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Selected Micronutrients in Cognitive Decline Prevention and Therapy

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Abstract Population aging is a worldwide demographic trend. Consequently, the prevalence of chronic age-related conditions such as clinically diagnosed neurological diseases, cognitive decline, and dementia will significantly increase in the near future. The important role of diets and healthy lifestyle as preventative of neurodegenerative diseases is widely accepted nowadays, and it may provide preventive strategies in very early, non-symptomatic phases of dementia well, especially because there are still no effective treatments for it. In this article, we review the known effects of selected micronutrients on the aging brain and we propose strategies for dietary improvements.

Keywords Cognitive decline · Micronutrients · Vitamins · Polyphenols · Alzheimer's

Introduction

Population aging is a worldwide demographic trend. According to the WHO, by 2040, the proportion of world population aged ≥65 is believed to reach 1.3 billion (14 % of the total). Consequently, the prevalence of chronic age-related conditions such as heart problems, clinically diagnosed neurological diseases, cognitive decline, and dementia will significantly increase. Diets rich in fresh fruit, vegetables, and unsaturated fats, and low in simple sugars and salt and highly processed foods, are generally associated with a reduced risk of developing several diseases such as type 2 diabetes, cardiovascular disease, neurodegeneration, and many forms of cancer. Shared risk factors for both Alzheimer's disease (AD) and vascular diseases such as atherosclerosis, stroke, hypertension, transient ischemic attacks, cardiac disease, and apolipoprotein E_4 (APOE e_4) genotype, obesity, and diabetes play important roles in the etiology of neurodegenerative diseases such as AD [1]. These vascular risk factors may increase the risk for AD by promoting inflammation, cerebral vascular disease, white matter lesions, hippocampal sclerosis, and mitochondrial dysfunction [1]. The important role of diets and healthy lifestyle as preventative of vascular diseases is widely accepted nowadays, and it may provide preventive strategies in very early, non-symptomatic phases of dementia as well, especially because there are still no effective treatments for AD. Recent focus is therefore on the early, asymptomatic phase of the disease especially on the (cerebro)vascular risk factors like atherosclerosis, hypertension, and obesity, etc., being modifiable via changes in lifestyle factors such as diet [2]. Recently, the Mediterranean diet has been shown in several prospective worldwide studies to be inversely associated with cardiovascular disease (CVD) and to be a strong protective factor against hypertension, obesity, and AD [3].

Of note, the Mediterranean diet (but also the Japanese diet [4]) is rich in micronutrients that derive from plant foods. In this respect, it has been suggested that adequate intakes of micronutrients, either consequent to a correct diet or through supplementation, might afford the elderly protection from neurodegeneration. In the cardiovascular realm, this has been referred to as the "metabolic tune-up," which should result in a marked increase in health at little cost [5]. In this article, we review the known effects of micronutrients on the aging brain

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and remark that this is a subject worth addressing in preventive medicine. Even though long-chain polyunsaturated fatty acids such as docosahexaenoic acid (DHA) are neuroprotective [6, 7] and have been suggested in cognitive decline prevention [6], we did not include them in this review because their suggested intake (around 500 mg/day, see ISSFAL.org for example) does not classify them as "micro" nutrients.

Alzheimer's Disease—Etiological Summary

AD is an irreversible neurodegenerative disorder which stems from the interaction between multiple factors that induce progressive memory loss and cognitive decline, exacerbated by neurotransmitter deficits. Neuropathologically, AD is characterized by the presence of extracellular senile plaques containing amyloid β peptides (Aβ) and intracellular neurofibrillary tangles of hyperphosphorylated tau protein [8]. The Aβ peptide is formed from amyloid protein precursor (APP) by sequential enzymatic processing, in which different β-secretases and γ-secretase are involved [9]. Moreover, Aβ aggregations are also tightly linked to increased oxidative stress. Oxidative stress is accompanied by mitochondrial dysfunction, pronounced inflammation, gliosis, axonal degeneration, and impairment of synaptic transmission that ultimately end in progressive neuronal loss, predominantly by apoptosis [10]. In summary, AD is a multifactorial disorder that must be addressed via a multidisciplinary approach, including proper nutrition and/or supplementation.

Vitamin C and AD

Vitamin C or ascorbic acid (AA) is a powerful water-soluble antioxidant present mainly in citrus fruits, strawberries, kiwis, and some green leaf vegetables such as spinach and broccoli. It is an essential nutrient for humans given that we are incapable of producing the enzyme gulonolactone oxidase needed to synthesize AA from glucose [11]. Of note, a plethora of biochemical processes are dependent on AA, particularly in the brain that is able to store AA in great amounts. In fact, only the adrenal glands contain similar concentrations of AA. AA plays critical roles in brain development and myelin formation [12], actively participates in the synthesis of neurotransmitters such as enzyme cofactors, and it is one of the most potent antioxidant agents in the organism [13, 14]. It should be noted that AA could represent an excellent therapeutic candidate in those neurodegenerative disorders characterized by increased oxidative stress such as AD. Some AD animal studies have been carried out in order to elucidate the mechanisms by which AA affects cognitive function and neurodegeneration. Murakami et al. [15] showed that AA attenuates Aβ oligomerization in APP transgenic mice. Likewise, Harrison et al. [16] observed that short-term high-dose AA infusion (125 mg/kg) in APP/PSEN1 and wild-type mice modifies behavior, favoring spatial learning and memory. Currently, a study—carried out in an AD mice model that is unable to produce its own AA—reported that a high AA dose decreases amyloid plaques burden in cortex and hippocampal brain of these mice. Therefore, this suggests that AA could protect against AD [17].

Along the same lines, numerous studies have reported that AD patients show low plasma concentrations of AA [18]. Thus, the majority of clinical trials have focused on assessing whether there is a true relationship between AA deficiency and risk of developing AD. Some such trials reported negative correlations between plasma AA levels and grade of decline cognitive. However, other studies proposed that plasma AA levels are not associated with age-related cognitive impairment [19, 20]. This discrepancy might be due to several reasons. First, plasma AA levels are dependent on daily intake, and thus, they are not truly representative of long-term consumption [21]. Second, although AA is highly concentrated in the brain, there is no association between AA brain content and plasma levels, at least according to spectroscopic assays with MRI imaging [22], a non-invasive technique. Third, there are genetic (e.g., carriers of AA expression) and non-genetic (e.g., age) factors that modulate AA absorption and assimilation in subsets of the population [23, 24]. This could explain why during recruitment, some control participants without signs of clinical scurvy actually exhibited AA deficiency according to plasma levels.

Hence, keeping in mind the aforementioned, many publications suggested that AA supplements might decrease the risk of developing AD or treat it altogether [25, 26]. Yet, another subset of assays found no relationship between the intake of vitamin C from food or supplements and reduced likelihood to develop AD [27]. Moreover, Gu et al. [28] reported that AA intake does not affect plasma Aβ levels or its related mechanism. Therefore, the available literature about the beneficial effects of diet supplementation with AA for preventing or treating AD is inconclusive.

Furthermore, in order to understand the precise role of AA in AD, we would need to carry out more clinical trials, paying more attention to their design and to the recruitment of participants, e.g., based on basal AA levels. Also, future assays should consider AA levels in CSF rather than plasma as a more important marker of AD.

Vitamin B and AD

B vitamins are a group of eight water-soluble vitamins that control a great variety of metabolic activities [29, 30]. Although their names are similar, all of them are chemically very distinct. The main dietary sources of this group of vitamins are meats, legumes, whole grains, potatoes, bananas, chili peppers, and a wide catalogue of unprocessed products. However, it is important to note that vitamin B_{12} (aka cobalamin) is not

present in plant foods [29]. In this review, we focus on the role of folate and vitamin B_{12} in AD. Folate is the most important methyl group donor for maintaining integrity of DNA and mitochondrial DNA, and vitamin B_{12} acts as cofactor in methylation and DNA synthesis. Hence, multiple acceptors are methylated through the folate- and vitamin B_{12}-dependent methionine-homocysteine cycle [31, 32]. Deficiency of these vitamins triggers neurological disorders such as memory loss, cognitive impairment, neuropathy, myelopathy, and sensory neuropathy [33]. It is well-known that increased homocysteine levels in serum or urine are markers of folate and vitamin B_{12} deficiency [34]. Homocysteine is a non-protein amino acid, which derives from methionine metabolism as regulated by B vitamins. Hyperhomocysteinemia (HHcy) impairs DNA and mitochondrial DNA, causing oxidative stress and ROS production as well as increased cytosolic calcium, which induce neuronal death [35]. Recent clinical trials have reported that HHcy is involved in cognitive decline and the development of AD [36, 37]. Therefore, understanding the mechanism(s) responsible for the association between HHcy and AD could provide practical means to prevent or reduce the risk of AD development. Zhang et al. [38] reported augmented amyloidogenesis following direct injection of homocysteine into animal brains. A recent study has demonstrated that a folate-, vitamin B_6-, and B_{12}-deficient diet induces HHcy in an AD-like mouse model and is associated with a significant acceleration of their amyloidotic phenotype [39]. Furthermore, it would be expected that an intervention with diets supplemented with folate or vitamin B_{12} could prevent o decrease the risk of developing AD. Accordingly, Haan et al. [40] suggested that the risk of homocysteine-induced dementia or cognitive decline might be modified by vitamin B_{12} supplementation. A small subset of dementias that are reversible with vitamin B_{12} has been observed, and it must be underscored that this treatment is inexpensive and safe [41]. However, the majority of clinical trials seem to indicate that vitamin B_{12} intervention does reduce homocysteine concentrations, but that this does not lead to any benefit in terms of cognition even after long-term of supplementation [42]. In summary, accumulated evidence indicates that vitamin B_{12} therapy does not improve cognition in patients without preexisting deficiency. Likewise, trials of folic acid supplementation, either alone or in combination with other B vitamins, reported limited or no effect on measures of cognitive function [43]. Of note, the observed discrepancy might be due to short treatment periods, because degenerative processes often take several years before the first symptoms appear. Therefore, we would need to recruit patients with severe vitamin B_{12} or folate deficiency. Also, we need to consider that the doses of folate and vitamin B_{12} should lead to serum concentrations that greatly exceed normal values in order to observe some effect. This is of particular concern in the elderly, where cobalamin is poorly absorbed [29], leading to acquired vitamin B_{12} deficiency and marginal status in this population subset. Thus, appropriate strategies to monitor B_{12} status and increase its absorption should be implemented.

In conclusion, further intervention studies in large samples with extended periods of follow-up are required. This will allow for further investigation of the role of vitamin B_{12} or folate in the onset or progression of AD.

Vitamin A and AD

Vitamin A or retinol is a lipophilic micronutrient present in many foods from both vegetal and animal origins. In particular, adequate consumption of carrots, broccoli, pumpkin, dairy products, liver, and eggs provides the recommended daily allowance of vitamin A, i.e., 900 μg (3000 IU) for men and 700 μg (2300 IU) for women. Nevertheless, vitamin A can also be synthetized in the brain [44]. Vitamin A is also named retinol because it participates in the synthesis of retinal pigments, which are essential for eyesight. Retinoid is a generic term that includes vitamin A and its natural as well as synthetic analogs. A wide range of biological activities and processes are modulated by retinoids which bind to two classes of nuclear receptors, namely retinoic acid receptors and retinoid × receptors. The brain expresses various isoforms of these receptors [45]. Accumulated evidence demonstrates that retinoids play an important role in processes strongly related to AD such as production of amyloid beta, inflammation, neurotransmission, and neurogenesis [46]. In addition, the synthesis of retinoid acid is inhibited by the amyloid beta peptide, thus exacerbating AD pathology [47]. Some authors have shown that vitamin A possesses antioxidant, neuronal-protective, and antioligomeric effects in in vitro and in vivo models of AD [48]. In the same way, disruption of the retinoid-signaling pathway in adult rats caused an accumulation of amyloid beta in the brain [49]. Moreover, vitamin A deficiency induces a downregulation of retinoid receptors, impairing short- and long-term memory and even potentiating depression in mice [50]. Likewise, preclinical studies of retinoids in transgenic mouse models of AD showed that retinoic acid decreased activation of microglia and astrocytes and improved spatial learning and memory [51]. Vitamin A-deprived mice showed a loss of hippocampal long-term potentiation, which was fully reversible by standard diet or direct administration of retinoic acid [52]. Thus far, all studies seem to support the hypothesis that vitamin A is an important molecule in the prevention and therapy of AD.

Lopes da Silva et al. [53] have demonstrated that these differences are due to the fact that the AD and control populations presented different nutritional status when they were recruited. However, when this difference is taken into consideration, AD patients exhibited significantly lower vitamin A status with respect to the control cohort. Theoretically, therapies with retinoids could be used to mitigate the vitamin A

deficit and, in turn, prevent AD. Along these lines, numerous preclinical studies carried out in mouse models of AD showed that administration of all-*trans* retinoic acid (ATRA) decreases amyloid accumulation and tau hyperphosphorylation and improves cognitive decline by gene expression modulation of different molecules involved in these activities [51, 54]. Similar observations have been reported with tamibarotene (AM-80) and acitretin, synthetic retinoid acid analogs which upregulated ADAM10, an enzyme implicated in non-amyloidogenic processing of APP [55]. Several phase II clinical trials (NCT01120002 and NCT01078168 clinical trials.gov identifier) are ongoing, in order to test the effects of retinoids in patients with AD. However, it should be underscored that the administration of retinoids may trigger some adverse reactions in certain patients. ATRA is extremely toxic at its chemotherapeutic dose of 45 mg/m^2/day, even at 90 days after treatment initiation; therefore, its use is limited in older populations, who are—however—more prone to develop AD. Moreover, prolonged retinoid usage produces gastrointestinal hemorrhage and abdominal pain [55], and extreme caution must be exerted.

In conclusion, the evidence available from preclinical studies shows that retinoids possess antiapoptotic, antioxidant, pro-differentiative, antiamyloidogenic, and antiinflammatory activities. Thus, vitamin A and its analogs might be considered as potential candidates for AD therapy. Yet, more clinical trials and toxicity assays are needed to elucidate the therapeutic role of vitamin A in AD.

Vitamin D and AD

Vitamin D belongs to the group of fat-soluble vitamins and is responsible for the intestinal absorption of various ions. It is also involved in calcium homeostasis and metabolism. Vitamin D is chiefly synthesized in the skin, following exposure to sunlight. In fact, fish and eggs are only foods that contain a vitamin D in noteworthy concentrations. Vitamin D from cutaneous synthesis and dietary intake is activated by hydroxylation in liver and kidney, producing 1,25-dihydroxyvitamin D that is the main circulating metabolite of vitamin D [56]. This molecule executes its functions by binding to its vitamin D-specific receptor. Many studies have reported that vitamin D presents a high affinity to this receptor in several brain regions and different cellular types; also, it has been demonstrated that the vitamin D receptor is widespread in the human brain. As an example, Eyles et al. described the existence of vitamin D receptors in the hippocampus, one of the main brain regions affected by AD [57]. Further, vitamin D signaling is involved in brain developing and function.

On the other hand, it is well known that the elderly are at a high risk of developing vitamin D deficiency due to decreased cutaneous synthesis [58] and dietary intake [59]. However, the intestinal absorption of vitamin D is not affected by age [60]. Until date, many clinical trials have found a strong association between low vitamin D concentrations and an increased risk of all-cause dementia and AD. All authors agree that vitamin D supplementation might have protective effects [61, 62]. Preliminary in vitro studies showed that vitamin D increases clearance and Aβ phagocytosis by macrophages of AD patients and reduces amyloid-induced cytotoxicity and apoptosis in primary cortical neurons [63]. The administration of 1,25-dihydroxyvitamin D decreases cerebral Aβ accumulation and improves cognition in mouse models of AD [64]. Based on these findings, several clinical trials have been carried out to evaluate the effects of vitamin D supplementation on cognition in elderly patients. The results obtained thus far are controversial, as there is discrepancy about the methods used to evaluate cognition decline, the treatment period, and doses and form of vitamin D: The literature shows that vitamin D_3 is more bioavailable than vitamin D_2. Furthermore, some authors suggest treating older patients with higher dose of vitamin D in order to ascertain if there is any neuroprotective effect of this vitamin [65]. Hence, more clinical trials should be carried out in order to confirm whether vitamin D supplementation could be used to delay or prevent the onset of AD in older adults.

Vitamin E and AD

Vitamin E was first described by Evans and Bishop [66] as a family of lipid-soluble compounds that encloses four tocopherols and four tocotrienols: α (alpha), β (beta), γ (gamma), and δ (delta): All of them are referred to as vitamin E. The tocopherols are saturated forms of vitamin E, whereas the tocotrienols are unsaturated and possess an isoprenoid side chain. α-Tocopherol is the most abundant biologically active form in nature [67]. The majority of vegetable oils are rich in all four tocopherol forms in different proportions, and tocotrienols are found in certain cereals and seeds such as wheat germ, oats, hazelnuts, maize, sunflower seeds and palm oil, rice bran oil, and poppy seed oil [68]. Numerous studies have shown the antioxidant properties of the vitamin E in a large variety of pathologies such as cancer, cardiovascular, and neurodegenerative alterations [69–71]. Vitamin E is able to scavenge free radicals converting them in less reactive compounds, favoring the cells' normal function. However, recent studies have demonstrated that vitamin E also possesses important activities non-related to its antioxidant activity [72]. Vitamin E inhibits or activates several enzymes involved in different signaling cascades and also modulates the expression of some genes [73]. Moreover, some vitamin E forms have been attributed antiinflammatory effects [74]. Therefore, its ample array of biological activities could explain, in part, the beneficial effects of vitamin E on various pathologies whose

triggering agents are totally different. In this review, we focus on the effects of vitamin E in Alzheimer's disease. It is widely accepted that the extracellular deposits of amyloid beta peptide and neurofibrillary intracellular tangles of hyperphosphorylated tau protein are the foremost etiological agents of AD. A recent study described how vitamin E prevents the activation of p38MAPK, whose activity is essential for phosphorylation of neuronal tau molecules [75]. In the last decade, the combination of in vitro and in vivo experiments has suggested a protective antioxidant role of vitamin E in the AD context [76]. Administration of vitamin E encapsulated into nanospheres decreases levels of amyloid beta-induced reactive oxygen species in the SH-SY-5Y human neuroblastoma cells [77]. Also, this vitamin protects against the oxidation-mediated decrease of synaptic proteins involved in neurotransmission, hence delaying cognitive decline [78]. Additionally, in vivo studies of AD are suggesting that vitamin E modulates the abnormal inflammatory response associated to this disease [79]. Nevertheless, apart from antioxidant and antiinflammatory properties, other studies have attributed certain antiamyloidogenic actions to vitamin E, because it decreased Aβ levels and the global volume of senile plaques in the early stages of AD [80]. According to Huebbe et al., α-tocopherol is able to modulate amyloid precursor protein processing by regulating mRNA concentrations of secretase enzymes [81]. Therefore, when considering these studies, we can postulate that vitamin E might be useful in treating AD based on its beneficial properties here described. In consonance with this conclusion, it has been shown that long-term feeding of rats with a diet supplemented with vitamin E protects against age-related cognitive decline [82]. However, this conclusion has not been undoubtedly confirmed by current clinical trials. If any, all of the clinical evidence obtained thus far concedes that there is an inverse correlation between vitamin E plasma concentrations and progression rate of AD [18]. Therefore, it is reasonable to expect that a diet enriched or supplemented with vitamin E would improve cognitive impairment or its progression to AD. A prospective study from Morris and colleagues reported that individuals with higher vitamin E intake from diet and supplements showed reduced cognitive decline and risk of developing AD when compared to control, i.e., low vitamin E intake individuals [83]. In a similar study, the authors recorded a lower risk of developing AD in individuals consuming foods rich in vitamin E [26]. Likewise, a cohort study evaluated the relationship between AD and the plasma concentrations of all vitamin E forms; the authors reported an association between low plasma tocopherol and tocotrienol levels and increased probability to develop AD [83]. Indeed, epidemiological studies report that vitamin E from food sources, i.e., the more bioavailable [84] natural form is more effective at preventing age-related neurodegenerative disorders than dietary supplementation [85]. Congruently, several clinical trials have indicated that vitamin E supplementation has no beneficial effects against cognitive impairment or the progression to AD [86, 85]. In brief, there appears to be some discrepancy about the putative beneficial effects of vitamin E in patients with AD. Some explanations have been proposed to explain, in part, these controversial results. Firstly, the criteria to recruit patients with AD are different among the various clinical trials. The vitamin E dose, period of treatment, and the tests employed to evaluate cognitive impairment are very variable between the different trials. Further, in majority of trials, vitamin E supplements were α-tocopherol and the other forms have not been not employed. A recent study has demonstrated that tocotrienols are more potent radical scavengers than α-tocopherol [68]. It has also demonstrated that γ-tocopherol has greater antiinflammatory property than α-tocopherol [87]. Consequently, the inconclusive results obtained from clinical trials might be partly due to the fact that the investigators did not take into consideration these aspects. One final issue that deserves attention is the fact that the systemic antioxidant actions of vitamins E and C have never been clearly demonstrated in humans; therefore, we should be careful when we attribute the purported beneficial effects of these vitamins to mere antioxidant activities.

In conclusion, additional clinical trials should be carried out with other forms of vitamin E in order to elucidate its potential beneficial properties toward AD treatment and prevention.

Vitamin K and AD

Vitamin K belongs to the fat-soluble vitamin group. There are two biologically active forms (K_1 and K_2) and other synthetic analogs (K_3, K_4, and K_5). Vitamin K_1 (phylloquinone) is the most common form of vitamin K and is present in several plants, especially in leaf vegetables, certain vegetable oils, and in fruits, tubers, and seeds. Vitamin K_2 or menaquinone occurs in animal products such as meat, eggs, cheese, and curd [88]. With respect to its analogs, vitamin K_3 or menadiones is a synthetic molecule used to treat vitamin K deficiency and as food supplement [88, 89]. All these forms of vitamin K possess antihemorrhagic property and participate in bone metabolism [90], even though other novel pharmacological and therapeutic activities have been discovered in recent years, including antioxidant and repressor of vascular calcification and neurological disorders associated to aging. Likewise, Allison has been the first one who reported that vitamin K deficiency is associated with AD pathogenesis,

because—in that study—plasma concentrations of vitamin K were lower in patients with a high genetic risk factor for developing AD than in healthy patients with the same age [91]. Of note, vitamin K deficiency promotes collagen mineralization in the intima and, thus, loss of vasomotion [92]. A recent clinical trial found that patients with early stage Alzheimer's disease consumed less vitamin K than did cognitively intact control subjects, which explains the vitamin K deficiency recorded in these patients [93]. Additionally, other studies have demonstrated that such hypovitaminosis is related to the greater prevalence of hip fractures observed in patients with AD [94]. Finally, in vitro and spectrometric assays have demonstrated that vitamin K_3 analogs inhibit Aβ aggregation and protect cells against Aβ-induced cytotoxicity [95]. Hence, accessible evidence is indicating that vitamin K could play a pivotal role in AD; there is also no current evidence that long-term administration of vitamin K produces undesirable effects. The efficacy of exposure to sunlight and of a diet supplemented with calcium, vitamin K_2, and vitamin D against hip fractures—which afflict AD patients—has been demonstrated [96], even though it is impossible to ascertain the individual contributions of these micronutrients. Further, no clinical trials assessed the potential antiamyloidogenic effects of vitamin K in patients with AD, notably in their quintessential cognitive decline. In summary, vitamin K appears to be a promising agent in AD therapy, but more in vitro and in vivo studies together with appropriate clinical trials should be carried out to discern the true role of this molecule as a viable treatment of AD.

(Poly)phenols and AD

In addition to vitamins, humans also eat fairly large amounts of (poly)phenols, which might play some healthful roles on neurodegenerative disorders [97]. Some of these compounds indeed improve certain pathologic features of AD in animal models, likely because of their mitochondria-augmenting activities [97]. (Poly)phenols from different fruits and beverages such as blueberries, grapes, apples, turmeric, green and black teas, wine, coffee, and cocoa possess multiple health activities, which may—theoretically—reduce the risk of AD [97]. It has been reported that phenolic compounds from bilberry and blackcurrant extracts possess antiamyloidogenic activity and alleviate behavioral abnormalities in a mouse model of AD [98]. Also, antiinflammatory properties have been granted to apple and green tea beverages, because they decrease proinflammatory cytokine levels in initial phase or moderate phase AD patients [99]. Tea, whether green or black, is rich in (poly)phenols endowed with in vitro antioxidant activities, which have been suggested to explain their putative neuroprotective actions. Nonetheless, other properties have been attributed to such neuroprotective and antiamyloidogenic (poly)phenols [100, 101].

Several epidemiological reported a reduction of dementias and Alzheimer's risk associated with moderate alcohol use, as compared with abstainers, with extents of risk reduction that vary among studies and meta-analyses [102]. Mechanistically, ethanol is able to reduce synaptic damage induced by beta-amyloid and synuclein [103]. Also, some in vitro studies reported that resveratrol possesses antiamyloidogenic activity, reducing the level of secreted or intracellular Aβ peptides [104]. Moreover, this (poly)phenol is able to reduce—still in vitro—the oxidative stress typical of AD, by reducing neuronal death and suppressing activation of astrocytes and microglia [105]. Despite these encouraging in vitro data, it is very unlikely that resveratrol is responsible for the preventive activities of wine, because (1) wine contains resveratrol in trace amounts [102]; (2) risk reduction is not exclusive to wine and is seen across all alcoholic beverages [102]; and (3) resveratrol is not bioavailable and its human activities are questionable to say the least [106, 107].

Another (poly)phenol-rich food item that is attracting attention is turmeric, whose rhizome contains the yellow pigment curcumin, which is used as food preservative and spice. Substantial in vitro evidence indicates that curcumin has antiamyloidogenic, antioxidant, and antiinflammatory properties, all of which suggest its potential to prevent AD [108]. Frautschy et al. [109] suggested that curcumin might prevent Aβ-mediated synaptic deficits, because curcumin-fed/Aβ-injected rats exhibited better memory function compared to Aβ-injected rats. Again, curcumin is poorly bioavailable, and its human activities remain to be fully proven.

Along the same lines of research, coffee, a complex mixture of (poly)phenolic components, diterpenes and caffeine, might possess beneficial effects on cognitive and neurological health. Some preclinical studies have demonstrated that chlorogenic acid, the main phenol present in coffee [110], prevents Aβ-induced oxidative stress and exerts neuroprotective effects by inhibiting overactivated neuronal enzymes responsible for the hydrolysis of neurotransmitters [111, 112]. Likewise, clinical studies suggest that chlorogenic acid supplementation could protect against cognitive degeneration [113]; however, no formal and well-controlled studies have been performed to date to confirm or disprove this hypothesis. Also, it is currently very difficult to discriminate the effects of coffee (poly)phenols such as chlorogenic acid from those of caffeine. In synthesis, the evidence pro or against neuroprotective effects of coffee intake is still inconsistent [114].

Finally, cocoa and chocolate contain (poly)phenols in copious amounts, together with some other compounds with potential biological activity [115]. It has been shown that polyphenols from cocoa interact with signalization cascades that lead to the inhibition of neuronal death by apoptosis and promote neuronal survival and synaptic plasticity [116]. In

addition, cocoa preserves murine cognitive abilities during aging, lowering the risk of developing AD [117]. It has been suggested that cocoa (poly)phenols activates the brain-derived neurotrophic factor (BDNF) survival pathway because of their antioxidant properties [116]. One aspect that needs elucidation is when consumption of cocoa and chocolate should be initiated to generate beneficial effects (if any) on age-dependent cognitive decline and neurodegenerative diseases [118].

It is noteworthy that no human intervention studies of green and black tea, wine (poly)phenols, curcumin, or cocoa in AD have been reported. Therefore, the extrapolation of in vitro and in vivo (animals) studies to the human situation still requires properly designed clinical trials.

Conclusions

Age-related cognitive decline is one of the major health challenges we are facing. Indeed, life expectancy is constantly increasing worldwide, which provokes major social imbalances as well as an increased burden on the national health care systems. There are currently no viable pharmacological tools to treat cogitive decline; therefore, several multidisciplinary preventive approaches to this disorder are being developed. Certainly, the implementation of correct diets and/or the use of adequate supplements appears of paramount importance in the elderly. Nevertheless, there are very few controlled and good-quality studies addressing the variegated effects of some dietary or pharmacological agents on mild cognitive decline and neurodegeneration as associated with age. In the case of micronutrients (as reviewed here), most of the available evidence comes from epidemiological and in vitro studies and clearly underscores the need to follow healthful diets and proper lifestyles, starting early in life. While attention is habitually paid to the macronutrient profile of diets and to caloric intake, emphasis should also be placed on essential fatty acids and micronutrients, namely vitamins and polyphenols, whose role appears to be crucial in AD prevention. Also, we might need to emphasize the potential preventive activities of some micronutrients in other forms of cognitive decline: Conceivably, milder forms might benefit the most from proper micronutrient intake.

One unresolved issue is whether lower serum concentration of several nutrients is due to disease-specific mechanism or due to the often poor nutritional intake and thus status of AD/dementia patients (or both). Yet, we still need properly executed clinical trials with reliable markers of cogitive decline; however, the possibility to formulate evidence-based nutraceuticals/supplements/functional foods targeted at the elderly should find a pertinent place in the “healthy aging” decalogue.

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