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Effect of ketogenic diet on alzheimer's disease to improve cognitive function: A literature review

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Abstract

Background: Alzheimer's is the most common cause of neurodegenerative dementia which is characterized by reduced cognitive function. Alzheimer's disease is a serious global problem because so far no effective treatment has been found to prevent it. Improving diet can be used as therapy to prevent cognitive decline. The ketogenic diet is one of the recommended therapies because it is neuroprotective.
Purpose: To review several studies related to the effect of giving a ketogenic diet in improving cognitive function in people with Alzheimer's.
Method: This study used the literature review method using the PRISMA protocol. Literature searches were conducted online, sourced from Scopus, Science Direct, PubMed, ProQuest, and SpringerLink databases by entering a number of relevant keywords. The key words are "ketogenic diet" AND "alzheimer's disease" AND "cognitive function" OR "improves cognition". The conditions for the inclusion of the reviewed articles are publications for the last five years (2018 - 2023), in English, open access, and include research articles or original articles. The feasibility of this study was assessed by applying the PICO framework, including the samples used were humans or experimental animals suffering from Alzheimer's, the sample received a ketogenic diet intervention.
Results: Showed an effect of the ketogenic diet on cognitive function in Alzheimer's patients. There were four articles reviewed where all articles examined the effect of giving a ketogenic diet on cognitive function in Alzheimer's sufferers. The ketogenic diet is a high-fat, low-carb diet that promotes the process of ketogenesis. The resulting ketone bodies, such as acetoacetate and β-hydroxybutyrate can meet the energy needs of brain cells and improve memory performance. The chronic effect of giving a ketogenic diet has been shown to increase cognitive test scores. However, acute administration of the ketogenic diet is still not known with certainty.
Conclusions: The chronic intervention of the ketogenic diet has a positive effect on improving the cognitive function of Alzheimer's sufferers. The ketogenic diet has been shown to be safe, feasible, and recommended as a treatment method for Alzheimer's patients.

Keywords: Alzheimer's Disease; Cognitive Function; Improved Cognition; Ketogenic Diet

INTRODUCTION

Alzheimer's disease is the most common cause of neurodegenerative dementia, characterized by progressive decline in cognitive function and memory (Das, Chakrabarti, Zulkipli, & Hamid, 2019). This disease has become a significant public health concern, as it has affected 50 million people worldwide (Rusek, Pluta, Ułamek-Kozioł, & Czuczwar, 2019). The cases of Alzheimer's dementia are projected to increase to 76 million cases by 2030, in line with the rise in average life expectancy (Xu, Jiang, Wu, Liu, Deng, Zhang, & Zhu, 2022).

Pathologically, Alzheimer's is characterized by progressive accumulation of extracellular beta-

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amyloid plaques and intracellular tau protein accumulation, or neurofibrillary tangles (Caselli, Beach, Knopman, & Graff-Radford, 2017). These accumulations result in synaptic and neuronal loss, leading to progressive decline in cognitive function and memory (Torosyan, Sethanandha, Grill, Dilley,Lee, Cummings, & Silverman,2018).

Generally, Alzheimer's patients experience mitochondrial dysfunction and disrupted brain glucose metabolism (Swerdlow, 2011). Mitochondrial dysfunction, as an organelle responsible for cellular respiration, alters the formation of amyloid precursor protein into pathogenic beta-amyloid fragments (McDonald, & Cervenka, 2018). Additionally, impaired glycolysis is related to cognitive decline due to reduced glucose transporter (GLUT-1) regulation in the brain (Koppel & Swerdlow, 2018). Alzheimer's patients exhibit lower brain insulin signaling and insulin receptor levels compared to healthy control groups (Kullmann, Heni, Hallschmid, Fritsche, Preissl, & Häring, 2016), leading to brain insulin resistance (Phillips, Deprez, Mortimer, Murtagh, McCoy, Mylchreest, & Schepel, 2021). Previous clinical studies have shown that insulin resistance in brain tissues could contribute to Alzheimer's disease (De la Monte, 2017).

Alzheimer's disease presents a serious global health issue, as there is no effective treatment to halt its progression (Holtzman, Morris, & Goate, 2011). Therefore, preclinical and clinical studies have suggested that changes in diet and lifestyle play a crucial role in Alzheimer's treatment (Barnard, Bush, Ceccarelli, Cooper, De Jager, Erickson, & Squitti, 2014). One dietary approach for preventing cognitive decline in Alzheimer's is the ketogenic diet (Rusek, Pluta, Ułamek-Kozioł, & Czuczwar, 2019).

The ketogenic diet is high in fat and low in carbohydrates, reducing carbohydrate intake to ≤10% of energy requirements (Taylor, Sullivan, Mahnken, Burns, & Swerdlow, 2018). The goal of the ketogenic diet is to induce a systemic shift from glucose metabolism to fatty acid metabolism, producing ketone bodies, mainly acetone and β-hydroxybutyrate (Ota, Matsuo, Ishida, Takano, Yokoi, Hori, & Kunugi, 2019). Alzheimer's patients experience insulin resistance in brain cells and reduced glucose utilization as brain energy source (Castellano, Nugent, Paquet, Tremblay, Bocti, Lacombe, & Cunnane, 2015). Ketone bodies act as the main energy source for neurons, replacing glucose (McDonald, & Cervenka, 2018). Ketone bodies generate more energy per unit of oxygen than glucose (Phillips, Deprez, Mortimer, Murtagh, McCoy, Mylchreest, & Schepel, 2021). Moreover, the ketogenic diet's effects can regulate mitochondrial biogenesis and induce gene expression in the citric acid cycle, enhancing energy production in neurons (Bough, Wetherington, Hassel, Pare, Gawryluk, Greene, & Dingledine, 2006). The purpose of this article is to review several studies on the effects of ketogenic diet therapy in improving cognitive function in both animal models and Alzheimer's patients, providing a literature review for further research.

RESEARCH METHOD

This study employs a literature review method using the PRISMA (Preferred Reporting Item for Systematic and Meta-analysis) protocol. Literature review involves identifying and analyzing valid research facts on a specific topic. The focus of this study is related to the effect of the ketogenic diet in improving cognitive function in Alzheimer's patients. Online literature search was conducted from sources including Scopus, Science Direct, PubMed, ProQuest, and SpringerLink, using relevant keywords such as "*ketogenic diet*" AND "*alzheimer's disease*" *OR* "*neurological disease*" OR "*dementia*" AND "*cognitive function*" OR "*cognition*" OR "*improves cognition*".

Inclusion criteria encompassed articles published within the last 5 years (2018-2023), written in English, open access, and categorized as research or original articles. Articles were screened based on title and abstract relevance, eliminating irrelevant articles. Duplicates were also removed. The study's eligibility was assessed using the PICO framework, including samples of Alzheimer's patients who received ketogenic diet intervention, and demonstrating the diet's effect on cognitive function. The research process utilizing the literature review method is depicted in the PRISMA diagram in Figure 1 below.

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RESEARCH RESULTS

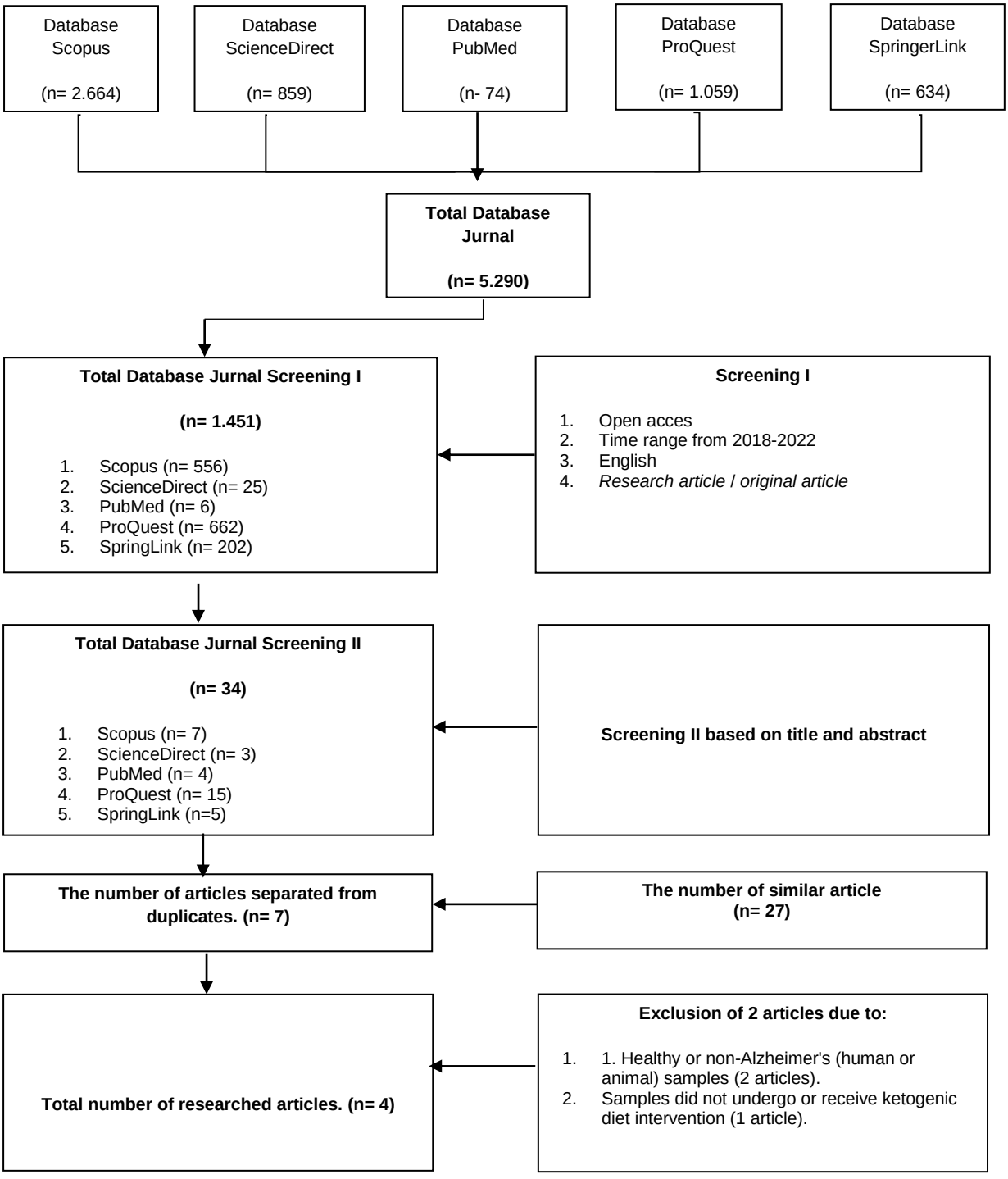

Figure 1. Prisma flow diagram

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Tabel 1. Result of Article Searching

Author/Title	Research Purpose	Intervention	Research Results	Conclusion
(Xu, Jiang, Wu, Liu, Deng, Zhang, Peng, & Zhu, 2022) Ketogenic diet ameliorates cognitive impairment and neuroinflammation in a mouse model of alzheimer's disease	To determine the impact of the ketogenic diet on cognitive function and pathology in 5XFAD mice, an experimental animal model validated to experience Alzheimer's disease.	The intervention was administered to 7-month-old male 5XFAD mice over a period of 4 months. Group 1 received a ketogenic diet formula containing 76% fat, 16% protein, 3% carbohydrates, and 5% dietary fiber of energy. Group 2 received a standard diet containing 12% fat, 23% protein, and 65% carbohydrates. Ketogenic diet was given to 7-month-old and 9-month-old male 5XFAD mice for a duration of 2 months.	After 4 months of ketogenic diet administration, there was an improvement in cognitive function evident from the increased number of neurons and synapses, along with reduced neural inflammation, amyloid plaques, and microglial activation. Conversely, the group receiving the standard diet did not experience enhanced cognitive function and instead exhibited decline. A shorter duration of ketogenic diet intervention (2 months) demonstrated a weaker effect compared to the 4-month intervention. Initiating the ketogenic diet at the age of 9 months did not show significant improvement in cognitive function.	The administration of the ketogenic diet yields a positive effect on the improvement of cognitive function and Alzheimer's disease histopathology.
(Phillips, Deprez, Mortimer, Murtagh, McCoy, Mylchreest, & Schepel, 2021) Randomized crossover trial of a modified ketogenic diet in alzheimer's disease	A randomized crossover trial aimed to investigate the impact of modified ketogenic diet on enhancing cognitive function, daily functioning, and quality of life in Alzheimer's patients at Waikato and Hamilton Hospitals in New Zealand.	There were 2 trial periods conducted with 26 Alzheimer's patients. In the first period, the sample received a modified ketogenic diet intervention (58% fat, 29% protein, 6% carbohydrates, and 7% fiber) for 12 weeks. In the 10-week washout period, patients continued with a control diet (11% fat, 19% protein, 62% carbohydrates, and 8% fiber) for 12 weeks. During each trial period, assessments of ACE-III, ADCS-ADL, and QOL-AD were conducted in the 6th and 12th weeks.	Out of 26 patients, only 21 patients completed the ketogenic diet (81%) Over the course of 12 weeks of ketogenic diet intervention, patients reached a state of ketosis, as indicated by the average level of β-hydroxybutyrate reaching 0.95 ± 0.34 mmol/L. During the two 12-week trial periods, compared to the control diet, patients on the ketogenic diet showed an increase in the average ADCS-ADL score (+3.13 ± 5.01 points, P = 0.0067), QOL-AD score (+3.37 ± 6.86 points, P = 0.023), and ACE-III score also increased but not significantly (+2.12 ± 8.70 points, P = 0.24).	The modified ketogenic diet can be applied to Alzheimer's patients for 12 weeks due to its high level of retention, compliance, and safety. Additionally, the ketogenic diet has been shown to improve daily functioning and quality of life.

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(Ota, Matsuo, Ishida, Takano, Yokoi, Hori, & Kunugi, 2019) Effects of a medium-chain triglyceride-based ketogenic formula on cognitive function in patients with mild-to-moderate alzheimer's disease	Testing the effects of medium chain triglyceride (MCT)-based ketogenic formula on cognitive function in Alzheimer's patients.	Administration of a 50-gram ketogenic formula containing 20 grams of MCT was given to 20 patients with mild Alzheimer's disease, followed by a neurocognitive test after 120 minutes.. Administration of a 50-gram ketogenic formula containing 20 grams of MCT to 20 patients with mild Alzheimer's disease for 12 weeks, with monthly neurocognitive testing	**Experiment** 1: There was a significant increase in plasma levels of acetoacetate and β-hydroxybutyrate compared to the placebo group. However, no significant differences were found in cognitive test scores between the ketogenic formula and placebo formula administration. **Experiment 2:** 16 out of 20 patients completed the trial for 12 weeks. Over the 12-week period, there was a significant improvement in the digit-symbol coding and immediate logical memory tests compared to baseline scores before the intervention. Moreover, by week 8, an increase in test scores was already observed.	The acute effects of consuming ketogenic formula on cognitive function in Alzheimer's patients have not been conclusively proven. However, chronic consumption of ketogenic formula for 2-3 months is recommended as it has shown positive effects on working memory, short-term memory, and processing speed in Alzheimer's patients.
(Taylor, Sullivan, Mahnken, Burns, & Swerdlow, 2018) Feasibility and efficacy data from a ketogenic diet intervention in alzheimer's disease	Explaining and evaluating the feasibility of the very high fat-ketogenic diet (VHF-KD) intervention in enhancing cognitive function in Alzheimer's disease patients.	Fifteen Alzheimer's disease patients (seven CDR 0.5, four CDR 1, and four CDR 2) were provided with VHF-KD intervention supplemented with MCT (70% fat, 20% protein, and 10% carbohydrates) for three months. Subsequently, the intervention was stopped, and they resumed their regular diet for one month (one-month washout period).	Out of the 15 Alzheimer's patients, 5 individuals discontinued the intervention and stopped in the first month (dropout rate of 33%). One CDR 0.5 patient and all CDR 2 patients exited the intervention. The administration of VHF-KD proved feasible for patients with CDR 0.5 and CDR 1 due to the appropriate macronutrient ratio targets, increased urine and serum ketone levels, and completion of the intervention. Administering VHF-KD showed improvements in cognitive assessment. Conversely, during the intervention cessation phase, no objective improvements were observed.	The ketogenic diet intervention with MCT supplementation demonstrates feasibility and efficacy as a therapy for Alzheimer's disease patients. There is a significant improvement in cognitive scores among patients who adhere to this diet.

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DISCUSSION

The first phase of the literature review began with a keyword search in the Scopus, Science Direct, PubMed, ProQuest, and SpringerLink databases, resulting in 5,290 articles. Then, in the first screening phase, these articles were selected according to inclusion criteria, yielding 1,451 articles. This was followed by the second screening phase, where articles from the first screening were re-evaluated based on title and abstract suitability, resulting in thirty-four articles.

To assess literature validity, articles meeting exclusion criteria, such as those from the same research, were excluded, resulting in seven articles. Additionally, articles using samples (human or animal) that were healthy and did not undergo a ketogenic diet intervention were excluded, resulting in four articles. These four articles were then subjected to journal analysis. The results of the journal search are presented in table 1 below.

All articles examined the effects of ketogenic diet intervention on Alzheimer's patients. One of the effects tested was related to cognitive function improvement. Out of the four reviewed journals, only one article used an animal sample. Three articles demonstrated positive effects of ketogenic diet intervention on cognitive function. Other research showed cognitive improvement following ketogenic diet intervention, though not significant. It was explained that 2-3 months of intervention yielded positive effects on Alzheimer's patients' cognitive improvement, but the acute effects of ketogenic diet on Alzheimer's patients' cognitive function remained uncertain (Phillips, Deprez, Mortimer, Murtagh, McCoy, Mylchreest, & Schepel, 2021; Ota, Matsuo, Ishida, Takano, Yokoi, Hori, & Kunugi, 2019).

Alzheimer's disease is the most common cause of neurodegenerative diseases, accounting for 80% of all dementia cases (Khoury, & Ghossoub, 2019). Alzheimer's disease leads to brain cell damage and decreased memory, thinking, and learning capabilities. Symptoms typically begin mildly and worsen over time, resulting in difficulties in physical activities and consciousness loss (Mirzaei, & Adeli, 2022). Early Alzheimer's symptoms usually involve short-term memory loss affecting daily activities (Lange, Lange, Makulska-Gertruda, Nakamura, Reissmann, Kanaya, & Hauser, 2017). Cognitive deficits result from neuron loss, neurofibrillary tangles degeneration, and progressive synaptic dysfunction (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011). National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA) state that Alzheimer's can be detected before clinical dementia symptoms manifest, through neuropsychological tests detecting signs of pathology accumulation such as β-amyloid deposits and neurofibrillary tangles (NFTs) or tau protein (Rajan, Wilson, Weuve, Barnes, & Evans, 2015).

The exact cause of Alzheimer's remains uncertain. Effective treatments to prevent Alzheimer's have not been found yet (Mirzaei, & Adeli, 2022). Therefore, addressing modifiable risk factors is considered the most successful way to prevent Alzheimer's (McGrattan, McGuinness, McKinley, Kee, Passmore, Woodside, & McEvoy, 2019). Alzheimer's risk factors include aging, genetics, and environment (Mirzaei, & Adeli, 2022). In this context, environmental factors like diet intervention are potential preventive measures (Barnard, Bush, Ceccarelli, Cooper, De Jager, Erickson, & Squitti, 2014). Proper diet intervention is shown to have the potential to prevent cognitive decline during aging (Smith, Blumenthal, Babyak, Craighead, Welsh-Bohmer, Browndyke, & Sherwood, 2010).

One recommended neuroprotective dietary therapy is the ketogenic diet (Omar, 2019). This literature review focuses on the impact of the ketogenic diet on cognitive improvement in Alzheimer's patients. Research conducted at the Jackson Laboratory on the effect of ketogenic diet intervention on cognitive dysfunction and nerve cell inflammation in male 5XFAD mice validated to have Alzheimer's disease showed that the ketogenic diet had a positive effect on cognitive function enhancement and Alzheimer's histopathology (Xu, Jiang, Wu, Liu, Deng, Zhang, & Zhu, 2022). The ketogenic diet provided to the test animals matched the caloric content of the standard diet consumed by wild mice daily. The ketogenic diet's nutritional content included 76% fat, 16% protein, 3% carbohydrates, and 5% dietary fiber in kcal. The experiment's first phase involved seven-month-old 5XFDA mice undergoing different treatments over

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four months. The first group received ketogenic diet intervention, while the control group was given a standard diet containing 12% fat, 23% protein, and 65% carbohydrates in kcal. The research results showed that the four-month ketogenic diet intervention improved cognitive function, as seen in improved synapse and nerve cell numbers, reduced nerve inflammation, decreased microgliosis, and diminished Aβ-amyloid deposition (Xu, Jiang, Wu, Liu, Deng, Zhang, & Zhu, 2022). In contrast, the control group showed no significant cognitive improvement. The ketogenic diet is high in fat and low in carbohydrates, promoting ketogenesis (Cunnane, Nugent, Roy, Courchesne-Loyer, Croteau, Tremblay, & Rapoport, 2011). This shift causes brain cells to rely on ketone bodies (Xu, Jiang, Wu, Liu, Deng, Zhang, & Zhu, 2022). Ketone bodies can supply most of the basal energy needs of nerve cells and up to about half of oxidative requirements, depending on neuron activity (Chowdhury, Jiang, Rothman, & Behar, 2014). Several studies suggest that after a 6-week intervention period, the low-carbohydrate diet group showed improved verbal memory performance compared to the high-carbohydrate diet group. This is attributed to the positive correlation between ketone bodies and memory performance (Krikorian, Shidler, Dangelo, Couch, Benoit, & Clegg, 2012).

Several experiments were conducted to examine the timing and duration effects of the ketogenic diet on cognitive function. A two-month ketogenic diet was administered to seven-month-old and nine-month-old male 5XFAD mice. The research reported that the shorter intervention period (2 months) led to enhanced working memory, but only slight spatial learning and memory improvement compared to the earlier four-month ketogenic diet intervention. Similarly, the two-month intervention starting at age nine months showed no beneficial effects (Xu, Jiang, Wu, Liu, Deng, Zhang, & Zhu, 2022). This indicates that an appropriate ketogenic diet intervention protocol is crucial for improving cognitive function in Alzheimer's patients.

Three articles used Alzheimer's patients as research subjects. Research conducted suggests that the ketogenic diet may be a suitable and effective treatment method for Alzheimer's patients. This is supported by the finding that a 12-week ketogenic diet intervention had high retention, safety, and compliance rates. Out of 26 patients, 21 (81%) completed the ketogenic diet, with almost half opting to continue it after the trial (Phillips, Deprez, Mortimer, Murtagh, McCoy, Mylchreest, & Schepel, 2021). This proportion is higher than in previous studies, possibly due to customizing the ketogenic diet to patient preferences, offering affordable and palatable menus (Taylor, Sullivan, Mahnken, Burns, & Swerdlow, 2018). Regarding cognitive tests, patients on the ketogenic diet showed an ACE-III cognitive score increase of 2.12 ± 8.70 compared to the control diet group. This increase was not significant and could be attributed to the COVID-19 lockdown policy at the time (Phillips, Deprez, Mortimer, Murtagh, McCoy, Mylchreest, & Schepel, 2021). Lockdown might have caused stress for those struggling to adapt to the ketogenic diet's lifestyle changes.

Medium Chain Triglycerides (MCTs) found in coconut and palm oil are fats metabolized into ketone bodies. In fasting or ketogenic diet conditions, the liver produces ketone bodies as brain energy sources (Hasselbalch, Knudsen, Jakobsen, Hageman, Holm, & Paulson, 1994). Ketone bodies have neuroprotective effects on the brain, enhancing cognitive function (Paoli, Bianco, Damiani, & Bosco, 2014).

Research indicated that acute ketogenic formula administration increased plasma acetoacetate and β-hydroxybutyrate levels compared to the control formula, though not significantly. Further research explored the chronic effects of ketogenic formula intervention. Significant improvements were found in digit-symbol coding and immediate logical memory compared to pre-intervention scores. Even by week 8, improvements in these test scores were evident (Ota, Matsuo, Ishida, Takano, Yokoi, Hori, & Kunugi, 2019).

Similar results were obtained from a study involving 15 Alzheimer's patients. Administering very high fat-ketogenic diet (VHF-KD) with MCT supplementation for three months indicated increased cognitive scores among compliant patients. The study also linked cognitive improvement with elevated ketone bodies, particularly β-hydroxybutyrate (Taylor, Sullivan, Mahnken, Burns, & Swerdlow, 2018).

Five patients withdrew from the study as they were unable to complete the VHF-KD. No serious

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side effects occurred following diet implementation. Minor complaints were limited to diarrhea. Despite this, laboratory tests and electronic electrocardiograms confirmed the safety of VHF-KD application, showing that Alzheimer's patients adhering to and tolerating the diet for a minimum of three months experienced no significant issues.

CONCLUSION

Based on the reviewed journals, it can be concluded that ketogenic diet intervention for 3-4 months can effectively improve cognitive function in Alzheimer's patients. However, the acute effects of ketogenic diet on cognitive improvement are still uncertain. Two out of four articles demonstrate that ketogenic diet intervention with MCT supplementation can enhance Alzheimer's patients' cognitive scores. Furthermore, three out of four articles suggest that the ketogenic diet is safe, suitable, and recommended as a treatment method for Alzheimer's patients. Nonetheless, improper ketogenic diet implementation might result in minor side effects. Therefore, Alzheimer's patients need to follow proper intervention protocols and recommendations.

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