Exploring the Influence of Diet on Alzheimer's Disease: A Comparative Review of Ketogenic and Mediterranean Diets

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Abstract

Alzheimer's Disease (AD) is a leading cause of dementia, marked by progressive cognitive decline. The disease affects nearly 7 million Americans alone, indicating that the disease is widespread and a genuine problem. AD has many genetic causes, which leads to the formation of aberrant protein buildup in the brain, preventing information from being transferred. While genetics is considered to be the leading contributor of AD, it is not the only factor, as genetic AD does not include all cases. This suggests that there are possibly environmental causes that could lead to the development of AD, such as diet and other lifestyle choices. This review focuses on the diet aspect of the environmental causes, hoping to explore the relationship between the Ketogenic diet and the Mediterranean diet on the progression and prevention of Alzheimer's disease.

Introduction: Alzheimer's Disease

Alzheimer's Disease (AD) is a neurodegenerative disorder which is characterized by a progressive cognitive decline, memory impairment, and the deterioration in daily functioning. AD is the leading cause of dementia globally, affecting millions of individuals, namely in 65 years of age and older (National Institute on Aging). Additionally, AD also poses a significant social and economic burden due to the medicine required and the physical and emotional strain on both patients and their families.

The disease follows a symptomatic course as depicted by Braak and Braak (2006), dubbed Braak Staging. In stages 1 and 2, the brain can be found to have small tau buildup in the transentorhinal and entorhinal zones, marking the earliest indication of AD. In Stages 3 and 4, these lesions extend into the neocortex of the fusiform and lingual gyri, which begins to slightly affect language, and it is in these two stages that the disease becomes more prominent and the lesions become deeper. In the stages of 5 and 6, the lesions extend into more parts of the brain, such as the occipital and frontal lobes. It is in these stages where the disease becomes characterized as severe dementia, and is the last stage prior to the inevitable demise of the patient (Braak et. al. 2006).

AD is associated with the aberrant accumulation of the two hallmark proteins in the brain: beta-amyloid (Aβ) plaques and tau tangles (Long and Holtzmann 2019). While currently unknown regarding their function in the human body, Aβ plaques are extracellular deposits made up primarily by insoluble beta-amyloid peptides. These peptides disrupt neuronal communication and trigger inflammatory responses, which contribute to the inevitable death of an Alzheimer's patient (Long and Holtzmann 2019). The tau tangles consist of hyperphosphorylated tau protein aggregates within neurons, accomplishing the same function as Aβ plaques by disrupting cellular transport mechanisms which lead to neuronal degeneration (Long and Holtzmann 2019). AD has also been found to be influenced by microglia and astrocytes, which are neuronal support cells of the brain. Both microglia and astrocytes initially exhibit neuroprotective properties. However, as AD becomes more severe in a patient, microglia start to release astrocyte-activating signals, causing proteins such as interleukin-1 to produce

more Aβ, creating a negative feedback loop (Di Benedetto et. al 2022) and a chronically inflamed brain state.

AD can also be caused by genetic factors, which facilitate the appearance of tau tangles, Aβ deposition, and neuroinflammation. The largest genetic risk factor for late onset AD is currently the APOE gene, which can lead to a 2-3 times increased risk if a person has one APOE4 gene. This is increased to 8-12 times increased risk if a person has two APOE4 genes, one from both parents. (Mayo Clinic 2023). In early onset AD, gene mutations in APP, PSEN1, PSEN2 will likely cause the contraction of AD before age 65 (Mayo Clinic 2023).

While early onset AD is mostly determined by specific gene mutations, late onset AD is also significantly influenced by environmental causes such as dietary and lifestyle choices. The primary purpose of this review is to explore the connection between these dietary choices and AD. Since AD affects millions of people globally, expensive treatments cannot always be the answer for many of these individuals. Many of the current options are exorbitantly expensive and have largely mediocre results with harsh side effects, making these current treatments not only a financial burden, but also unusable. By understanding how individuals can prevent the onset of AD, these people can have a genuine chance of fighting the disease from an early age.

Ketogenic Diet and Alzheimer's Disease

Ketogenic Diet: Introduction

The Ketogenic Diet (KD) is a method of nutrition where the individual aims to activate ketone bodies (beta-hydroxybutyrate, acetoacetate and acetone) which leads to a condition called ketosis. In ketosis, ketone bodies are used peripherally as an energy source made by the liver using stored fat when glucose is not readily available (LeWine 2024), thus, in theory, burning more fat. The KD is focused on the practice of maximizing energy acquisition from fats and largely minimizing the grams of carbohydrates eaten daily to no more than 50 grams (LeWine 2024). Protein is limited to roughly 75 grams in a daily diet, which can be adjusted according to a person's exact daily needs (LeWine 2024). As a result of following these highly specific ratios, the body undergoes a fast-like condition known as ketosis. The fasting leads to the use of the ketone bodies as the main energy substrate because the body has switched off of glucose and has begun to utilize fat, the place where ketone bodies are derived from, as the energy source (LeWine 2024). Therefore, the KD differentiates itself from other diets due to its characteristic fasting without most of its negative effects. The KD has one major side effect in that the process of drastically changing diets causes many individuals to experience a condition known as the ketogenic flu or the carb flu. This condition is caused by the change in diet from, likely, high carbs to a miniscule amount and drastically increasing fat intake (Kubala 2023). This change causes withdrawal-like symptoms in some, such as nausea, vomiting, and weakness (Kubala 2023). While this condition may not present itself in all individuals who follow the diet, it is an important side effect to consider.

Ketogenic Diet and Alzheimer's Disease: Published Work

One of the largest methods by which individuals can prevent AD is by adjusting their lifestyle so that they can have the best chance of staying healthy. One of these adjustments could be the adherence to the Ketogenic Diet (KD). One study showcases how KD contributed to the development of the mitochondria in healthy, 14-month old female mice. KD was shown to increase mitochondrial mass and kynurenine aminotransferase (KAT) levels in certain muscles. KAT transforms kynurenine to kynurenic acid. Initially, kynurenine is toxic to the brain when forming quinolinic acid as it can cross the blood-brain barrier (Pathak et al. 2022). In KD, KAT

transforms this noxious kynurenine to kynurenic acid, which cannot cross over the blood-brain barrier, it prevents the formation of the neurotoxic quinolinic acid (Pathak et al. 2022). This study showcases how KD, can prevent the decline of cognitive function through metabolic and mitochondrial enhancements.

Another study implemented the use of a medium-chain triglyceride (MCT)-based ketogenic formula, a specialized nutritional composition designed to induce and maintain a state of ketosis in the body, in 20 Japanese individuals who had mild-moderate AD (Ota et al. 2018). The study revealed that over a 12 week period, some patients exhibited improvements in verbal memory and processing speed. This study further highlights how KD could significantly improve cognitive function, possibly preventing the worsening of AD.

Building upon the MCT-based KD, another study regarding the effects of KD on mice that were fed a high-fat-high-cholesterol (HFHC) diet for 16 weeks was conducted (Lin et al. 2022). This study revealed that after switching to the KD for 8 weeks, the mice who were previously fed a HFHC diet exhibited a large improvement in spatial learning and memory performance compared to those on only the HFHC diet. The study also revealed that following the change to the KD, the mice had lower inflammation markers (NF-κB and TNF-α) and proteins (GFAP, APP and phosphorylated tau) linked to AD. This study goes further into the MCT based KD, and highlights how the traditional American diet, which has a great resemblance to the HFHC diet, could be a significant contributor to AD development.

Another study by Jacopo Lucente and his peers was conducted on aged mice with the focus of identifying the role of Beta-Hydroxy-butyrate (BHB), a ketone body, the very energy source that KD aims to utilize, on AD development (Lucente et al. 2024). The study compared the experimental group, which was fed KD, and the control group of mice, for 7 months and revealed that the mice who were fed the KD showcased a higher long-term-potentiation (LTP), which indicates that the mice fed KD exhibited better synaptic memory, without affecting Amyloid-Beta levels. The same study also revealed, through RNA sequencing, that KD increased the efficacy pathways related to synaptic plasticity, highlighting how the KD could be a viable lifestyle adjustment for the prevention of AD, especially when bolstering the ketone body BHB.

A different study, conducted in 2009 (Mohamed et al. 2009), delved into how KD impacted sexually mature male obese rats in their weight and Alzheimer's markers such as the amyloid precursor protein (APP). The study showcased that after being fed the KD, the obese rats exhibited significant weight loss and reduced brain APP and apolipoprotein E4. This study suggests that the KD may have neuroprotective properties and could be a genuinely viable option for the prevention of Alzheimer's disease because the KD reduces APP, leading to less plaque formation, meaning a better guard against AD.

A different study was conducted by Ximin Yang and Baochua Cheng regarding the effects of KD on MPTP, a chemical to induce Parkinson's disease-like symptoms, treated mice and observed how the diet impacted these mice (Yang and Cheng 2010). The study highlighted how KD decreased chronic microglia activation. Typically, this inflammation leads to the release of proinflammatory cytokines and reactive oxygen species, which can damage neurons and exacerbate neuroinflammation (Di Benedetto et al. 2022). While the study focused on Parkinson's disease, chronic microglia activation is common in both Parkinson's and AD, therefore, the study further suggests that KD may exhibit neuroprotective properties and anti-inflammatory benefits, possibly making it a valuable intervention for the prevention of AD.

Mediterranean Diet and Alzheimer's Disease

Mediterranean Diet: Introduction

In addition to the KD, the Mediterranean diet (MD) could also be a viable diet to implement in the prevention of Alzheimer's disease. MD is one of the most well known diets in human history. MD is rooted in the traditional dietary patterns of countries during the 1960's surrounding the Mediterranean Sea, such as Greece and Spain (Guasch-Ferré and Willet 2021). The diet is characterized by the consumption of plant-based foods, including fruits, vegetables, legumes, nuts, and whole grains, all of which supply the human body with a rich source of dietary fiber, vitamins, minerals, and antioxidants (Guasch-Ferré and Willet 2021). Many of the meals within MD predominantly use a high amount of olive oil as the primary source of dietary fat, benefitting cardiovascular health (Guasch-Ferré and Willet 2021). In addition to these nutritional guidelines, MD also encourages followers to adopt a more social lifestyle. This change entails individuals becoming more physically active and participating in more conversations with their peers, which has been shown to activate the brain (Guasch-Ferré and Willet 2021). Followers of MD are encouraged to limit dairy consumption (such as cheese and yogurt) and no more than 4 eggs a week. Much of the protein that is acquired in this diet is from fish and other seafood, in addition to plant-based proteins. This dietary pattern also emphasizes the importance of moderate wine consumption, particularly red wine. Red wine, when consumed with meals, is believed to confer additional cardiovascular benefits due to its polyphenol content (Ditano-Vázquez et al. 2019). MD is shown to be significantly helpful in preventing severe diseases such as cancer, diabetes, and stroke (Cleveland Clinic). In addition to these benefits, MD is thought to be beneficial to the prevention of Alzheimer's disease (AD). Both the olive oil consumption and light red wine consumption exhibit neuroprotective properties, highlighting the efficacy of these 2 aspects in MD for Alzheimer's prevention and/or inhibition. (Silva et al. 2023). Additionally, the omega-3 fatty acids in fish contribute to neuroprotection and are believed to reduce amyloid plaque formation, a hallmark of Alzheimer's pathology (Zhang et al. 2011). The holistic lifestyle associated with MD, including physical activity and social interaction, further supports cognitive health, making it a promising dietary choice for Alzheimer's prevention.

Mediterranean Diet and Alzheimer's Disease: Published Work

Given these benefits provided by MD, many studies have been conducted to determine the relationship between MD and AD. One study experimented with eighty-seven participants with normal cognition or mild cognitive impairment and they fed them either the MD or a traditional western diet (WD) which includes high fat and sodium (Hoscheidt et al. 2022). The study showcased how following the MD diet for 4 weeks, the CSF to amyloid-beta ratios increased in those with normal cognition (Hoscheidt et al. 2022). A Higher CSF:Aβ ratio indicates a lower risk of amyloid plaque formation in the brain, which is associated with AD (Hoscheidt et al. 2022). The study also showcased how following the implementation of the western diet for the same 4 weeks, the opposite effect was observed in those with normal cognition: CSF:Aβ ratios had decreased, highlighting how a western diet could be a major factor in the formation of Aβ plaques, which could lead to AD (Hoscheidt et al. 2022).

Rubia Ortí et. al conducted a study in 2018 with the intent to identify the effect of a coconut oil-enriched MD would have on those with AD. The study, conducted on 44 patients with AD, revealed that the group which consumed the coconut-rich MD had improved episodic memory, temporal orientation, and semantic memory, highlighting how a coconut enriched-MD plan could prevent AD from worsening in those with AD (Rubia Ortí et al. 2018).

In a known study conducted by Elena H. Martinez-Lapiscina et. al., researchers investigated the effect of different variations of the MD on cognitive function in humans with

cardiovascular risk. The study found that of the 522 participants with high vascular risk, which means that these participants were at risk of developing conditions that impact the blood vessels, those who consumed the extra-virgin olive oil variation and the mixed nuts variation of the MD had higher Mini-Mental State Examination (MMSE) and Clock Drawing Test (CDT) scores. High MMSE scores usually indicate that a patient is having no issues and usually means that the patient is not experiencing any form of dementia. Similarly, an accurate clock drawing usually means that a patient is exhibiting no symptoms of dementia. However, low MMSE scores and a poorly drawn clock can indicate that a patient could be exhibiting dementia symptoms and could be a potential reason to check for AD (PsychDB and HealthDirect).

Discussion

The studies reviewed, including those on the Ketogenic diet (KD) and Mediterranean diet (MD) consistently demonstrate significant implications for Alzheimer's disease (AD) prevention and management through dietary adjustments. The KD, characterized by its ability to significantly reduce neuroinflammation, shows promise in improving cognitive function and reducing AD markers in both animal models and human studies. The increase in ketone bodies showcase how the KD could protect against neurodegeneration. Additionally, the MD, rich in antioxidants and anti-inflammatory compounds like olive oil, shows similar promise in the same manner. In the studies conducted, the MD highlighted how the diet could also be a contributing force against the worsening of AD. These findings underscore the critical role of dietary patterns in modifying AD risk factors and potentially delaying disease progression.

For individuals with or without AD, adopting diets like the KD or MD could offer significant benefits in preserving cognitive function and reducing AD risk or progression. While it may be difficult to modify a daily diet to a strict lifestyle, the benefits seem to overwhelmingly outweigh the drawbacks. The prevention of AD is a large benefit in the human body and based on the studies conducted, it seems that one of these two diets could be the answer to the problem. However, it is important to note that while the KD has shown potential benefits, it can be less approachable and harder to adhere to than the MD.

While this review discusses the many studies regarding diets and their effect on the prevention of AD, continued research in these fields holds great promise for the treatment of AD and should be prioritized in the future. The research in this sector should certainly focus on long-term efficacy to prevent AD. For example, research should focus on understanding the long-term effects of diet on the degenerating brain, as AD is a progressive neurodegenerative disease and long-term studies can reveal whether dietary interventions can slow disease progression, delay onset, or reduce severity over time. These studies all showcase how the dietary interventions showed effects within a few years, but none highlighted the effects far into the future. It is possible that long-term usage of these diets may be detrimental to other areas of health or eventually lose potency. However, it is also possible that long-term diet use continues to have positive impacts on disease outcome. More studies will determine which outcome is more likely.

Conclusion

AD seems to be a scary situation at a global level and there is an increased need to prevent it in both clinical settings and lifestyle aspects. For those who currently have AD, hyperinflated medicines that cost upwards of tens of thousands of dollars are often the only treatment option (Hull and deBlecourt), thus causing even more burden and stress. Furthermore, these drugs have been shown to have mediocre outcomes at best (Hull and deBlecourt). While waiting for better drugs to hit the market, dietary interventions that could work

to reduce the prevalence of AD are significant in that they can mitigate this macabre reality. The KD, while a difficult diet to follow, shows promise in preventing AD because of its reduction in neuroinflammation. Similarly, the MD shows promise in its use of olive oil and its beneficial relationship with cognitive function. If AD can be prevented using simple dietary interventions, the next challenge would be to spread awareness of the positive effects of KD and MD and work to educate people to make changes to their current lifestyle. This would eventually save individuals thousands of dollars in Alzheimer's medication because they would have been saving their health from the previous years. Prioritizing accessible dietary interventions such as KD or MD offer a promising pathway to the prevention of AD while also potentially alleviating its economic and personal toll.

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