The role of diet in preventing and reducing cognitive decline

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ABSTRACT

Purpose of Review

This review summarizes the most recent evidence regarding the effects of diet in preventing and reducing age-related cognitive decline and neurodegenerative diseases.

Recent Findings

Recent evidence indicates that nutraceuticals and whole diet approaches may protect against the development of age-related cognitive decline and pathological neurodegeneration. The neuroprotective effects are diverse depending on the nutrient employed and may involve a reduction of neuroinflammation, an activation of the endogenous antioxidant defence system and a modulation of the gut microbiota structure and function.

Summary

This review summarizes the existing evidence in favour of diet as a viable alternative approach to directly impact cognitive decline and neurodegenerative disease. The single nutrient (polyphenols, B vitamins, long-chain polyunsaturated fatty acids) versus whole diet approach (Mediterranean diet, DASH, MIND, Nordic, ketogenic) is presented and discussed. Potential mechanisms of action underlying the beneficial effects of these diets are also described. Implementation of large-scale preventive interventions based on dietary patterns identified as being beneficial to brain health should be a research and public health priority, ideally in conjunction with other health-promoting lifestyle factors.

Keywords: Brain, Alzheimer's disease**,** nutrition, ageing, dementia

INTRODUCTION

It has been estimated that 50 million people worldwide suffer from Alzheimer's disease (AD), the most common type of dementia. If no breakthrough can be made to prevent the disease or delay its onset, the number of patients is anticipated to reach 152 million by 2050 (1). Assuming a curvilinear association between age and dementia risk, a 2 year delay in onset would reduce population incidence by 22% by 2047 (2), resulting in 25 million fewer cases worldwide (3). Existing drug treatments for neurodegenerative conditions rarely curtail the underlying disease processes, and consequently there is an urgent need to develop alternative strategies to directly prevent, slow, and even stop neurodegeneration. Lifestyle strategies such as nutritional interventions have potential to be a safe, cheap, and effective alternative to protect against age-related cognitive decline and neurodegeneration, resulting in significant personal and societal benefits (4). This review aims to summarise the existing evidence in favour of diet either in form of nutraceuticals or whole diet as a viable alternative approach to directly impact cognitive decline and neurodegenerative disease. Some mechanistic considerations will also be described.

NUTRACEUTICALS

Accumulating evidence indicates that nutraceuticals such as polyphenols, B vitamins, polyunsaturated fatty acids (PUFAs) and other nutritional components can have beneficial effects on cognitive impairment associated to normal aging and/or neurodegenerative diseases like AD. We will describe below the impact of such nutritional components on brain functions.

Polyphenols

Polyphenols are a large family of phytochemicals widely distributed in the plant kingdom and present in fruits, vegetables, nuts, seeds, flowers and other plants used for human

consumption. They can be classified according to the number of phenol rings presented and the structural components that bind these rings in phenolic acids (hydroxycinnamic and hydroxybenzoic acids), flavonoids (benzene rings) and less common stilbene and lignans, although other categorizations exist (5). Previous research has demonstrated that different purified polyphenols such as resveratrol, curcumin, anthocyanin, ferulic acid, catechin and epicatechin were able to prevent cognitive decline in experimental animal models of aging and degenerative diseases (6-10). A plethora of observational and intervention studies observed a positive correlation between cognitive decline and the supplementation of different products rich in polyphenols like cocoa, berries, green tea and grape (11-15). However, not all studies investigating the effects of polyphenols on cognitive decline reported positive results. A recent meta-analysis of 34 clinical trials concluded that although some polyphenols might improve specific markers of cognitive status, definitive recommendations for the use of these compounds in the prevention of cognitive decline are currently not applicable (16). This is partly due to differences between individuals in the absorption, distribution, metabolism and excretion of bioactive compounds (17) as well as to heterogeneity in their biological response (18). The major determinants responsible for the between-subject variability may include genetic (Single Nucleotide Polymorphisms) and non-genetic factors (gut microbiota composition, sex, age, dietary habits, etc) which are only beginning to be explored and may differ depending on the compounds (19).

B-Vitamins

B vitamins have been suggested to have a positive effect on cognitive functions thanks to their ability to counteract the increase of homocysteine during aging that is related to cognitive impairment (20, 21). A randomized, double blind, placebo controlled study that involved 818 participants aged 50–70 years, evidenced that a supplementation of 800 μg/day of folic acid significantly improved domains of cognitive function that tend to decline

with age (22). The clinical trial (VITACOG) demonstrated that B-vitamin supplementation (folic acid 0.8 mg, vitamin B_6 20 mg, vitamin B_{12} 0.5 mg) for 2 years in participants aged 70 years and over with MCI reduced average brain atrophy rate (23, 24), ameliorated global cognition, episodic memory and semantic memory (25). Furthermore, the Singapore Chinese Health Study including 16,948 participants showed that higher dietary intakes of riboflavin and folate in midlife were associated with a lower risk of cognitive impairment in later life in the Chinese population (26). However, a recent meta-analysis evidenced conflicting results on cognitive outcomes of B-vitamin supplementations due to the great variability of the existing trials in terms of type of supplementations, population sampled, study quality, and duration of treatment (27).

Long chain polyunsaturated fatty acids (LC-PUFAs)

Neuronal cell membranes are particularly enriched in LC-PUFAs, important for the optimal development and function of the brain and the nervous system (28). The two most important types of LC-PUFAs in the human brain are eicosapentaenoic acid (EPA: 20:5 ω-3) and docosahexaenoic acid (DHA: 22:6 ω-3) (29). Although different studies evidenced an association between endogenous low levels of omega-3 and cognitive impairment and Alzheimer's disease (30, 31), the effects of ω-3 LC-PUFAs supplementation on cognitive outcomes in randomized clinical trials remain controversial. In a randomized, double-blind, placebo-controlled study, healthy older adults (62-80 years) with subjective memory impairment receiving 2.4 g/d PUFAs for 24 weeks induced an increase in working memory performance (32). The administration of DHA-enriched meals to subjects (n = 75; 88.5 ± 0.6 years) with cognitive impairment, living in nursing homes, protected against age-related cognitive decline (33). On the other hand, in a recent very large trial involving 1680 participants, a daily dose of 800 mg DHA and 225 mg EPA had no significant effects on cognitive decline over 3 years in elderly people aged 70 years or older with memory

impairment (34). A meta-analysis of prospective cohort studies found no statistical evidence for an inverse association between ω-3 LC-PUFAs intake and risk of dementia or AD (35). Yassine et al. (36) suggested that the different outcomes of the ω-3 supplementations studies on cognitive decline may be, in part, explained by the interactions among DHA, *APOE* genotype, and stage of AD pathologic changes. They demonstrated that DHA supplementation in predementia but not in AD dementia may reduce the risk for or delay the onset of AD symptoms in *APOE4* carriers.

DIETARY PATTERNS

An increasing number of studies are highlighting the synergic effect of different natural compounds when administered in combination (37-39). Taking into account the complex biological mixture of different components of the diet, it has been suggested that the use of a diet approach rather than the supplementation of single components might help to prevent/counteract cognitive decline in elderly people.

Mediterranean diet

The Mediterranean diet (MeDi), the traditional dietary pattern followed by people residing on the shores of the Mediterranean Sea, is characterized by a high intake of vegetables, legumes, fruits, cereals, fish, and extra virgin olive oil, moderate consumption of alcohol and low-to moderate intake of meat and dairy products. It is undoubtedly the most extensively studied dietary pattern, and more and more evidence suggest a potential protective role against cognitive decline and dementia.

Two clinical trials (40, 41), part of the larger trial PREDIMED (42), investigated the effect of MeDi in combination with nuts or extra virgin olive oil (EVOO) and found improved cognitive function with the MeDi supplemented with either EVOO oil or nuts vs. low-fat diet. These trials, despite having a realistically long follow-up (4·1–6·5 years), have the limitation to

consider relatively few participants. The key role of EVOO in relation to the positive effects of the MeDi was reinforced by the findings of Mazza et al. (43) who observed improved cognitive functions in elderly following the MeDi in which all the oils were substituted with EVOO for 1 year in respect to subjects following the MeDi alone.

Different meta-analyses evidenced a positive effect of MeDi on cognitive function. In particular, Sofi et al. (44) reported a 13% reduced risk of neurodegenerative diseases in individuals who most adhered to the MeDi. Similarly, Psaltopoulou et al. (45) evidenced that moderate and high adherence to MeDi is consistently associated with reduced risk for cognitive impairment. However, not all the studies totally agreed on the Medi positive effects on cognition. A systematic review reported that most of the randomized controlled trials published until 2018 found no significant association between MeDi and reduction of cognitive decline, and very few showed a small effect sizes (46). However, significant and clinically meaningful effect sizes were found for cognitive composites in the largest and most robust trial, indicating promising scope for future well-designed trials.

DASH diet

The Dietary Approaches to Stop Hypertension (DASH) diet was initially designed to prevent hypertension and is relatively low in saturated fat, total fat, and cholesterol; moderately high in protein; and high in minerals and fibres (47). Of the three studies which investigated the effect of DASH diet on cognitive function in the elderly, two studies reported a positive outcome (48, 49), meanwhile one did not evidence any effects (50). In particular, a study including 923 elderly men and women reported modest but positive links between the highest tertile of DASH diet adherence and lower rates of AD (49). The Nurse's Health Study observed that a higher adherence to DASH diet was associated with improved global cognition and verbal memory (48). On the contrary, the Women's Health Initiative Memory Study (WHIMS) (50) reported that DASH diet adherence was not associated with a lower

incidence of MCI or dementia in old women. The impact of DASH diet on cognition is just beginning to be explored and further research is necessary before we could draw solid conclusion.

MIND diet

The MIND diet is a combination of the MeDi and DASH diets but with slight modifications taking into account the best evidence for neuroprotection. Three cohort studies evidenced a positive effect of MIND diet on cognitive function. For example, Morris et al. showed that MIND diet score was associated with a slower rate of cognitive decline equivalent to 7.5 years of younger age among the participants in the top third of MIND diet scores compared with the lowest third (51). In a subsequent study, they found that high and moderate adherence to MIND diet was associated with a decrease in AD risk (49). The US Nurse's Health Study investigated the effect of the MIND diet on 16,058 older women aged 70 and over for 6 years and found that long-term adherence to the MIND diet was moderately associated with better verbal memory in later life, but not association was evidenced with global cognition, verbal memory or telephone interview of cognitive status (52). Future studies using the MIND diet should be conducted within populations at greater risk of cognitive decline.

Nordic diet

The Nordic diet attempts to reflect the diet consumed in Nordic countries and is characterized by high intakes of fish, apples and pears, cabbages, root vegetables, whole grains from oat, barley and rye, berries, low-fat dairy products, potatoes and rapeseed oil (53). A large population-based cohort study that followed a total of 2223 dementia-free adults aged ≥60 for 6 years observed that moderate to high adherence to Nordic diet was more closely associated with less cognitive decline than moderate to high adherence to the

other healthful dietary pattern such as MeDi, DASH and MIND (54). Another study carried out in subjects aged 57–78 years revealed that better adherence to the Nordic diet had been associated with higher scores in global cognition over a 4-year study period after adjustment for demographic and lifestyle factors in individuals with normal cognition (55). Consumption of a Nordic diet appears to display a positive association with cognition in individuals with normal levels of cognition, however, whether such might improve cognition in population with cognitive decline remains to be established.

Ketogenic diet

In the last years, different studies suggested the ketogenic diet (KD), characterized by high fat, moderate protein and very low carbohydrate composition, as a tool to prevent the consequences of age-related cognitive decline. In aged rats the KD improved cognitive performance under normoxic and hypoxic conditions, meanwhile motor performance where not affected (56). Two studies carried out in mice found that KD initiated in young adulthood extend midlife longevity and improve cognition (57, 58). A recent study, observed that a late-life KD intervention improved behaviour on both the elevated figure-8 maze alternation task and on cognitive dual task that required working memory while simultaneously performing a bi-conditional association task in rats (59). Such data were recently confirmed in a preliminary human study, demonstrating that the generation of even trace ketones might enhance episodic memory and patient-reported vitality in very early AD (60). Future studies are however necessary to confirm these preliminary results.

MECHANISMS UNDERLYING THE IMPACT OF DIET

Several studies support a relationship between neuroinflammation and nutrients, foods or dietary patterns, taking into account the synergistic or antagonistic biochemical interactions among nutrients as well as the different food sources of the same nutrient. Natural

antioxidant compounds found in plant foods and particularly those found in berries (such as strawberry, blueberry, blackcurrant, blackberry, blueberry and mulberry) have been proposed to exert a multiplicity of neuroprotective actions within the brain, including a potential to protect neurons against injury induced by neurotoxins, an ability to suppress neuroinflammation and a potential to promote memory, learning, and cognitive functions (61-63). Whether the dietary bioactive compounds can cross the Blood Brain Barrier (BBB) in order to play a direct anti-inflammatory or pro-inflammatory effect on microglia and/or other Central Nervous System (CNS) cells is still unclear. Another hypothesis is that they may trigger a peripheral reaction that indirectly induces a CNS response. The subsequent synthesis of cytokines may drive microglia polarization and promote immune-to-brain signalling (64).

The ketogenic diet, originally developed for the treatment of epilepsy in non-responder children, is spreading to be used in the treatment of many diseases, including older adults at risk for AD (65). The main activity of the ketogenic diet has been related to improved mitochondrial function and decreased oxidative stress. beta-Hydroxybutyrate, the most studied ketone body, has been shown to reduce the production of reactive oxygen species (ROS), and to improve mitochondrial metabolism. In particular, it stimulates the cellular endogenous antioxidant system with the activation of nuclear factor erythroid-derived 2-related factor 2 (Nrf2), modulates the ratio between the oxidized and reduced forms of nicotinamide adenine dinucleotide (NAD^+/NADH) and increases the efficiency of electron transport chain through the expression of uncoupling proteins. Furthermore, the ketogenic diet performs anti-inflammatory activity by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome as well as by inhibiting histone deacetylases (HDACs), therefore improving memory encoding (66, 67).

In order to combat oxidative stress and produced ROS, ascorbic acid and vitamin E have been extensively used. Whilst their combined use has provided positive results, the single use of ascorbic acid, despite encouraging results obtained in vitro and in vivo, has not proven to be particularly useful in the treatment of AD, although its deficiency plays an important role in accelerating amyloid accumulation (68). Ascorbic acid also affects inflammageing by decreasing the amount of IL-6 and IL-8, two cytokines involved in the production of ROS (69, 70).

Research over the past two decades has indicated that the gut microbiome and it's interaction with dietary compounds have important implications for human health (71). Polyphenols, for example, favour the growth of beneficial symbiotic bacteria and counteract the growth of pathogens (61). Similarly, omega-3 fatty acids and KD were also reported to affect microbiota composition and function in middle-aged, healthy volunteers (72) and MCI patients respectively (73). Mechanisms may involve the production of short-chain fatty acids (SCFAs), branched-chain amino acids, and gut hormones. SCFAs, including acetate, butyrate, propionate, and lactate, can enter the circulatory system, and it is plausible that they may signal to the brain via this route (74).

CONCLUSION

Much evidence underlines the importance of diet in promoting health; it has been shown that nutritional protocols can direct the course and the outcomes of different pathologies affecting the central nervous system. The implementation of clinical trials will confirm the effectiveness of nutritional protocols developed not only for a specific disease but also for the demands of every single patient. Implementation of large-scale preventive interventions based on dietary patterns identified as being beneficial to brain health should be a research and public health priority, ideally in conjunction with other health-promoting lifestyle factors.

ACKNOWLEDGEMENTS

None

FINANCIAL SUPPORT AND SPONSORSHIP

Sapienza Ateneo 2018 to Rita Businaro

CONFLICTS OF INTEREST

None

KEY POINTS

- Dietary interventions are effective strategies against age-related cognitive decline and neurodegeneration

- Individual nutritional components such as polyphenols, B-vitamins and long chain polyunsaturated fatty acids can have beneficial effects on cognitive performance

- Different dietary patterns are suggested to exert a positive effect against cognitive decline in the elderly

- Mechanisms may involve a reduction in neuroinflammation, an increase in endogenous antioxidant defence and a modulation of the gut microbiota structure and function.

- Research should focus on large-scale preventive interventions ideally in conjunction with other health-promoting lifestyle factors.

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