheimer's disease [21, 22]. A similar observation has been found in humans [23]. Nowadays, one of the well-recognized cardiovascular disease risk factors are carried by foods including lipids and lipoproteins (low-density lipoprotein LDL and high-density lipoprotein HDL cholesterol and triacylglycerol) [24]. For example, atherosclerosis, a cardiovascular disease, is recognized as an important age-related disease caused by some elevated concentrations of oxidatively modified LDLs which generate free radicals. This suggests that good nutrition might prevent the onset of age-related cardiovascular diseases.

There is a link between factors (ROS production, CR or DR) described in the precedent lines and endocrine signaling pathway [25]. Indeed, ROS production and nutritional intervention (DR or CR) involve upstream nutrient signaling pathway changes including in the insulin/IGF-1 axis and the mammalian target of rapamycin (mTOR) signaling pathway [18, 25]. In agreement with this, in a study released in 2013, an altered neuroendocrine pathway during a prolonged starvation study in animals has been reported [18], reinforcing the previous statement. This benefit effect is based on the reduction of an adipose cell hormone called leptin that helps regulate energy balance by inhibiting hunger. Those findings underscore a central role of endocrine system mediated by the nutrition state, as a master regulator of the aging process.

Several alterations in gene expression are linked to aging [26–28]. This change is observed in skeletal muscle, brain, and heart, exposing the whole organism to developing an age-related disease. Aging selectively increases inflammatory and oxidative stress transcripts and downregulated genes involved in ROS production [29]. Accordingly, genes that have been reported to change during aging are particularly involved in the process of food absorption and in the modulation of nutrient signaling pathways.

Through all these theories of aging, it has become evident that food intake or nutrition state is in the center of the aging process, and this appeals for diet adjustment for better aging without any age-related diseases.

Aging and Physiological Consequences

Physiological changes observed during aging are the manifestations of synergetic dysfunctions of several cell components including mitochondria, lysosome, and endoplasmic reticulum. This dysfunction leads to a loop of consequences characterized by ROS production, dysfunction of the clearance systems and accumulation of wastes within the cytoplasm, and cell damages. In the tissue level, there is a dysfunction of the hormonal production, changes in the cell activity and communications, loss of synapses, and excitotoxicity in the neuronal tissue. On the clinical level, troubles are described such as frailty, malabsorption of essential nutrients, and sarcopenia [30].

Frailty, for example, is a late-stage of life syndrome that results from reaching a threshold of decline across multiple organ systems [31]. Depending on the frailty definition and evaluation tool, frailty prevalence ranges between 4.0 and 59.1% in community-dwelling people aged ≥ 65 years [32•]. As the population ages, frailty represents increasingly important public health concerns and has an incremental effect on health expenditures (additional ± €1500/frail person/year) [33, 34]. Because of the major clinical and economic burden, it is critical to find efficient, feasible, and cost-effective interventions to prevent or slow down frailty in order to avoid or diminish the adverse outcomes and maintain or improve quality of life [31]. Frailty is possibly reversible or modifiable by interventions. Previous research on non-pharmacological interventions such as physical exercise and nutritional interventions showed promising effects on frailty status, functional outcomes, and cognitive outcomes [35]. These interventions can be combined with each other or with other (e.g., pharmacological, hormonal, or cognitive) therapies to prevent or treat frailty [36].

Besides, it is known that low stomach acid can affect the absorption of nutrients, such as vitamin B12, calcium, iron, and magnesium. This might worsen the nutrient deficiencies already observed in older people. For example, in an article reviewing the relationship between oral status and nutrition, examples were given of studies showing a decrease in vitamin, fruit, and vegetable intake and increase in carbohydrates in the elderly due mainly to tooth loss. This situation explained the obesity observed in edentulous elderly people by further studies exposed in the review. In other cases, the situation is transformed into low body weight due to the inability to chew, the loss of appetite, or mouth dryness observed in elderly [37]. In another article reviewing the changes observed during aging and their association with malnutrition, the obesity observed in the elderly is explained by the loss of lean muscle and sarcopenia. This loss in muscle happens in healthy and non-healthy patients, suggesting this to be a metabolic issue and not a disease one. Sarcopenia is also the cause behind a reduced total body water content (dehydration) and it is caused by the lack of exercise that is frequent in the elderly [38]. Dehydration is one of the causes behind intractable constipation observed in this population. And, constipation has been associated with a decreased quality of life: paranoid ideations, hostility, and obsessive-compulsive disorder, anxiety disorders and depression, somatization, psychosis. Considering the fact that old people are already experiencing a feeling of unwantedness due to the fact that they no longer feel useful to their communities and/or are living in caring houses, constipation may lead them to a worse psychological health [39]. Psychological illness has also been associated with a deficiency in mineral intake. A study performed in Japan has demonstrated the relation between depressive symptoms in working adults aged 19 to 69 years and the intake of minerals. It showed that higher intake of magnesium, calcium, iron, and zinc was associated with lower depressive symptoms, suggesting to augment the intake of those minerals in diet [40].

The precedent findings suggest that the contents of food for the elderly, e.g., water, minerals, vitamins, fiber, and proteins, should be checked or supplemented to make sure there is a higher input in comparison with that of a younger adult and that the energy intake (due mainly to carbohydrates) must be reduced to a minimum. A particular focus is put on some vitamins and minerals due to their importance in the human body in general and in elderly people in particular. These are vitamins (A, C, D, E, K, B6, B12, folates), minerals (copper, iron, selenium, magnesium, manganese, zinc, calcium, sodium, iodine), proteins, and water.

Nutritional Needs During Aging

Minerals

Intake of iron (Fe) in elderly must be checked to make sure it meets the daily intake (Table 1) due to the fact that iron deficiency is highly observed in aged people. In fact, studies found the prevalence of anemia is 3 to 25% in the elderly living in their communities. Anemia could lead to various illnesses such as frailty and decreased physical performance, reduced muscular strength with increased risk of falls, cognitive decline and dementia, and increased mortality risk in longitudinal studies [57]. Iron is helped in its function in the formation of hemoglobin by copper (Cu).

In comparison to Fe, Cu deficiency is not frequently reported in the elderly; studies have instead reported an increase in serum copper level. This increase has been investigated and it has been demonstrated that Cu has an interconnection with zinc (Zn) levels in the human body. In the elderly, the increase in Cu levels might be due to nutritional intake, oxidative stress, pro-inflammatory stimuli, and cellular senescence [58]. The copper to zinc ratio (CZr) has been developed to check the two nutrients and evaluate their effects on the human body. Recommendations have come out of such studies. Indeed, it has been proven that a CZr over 2 in the elderly is associated with an inflammatory response or a decreased nutritional Zn status, with debilitating conditions, and with the risk of cardiovascular disease death, malignancy, and all-cause mortality [58]. The CZr should therefore regularly be controlled in people aged 60 and over. The strong relation between zinc and copper is due to the fact that zinc is involved in almost the same functions as Cu (Table 1).

Zinc (Zn) could be found in a variety of foods such as grain products, milk and dairy products, meat and alternatives, and fish and seafood (Table 1). A study performed in the elderly in the USA has demonstrated a correlation between the levels of Zn in blood and the immune system. Indeed, Zn supplementation significantly increased anti-CD3/CD28 and phytohemagglutinin-stimulated T cell proliferation, and the number of peripheral T cells [59]. Another study performed in Australia has found that Zn supplementation in an elderly population with low zinc status has induced a decrease in genomic stability biomarkers, in the name of the micronucleus frequency, the tail moment, the tail intensity, and the telomere base damage [60]. In a study performed in a mouse model, Zn deficiency induced aberrant immune cell activation and differentiation in the absence of differentiation signal leading to an enhanced (not needed) pro-inflammatory response of the organism [61]. Those studies confirm the role of Zn in the improvement of the immune system, and the protection of cells against malign development. Just like Zn, selenium (Se) helps the immune system and thyroid function (Table 1).

A study performed in the elderly Danish population to investigate the long effects of Se supplementation after 6 months and 5 years has revealed a decrease of the total cholesterol levels in the blood of patients supplemented in comparison with the control group [62]. In a review describing the investigated effects of selenium and its derivative on epigenetics, it has been found that, among other effects, Se caused a reversible alteration of the cell heterochromatin status and also changed the DNA methylation status of individual genes with roles in fetal development, including Hnf4α (hepatocyte nuclear factor 4α), Aebp2 (AE binding protein 2), Prickle 2 (prickle homolog 2), and Rnd2 (Rho family GTPase 2), without compromising the cell potential to form embryonic bodies, showing an interesting link between Se and tissue-specific differentiation. In the same review, Se has been described like other nutrients, to induce or to be associated with changes to histone marks, thereby possibly affecting health outcomes. Interference of nutrients with histone marks can principally occur through modulation of histone-modifying enzyme activity/expression and via interference with substrate availability. But studies reviewed are not sufficient to establish the clear effects of selenium on epigenetics [63]. Another study performed in Sweden to check the effect of Se and Q10 supplementation over 4 years in elderly people on cardiovascular mortality has shown a decreased mortality due to cardiovascular disease. Besides, 6 years after the 4 years supplementation, the reduced mortality due to cardiovascular disease was also maintained [64••]. Selenium (Se) just like manganese (Mn), iodine (I), and magnesium (Mg) could be found in cereals and also in other types of food (Table 1).

Mn and I are also implied in neuronal activities, as suggested by their role and functions (Table 1). In a review on studies investigating the relationship between Alzheimer's disease (AD) and mild cognitive impairment (MCI), a meta-analysis of the studies has shown that patients with AD and MCI have low Mn serum levels in comparison to the controls [65]. Concerning iodine, both its deficiency and excess are generally observed in aged people, leading to hypothyroidism or hyperthyroidism and auto-immune thyroid disease [66]. It suggests that in comparison with many other nutrients where deficiency is highly observed in the elderly, in the case of iodine, serum levels should be checked before emphasizing any means to augment its level in the organism (Table 1).

Calcium and magnesium are the two most important divalent intracellular cations in the organism [50]. They have synergistic effects in a certain number of biochemical reactions and physiological functions in the human body [67].

Both of them could be provided by different types of food and also through supplements (Table 1). Mg supplements have, in fact, been used in clinical trials. For example, healthy elderly women were supplemented with Mg in a region of

Table 1 Vitamin and mineral needs in the elderly. *µg* micrograms, *mg* milligrams, > superior to, < inferior to

Mineral/vitamin	Age	Daily need		Sources	Role in the human body
		Men	Women		
Iron	> 51	8–45 mg		Vegetables and fruits (spinach, tomato, edamame and baby soybeans, lima beans, asparagus, hearts of palm, potato with skin, snow peas, turnip or beet greens, prune juice, apricots, beets, kale, green peas); grain products; cereals; meat and poultry; fish and seafood; beans; eggs [41, 42]	Formation of hemoglobin (binds oxygen and transports it all over the body) in red blood cells Main component of enzymes named cytochromes (oxidative metabolism; synthesis of steroid hormones and bile acids; detoxification of foreign substances in the liver; signal controlling in some neurotransmitters, such as the dopamine and serotonin systems in the brain) [43, 44]
Copper	> 51	900–10,000 µg		Organ meats (beef, lamb, goose, duck liver and kidneys); seafood (mollusks, oysters); nuts (almonds, cashews); seeds; whole grains (soy, beans); cocoa [41, 42]	Active site of many metalloenzymes: ceruloplasmin (a plasma glycoprotein, antioxidant), dopamine-β-monooxygenase (conversion of dopamine to norepinephrine), cytochrome-c-oxidase (terminal mitochondrial electron carrier), lysyl oxidase (oxidative deamination of peptidyl lysine), Cu-Zn-superoxide dismutase (cytosolic protein speeding up the dismutation of superoxide) and tyrosinase (conversion of tyrosine into melanin) Synthesis of white cells [45]
Zinc	> 51	11–40 mg		Grain products (wheat, cereals, rice); milk and dairy products (cheese, yoghurt); meat and alternatives (liver, beef, veal, lamb, pork, turkey, chicken, baked beans, tempeh/fermented soy product, sunflower seed, cashew, tofu); fish and seafood (oysters, carbs, octopus, lobster, anchovies, shrimp) [41, 42]	Major metabolic pathways concerned with protein, lipid, carbohydrate, and energy metabolism and essential for cell division and, consequently, for growth, tissue repair, and normal reproductive development Normal growth and development for all ages Immune system and wound healing [43]
Selenium	> 51	55–400 µg		Vegetables and fruits (mushrooms); grain products (couscous); milk and dairy products (cheese, yoghurt, milk); meat and poultry (liver, bacon, chicken, beef, lamb); nuts and seeds; fish and seafood (halibut, herring, bass, cod, mackerel, tilapia, tuna, oysters, pike or grayling, salmon, sardines, crab) [41, 42]	Antioxidants' reactions: component of one of the most important enzymes of such reactions, glutathione peroxidase Immune system and the thyroid function [42]
Manganese	> 51	2.3 mg	1.8 mg	Oats, wheat, pecans, soybeans, rye, barley, quinoa, garlic, cloves, brown rice [41, 42]	Cofactor for a variety of enzymes, including arginase, glutamine synthetase (GS), pyruvate carboxylase, and Mn-dependent superoxide dismutase (Mn-SOD) which play important roles in development, digestion, reproduction, antioxidant defense, energy production, immune response, and regulation of neuronal activities [46]. MnSOD plays a major role in the antioxidant system of the organism, due to its location in the mitochondria where it scavenges the superoxide O^{-}_{2} [47] Essential component of the superoxide dismutase mimetic manganese (III) tetrakis (92)-benzoic acid porphyrin (MnTBAP), an antioxidant which has been shown to limit weight gain during short-term high-fat feeding without preventing insulin resistance and also to treat pre-existing obesity and insulin resistance in mice [48]
Iodine	> 51	150–1800 µg		Cereals grains; fish (haddock, cod, plaice, salmon fillet, canned tuna); shellfish (prawns,	Essential component of thyroid hormones, essential to brain development [49]

Table 1 (continued)

Mineral/ vitamin	Age	Daily need		Sources	Role in the human body
		Men	Women		
				scampi); eggs, meat and poultry, bread, fruits, vegetables; fortified cereals [41, 42]	
Magnesium	> 51	320–350 mg		Fruits and vegetables (tamarind, spinach, pear, Swiss chard, okra); grain products (cereals, quinoa); cereals (peas, soybeans, soy nuts, lentils); nuts and seeds (almonds, cashews, pine nuts, sunflower seeds, sesame seeds, hazelnuts); fish and seafood (salmon, chinook, halibut, mackerel, pollock, crab) [41, 42]	Complexation with ATP, required for many enzymes such as kinases which are involved in phosphorylation reactions that transfer a phosphoryl group from ATP to an acceptor molecule [50] Carbohydrate metabolism: regulation of rate-limiting enzymes involved in glycolysis, glucose homeostasis, and insulin action including both insulin receptor responses (tyrosine kinases) and the insulin-signaling cascade Stabilizing role for proteins, nucleic acids, and biological membranes Bone metabolism/remodeling: calcium absorption, i.e., calcitonin stimulation, parathyroid hormone secretion, osteoblast adhesion, and bone formation [50] Intracellular signaling: regulation of ion channels and transportation, processes which are important for muscular and neuronal excitability and activity [50]
Calcium	51–70 > 51 > 71	1200–2000 mg 1200–2000 mg	 1200–2000 mg	Milk and milk products (fat-free or low-fat), some forms of tofu, dark-green leafy vegetables (collard greens and kale), soybeans, canned sardines and salmon with bones, calcium-fortified foods and calcium supplements (calcium citrate and calcium carbonate) [41, 42]	Vascular contraction, vasodilation, muscle functions (maintenance and integrity of skeletal muscles), bone formation, nerve transmission (control of nerve excitability), intracellular signaling, and hormonal secretion [51]
B6	> 50	1.7 mg	1.5 mg	Fortified cereals, whole grains, organ meats (liver), fortified soy-based meat substitutes [41, 42]	Catabolic metabolism (leading to the generation of energy) and anabolic metabolism (resulting in the construction and transformation of bioactive molecules) [52]
B12	> 50	2.4 μg		Meat, fish, poultry, milk, and fortified cereals [41, 42]	
B9	> 50	400 μg		Dark-green leafy vegetables like spinach, beans, and peas, fruits like oranges and orange juice, and folic acid from fortified flour and fortified cereals [41, 42]	
C	> 50	45 mg		Fruits (citrus fruits and juices, cantaloupe, honeydew melon, cherries, kiwi fruits, mangoes, papaya, strawberries, tangelo, watermelon) and vegetables (tomatoes, cabbage, broccoli, Brussels sprouts, beansprouts, cauliflower, kale, mustard greens, red and green peppers, peas, tomatoes, potatoes), supplements [41, 42]	Exists in the human body under the form of ascorbate which acts as a co-substrate of many enzymes essential to the functioning of the human body: redox balance (donation of electrons); recycling mechanisms (avoid loss of antioxidants through dismutation reactions); neuronal differentiation, maturation, and survival (increase the expression of genes involved in the process); catecholamines (dopamine and norepinephrine) biosynthesis (modulation of the neurotransmission, learning and memory), etc. [53]
A	50–65 > 65	300 μg 300	270 μg	Vitamin A is found in animal products (glandular meats, liver and fish liver oils, egg yolk, whole milk and dairy products, fortified cereals, fortified condiments, fortified fats and oils). Pro-vitamin A carotenoids are found in green leafy vegetables (spinach, amaranth, and young leaves from various sources); yellow vegetables (pumpkins,	Normal functioning of the visual system Growth and development Maintenance of epithelial cellular integrity, immune function, and reproduction [44]

Table 1 (continued)

Mineral/ vitamin	Age	Daily need		Sources	Role in the human body
		Men	Women		
				squash, and carrots); yellow and orange non-citrus fruits (mangoes, apricots, and papaya); red palm oil; indigenous fruits (burití and thatis in Brazil, gấc in Vietnam), fortified food [41, 42]	
D	50–70 > 70	600–4000 IU 800–4000 IU		Fatty fish, fish-liver oils, fortified milk and milk products, and fortified cereals [41, 42]	Homeostasis of calcium and phosphorus (necessary for proper bone mineralization and in nerve conduction and all general cellular functions of the body) Muscular system (stimulation of the proliferation and differentiation of muscle cells) Modulation of the transcription of cell cycle proteins which decrease cell proliferation and increase cell differentiation of a number of specialized cells of the body (e.g., osteoclastic precursors, enterocytes, keratinocytes, etc.) [44, 54]
E	> 50	15–1000 mg		Vegetables (spinach leaves, dandelion leaves, tomatoes, chard, turnip leaves, red pepper); fruits (avocado); cereals; eggs; fish and sea fruits (eel, herring, sardines, tuna); nuts and seeds (kernels, hazelnuts, peanuts, pine nuts, Brazil nuts); meats, fats, and oils (vegetable oils); fortified oils and cereals, supplements [41, 42]	Prevention of oxidative stress: α-tocopherol prevents the formation of new radicals and Ω-tocopherol scavenges and neutralizes the already formed radicals Protection of cell membrane Immunity (regulation of platelet aggregation and protein C kinase activation) [55]
K	51–65 > 65	55 μg 65 μg	65 μg	Vegetables (spinach leaves, dandelion leaves, cabbage, chard, turnip leaves, mustard leaves, beet leaves, lettuce, onion); vegetable oils (peanut oil, corn oil, sunflower oil, and safflower oil); fruits (kiwi, rhubarb, avocado, cornflower); eggs, meat, tuna, soybeans; fortified oils and cereals [41, 42]	Blood clotting, calcium transport, bone density, and prevention of calcium deposits on blood vessels [56]

Italy for over 12 weeks and their physical performance investigated during a randomized controlled trial. Results have shown a clear amelioration of the Short Physical Performance Battery (SPPB) in the treated group in comparison with the controlled group, with more evident results with participants with a deficiency in the recommended dietary Mg intake [68]. In a clinical study run in Mexico to evaluate the effect of magnesium supplementation in adults aged 30 to 65 years old with hypomagnesemia and newly diagnosed with prediabetes, plasma glucose levels have been reduced, and the glycemic status of the adults improved [69]. An observational study in elderly men (40 to 86 years old) presenting acute aortic dissection was carried out in Milan for over 19 years. Levels of Mg and Calcium (Ca) were investigated and found to be lower in the sick elderly men group in comparison with the healthy control group. In addition, levels of all the pro-coagulant and pro-inflammatory mediators analyzed, including sP-sel, D-dimer, TNF-α, IL-6, and CRP, were high. The findings suggest that low Mg and Ca in acute aortic dissection elderly patients may contribute to altering normal endothelial physiology and also concur in changing the normal concentrations of different mediators involved in vasodilatation and constriction, associated with acute aortic dissection [67].

In a published review where many of such studies involving Ca have been meta-analyzed, it came out that Ca supplements have helped prevent fracture (total and vertebral) in some studies, but data were not sufficient to consistently affirm that Ca supplement can prevent the risk of fracture in the elderly [70]. The result is supported by another review on the role of combined vit D and calcium. Indeed, vitamin D has been reported to facilitate absorption of Ca in various studies, suggesting the synergistic effect both could have on bone formation. However, the review by analyzing all the studies on fractures in elderly and effects of Ca or vit D, or both, did not find a correlation between the supplementation of vit D and Ca and its effects in the elderly on fracture prevention [71••]. Based on these facts, the long-aged recommendation about simultaneous supplementation of vit D and Ca to keep bones strong and healthy needs to be interrogated and investigated further in the different ages so that clear recommendations could be made.

Those nutrients are altogether needed as they increase synergistic reactions. Recommendations are made on the daily intakes, but in some cases, the daily intakes should not exceed as they might lead to other health injuries (Table 1).

Vitamins

Vitamin D is a member of other types of nutrients called vitamins which are also essential in older ages. They exist in two types: hydro-soluble vitamins (vitamin B complex group and vitamin C) and liposoluble vitamins (vitamins A, D, E, and K).

Vitamins B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folate), and B12 (cobalamin) form the group of B complex vitamins. Among them, vitamins B6, B9, and B12 have driven importance because they have been discovered to have synergistic interaction in the recycling of homocysteine in the methionine cycle. And, homocysteine levels were noticeably high in the plasma of people suffering from cardiovascular disease, Alzheimer's, and dementia, due to the absence or deficiency of the recycle of homocysteine by those three vitamins [52]. Consequently, vitamins B6, B9, and B12 are the ones among B complex vitamins to be primarily recommended in the elderly, to prevent or reduce the severity of the preceding diseases (Table 1). In contradiction to this recommendation, a clinical study performed in Hong Kong, to investigate the effect of supplementation in vitamin B12 on cognitive decline in diabetic elderly patients with borderline vitamin B12 status, came to the conclusion that vit B12 did not reduce cognitive decline in those patients [72]. However, a rushing conclusion could not be drawn because the trial has not investigated the simultaneous supplementation effect of the three vitamins (vitamins B6, B9, and B12) on cognitive decline. Besides, one study is not sufficient to question the recommendation made. Vitamins B6, B9, and B12 could be found from a variety of sources: fruits, vegetables, cereals, etc. (Table 1). Vitamin C is also involved in neurophysiology where it plays different functions (Table 1). The daily intake could be achieved through supplementation and/or food sources (Table 1).

In contrast to vitamin B group and vitamin C; vitamins A, D, E, and K are fat-soluble vitamins.

Vitamin A (retinol) has been demonstrated in vitro to possess anti-aging effects on naturally aged skin in vivo through improvement of the homeostasis of epidermis and dermis by stimulating the proliferation of keratinocytes and endothelial cells, and activating dermal fibroblasts [73]. Vitamin A has also been clinically proven to have effects on cancer cells. For example, polymer-stabilized nanoparticles from synthetic retinoid ST1926-NP (synthetic retinoid ST1926, a derivative of vitamin A) were proven to express an antitumor effect in acute myeloid leukemia in xenograft mice [74]. By performing a post-mortem study on elderly patients who died from ischemic cardiovascular disease (ICVD), Lima and collaborators have found that ICVD-increased body weight and liver weight were due to a failure in the storage of retinol in the liver [75].

In a review on studies carried out on the second liposoluble vitamin, vitamin D relation and frailty in aged people, it came out that low levels of this vitamin increased the risk of frailty in the elderly [76]. Another review, which meta-analyzed published data investigating the relation between the vitamin D and diabetes in older people, found that the risk of diabetes was higher in patients with low levels of vitamin D [77]. The same type of review studying the relation between systemic inflammation and vitamin D shows in a certain degree that supplementation of vitamin D improved the inflammatory status. But the data investigated are not sufficient and well documented to make a clear connection between elderly inflammatory status improvement and levels of vitamin D in the serum.

Vitamin E or tocopherol, the third liposoluble vitamin, has various functions (Table 1). The role of vitamin E in immunity was demonstrated by an in vitro study performed on polymorphonuclear leukocytes (PMNs, leukocytes involved in the fight against disease, particularly infectious diseases) isolated from young and older patients suffering from pulmonary infection. After isolation, PMNs were treated with α-tocopherol and drawn to migrate across lung epithelial cells after infection by *Streptococcus pneumoniae*. Results obtained showed that PMNs treated with α-tocopherol were more efficient in killing the bacteria in comparison with their younger counterparts and with the controls [78]. A review on vitamin E and Alzheimer's disease presented several researches where vitamin E has been demonstrated to reduce the decline of cognitive abilities in aged people and also Alzheimer's disease [79].

Vitamin K, the last one of the vitamin ADEK group, exists under 3 natural forms and one synthetic: vitamin K1, vitamin K2, menaquinone-7 (MK-7); vitamin K2, menaquinone-4 (MK-7), and vitamin K3 (menadione, synthetic). In a clinical research run in the Mediterranean area to study the relation between vitamin K levels and mortality in aged people at risk of cardiovascular disease (CVD), it was found that by augmenting intake of vitamin K, the risk of cancer, CVD, and all-cause mortality was lower [80]. In a case-control study investigating the relation between hip fracture in the elderly and their status of vitamins K and D, it was discovered that those vitamin levels were lower in hip fracture patients compared with controls [81].

Vitamins are also essential in the nutrition of elderly people. They also act synergistically with minerals to prevent aged people from a certain number of deficient physiological conditions and ailments.

Protein Intake, Fiber Intake, and Rehydration

Aged people reduce their physical activities with consequences on muscles [82]. Indeed, decreased physical activity associated with aging leads to the deterioration of muscle mass and function called sarcopenia [82]. Sarcopenia is accelerated by chronic and acute illnesses [83–85]. Moreover, aged people suffer poor appetite at the same time, reducing their protein intake [86]. Older adults, with limited resources, reduced appetite, and physical and environmental limitations, could find it challenging to consume high-quality proteins regularly [87]. It is noteworthy that aging does not impair the ability to synthesize muscle protein after consumption of high-quality protein-rich food [88, 89]. Experts therefore recommend older adults to consume between 25 and 30 g of high-quality protein at each meal [90].

National surveys of dietary intake highlight that the dietary fiber consumption of older adults is often lower than recommended levels [91]. Fiber-rich meals are known to provide not only nutrients such as vitamins, minerals, and antioxidants, but they also are sources of benefits such as improved gastric motility, improved glycemic control, and reduced cholesterol [92]. There is a need to carefully evaluate frail older adults and those with poor appetite in order to prevent high-fiber diets from leading to excess satiety which in itself could lead to overweight [92]. Fluid intake should be considered as well in both recommendations and evaluations on nutritional status [92]. Indeed, adequate water consumption is also important with aging, as the body becomes less able to recognize dehydration signs. Daily water consumption is set to prevent the effects of dehydration by replacing normal daily losses [91]. Daily total (from drinks and food) fluid recommendations range from 2.5 to 3.4 L for men and from 2 to 2.8 L for women [93–95].

Factors Affecting Food Intake: Disability, Caregiver, Living Arrangements, and Physical Activities

Disability often affects diet quality. Physical functioning problems are more frequent in older people than in younger ones [96]. It was reported that 42% of people aged 65 years suffered a functional limitation with higher proportions of women and poor people [96, 97]. Some diseases like stroke (20% of the survivors), diabetes (11%), and ischemic heart disease (10%) increase the risk of functional limitations in older adults who require help in performing activities of daily living (ADLs) [98]. Moreover, 7% of older adults living with arthritis require help performing ADLs; given its prevalence in the elderly (52%), the number of patients needing assistance is quite high [98]. Older people living with disabilities should benefit of the assistance of relatives or caregivers. It is therefore important for the latter to be aware through sensitization and trainings of the nutritional needs of the aged people. And it becomes important that persons taking care of the aged people are aware of the types of alimentation they need. Senior housings are rapidly growing, even if there are still gaps in their services [92]. It is then a duty for public authorities to guarantee aged people a minimum of adequate conditions. It was also established that exercise counteracts depression, alterations in gastrointestinal functioning, and anorexia which are common in older adults, especially those under therapies such as corticosteroids [92].

Conclusion

Nutrients and their metabolites obtained from food intake control key biological processes including enzymatic activities, energy balance, and genome stability throughout the life cycle. As aging is the period when all these processes decline, a strong connection has been made between nutrition and aging or age-related disorders. This review about nutrition and aging summarizes studies and researches discussing the role of nutrition on aging and age-related disorders and how these can be mitigated by nutrients. The issue underscored the necessity to have an appropriate diet to maintain a normal function of the body without any-age related disorders. Interestingly, intake of macronutrients as proteins or micronutrients such as magnesium, vitamins, and selenium is suggested to ensure healthy aging and lifespan extension, since these have an impact on aging factors including redox control, endocrine pathway, and energy balance. The proportion of the elderly in the world is currently at the highest level in the history of mankind, and it is estimated that this level will continue to grow steadily, thus this urge for further investigation to identify the molecular targets and pathways by which nutrition components act to delay the aging process.

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Compliance with Ethical Standards

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•• Of major importance

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