**THE MEDITERRANEAN DIET IMPACT ON PREVENTION AND TREATMENT OF COGNITIVE DECLINE**

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**THE MEDITERRANEAN DIET IMPACT ON PREVENTION AND TREATMENT OF COGNITIVE DECLINE (Abstract):** The world’s population aged over 60 years is predicted to double in the next 50 years. Increased age makes us vulnerable to various neurodegenerative pathologies among them cognitive impairment and dementia. The economic and social burden of caring for persons with cognitive decline is increasing, and to date there are no effective pharmacologic agents to prevent or treat the disease or even its precursor stages. Identifying simple and effective interventions, like modifiable risk factors to prevent cognitive decline and dementia is likely to be an important strategy for delaying the onset, and reducing the number of patients is a major public health priority. There is growing evidence that diet-a modifiable risk factor- could be one component of an effective prevention strategy against cognitive decline, although no firm conclusion can be drawn at this point. A healthy Mediterranean diet (MeDi), rich in fruit, vegetables, whole grains, nuts, olive oil, and fish may be neuroprotective. Greater adherence to the MeDi is associated with slower rate of cognitive decline and lower risk of cognitive impairment and dementia, but findings are conflicting, mainly due to significant heterogeneity between studies in terms of populations studied and methods used to assess diet and cognition. All these reasons highlight the need for randomized clinical trials and for further research. **Keywords:** COGNITIVE IMPAIRMENT, NUTRITION, MEDITERRANEAN DIET.

Aging is a normal and physiological process. Genetic studies claim that we are born with a genetic determined cognitive reserve which is affected as we get older by environmental and external factors resulting in a decline. Epidemiological studies predict that the number of persons affected by cognitive decline will double every 20 years and reach 106.8 million, affecting 1 out of 85 persons by 2050. Therefore, is a growing public health concern with significant socioeconomic burden, being one major cause of death and disability worldwide (1).

Cognitive impairment can be influenced by several factors and the potential effect of nutrition has become a topic of increasing scientific and public interest (2).
recent years, there has been increasing evidence supporting the role of nutrition in and that to achieve a benefit, an intervention would likely need to be started in the preclinical stage. Emerging evidence suggests an association between dietary habits and cognitive performance (3). Nutrients and diets, together with other aspects of daily living (such as exercise), can affect multiple brain processes by regulating neurotransmitter pathways, synaptic transmission, membrane fluidity and upregulating genes for maintaining synaptic function and plasticity (4).

A common approach to explore the impact of nutrition is studying dietary patterns comprising combinations of nutrients and foods. A frequently studied dietary pattern is the Mediterranean diet, which is rich in fruits and vegetables and unsaturated fatty acids and has been proven to have vascular and anti-inflammatory benefits and may be neuroprotective (5). It was first described by Dr. Walter Willet from Harvard University in 1990 and recognized as UN cultural patrimony in 2013. Its definition consists in recommendations regarding the number of portions per day of different classes of nutrients. It favors the consumption of whole grains, fruits and vegetables, olive oil, fish, nuts and dairy over red or processed meat products and refined sweets. It also recommends increased water consumption and 1 or 2 glasses of red wine per day. The Mediterranean dietary pattern refers not only to the type of food consumed, but also to lifestyle and the social customs associated with the way of eating. It therefore seems reasonable to assume that this pattern of healthy eating can modify cognitive status and reduce the prevalence of cognitive impairment, and mood disturbances in the elderly population (6).

THE ADHERENCE TO THE MEDITERRANEAN DIET

The Mediterranean Diet was largely studied due to its effect in many pathologies. Cognitive decline means brain aging which involves neurodegeneration with loss of synapses and neurons, increased oxidative stress, inflammation and vascular impairment. The primary foods of the Mediterranean diet contain bioactive nutrients and phytochemicals like polyphenols, flavonoids, vitamins, minerals and fiber, arginine and antioxidants with anti-inflammatory proprieties and neuroprotective effect (7). The fish and olive oil contain a lot of omega 3 acids (polyunsaturated fatty acids), part of the neural membrane functioning, increase the activity of antioxidation enzymes, protecting against oxidative stress, neuronal death and the formation and aggregation of amyloid in the brain (8).

Prospective studies have shown that populations with higher adherence to MeDi exhibit lower risk of cardiovascular diseases (9). Reduced inflammation and improved endothelial function produce vasodilatation and increased cerebral blood flow, reducing oxidative stress and neuronal cell death. Interventional studies have reported improvements to blood pressure, lipid profiles, insulin sensitivity, CRP levels and oxidative stress. (10).

Greater adherence to the Mediterranean diet has been associated with a lower rate of cognitive decline in many observational and interventional studies (11). The international recommendations for globally applicable dietary guidelines were translated into the Healthy Diet Indicator (HDI) by the World Health Organization (WHO) in 1990 (12). The HDI based on initial WHO recommendations has been associated with a lower prevalence of cognitive impairment. There-
fore, the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) which included 3 population-based cohorts: Survey in Europe on Nutrition and the Elderly, a (SENECA), Rotterdam Study (RS), Nurses’ Health Study (NHS) totaling 21,837 men and women from Europe and US concluded that a higher HDI score was not related to reduced rates of cognitive decline in European and American older adults (13).

Beside many studies regarding the association between Mediterranean style of eating and cognitive decline, there are a few meta-analyses which gather and select the most important data about this subject. Researchers from Mayo Clinic, USA, screened 664 studies through November 2012, aiming to determine whether there is an association between the Mediterranean diet (MeDi) and cognitive impairment. Only five studies met the eligibility criteria and showed that higher adherence to the MeDi reduced the risk of mild cognitive impairment with 33%. Results also suggested that a higher adherence to the MeDi is associated with a significant reduced risk of developing Alzheimer disease, and a reduced risk of progressing from mild cognitive impairment to dementia (14).

Living on a Mediterranean diet also reduces the risk of stroke, depression, cognitive impairment and Parkinson disease. Higher adherence to MeDi has protective action and is consistently associated with reduced risk for stroke, mainly ischemic and in the male population. Moderate adherence was linked to reduced risk for depression (15). Not living in the Mediterranean area has not been an impediment for the benefit of MeDi on cognition. Lower adherence to a Mediterranean diet was associated with higher AD and mild cognitive impairment compared to healthy subjects in an Australian population (16). An analysis conducted in a group of healthy elderly Swedish men and women, showed that adherence to MeDi was positively associated to healthier cognitive aging, even though no association was found between Mediterranean score and cognitive function or brain volume measured by magnetic resonance (17).

Not all studies favor the benefit of MeDi. For example, results from the cognitive sub-study of the Women’s Health Study reported no association of the Mediterranean diet with cognitive decline. Differences in methodologies used to assess adherence, different sample size, the heterogeneity of groups or populations tested and poor reliability of food questionnaires, among other factors may be the reason why some studies have found no correlation between adherence to a Mediterranean diet and delayed or reduced cognitive decline (18).

PREVENTION WITH THE MEDITERRANEAN DIET

Successful aging depends on the homeostatic reserves of different physiological systems. Recent literature states that MeDi has also effects on cognitive frailty. This novel entity represents a critical intermediate status of the aging process that is at increased risk for negative health-related events and it is starting to be investigated also in association with nutrition (19). There is not a clear understanding of the pathways converging into frailty, but it seems that the losses imposed by ageing, the impact of acute or chronic disease, and the own genetic endowment of the individual may have important roles (20). The potential for reversibility of frailty and its
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different phenotypes suggests that these clinical features may be important for secondary prevention in neurodegenerative diseases. Studies have reported an inverse association between adherence to a Mediterranean diet and lifestyle and prevalence of frailty (21).

Preventing cognitive decline is the subject of recent research. One of them investigated the association between MeDi and the prevention of mild cognitive impairment (MCI) and the progression from MCI to Alzheimer disease (AD) in a multi-ethnic community in New York. 1,393 cognitively normal participants were included from whom 275 developed MCI and 106 were diagnosed with AD for 4.5 years. Subjects that consumed MeDi had 28% less risk of developing MCI and 48% less risk of developing AD compared to control. In the end, there was a significant protective effect of MeDi against MCI and AD, and even a reduced risk of MCI conversion to AD. Studies looked deeper into the effects of MeDi on the domains of cognitive function of healthy older adults, respectively on memory and executive function. In a meta-analysis with 41,492 participants where the primary outcome was cognitive function, but divided into domains of memory and executive function results revealed a significant association between MeDi and older adults’ episodic memory and global cognition, but not working or semantic memory. Also, compared with controls, the MeDi improved delayed recall, working memory and global cognition, but not episodic memory, immediate recall, attention, processing speed or verbal (22).

A study published this year investigated the associations of MeDi and its components with magnetic resonance imaging measures of cortical thickness for the four lobes separately and averaged. Higher MeDi score was associated with larger frontal, parietal, occipital, and average lobar cortical thickness and higher adherence to MeDi was associated with larger cortical thickness. While higher legume and fish intakes were associated with larger cortical thickness, especially parietal and precuneus, higher carbohydrate and sugar intakes were associated with lower entorhinal cortical thickness. This study opens new paths for research, but these novel findings need cross-sectional and prospective studies for validation (23).

Another proposed neuroprotective dietary pattern, the Mediterranean-DASH diet Intervention for Neurodegeneration Delay (MIND diet), has been recently described. The MIND diet is a modified version of MeDi but incorporates additional foods based on current evidence in the study of the effect of diet on dementia. In some population-based studies MIND score was more predictive of cognitive decline than MeDi score, and higher MIND scores were associated with lower risk of Alzheimer disease. These results show that greater adherence to MeDi and MIND diet patterns are associated with better overall cognitive function in older adults and lower odds of cognitive impairment, which could have important public health implications for preservation of cognition during aging (24).

THE THERAPEUTIC ROLE OF THE MEDITERRANEAN DIET

The literature available today is also focused on nutritional therapy or intervention, in delaying the neurodegeneration processes with various nutrients and diets. Regarding this new goal, a recent parallel-group randomized clinical study investigated 447 participants on a Mediterranean diet.
if it influences cognitive status compared with a control diet for 6 years. The Prevención con Dieta Mediterránea (PREDIMED) study used neurocognitive testing at inclusion and at the end of the study, among which the Mini-Mental State Examination, Rey Auditory Verbal Learning Test (RAVLT), Wechsler Scale and the Color Trail Test (CTT). The participants were randomly assigned to MeDi supplemented with extra virgin olive oil (1L/week), MeDi supplemented with mixed nuts (30 g/d), or a control low fat diet. The follow-up was available only to 334 participants after intervention and data showed that the group allocated to MeDi plus olive oil scored better on the RAVLT, MMSE and Color Trail Test compared with controls; no between-group differences were observed for the other cognitive tests. The MMSE and CTT scores were also higher for participants allocated to MeDi and nuts versus control. In the end, the investigators concluded that, although not in all cognitive tests, a Mediterranean diet supplemented with olive oil or nuts is associated with improved cognitive function per se, but also compared with a low-fat diet (25).

Furthermore, actions are taken in the medical world to use diets as interventional strategies in treating different diseases. This year, the BRIDGE (Building Research in Diet and CoGnition) randomized controlled trial started and aims to investigate the effect of MeDi, with and without weight loss, on cognitive functioning in obese older adults (BMI ≥ 30 kg/m² and ≤ 50 kg/m², age ≥ 55 years). They will be randomized in a 2:2:1 allocation scheme to: Typical Diet Control; MeDi alone, without weight loss; or MeDi lifestyle intervention to promote weight loss and weight loss maintenance. Both MeDi intervention groups will meet for one individual session and 27 group sessions over an 8-month period. Individuals in the control group will not receive instruction on changing lifestyle habits. Outcomes will be assessed at baseline, 8 and 14 months. The primary outcome is cognitive functioning; secondary outcomes will include changes in body weight, diet, cardiovascular, metabolic, and inflammatory biomarkers (26).

Regarding the MeDi role in treating cognitive decline, the group led by Samieri showed that MeDi postpones cognitive aging with 1 year and reduces the risk of MCI and the conversion rate from MCI to dementia. Before that, Feart et al stated that there is a therapeutic window of 5 years before the clinical diagnosis of Alzheimer’s disease in which MeDi can be used as a therapeutic strategy with very good effects on the cognitive function (27). The cognitive decline may be also reduced by lowering the cardiovascular risk, mission in which MeDi has already proved efficient, by lowering blood pressure, cholesterol, lipids, body weight and supporting the pharmacological treatment in many metabolic diseases (28).

CONCLUSIONS

In our opinion nutrition plays a decisive role in the maintenance of cognition, thus successful brain aging is an achievable goal for dietary therapies. We reviewed studies that highlight the implication of epigenetic nutritional events in modulating the cognitive abilities and that raises the possibility of dietary manipulations as a viable strategy for treating brain related pathology. In our review evidence is suggestive of a neuroprotective role for the Mediterranean Diet, but variation between studies makes it difficult to draw firm conclusions. Further
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Investigation is needed to determine whether the MeDi represents an optimal dietary pattern for protection against neurodegeneration in representative populations.

Our conclusion is that higher adherence to Mediterranean Diet is associated with slower cognitive decline and lower risk of developing Alzheimer disease. Long-term randomized controlled trials promoting a Mediterranean Diet and life style may help establish whether improved adherence helps to prevent or delay the onset of Alzheimer disease and other types of dementia. What we are sure and has been proved is that in brain aging and preventing cognition decline a multidomain intervention is required including proper nutrition, supported physical exercise and updated pharmacological treatment.

REFERENCES


## NEWS

**PREDICTING GESTATIONAL DIABETES MELLITUS THROUGH SERUM SEX HORMONE BINDING GLOBULIN LEVEL**

A group of researchers conducted a study that assessed the sex hormone binding globulin (SHBG) as a valuable biochemical marker in predicting gestational diabetes mellitus (GDM). Circulating SHBG levels are inversely associated with insulin resistance. In this case controlled study were included 90 pregnant women, 45 women with GDM and 45 matched controls. They measured the serum SHBG levels by Enzyme-linked immunosorbent assay (ELISA) method between 24 and 28 weeks of gestation. Compared with the control group, SHBG concentrations were significantly lower in the GDM group; 23nmol/L vs. 78 nmol/L. The authors concluded that patients with GDM have lower circulating levels of SHBG than normal glucose tolerance pregnant women, so circulating concentrations of SHBG represent a potentially useful new biomarker for prediction of risk of GDM. (Tawfeek MA, Alfadhli EM, Alayoubi AM, El-Beshbishy HA, Habib FA. Sex hormone binding globulin as a valuable biochemical marker in predicting gestational diabetes mellitus. *BMC Women's Health* 2017; 17: 18 DOI: 10.1186/s12905-017-0373-3)

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