

Effect of Nutrition on Aging

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Choosing low carbohydrate diets or diets rich in vegetables, fruits, nuts, cereals, fish, and unsaturated fats, containing antioxidants, potassium, and omega-3 decreased cardiovascular diseases and obesity risk, protected the brain from aging, reduced the risk of telomere shortening, and promoted an overall healthier life. Since the biological processes of aging cannot be controlled, changing one's nutritional patterns is crucial to prevent the emergence and development of diseases, boost longevity, and, mostly, to enhance one's quality of life and promote healthy aging.

healthy aging

nutrition

cardiovascular disease risk

biomarkers

1. Introduction

Aging is the gradual process of natural changes that occur throughout the human lifespan. This process begins in early adulthood; throughout the years, many mental and bodily functions begin to slowly decline, resulting in health issues, such as increased morbidity and decreased fertility . Over the years, life expectancy has risen, with approximately 8% of the world population being over 65 years old, and in approximately 30 years, this number is expected to double . However, this does not necessarily mean that people experience better health in their later years when compared with other generations ^{[1][1]}.

In fact, despite the life expectancy increase, aging is a mechanism that has multifaceted features that are linked: molecular, cellular, physiological, and functional levels that ultimately lead to chronic diseases ^[3]. At the molecular level, aging is represented by genomic instability, telomere attrition (as they tend to shorten), epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, stem cell exhaustion, and altered intercellular communication, which are believed to be decisive to determine one's lifespan ^[4]. These risk factors might impact the cellular level by deregulating signaling; thus, causing cellular senescence and mitochondrial dysfunction ^[5]. Consequently, the physiological and functional levels weaken, triggering the development of chronic inflammation, alterations in energy metabolism, such as variations in insulin sensitivity, undermining neuronal ^[6], and sensory functions, mainly visual, auditory, and touching (or movement) ^{[7][8]}. On a physical level, hair normally turns white, thinner, and takes longer to grow, and the skin becomes less elastic and more wrinkled, as a result of less efficient vitamin D synthesis ^[9]. Moreover, there are some factors that are usually associated with specific disorders that might appear: hyperglycemia, hypercholesterolemia, and hypertension ^[10]. Altogether, these effects give rise to numerous age-associated disorders that result from these alterations, such as sarcopenia, represented by the decline in skeletal muscle mass, and, therefore, weakening physical functioning, which is derived from chronic

inflammation, hormonal changes, cell dysfunction, an unhealthy diet, lack of physical activity [11], neurodegenerative diseases, heart diseases, diabetes, and cancer [12][13].

Despite the biological changes associated with aging, there are risk factors, such as lifestyle and dietary patterns [14][15], which, if altered, can promote healthy aging, and are characterized by the development and maintenance of the functional abilities that enable one's wellbeing [16]. Healthy lifestyles promote the maintenance of cognitive abilities and boost the immune system [14][15][17][18]. Studies show that adoption of a Mediterranean diet, characterized by a decreased consumption of saturated animal fat and red meat and a higher intake of fruits and vegetables, along with maintaining a healthy weight and reducing salt intake [19][20][21][22], and lifestyle changes, such as engaging in physical and social activities and reducing smoking and alcohol consumption, can significantly modulate the inflammatory state of the body. Consequently, general health improves throughout the diverse stages of life [19][23][24]. It is also believed that these key factors may be viewed from a life-course perspective since a change of these routines can shape the rate at which human cells or organs enter in senescence, delay the onset of chronic diseases, and promote mobility, mental function, and wellbeing [19][25]. However, the main “gaps” remain as to what types of diets or what food components could actually improve healthy aging, and what biomarkers are modulated by the diet and associated with chronic diseases, in order for them to be considered more when evaluating or preventing the incidence of these diseases.

2. Effect of Nutrition on Aging

Avoiding unhealthy habits, mainly concerning diets, may improve life quality and promote healthy aging (Figure 1 and Figure 2).

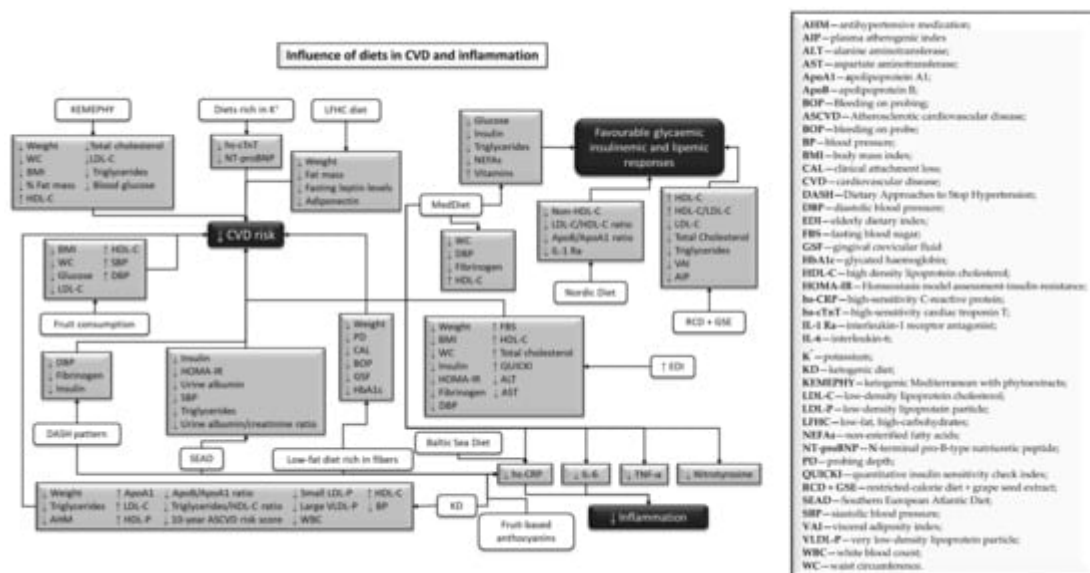


Figure 1. Influence of diets in cardiovascular diseases hallmarks and inflammation.



The ketogenic diet (KD) reduced CVD risk by improving CVD biomarkers (**Figure 1**) in T2D patients and decreasing inflammation [26]. It also prevented brain aging (**Figure 2**) by avoiding the destabilization of brain network and network switching [27]. Network stability is represented by the ability of the brain to maintain functional communication between its regions, and when this process is affected, network switching occurs from the largescale reorganization of the network modules. Moreover, the Mediterranean diet (MedDiet) regulated the relationship between genetic risk factors and cognition [28], protecting participants with specific variants of the *CR1* gene (without A minor allele of the rs3818361), the *CLU* gene (with T minor allele of the rs11136000), the *PICALM* gene (with T minor allele of the rs3851179), and both non-ApoE4 and ApoE4 carriers. Variations in this diet, such as the modified Mediterranean–ketogenic diet (MMKD), prevented cognitive decline (**Figure 2**) in adults with Alzheimer’s disease (AD) risk, by increasing amyloid-beta 42 (A β 42) and decreasing tau expression [29].

The mediterranean diet (MedDiet) demonstrated beneficial effects in several key points. The role of the dietary inflammatory index (DII) used this diet in telomere shortening (**Figure 2**) [32]. An anti-inflammatory diet, rich in antioxidants, could reduce the rate of telomere shortening, by improving telomerase activity [33] in individuals at high risk of CVD [32][34][33][35]. In addition, diets rich in fibers, vegetables, and fruits, and poor in meat, dairy products, and PUFAs, as well as waist circumference (WC) reduction, are beneficial in improving leukocyte

telomere length (**Figure 2**) [34][36][37]. In contrast, consumption of ultra-processed foods (UPFs) and processed meat was negatively associated with MedDiet adherence, and it was positively related with a higher risk of having shorter telomeres (**Figure 2**) [38][39][40]. UPF was also linked to an increased risk of CVD, ischemic heart disease (IHD)/cerebrovascular disease, and all-cause mortality (**Figure 2**) [40].

The adoption of a KD reduced CVD risk, by improving CVD biomarkers (**Figure 2**) in T2D patients, and decreased inflammation [41][42][43][44]. Since inflammation has a role in every facet of CVD pathogenesis [45] and hs-CRP and WBC count are well-established markers of inflammation and risk factors for CVD [46][47], the decrease of these markers in the CCI indicated that inflammation was diminished after 1 year of intervention. KD also protected brain aging (**Figure 1**) by avoiding the destabilization of the brain network, which is what happens when glucose is used as fuel [48]. These stabilizing effects of nutritional ketosis were replicated when exogenous ketones were administered, suggesting that they were specifically due to glucose metabolism rather than ketone body metabolism [48]. Furthermore, it supports the hypothesis that there are some beneficial neural effects associated with the hypocaloric state; intermittent fasting and severe caloric restriction may result from the use of ketone bodies by the brain [49].

The MedDiet modulated the impact of genetic risk factors on cognition (**Figure 2**) [28]. The variants studied have been associated as risk factors for AD [50][27][29] and cognitive decline, mainly with poor memory performance in population-based studies [51][26]. The MedDiet has already been revealed as protective in cognitive functioning [52], cognitive decline [53], and the development of mild cognitive impairment and dementia [54][55]. Daily intake of green tea catechins also demonstrated beneficial effects on the working memories in adults [31][56][57]. The MMKD prevented cognitive decline (**Figure 2**) in adults with Alzheimer's disease (AD) risk, by increasing A β 42 and decreasing tau expression [58]. Moreover, a high diet quality that prioritizes foods that are the base of the KD and MedDiet, allied to a diverse vegetable intake, was linked to a decrease of cognitive decline risk [30]. This was supported by previous studies that demonstrated that dietary interventions had a huge impact on cognitive deterioration [59]. Additionally, this protective effect may be due to individual characteristics of foods. Antioxidants and phenolic compounds can minimize oxidative damage and inflammation, and boost neuronal antioxidant defenses [60][61].

The MedDiet was used to assess the role of DII in telomere shortening, proving that an anti-inflammatory diet or one rich in antioxidants could reduce the rate of telomere shortening in individuals at a high risk of CVD [32]. Studies that evaluated adherence to the MedDiet achieved the same conclusions [34][33][35][62][63][64][65].

Higher consumptions of vegetables [36] and diets rich in fibers [34][37] were also positively associated with leukocyte telomere length, as well as lower WC, whereas SFAs were negatively linked [36]. Thus, an anti-inflammatory diet can avoid telomere shortening and, consequently, reduce the impact of aging and cancer development [66]. In contrast, consumption of UPF and processed meat was linked to an increased risk of having shorter telomeres [38][39]. UPFs are industrial formulations of food-derived substances (oils, fats, sugars, starch, protein isolates) that include flavorings, colorings, emulsifiers, and other cosmetic additives [38]. UPFs have been linked with several diseases, such as hypertension [67], obesity [68], MetS [68], T2D [69], and cancer [69]. Higher total intakes of salt,

saturated fat, and sugar, as well as inadequate intakes of fiber and minerals, could explain the association between UPF consumption and the risk of developing short telomeres. [70].

The MedDiet [71][72][73], or its components [74][75], RCD, allied to daily consumption of GSE [76], DASH patterns [77], LFHC diet [78], the Baltic Sea diet [79], the Nordic diet [80], SEAD [81], the KEMEPHY diet [82], or the use of EDI scores to assess MedDiet adherence [83], promoted decreased inflammatory markers and improved cardiometabolic risk factors (**Figure 1**), including components that belong to MetS. MetS is one of the most significant risk factors associated with CVD [84][85] and it is defined as having at least three of the following characteristics: (i) central obesity, (ii) increased serum triglyceride levels, (iii) low HDL levels in the blood, (iv) cholesterol levels, (v) hypertension, and (vi) higher fasting blood glucose levels [85]. Since these diets are very similar, this might explain the similar results. In several studies, researchers note that the MedDiet is able to prevent CVD [20][22][86][87]; this effect is due to the combination of different foods that have anti-inflammatory properties. The DASH diet pattern was already established as a potential treatment for hypertension [88], to reduce both fasting and postprandial insulin concentrations [89], and CRP levels [90][91]. The KEMEPHY diet, by inducing a physiological ketosis through elevated ketone bodies present in blood or urine [92], stimulates positive changes in cardiovascular risk factors and body composition [93].

SEAD, just like the MedDiet, is rich in folate and vitamin C from vegetables, as well as omega-3 fatty acids from fish; these compounds have already been connected with reduced insulin [94][95] and low hs-CRP [96]. This inflammatory marker was also reduced in this diet, suggesting that it may reduce CVD risk (**Figure 1**). The Baltic Sea diet also promotes the reduction of CRP concentrations (**Figure 1**), due to the presence of Nordic fruits and berries and cereals [79]. They contain antioxidant components, such as polyphenols, minerals, vitamins, and dietary fibers, which diminish these levels and the release of E-selectin [97][98]. This molecule is produced and released into circulation during endothelial injury, and its reduction improves endothelial function [98]. The healthy Nordic diet decreases IL-1 Ra [80], which is one of the most sensitive inflammatory markers, in obesity and MetS. It has been associated with high intakes of SFAs and lower consumption of berries, fruits, and whole-grain products [99][100][101]. Moreover, higher levels of IL-1 Ra have been revealed to predict T2D and the progression of MetS to T2D [99]. In addition, this healthy Nordic diet promotes the reduction of non-HDL-C and LDL-C, which are designated to have an important impact on CVD morbidity and mortality [102][103]. CVD risk is also attenuated by high intakes of potassium (**Figure 1**) due to its nonlinear association with CVD biomarkers (**Figure 1**) [104][105][106], which is supported by previous studies [107][108][109], thus endorsing the World Health Organization (WHO) recommendation that adults increase their potassium intake [110]. In contrast, CVD, IHD/cerebrovascular disease, and all-cause mortality was linked to UPF consumption [40][111][112][113].

The MedDiet also decreases risk factors associated with other comorbidities (**Figure 2**), such as hepatic steatosis [72], atherothrombosis [114], oxidative stress, by promoting the excretion of urinary metabolites [115], and, allied to virgin olive oil, demonstrates protective effects on bone tissue, by increasing serum osteocalcin [116].

The MedDiet, allied to a supplementation of CoQ, was shown to protect DNA from oxidative damage (**Figure 2**) by reducing the activation of p53 [117] and, consequently, the expression of genes involved in p53-dependent DNA

repair were downregulated [118]. Previous studies demonstrated that DNA damage plays an important role in the pathogenesis of atherosclerosis (buildup of fats, cholesterol, and other substances in and on the artery walls), as well as other aging-related diseases [119]. As for diets rich in PUFAs—CoQ supplements have been shown to mitigate oxidative and lipid peroxidation chain reaction damage [120][121], regenerate other antioxidants, such as α -tocopherol and ascorbate [122][123][124], and reduce CVD risk and inflammation [120]. The fatty acid content of cellular membranes and fluids is linked to oxidative stress, so it was expected that MedDiet + CoQ helped prevent this event [125][126][127]. Furthermore, recent research has shown that changes in the expression of p53 and the p53-regulated DNA damage response genes, such as *gadd45a* and *mdm2*, can be used as genotoxic and carcinogenic stress markers [128][129]. This diet also has an additional influence on the inflammatory response and ER stress [130], since it reduces the p65, IKK-b, and IL-1b gene expression.

A low-fat diet rich in fibers has demonstrated protective effects on periodontal disease (**Figure 2**), by reducing its biomarkers in older adults [131]. This disease has already been associated with obesity [91][132].

In contrast, previous studies [133][134][135][136][137][138][139] have demonstrated that unhealthy habits, such as westernized diets (high intakes of red meat, processed foods, ‘fast-foods’, high-fat dairy products, snacks, and sugary soft drinks, and low intakes of fruits, vegetables, vitamins, and minerals), lack of physical activity, alcohol consumption, or smoking can potentiate the risk of development of diabetes, obesity, cardiovascular diseases, and cancer. Thus, even in the absence of traditional CVD risk factors (smoking, T2D, high BP, and elevated levels of cholesterol), weight-loss strategies should always be recommended in order to keep a healthy body weight to decrease CVD and other comorbidities risk.

3. Conclusions

Diets rich in vegetables, fruits, nuts, cereals, fibers, fish, unsaturated fats, containing antioxidants, vitamins, potassium, omega-3—and reducing red meat and UPF intake—could prevent obesity, CVD, and inflammation, and promote favorable glycemic, insulinemic, and lipidemic responses. Moreover, the MedDiet and KD, or a combination of these diets (MMKD), and increasing consumption of vegetables and green tea catechins, could improve one’s working memory and decrease destabilization of the brain network and the attention domain, preventing cognitive decline. Finally, the MedDiet, supplemented with CoQ or VOO, or a low-fat diet, also rich in antioxidants, could help to decrease the prevalence of atherothrombosis, hepatic steatosis, diabetes, and telomere attrition, as well as prevent oxidative and DNA damage. These diets can enhance one’s quality of life and increase life expectancy. Moreover, a putative panel of molecular markers (see **Figure 1** and **Figure 2**) would follow the impact of diet/nutrition alterations during aging.

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