

Food For Memory: A Review of the Effects of Diet on Alzheimer's Disease Progression

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ABSTRACT

The incidence of Alzheimer disease (AD) is rapidly increasing worldwide. Alzheimer's disease is a type of dementia characterized by progressive cognitive dysfunction. Though some studies suggest potential management options for preventing AD symptom progression, there is currently no absolute way to fully prevent Alzheimer's disease from occurring nor is there a curative treatment. Despite the few methods associated with preventing AD symptom progression, evidence strongly suggests that diet may play a role in slowing AD symptom progression and decreasing disease burden. In this review, we evaluated several diets to understand their respective association with AD symptoms and neuropathology. Overall, we found that the Mediterranean, Vegan, Vegetarian, Ketogenic and Paleo diets improve AD cognitive symptoms and decrease amyloid β peptide ($A\beta$), the principal toxic factor in AD. However, further research needs to be conducted to fully elucidate the relationship between these diets and AD.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects 25 million people worldwide (Qiu et al., 2009), and it is the most common form of neurodegenerative dementia in the United States (Soria Lopez et al., 2019). The prevalence of Alzheimer's disease in people aged 65-90 around the world is continually increasing as the population ages (Masters et al., 2015), and there is no cure for this disease. The symptoms of Alzheimer's disease begin with mild memory difficulties and as the disease progresses, there is increased cognitive impairment, increased neuronal loss, atrophy, and the presence of neuropathologic lesions (Mantzavinos & Alexiou, 2017). The diagnosis of AD is not confirmed until an autopsy is performed, and there are few biomarkers that are associated with AD ("Alzheimer's Disease," 2018).

Amyloid β peptide ($A\beta$) is the major biomarker and the main pathology used to identify AD in patients experiencing neurodegenerative signs and symptoms (Weller & Budson, 2018). $A\beta$, in its physiologic state, has two major functions: regulating synaptic activity and ensuring neuronal survival (Pearson & Peers, 2006). When $A\beta$ aggregates in neurofibrillary plaques, it can lead to increased neurotoxicity in the brain, potentially contributing to the pathogenesis of Alzheimer's and dementia (Chen et al., 2017). Reduced coffee consumption, reduced carbohydrate consumption or even increased vitamin intake may decrease the risk for Alzheimer's disease (Browne et al., 2019; Henderson et al., 2006; Larsson et al., 2017).

Though there are few therapeutic options to limit the neurofibrillary plaques (Sevigny et al., 2016) and cognitive decline, many studies have shown that diet and nutrition may prevent the progressive symptoms of Alzheimer's disease (Hill et al., 2019; Martha Clare Morris et al., 2015; Román, Jackson, Gadhia, et al., 2019).

However, of these diets, the Mediterranean diet may have the most potential in slowing cognitive decline and improving the symptoms of Alzheimer's disease by reducing $A\beta$ in the brain (Martha Clare Morris et al., 2015; Nagpal

et al., n.d.). Therefore, this review will explore the association between diet and Alzheimer's disease to further understand how different diets influence disease pathogenesis and symptom progression in Alzheimer's disease patients.

The Western diet

A vast majority of individuals in the United States follow a Western diet, which contains high amounts of processed ingredients, unhealthy trans fats, low micronutrient intakes, high ratio of carbohydrates to healthy fats (omega 3) and calorie dense foods (Cordain et al., 2005). This diet has been linked to the increased prevalence of Alzheimer's disease in westernized and developed countries (Martins et al., 2006). Epidemiological studies suggest that the Western diet contributes to an increased risk of Alzheimer's disease due to high fat and high cholesterol consumption (M. C. Morris et al., 2004; Puglielli et al., 2003). Additionally, recent animal studies have demonstrated an association between increased levels of amyloid β peptide in the brain and a high-fat diet (HFD) when compared to controls fed a standard diet (Amtul et al., 2011; Bracko et al., 2020; Jacka et al., 2015; Więckowska-Gacek et al., 2021). Further, researchers demonstrated that mice fed a HFD for four months displayed accelerated cognitive decline, increased A β deposits in the brain, and increased oxidative stress, all of which are hallmark signs of Alzheimer's disease (Thériault et al., 2016). Though these studies did not address the mechanism for which HFD alters Alzheimer's disease burden, several studies have linked unhealthy high fat consumption (predominantly triglycerides and not cholesterol per se) to neuroinflammation (Cavaliere et al., 2019; Duffy et al., 2019; Spencer et al., 2017). Neuroinflammation may be mediated by the ratio of omega fatty acids, where high levels of omega-3 fatty acids contribute to the prevention or improvement of cognitive symptoms in Alzheimer's disease (Thomas et al., 2015), and high levels of omega-6 fatty acids contribute to increased inflammation in the brain and progression of cognitive symptoms in Alzheimer's disease (Pegueroles et al., 2018; Simopoulos, 2016; Vasefi et al., 2019). Continually, the Western diet favors high dietary omega-6 fatty acid consumption (Patterson et al., 2012), tipping the balanced ratio towards an increase in neuroinflammation (Pegueroles et al., 2018; Simopoulos, 2016; Vasefi et al., 2019). Since a HFD has been shown to increase inflammation in the brain and increased neuroinflammation is a major contributor to AD pathogenesis (Thériault et al., 2016; Van Eldik et al., 2016), the Western diet may worsen AD symptoms and contribute to AD pathogenesis.

While studies provide strong evidence for the role of HFD and neuroinflammation in increasing AD amyloid beta and symptom burden, recent studies suggest that high sugar consumption also worsens Alzheimer's disease symptoms (Cao et al., 2007; Orr et al., 2014; Pase et al., 2017). In fact, one study has demonstrated an association between increased sugar intake and increased neurodegeneration (Pase et al., 2017); increased sugar intake led to decreased total brain and hippocampal volume and decreased performance on memory tests in animal models (Pase et al., 2017). Excess sugar intake has been associated with increases in mammalian target of rapamycin (mTOR) signaling, an energy homeostasis modulator and key nutrient sensor (Orr et al., 2014). Particularly, in Alzheimer's disease, dysregulation of mTOR signaling impacts the degradation of A β (Spilman et al., 2010), resulting in increased neurofibrillary plaque burden. Thus, excess sugar consumption through the Western diet, and subsequent hyperactivation of mTOR signaling, may promote AD A β accumulation and further symptom progression.

Few studies address the connection between diet and AD, while also addressing the mechanisms that contribute to disease pathogenesis and progression. However, based on the evaluation of recent studies concerning the Western diet, the high fat content, increased omega-6 fatty acids, and excess sugar consumed as part of the Western diet may all contribute to increased amyloid β accumulation in the brains of Alzheimer's patients, hence promoting Alzheimer's disease symptoms.

Ketogenic Diet

Ketogenic diets are high fat, low carbohydrate diets that move towards utilization of fat reserves and reducing utilization of carbohydrates to <10% of energy (Rusek et al., 2019). Ketogenic diets may affect some neuropathological changes in rodents may affect neuropathological findings and some biochemical changes due to exogenous β -OHB,

and MCT display reduced A β levels to 25% in the brain of rodents, protection from amyloid- β toxicity, and improved mitochondrial function (Auwera et al., 2005). The pathophysiological metabolic alterations observed in Alzheimer's include abnormal glucose metabolism uptake, diminished mitochondrial brain energy metabolism with increased inflammation including a reduction in tau and amyloid-beta dysfunction which is eventually associated with progression of dementia (Rusek et al., 2019). When Ketogenic diets are instituted, it can modulate the metabolic and signaling changes underlying the pathophysiology of neurodegenerative disorders (Rusek et al., 2019). Ketogenic diets have limited animal and human studies data but do show some good effects on cellular metabolism and improving mitochondrial function.

In Western diets, the concentration of total ketone like beta hydroxybutyrate supplies less than 5% of brain energy requirements but in contrast ketogenic diets induces a state of physiological ketosis and the utilization of beta hydroxybutyrate is toward a greater part of brain energy metabolism (Rusek et al., 2019).

Compared with glucose, ketones will help compensate for brain insulin resistance and deficient glucose metabolism, also upregulating mitochondria biogenesis and increasing neuron energy production (Rusek et al., 2019). However the long term effects of ketogenic diets increasing cardiovascular disease due to high fat consumption are limited. Also when studies that compared ketogenic with crossover to Mediterranean diets, like (Landry et al., 2021), adherence was an issue beyond when the diets were prepared and handed to participants as opposed to when they had to prepare food themselves and that is a significant issue and the authors do recognize the effects of ketogenic diets on long term outcomes and general health and well being.

The Vegan and Vegetarian diets

Because of the growing health concerns from consuming a Western diet long-term (Kanoski & Davidson, 2011; Kopp, 2019; Manzel et al., 2014), many individuals have sought diets that bypass meat and animal products such as the vegetarian and vegan diets, respectively. The vegetarian diet excludes meat, poultry or fish and is usually rich in carbohydrates, dietary fiber, folic acid, and a variety of daily vitamins and minerals (Key et al., 2006). Similar to the vegetarian diet, the vegan diet contains high levels of carbohydrates, daily vitamins and minerals, and dietary fiber, and only differs by the exclusion of all animal products including animal meat, eggs, and dairy milk (Craig, 2009). In a recent study, high consumption of vegetables was associated with a decreased risk of dementia and slower rates of cognitive decline as age progressed (Loef & Walach, 2012). In another study, those who consumed a diet containing animal products, including meat, were more than twice as likely to become demented than those who consumed a vegetarian diet (Giem et al., 1993). Further, in the same study, vegetarians demonstrated an association with delayed onset of dementia (Giem et al., 1993), suggesting that some component in meat plays a role in AD onset and progression.

Additionally, the consumption of red meat and animal fats have been linked to increased levels of oxidative stress and inflammation (Gardener et al., 2016; Kalmijn et al., 1997; Morrison et al., 2010). Elevated levels of cholesterol, oxidative stress, and inflammation have also been linked to the etiology of Alzheimer's disease, specifically the abnormal accumulation of amyloid β (Cheignon et al., 2018; Dyall, 2010; Haque, 2018). Since both the vegetarian and vegan diets lack animal fat derived from meats, these individuals have low plasma cholesterol concentration (Key et al., 2006) and reduced inflammation (Haghighatdoost et al., 2017). Therefore, the absence of animal products in the vegan and vegetarian diets, and subsequent lack of inflammation and low levels of cholesterol, may contribute to a delayed onset and slower progression of Alzheimer's disease pathogenesis and symptoms, respectively.

The Paleolithic diet

In contrast to the vegetarian and vegan diets, the paleolithic (paleo) diet hints at redesigning one's diet to mirror that of a hunter-gatherer, where processed foods, refined sugars, dairy, grains, and legumes are avoided (Tarantino et al., 2015; *Textbook of Natural Medicine*, n.d., Chapter 199). The paleo diet relies on grass-fed meat, fruit, and vegetables,

along with healthy saturated fats (Tarantino et al., 2015; *Textbook of Natural Medicine*, n.d., Chapter 199). Though the paleo diet has not been studied in direct relation to Alzheimer's disease, a recent study has shown that the paleo diet in type II diabetes mellitus patients improved glucose control and lipid profiles when compared with a conventional diet of moderate salt intake, low-fat dairy, whole grains, and legumes (Frassetto et al., 2015). Additionally, patients with higher insulin resistance at the start of the study showed the greatest improvement in insulin resistance after following the paleo diet for 14 days (Frassetto et al., 2015). Continually, insulin has been suggested to play a role in regulating two important factors involved in the pathogenesis of Alzheimer's disease: amyloid precursor protein (APP) and A β (Watson et al., 2003). These factors are important for the formation of senile plaques (Scheuner et al., 1996), which are pathological hallmarks of Alzheimer's disease. Several studies have implicated insulin resistance (IR) as a major risk factor for age-related cognitive decline, including AD (Mullins et al., 2017; Srikanth & Arvanitakis, 2018; Talbot et al., 2012). To prevent the aggregation of A β plaques, A β plaques need to be cleared, and insulin regulates this A β clearance (Plum et al., 2005). When insulin resistance is present, A β fibrils are formed and are not cleared, thus contributing to the increased A β burden seen in AD (Yamamoto et al., 2012).

Since the paleo diet has been implicated in lowering insulin resistance in individuals following the diet for at least 14 days (Frassetto et al., 2015), and increased insulin resistance plays a role in modulating APP and subsequently, increasing the formation of amyloid beta plaques in the brain (Yamamoto et al., 2012), the paleo diet may be a viable option to slow the progression of Alzheimer's disease. Though both animal and epidemiological studies have demonstrated the benefits of the paleo diet, more studies need to be performed to further understand the duration and long-term effects of the paleo diet on insulin resistance, A β formation and aggregation, and Alzheimer's disease symptoms and progression.

The Mediterranean diet

While the vegetarian, vegan, and paleo diets show potential benefits in mitigating the amyloid burden and cognitive decline associated with Alzheimer's disease, the Mediterranean diet has shown the most promise in alleviating the symptoms of Alzheimer's disease. The Mediterranean diet is mainly composed of fruits, vegetables, grains, olive oil and fish (Miranda et al., 2017), and it has been linked to preventing cardiovascular disease, stroke, cognitive decline and Alzheimer's disease (El-Hajj et al., 2021; Jimenez-Torres et al., 2021; Román, Jackson, Gadhia, et al., 2019). Numerous epidemiological studies have linked the Mediterranean diet to reducing the symptoms of dementia (Berti et al., 2018; Lourida et al., 2013; Opie et al., 2013; Petersson & Philippou, 2016; Plassman & Potter, 2018), including a reduction of A β plaques (Vassilaki et al., 2018). One study demonstrated that cognitively normal individuals who had a lower adherence to the Mediterranean diet showed increased cortical thinning in regions consistent with clinical AD patients when compared with those with higher adherence to the Mediterranean diet (Mosconi et al., 2014). Further, another study demonstrated that high sugar and carbohydrate consumption were linked to lower entorhinal cortical thickness, while adherence to the Mediterranean diet demonstrated greater frontal, parietal, and occipital cortical thickness (Staubo et al., 2017). Continually, another study demonstrated that adherence to a Mediterranean diet resulted in reduced cerebral AD pathology accumulation over time and slower cognitive decline (Rainey-Smith et al., 2018). When taken together, these studies suggest that consistent adherence to a Mediterranean diet may play a protective role in preventing tissue loss and AD pathology, thereby delaying or preventing the onset of Alzheimer's disease.

Studies have yet to determine why adherence to a Mediterranean diet results in improved cognition and a reduction in amyloid β . However, some studies suggest that olive oil, as part of the Mediterranean diet, may play a role in improving cognition and potentially preventing Alzheimer's disease (Román, Jackson, Reis, et al., 2019; Valls-Pedret et al., 2015). It has also been shown to increase cognitive performance and delay age-related cognitive decline (Valls-Pedret et al., 2015). Further, a recent study in mice demonstrated that high doses of olive oil can delay AD symptom onset and decrease A β accumulation, subsequently reducing the severity of symptoms (Grossi et al., 2014). Olive oil has been linked to antioxidant compounds, polyphenols, which may reverse disease, aging-related learning

and memory impairment (Rigacci, 2015). In addition to polyphenols, there is another component of olive oil that may protect against Alzheimer's disease: oleocanthal (Qosa et al., 2015). Oleocanthal is a phenolic secoiridoid component of olive oil and has been linked to preventing amyloid-beta and tau aggregation *in vitro* and enhancing the clearance of amyloid β from the brains of mice *in vivo* (Qosa et al., 2015). Further, this animal study investigated the effect of oleocanthal on the hallmark symptoms of Alzheimer's disease in a mouse model of AD and showed that the load of A β decreased in the hippocampal parenchyma and adjacent microvessels, both of which are essential for memory (Qosa et al., 2015). Additionally, more A β was cleared from the blood-brain barrier (Qosa et al., 2015), suggesting that the Mediterranean diet, through oleocanthal, may reduce Alzheimer's disease burden.

Based on recent evidence, it is evident that the Mediterranean diet plays a role in mitigating the effects of Alzheimer's disease on patients, potentially due to the oleocanthal and polyphenol components of olive oil. However, more studies are needed to validate the effects of these components on the pathophysiology underlying Alzheimer's disease.

Discussion

Our review explored the various effects of different diets on the progression of Alzheimer's disease and increased disease burden. While our review explored the Western, Ketogenic, Vegan, Vegetarian, and Paleo diets, we found that the Mediterranean diet was the most studied of these diets and may be the most beneficial in preventing the symptoms of Alzheimer's disease. One study, in particular, directly compared the Mediterranean diet to a high-carb, high-sugar diet similar to that of the Western diet (Staubo et al., 2017). However, this study failed to include other potential protective diets such as the paleo or vegan diets. Therefore, in order to determine the most effective diet in reducing amyloid β accumulation, reducing cognitive decline, and improving memory, population-based studies directly comparing these diets or a randomized control study where individuals already at risk of developing Alzheimer's disease are assigned various diet groups must be conducted.

Because the driving forces behind Alzheimer's disease are poorly understood, drug based interventions are difficult to study. Therefore, our review focused on how diet affects the brain, and we proposed potential links between diet, Alzheimer's disease, and pathophysiologic functions such as neuroinflammation, insulin resistance, and atrophy. The health benefits of each of these diets are well-established in the literature as are the pathophysiologic states in AD, allowing for us to link dietary components with pathophysiology associated with AD. However, the mechanism underlying diet and cognitive function is poorly understood. It is not known how diet may impair or improve a patient's ability to complete daily tasks that is seen in late-onset dementia.

Despite a thorough review of the literature and careful selection of diets, our study is limited in the types of diets reviewed. We chose to focus on the Mediterranean, Ketogenic, Western, Paleo, Vegan, and Vegetarian diets, though other diets such as a gluten-free, raw, low carb or no-sugar diet may also influence Alzheimer's disease onset and progression (Berger, 2017; Makhlof et al., 2018; Rusek et al., 2019). Additionally, few studies investigate the mechanisms underlying these diets. Though we propose several ways in which components of these diets may contribute to the prevention of Alzheimer's disease onset, progression, and disease burden, it is currently unknown how adherence to these diets truly exert their beneficial and protective effects. Despite the limitations and unknowns, our review demonstrates that there is a non-invasive, healthy and protective intervention for potentially mitigating the effects of Alzheimer's disease. In addition to the high sugar intake, perhaps of major significance is the issue of processed foods in chronic disease causation as noted by Leonard et al (Leonard & Robertson, 1994). These authors showed that pastoralists, foragers, agriculturalists all had normal body mass indices (BMI) but those consuming a Western type diet had significantly elevated BMI's (Leonard & Robertson, 1994).

Conclusion

There is evidence to suggest that the Mediterranean, Vegan, Vegetarian, Ketogenic and Paleo diets improve AD outcomes, decrease AD risk, delay cognitive decline onset, and reduce disease burden. However, the evidence remains limited, with only recently accomplished randomized controlled trials. However, randomized control trials do not provide direct mechanisms for how these diets promote their protective effects. Therefore, while existing studies suggest that these particular diets and their components positively influence Alzheimer's disease, more studies must be conducted in order to identify a key therapeutic target in which alterations in diet can effectively prevent and treat Alzheimer's disease and its associated symptoms.

Acknowledgments

I would like to thank my mentor Nicole Katchur for helping me with this project.

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