Impact of Mediterranean and Ketogenic Diets on Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is a neurodegenerative disease (NDD) characterized by cognitive decline and behavioral disorders. In recent years, the number of patients has been on the rise and the population is becoming increasingly younger, which has attracted widespread public attention. At present, research on the intervention of dietary patterns in AD patients is still in its early stages, but many animal and human experiments have shown that the Mediterranean diet (MD) and ketogenic diet (KD) can improve the pathological and physiological changes of AD patients, thereby slowing down the progression of related symptoms. However, the specific impact mechanism is still unclear. This article collects the relevant influencing factors and mechanisms of MD and KD on AD patients, and concludes that both different dietary patterns have significant positive effects on the treatment of AD patients. The purpose of this study is to reveal the pathogenesis of AD and deepen the public's understanding of AD. In addition, based on research results, scientific dietary guidelines can be developed for AD patients and susceptible populations to prevent and treat the occurrence and development of AD through dietary adjustments. Based on the fact that AD patients are mostly elderly, they have eating problems such as swallowing difficulties and anorexia. In addition to providing guidance on the dietary content of AD patients, teaching them how to adhere to a MD or a KD is also a crucial part of dietary therapy. Future research can also start from the implementation effect.

Keywords: Alzheimer’s disease; Mediterranean Diet; Ketogenic Diet.

1. Introduction

Alzheimer's disease (AD) is a degenerative disease of the central nervous system characterized by progressive cognitive impairment and behavioral damage. Patients may gradually lose their ability to live independently, posing a serious threat to their health and quality of life. In 2018, Alzheimer's International estimated that approximately 50 million people worldwide suffer from dementia, which is expected to double by 2050, with two-thirds living in low - and middle-income countries [1]. In recent years, clinical data has shown that AD is becoming increasingly younger and receiving widespread public attention. However, there is currently no recognized drug for the specific treatment of AD. With the continuous research on nutrition, more and more evidence supports the role of nutrition in AD. Thus people are beginning to link the treatment of such diseases with dietary patterns. Among them, the Mediterranean diet (MD) and ketogenic diet (KD) have been extensively studied. However, among studies examining these dietary patterns, there are discrepancies in the reported benefits.

The MD has been widely spread around the world since it was defined in 1960. Generally, the MD includes fruits, vegetables, bread and whole grains, as well as potatoes, beans, nuts and seeds. The MD also includes fresh vegetables, fruits and olive oil [2]. The ingredients mentioned above mainly provide carbohydrates, proteins and vitamins. Meanwhile, the MD does not include a lot of red meat, people who maintain the MD generally do not consume a large amount of animal protein and fat.

2. Pathological Mechanism of AD

AD is a neurodegenerative disease (NDD) characterized by cognitive decline and behavioral disorders, which mostly occurs in the elderly. The etiology of AD is very complex, and its pathological mechanism is still not fully understood. Current studies mainly believe that amyloid deposition, tau protein aggregation, apolipoprotein abnormality, vascular disease, heavy metal disorder, oxidative stress and genetic factors are the etiology of AD [3]. Among them, amyloid plaque aggregation and neurofibrillary tangles are the main pathological markers of AD [4]. Pathological accumulation of beta-amyloid protein is widely considered to be one of the main causes of AD [5].

3. KD & AD

3.1. Overview

KD is a nutritional method that increases the production of ketones (β - hydroxybutyrate, acetoacetate, and acetone) in the body through the intake of high fat and low carbohydrates, leading to ketosis. This effect is achieved by obtaining the maximum energy share from fat and minimizing the consumption of carbohydrates. The KD [6, 7]. As a dietary pattern, mimics the fasting state in the body but does not lead to the negative effects of hunger.

3.2. Mechanism of KD

More and more evidence suggests that it has the effect of improving cognitive function and delaying AD. The progressive impairment of cognitive function in AD patients is associated with reduced glucose uptake and metabolism. During AD, a decrease in the levels of two major glucose transporters, GLUT1 and GLUT3 [8], was observed in the brain. This is related to the excessive phosphorylation of tau protein and the density of neurofibrillary tangles in the brain, which are typical symptoms of AD. Toxic proteins accumulate in the brain, causing cognitive decline. A KD can provide ketones as a substitute metabolite for the brain, helping the body eliminate these toxic proteins.

In addition, insulin resistance is also a typical pathological feature of AD patients. Recent evidence suggests that insulin directly affects the neuropathological and behavioral characteristics of AD by influencing the memory related beta amyloid pathway and synaptic plasticity. The most commonly used method for measuring insulin resistance is to calculate the homeostatic model assessment insulin resistance (HOMA-IR) index [7]. Many studies have shown that due to the application of a KD, the index value significantly decreases, which directly confirms its impact on insulin resistance.

In recent years, studies have found that neuroinflammation has become the third major pathological feature of AD after A β deposition and NFTs. Neuroinflammation is an immune response activated by glial cells in the central nervous system, typically occurring under stimuli such as nerve damage, infection, and toxins, or under autoimmune effects. Multiple studies have shown that a KD can regulate the inflammatory response of AD patients through various molecular regulatory mechanisms. The KD diet affects anti-inflammatory effects by activating microglia, promoting apoptosis, and increasing the concentration of neuroprotective mediators, including neurotrophic factors such as neurotrophin-3 (NT-3), brain-derived neurotrophic factor (BDNF), and glial cell line derived neurotrophic factor (GDNF). And molecular chaperones (proteins that prevent peptide aggregation into potentially toxic molecules) [9, 10]. In addition, another mechanism of KD is the inhibition of histone deacetylases (HDACs), which play a role in altering chromatin structure and accessibility. β - OHB inhibits HDACs 1, 3, and 4 (class I and IIa) in vitro, leading to improved memory function and synaptic plasticity [11, 12]. In addition, ketones can inhibit the innate immune sensor nod like receptor 3 (NLRP3) inflammasome, which controls the activation of caspase-1 and inhibits the release of pro-inflammatory cytokines such as IL-1 β and IL-18 by limiting cell K+efflux [13-15].

AD patients also have mitochondrial dysfunction. Research has shown that a KD can induce the formation of new mitochondria by activating the mitotic regulatory pathway [16]. In addition, β - hydroxybutyrate provides components involved in respiratory chain reconstruction [12]; On the other hand, even in the case of damage to the first complex of the respiratory chain, it is possible to obtain energy from ketone bodies. After the improvement of mitochondrial function, it is also beneficial for the supply of energy to the brain.

The KD also has significant neuroprotective effects. For brain function, even in healthy individuals, an increase in beta hydroxybutyrate concentration is much more beneficial than glucose. This was confirmed in a study where injecting hydroxybutyrate into healthy individuals (until a concentration of 5.5 mmol/L was obtained) reduced brain glucose utilization by 14% and resulted in an increase of up to 30% in cerebral blood flow while maintaining oxygen consumption. The author directly suggests that ketones may have neuroprotective effects [17]. In addition, studies have shown that the application of KD can reduce demyelination caused by glucose deficiency, death of oligodendrocytes (producing myelin), and axonal degeneration through the regulation of β - hydroxybutyrate [18]. In recent years, the gut microbiota has become a popular research direction, and there is evidence to suggest that a KD significantly affects the remodeling of the gut microbiota. This is even more reasonable when considering the direct connection between the gut and the brain through the gut brain axis, where the microbiota can influence brain processes (i.e. neural transmission).

Although KDs have been proven to have therapeutic effects on AD patients in many studies, there is still a lack of large-scale clinical comparative trials. Currently, there are also studies that have found some adverse effects of KDs on AD patients, but they rarely occur and are usually caused by improper dietary adjustments. It should be remembered that the treatment methods for patients should be as individualized as possible.

4. MD & AD

4.1. Overview

KD is a nutritional method that increases the production of ketones (β - hydroxybutyrate, acetoacetate, and acetone) in the body through the intake of high fat and low carbohydrates, leading to ketosis. This effect is achieved by obtaining the maximum energy share from fat and minimizing the consumption of carbohydrates. As a dietary pattern, mimics the fasting state in the body but does not lead to the negative effects of hunger [19, 20].

4.2. Exact Factors: Omega-3 long-chain Fatty Acids (LCFAs)

The plant foods and fish included in the MD can provide rich polyphenols and Omega-3 LCFAs to improve vascular activity and brain blood supply, which has a positive impact on preventing and improving AD. Meanwhile, fish can also provide DHA, which is essential for brain function [21]. According to following research covering nearly 70,000 people, the participants do not express obvious brain blood supply and brain function decline crisis when they maintain the MD over 4.4 years [21].

Another research proved that the MD can provide rich polyphenols and unsaturated fatty acids including Omega-3 LCFAs to inhibit oxidative stress and neuroinflammation in the brain as well. Although it is unclear whether the diet has a direct effect on neurocognition or inflammatory immune guidance, the results clearly demonstrated the positive results. Elderly people who maintain the MD for at least 4 years have better cognitive improvement in a comparative test [22].

Dietary observation cases have expressed that Omega-3 has a positive effect on preventing or reducing the occurrence of AD. Further research has found that Omega-3 intake had inversely proportion with occurrence of the disease [23]. The result clearly indicated, AD has been linked to chemical and medical evidence of the omega-3s provided by the MD. Palimariciuc M, et al have discussed, the Omega-3 have neuroprotective properties by providing the brain with structural proteins and membrane lipids that support brain function. Additional, since the high membrane

fluidity is essential for maintaining synaptic integrity, the active support of omega-3 in this part mentioned above can ensure the integrity of synaptic and even neural function, then the Omega-3 effects in combating the abnormal brain function caused by AD [24]. More specific details indicated that eicosapentaenoic acid (EA) and docosahexaenoic acid (DA) closely related to Omega-3, and they are believed to not only affect healthy brain development and function, but they can also control the occurrence of neuro-inflammation, thus effectively ensuring healthy neurological function and mental health [25]. Hence, the Omega-3 provided by the MD have been widely observed to reduce the risk of AD by improving brain function and reducing neuroinflammation [26].

5. Discussion

More and more evidence shows that AD is a multifactorial disease. At present, the most widely used AD drugs include Acetylcholinesterase inhibitors, Donepezil, Galantamine Reminyl, Rivastigmine, and Memantine. However, these drugs have different degrees of toxic side effects, so people pay more and more attention to the study of dietary pattern on AD. Secondly, since the incidence of AD disease is positively correlated with the age of patients, and this part of the population generally cannot accept or adhere to the MD pattern and ketogenic-diet for a long time, how to make elderly AD patients adhere to these diet patterns is also worthy of attention [27,28]. Specific implementation plans are:

1) Provide attractive food: choose bright colors, strong smell of food, these characteristics can stimulate the patient's appetite. Appropriately increase the taste and texture of food, such as adding seasonings or using thick soups, to enhance the appeal of food.

2) Provide localization programs: Many elderly groups have low acceptance of dietary patterns different from their own regions, so diets with localized characteristics can be customized according to different regions and have the same nutritional components, so as to improve the acceptance of elderly patients.

3) Provide simple food choices: complex food types often become an obstacle to adhering to the dietary pattern, reduce the number and complexity of choices, and provide patients with some simple and understandable food options, such as providing two to three staple foods and several common non-staple foods, can greatly improve the probability of long-term adherence.

6. Conclusion

This paper uses the method of inductive review to summarize the current research progress on AD. It not only introduces the pathological mechanism of AD disease, but also focuses on the influence of MD pattern and KD pattern on the symptoms of AD patients, and introduces the principle of interference of two dietary patterns in AD disease. Studies have shown that the MD pattern and the KD pattern can play a positive role in the prevention and improvement of symptoms of AD.

KD can provide metabolic substitutes for the brain and help the body clean up toxic proteins in the brain, and the majority of studies believe that a significant reason for the decline in neurocognitive function of ad patients is the accumulation of toxic proteins in the brain of patients. Therefore, KD can improve the neurocognitive function of ad patients to some extent.

Although the pathogenesis of AD is not clear at present, it is certain that the MD pattern provides the high-quality protein and fat required by the brain to maintain the function of the brain, so the MD pattern can play a positive role in the prevention and intervention of AD, and because the incidence of AD increases with age, Healthy eating patterns can also provide essential vitamins and nutrients to older people.

Current research also has certain limitations, such as the KD, although it has been shown in many studies to be therapeutic in AD patients, but there is still a lack of clinical trials with large sample sizes.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

References

[1] Alzheimer's disease International. World Alzheimer Report 2018: The state of the art of dementia research: new frontiers. [Online] Available at: https://www.alzint.org/u/WorldAlzheimerReport2018.pdf [Accessed: 9th Sep 2020].

[2] Guasch-Ferré, M., & Willett, W.C. (2021). The Mediterranean diet and health: A comprehensive overview. Journal of Internal Medicine, 290, 549–566.

[3] Lu, Y.Y., Fang, Z.Z., Fan, Y.Y., Wang, B.W., Zheng, R.M., et al. (2023). Progress in the pathogenesis and drug treatment of Alzheimer's disease. Progress in Physiological Sciences, (02), 81–89.

[4] Adalbert, R., Nogradi, A., Babetto, E., Janeckova, L., Walker, S.A., Kerschensteiner, M., et al. (2009). Severely dystrophic axons at amyloid plaques remain continuous and connected to viable cell bodies. Brain, 132(Pt 2), 402–416.

[5] Chen, Z.Y., & Zhang, Y. (2022). Animal models of Alzheimer's disease: Applications, evaluation, and perspectives. Zoological Research, 43(6), 1026–1040.

[6] Liu, Y., Liu, F., Iqbal, K., Grundke-Iqbal, I., & Gong, C.X. (2008). Decreased glucose transporters correlate to abnormal hyperphosphorylation of tau in Alzheimer's disease. FEBS Letters, 582, 359–364.

[7] Dyńka, D., Kowalcze, K., & Paziewska, A. (2022). The role of ketogenic diet in the treatment of neurological diseases. Nutrients, 14(23), 5003.

[8] Liu, Y., Liu, F., Iqbal, K., Grundke-Iqbal, I., & Gong, C.X. (2008). Decreased glucose transporters correlate to abnormal hyperphosphorylation of tau in Alzheimer's disease. FEBS Letters, 582, 359–364.

[9] Maalouf, M., Rho, J.M., & Mattson, M.P. (2009). The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. Brain Research Reviews, 59, 293–315.

[10] Włodarek, D. (2019). Role of ketogenic diets in neurodegenerative diseases (Alzheimer's disease and Parkinson's disease). Nutrients, 11, 169.

[11] Bough, K.J., Wetherington, J., Hassel, B., Pare, J.F., Gawryluk, J.W., Greene, J.G., Shaw, R., Smith, Y., Geiger, J.D., & Dingledine, R.J. (2006). Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. Annals of Neurology, 60, 223–235.

[12] Peixoto, L., & Abel, T. (2013). The role of histone acetylation in memory formation and cognitive impairments. Neuropsychopharmacology, 38, 62–76.

[13] McDonald, T.J.W., & Cervenka, M.C. (2018). Ketogenic diets for adult neurological disorders. Neurotherapeutics, 15, 1018–1031.

[14] Pierre, K., & Pellerin, L. (2005). Monocarboxylate transporters in the central nervous system: Distribution, regulation and function. Journal of Neurochemistry, 94, 1–14.

[15] Youm, Y.H., Nguyen, K.Y., Grant, R.W., Goldberg, E.L., Bodogai, M., Kim, D., D'Agostino, D., Planavsky, N., Lupfer, C., Kanneganti, T.D., et al. (2015). The ketone metabolite beta-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. Nature Medicine, 21, 263–269.

[16] Hu, Z.G. (2009). Experimental study on the protective effect and mechanism of ketogenic diet on traumatic brain injury. (Doctoral dissertation). Nanjing University, Nanjing, China.

[17] Svart, M., Gormsen, L.C., Hansen, J., Zeidler, D., Gejl, M., Vang, K., Aanerud, J., Moeller, N. (2018). Regional cerebral effects of ketone body infusion with 3-hydroxybutyrate in humans: Reduced glucose uptake, unchanged oxygen consumption, and increased blood flow by positron emission tomography. PLOS ONE, 13(2), e0190556.

[18] Mu, J., Wang, T., Li, M., Guan, T., Guo, Y., Zhang, X., Zhang, G., & Kong, J. (2022). Ketogenic diet protects myelin and axons in diffuse axonal injury. Nutritional Neuroscience, 25, 1534–1547.

[19] Guasch-Ferré, M., & Willett, W.C. (2021). The Mediterranean diet and health: A comprehensive overview. Journal of Internal Medicine, 290, 549–566.

[20] Stefaniak, O., Dobrzyńska, M., Drzymała-Czyż, S., & Przysławski, J. (2022). Diet in the prevention of Alzheimer's disease: Current knowledge and future research requirements. Nutrients, 14(21), 4564.

[21] Román, G.C., et al. (2019). Mediterranean diet: The role of long-chain ω-3 fatty acids in fish; polyphenols in fruits, vegetables, cereals, coffee, tea, cacao, and wine; probiotics and vitamins in prevention of stroke, age-related cognitive decline, and Alzheimer's disease. Rev Neurol (Paris), 175(10), 724–741.

[22] McGrattan, A.M., McGuinness, B., McKinley, M.C., Kee, F., Passmore, P., Woodside, J.V., & McEvoy, C.T. (2019). Diet and inflammation in cognitive ageing and Alzheimer's disease. Current Nutrition Reports, 8(2), 53–65.

[23] Yassine, H.N., et al. (2023). Nutritional metabolism and cerebral bioenergetics in Alzheimer's disease and related dementias. Alzheimer's & Dementia, 19(3), 1041–1066.

[24] Palimariciuc, M., et al. (2023). The quest for neurodegenerative disease treatment—focusing on Alzheimer's disease personalized diets. Current Issues in Molecular Biology, 9, 45(2), 1519–1535.

[25] Naureen, Z., et al. (2022). Dietary supplements in neurological diseases and brain aging. Journal of Preventive Medicine and Hygiene, 63(2-3), E174–E188.

[26] Grant, W.B., & Blake, S.M. (2023). Diet's role in modifying risk of Alzheimer's disease: History and present understanding. Journal of Alzheimer's disease, 96(4), 1353–1382.

[27] Walsh, D.M., & Selkoe, D.J. (2004). Deciphering the molecular basis of memory failure in Alzheimer's disease. Neuron, 44, 181–193.

[28] Soodi, M., Saeidnia, S., Sharifzadeh, M., et al. (2016). Satureja Bachtiarica ameliorates beta-amyloid-induced memory impairment, oxidative stress, and cholinergic deficit in an animal model of Alzheimer's disease. Metabolic Brain Disease, 31, 395–404.