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REVIEW ARTICLE

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Importance of nutrological management and gut microbiota in alzheimer's disease: a systematic review

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Abstract

Introduction: In the context of neurodegenerative diseases, Alzheimer's disease (AD) is the most common form of dementia. It is estimated that more than 46 million people are affected worldwide. Several factors contribute to the risk of developing late-onset Alzheimer's disease, including advanced age, genetic factors, family history, history of head trauma, hypertension in midlife, obesity, diabetes, and hypercholesterolemia. Studies have shown the important role of the gut microbiota in controlling this condition, together with adequate nutrition. **Objective:** It was to analyze the relationship between dietary patterns, gut microbiota, micro and macronutrients, and cognitive disorders in Alzheimer's disease. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was conducted from May to August 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 140 articles were found. 75 articles were fully assessed and 30 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 15 studies with a high risk of bias and 25 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=89.5%>50%. It was concluded that several antioxidants found in a healthy natural diet can efficiently attenuate free radical attacks and neutralize dysregulated pro-oxidants, reducing oxidative stress and the induction of degenerative diseases such as Alzheimer's disease. Studies have found that plasma lipopolysaccharide levels in patients with Alzheimer's disease were three times higher than in healthy controls. Thus, increased concentrations of plasma lipopolysaccharide and fecal calprotectin indicate an altered intestinal barrier function and increased inflammation and intestinal permeability in patients with Alzheimer's disease.

Keywords: Alzheimer's disease. Gut microbiota. Nutrology.

Introduction

In the context of neurodegenerative diseases, Alzheimer's disease (AD) is the most common form of dementia. It is estimated that more than 46 million people are affected worldwide. Several factors contribute to the risk of developing late-onset Alzheimer's disease, including advanced age, genetic factors, family history, history of head trauma, hypertension in midlife, obesity, diabetes, and hypercholesterolemia **[1]**.

Currently, available drugs for the treatment of AD have only symptomatic effects, and there is an unmet need to prevent the onset of AD, as well as to slow the progression of the disease to mild cognitive impairment (MCI) in the absence of disease-modifying therapies. In the last decade, one of the hypotheses raised was the association between lifestyle factors, such as diet and eating habits, and the occurrence of AD and dementia. Dietary factors can affect the risk of cardiovascular disease (CVD), also influencing the risk of AD and dementia **[2]**.

A growing body of evidence suggests that certain diets are associated with a lower incidence of AD, so maintaining a healthy diet may have an impact on many of these potential risk factors for cognitive decline **[2]**. Therefore, high dietary monounsaturated fatty acids (MUFA) and n-3 polyunsaturated fatty acids (n-3 PUFA), high fish consumption, together with high antioxidant levels from fruits and vegetables and regulated gut microbiota, may have a beneficial effect on dementia risk **[3,4]**. However, the diet should be considered as a whole, consisting of a complex of nutritional principles, foods, micronutrients, and macronutrients that interact with each other. Indeed, combinations of foods and nutrients in certain patterns may act synergistically to provide stronger health effects than those conferred by their food components.

The National Association on Aging and Alzheimer's Disease (NIA-AA) guidelines for AD and cognitive decline due to AD pathology **[5]** introduced evidence suggesting a direct relationship between diet and dietary changes on brain structure and activity, thus opening the era of brain imaging biomarkers in nutritional epidemiology.

Therefore, the present study analyzed the relationship between dietary patterns, gut microbiota, micronutrients and macronutrients, and cognitive impairments in Alzheimer's disease.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 07/10/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 07/10/2024.

Search Strategy and Search Sources

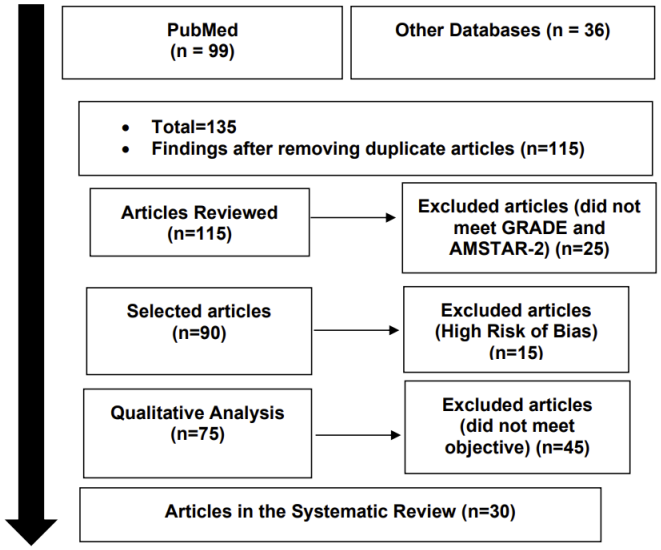
The literature search process was carried out from May to August 2024 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors (DeCS /MeSH Terms) were used: "Alzheimer's disease. Gut microbiota. Nutrologia", and using the Boolean "and" between MeSH terms and "or" between historical discoveries. The articles selected used the period from 2009 to 2023 as inclusion criteria, considering research from the last 13 years. All types of available studies were selected, including prospective, retrospective, case-control, cross-sectional studies, case reports, in vitro and in vivo studies, as well as systematic and literature reviews. Studies that did not correlate diet or microbiota with Alzheimer's disease or other cognitive diseases in their abstract were excluded.

Results and Discussion

Summary of Findings

A total of 140 articles were found that were subjected to eligibility analysis, and then 30 articles were selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in study types such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=89.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 15 studies with a high risk of bias and 25 studies that did not meet GRADE and AMSTAR-2.

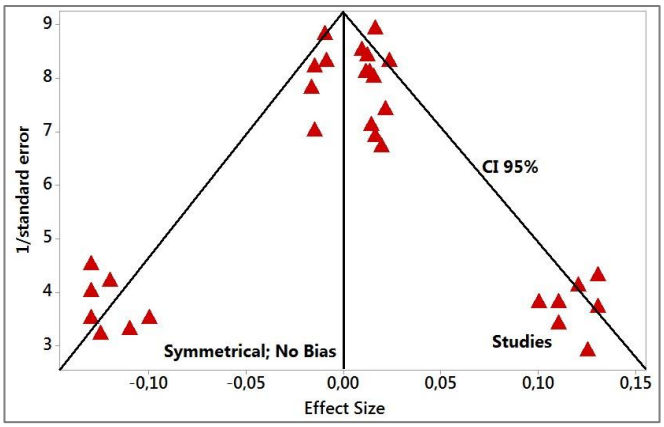
Figure 1. Flowchart showing the article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=30 studies).



Source: Own authorship.

Main Results

Cells gradually degenerate with aging. Cellular degeneration in aging is a highly complex process with several mechanisms and pathways involved [6]. During aging, cellular metabolic redox reactions occur that induce detrimental genetic and biochemical changes. Increased production of reactive oxygen species (ROS) and nitrogen damages cellular proteins, lipids, carbohydrates, and nucleic acids through oxidative stress, contributing to cellular degeneration during aging [7]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are short-lived, but increased redox reactions continuously generate new ROS and RNS, and are believed to contribute to the onset of several degenerative diseases, including cancer, diabetes, Alzheimer's, and Parkinson's [6].

Metabolic and physiological behavior changes rapidly with aging. Thus, highperformance cells and tissues, including postmitotic cells (brain and heart), are likely to be severely affected by ROS overload. This is one of the fundamental bases for the hypothesis of degenerative diseases induced by oxidative stress in the elderly [7]. Normal metabolic processes or cellular stresses continuously generate ROS and RNS and they accumulate over time. High levels of pro-oxidant impairment and weakening of antioxidant defense mechanisms are more common in the elderly, suggesting that the elderly population is more affected by associated degenerative diseases.

AD is a complex and chronic neurodegenerative disorder related to aging. The mechanisms of AD are largely unknown. Inflammation, intracellular release of calcium ions, autophagy, apoptosis, and, mainly, overproduction and aggregation (crosslinking) of Aβ peptides are believed to be involved in AD neurodegeneration [8]. Neuronal cells, among others, are particularly susceptible to degenerations induced by oxidative stress [9].

Neurons are metabolically active cells and use large amounts of oxygen, approximately one-quarter of the total oxygen consumed in the body, during metabolism. As a result, neuronal cells generate an enormous amount of ROS and RNS and are subject to free radical attacks. Compared to other cells, neurons comprise a low level of antioxidant defense molecules and contain a higher amount of polyunsaturated fatty acids prone to oxidation [9]. Lipid oxidation is one of the pathological markers found in AD brain tissue [7]. Highly oxidizable polyunsaturated fatty acids, such as arachidonic and docosahexaenoic acids, are present in the brain, and lipid peroxidation damages neuronal membranes, thus favoring damage to brain structures.

Pro-oxidant overload is associated with age-related degenerative diseases and antioxidant defense mechanisms may play vital roles in attenuating pro-oxidant activity and helping to prevent disease progression. Thus, enhancing antioxidant pathways and/or neutralizing pro-oxidants by exogenous antioxidants may provide viable preventive options for degenerative diseases [1].

Gut Microbiota, Diet, and Alzheimer's Disease

The health and diversity of the gut microbiota are directly dependent on food. The gut microbiota plays an important role in increasing or decreasing the risk of AD. The gastrointestinal tract, from the esophagus to the anus, is lined by a layer of epithelial cells, which form the intestinal mucosal barrier to protect the body from infection by pathogenic microorganisms and prevent particles, chemicals, bacteria, and other health hazards. They play important roles in protecting the health of the host **[10]**. When problems with intestinal permeability occur, which is called leaky gut, disruption of the intestinal barrier functions causes leaky gut accompanied by increased inflammatory levels and resulting in the occurrence of diseases **[11]**.

The integrity of the blood-brain barrier (BBB) is vital for brain development and function. In the past, it was believed that the BBB was impermeable and could prevent potentially harmful substances from entering the brain. It has recently been discovered that many substances can threaten the integrity of the BBB, causing all kinds of molecules, including proteins, viruses, and even bacteria, to enter the brain and threaten brain health **[12]**.

Changes in the gut environment can gradually destroy the brain's ability to protect it from toxic substances. Inflammation-induced by a leaky gut will result in a leaky brain, which is the increased permeability of the BBB. The disruption of the balance of gut microbiota is directly related to a leaky gut **[13]**. Stress, infection by pathogens, and antibiotics can destroy the gut microbiota and lead to increased intestinal permeability.

Lipopolysaccharide (LPS) is a combination of lipids and sugar and an important component of the cell wall of gram-negative bacteria. There are about 50% to 70% of gram-negative bacteria in the normal gut microbiota. LPS, which is an endotoxin, induces severe inflammation of the body if it enters the bloodstream. In healthy conditions, LPS is blocked from the bloodstream by the tight junctions that exist between intestinal epithelial cells **[13]**.

When intestinal permeability is increased, LPS finds its way into the bloodstream and results in inflammation. Therefore, blood LPS levels represent not only inflammation but also a leaky gut. Studies have found that plasma LPS levels in AD patients were three times higher than in healthy controls **[14]**. Increased plasma LPS and fecal calprotectin concentrations indicate altered intestinal barrier function and increased inflammation and intestinal permeability in AD patients. These results further confirm that the gut microbiota may participate in the pathogenesis of AD **[15]**.

As previously demonstrated, oxidative stress results in cellular damage. Therefore, seeking ways to promote antioxidant effects may prevent the occurrence of AD. Vitamin A and β-carotene may be key molecules for the prevention and therapy of AD, due to their ability to inhibit the formation of Aβ oligomers and fibrils. Lower serum and plasma concentrations of vitamin A and β-carotene have been observed in patients with AD, and higher plasma β-carotene levels have been associated with improved memory performance **[16]**. Another important vitamin in reducing Aβ oligomer formation and oxidative stress is vitamin C. Overall, there is a large body of evidence that maintaining healthy vitamin C levels may have a protective function against AD **[17]**.

B vitamins may contribute to AD by inhibiting oxidative stress and decreasing homocysteine concentrations **[18]**. High homocysteine concentrations have been associated with an increased risk of AD, and homocysteine has been significantly elevated in patients with AD; high-dose vitamin B6, B12, and folate supplementation reduce plasma homocysteine concentrations in patients with AD; homocysteine-lowering treatment may be a therapeutic target for AD **[19]**.

Vitamin D may have little association with Aβ mechanisms, and its potential association with AD may involve other pathways, such as antioxidant, vascular, anti-inflammatory, or metabolic pathways. A meta-analysis of 10 studies showed that AD cases had lower serum concentrations of vitamin D than matched controls **[20]**.

Current knowledge does not provide evidence for the role of selenium (Se) in the treatment of AD, but it is believed to have a possible preventive relevance, and selenium has been reported to play an important role in antioxidant defense. AD patients had significantly lower plasma selenium levels when compared to controls **[18]**.

Polyphenols are natural antioxidants that provide protective effects in AD through a variety of biological actions, such as interaction with transition metals, inactivation of free radicals, inhibition of the inflammatory response, modulation of the activity of different enzymes, and effects on intracellular signaling pathways and gene expression. A randomized, double-blind, controlled clinical trial of polyphenol supplementation in 100 individuals showed that polyphenols contained in antioxidant beverages may benefit AD patients by lowering homocysteine concentrations in AD patients **[21]**.

The study by Eskelinen et al., (2009) **[22]** followed 1,409 individuals in Finland aged 65–79 years for 21 years and found that people who drank three to five cups of coffee daily in midlife had a 65% lower risk of

AD compared to people who did not drink coffee or drank less than two cups per day.

The effect of coffee can be explained in two ways. First, the gut microbiota can easily digest the fiber in coffee beans and harvest its energy to aid their growth. At the same time, they can reduce the ratio of Firmicutes to Bacteroidetes bacteria, and this change in the ratio of Firmicutes to Bacteroidetes is associated with reduced inflammation. Second, the body's ability to utilize coffee polyphenols is also influenced by the gut microbiota to a large extent. After consumption, polyphenols need to be degraded by the gut microbiota into small molecules that are easily absorbed by the human body. Therefore, to obtain sufficient health benefits and increase the bioavailability and activity of polyphenols, it is necessary to have a healthy gut microbiota. The protective role of other antioxidants and nutrients may also depend on the balance of the gut microbiota to some extent. Healthy gut microbiota can increase their biological activity and utilization, and thus exert their maximum protective role on the brain and reduce the risk of AD **[13]**.

Increased monounsaturated fatty acid is associated with improved cognitive function, while increased saturated fatty acid is associated with worsened cognitive function. Monounsaturated fatty acids (MUFAs) and MUFA derivatives have antiinflammatory effects, and MUFA derivatives, including low molecular weight phenols, have been reported to have antioxidant effects. Data from a prospective study suggested that higher monounsaturated fatty acid intake is associated with less cognitive decline **[23]**.

A high intake of polyunsaturated fatty acids may be beneficial for AD. Dietary supplementation of omega-3 polyunsaturated fatty acids affects the expression of genes that may influence the inflammatory process. Dacosahexaenoic acid (DHA), the main form of omega-3 fatty acids, reduces Aβ production and pathological changes in animal models of AD. One study showed that omega-3 fatty acids slowed cognitive decline in elderly individuals without dementia **[24]**.

Diet is generally considered to be closely associated with the occurrence of AD. Omega-3 polyunsaturated fatty acids are vital for neuronal and brain functions. Low body levels of omega-3 may be associated with neurodegenerative diseases, including AD. The intestine is the primary site for absorbing fatty acids, and omega-3 absorption in the intestine is limited by a variety of conditions, including the fatty acid composition of the diet, the body itself, and the existing form of fatty acids **[25]**.

Dietary fatty acids are one of the main carbon sources for the gut microbiota. The gut microbiota can metabolize dietary fatty acids alter the fatty acid composition in the intestine, and eventually alter the body's fatty acid composition. The gut microbiota can also participate in the intestinal absorption of omega-3. Dietary fatty acids can also directly or indirectly modulate the composition of the gut microbiota and influence the host immune system. The composition of the gut microbiota changed significantly in mice fed an omega-3-enriched diet **[23]**.

The Western diet is characterized by a higher intake of red meat and processed products, refined grains, sweets, and desserts. The high-fat Western diet may contribute to the development of AD by affecting Aβ deposition and oxidative stress **[25]**. In contrast, a study of 3054 participants evaluated participants who consumed a healthy diet, defined as positively correlated with the consumption of fruits, whole grains, fresh dairy products, vegetables, breakfast cereals, tea, good fats, nuts, and fish and negatively correlated with meat, poultry, refined grains, animal fat, and processed meat. Participants with the highest compared to the lowest adherence to the healthy diet had better cognitive function **[26]**.

Furthermore, the Mediterranean diet, a typical diet of the Mediterranean region, is characterized by a high consumption of fruits, vegetables, cereals, bread, potatoes, poultry, beans, nuts, olive oil, and fish; a moderate consumption of alcohol (wine); lower consumption of red meat and dairy products. Adherence to the Mediterranean diet may not only affect the risk of AD but also mortality in the disease. A meta-analysis of eighteen cohort studies with 2,190,627 individuals showed that adherence to the Mediterranean diet was associated with a significant reduction in overall mortality and neurodegenerative diseases **[27]**. The Mediterranean diet appeared to benefit the health of patients with Crohn's disease, reflected by a tendency to reduce biomarkers of inflammation, in addition to normalizing the gut microbiota with increased Bacteroidetes and Clostridium and decreased Proteobacteria and Bacillaceae **[28]**. The Mediterranean diet may play important roles in disease control, including the treatment of AD by balancing the gut microbiota **[29,30]**.

Conclusion

It was concluded that several antioxidants found in a healthy natural diet can efficiently attenuate free radical attacks and neutralize dysregulated pro-oxidants, reducing oxidative stress and the induction of degenerative diseases such as Alzheimer's disease. Studies have found that plasma lipopolysaccharide levels in patients with Alzheimer's disease were three times higher than in healthy controls. Thus, increased plasma lipopolysaccharide and fecal calprotectin

concentrations indicate altered intestinal barrier function and increased inflammation and intestinal permeability in patients with Alzheimer's disease.

CRediT

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