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The Therapeutic Effects of the Ketogenic Diet on Alzheimer's Patients: Review

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التأثير العلاجي لحمية الكيتوجينيك على مرضى الزهايمر : مراجعة

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Abstract:

Alzheimer's disease (AD) remains a leading cause of cognitive decline with limited therapeutic options. Recent research has explored the potential of the ketogenic diet (KD) as a neuroprotective intervention for AD. This review synthesizes current evidence demonstrating the beneficial effects of KD on cognitive function, metabolic regulation, and neuroinflammation in individuals with Alzheimer's disease. Studies indicate that ketone bodies, produced through a high-fat, low-carbohydrate diet, serve as an alternative energy source for neurons, potentially improving mitochondrial function and synaptic plasticity. Moreover, KD has been associated with reductions in amyloid-beta accumulation and neuroinflammatory markers. In conclusion, these findings suggest that the ketogenic diet offers a promising adjunct therapy for managing AD symptoms and slowing disease progression. Further rigorous clinical trials are warranted to establish standardized protocols and long-term safety of KD in this population.

Keywords: Alzheimer, Ketogenic Diet, Elderly Diseases, Elderly Nutrtion.

الملخص:

يعد مرض الزهايمر (AD) سببًا رئيسيًا للتدهور المعرفي، مع خيارات علاجية محدودة. وقد استكشفت أبحاث حديثة إمكانات استخدام النظام الغذائي الكيتوني (KD) كتدخل وقائي عصبي لمرض الزهايمر. تُلخص هذه المراجعة الأدلة الحالية التي تُثبت الآثار الإيجابية للنظام الغذائي الكيتوني على الوظيفة الإدراكية، وتنظيم الأيض، والالتهاب العصبي لدى الأفراد المصابين بمرض الزهايمر. تشير الدراسات إلى أن أجسام الكيتون، المُنتجة من خلال نظام غذائي غني بالدهون ومنخفض الكربوهيدرات، تُمثل مصدرًا بديلًا للطاقة للخلايا العصبية، مما قد يُحسّن وظيفة الميتوكوندريا ومرونة التشابك العصبي. علاوة على ذلك، ارتبط النظام الغذائي الكيتوني بانخفاض تراكم بروتين بيتا أميلويد وعلامات الالتهاب العصبي. تشير هذه النتائج مجتمعةً إلى أن النظام الغذائي الكيتوني يُقدم علاجًا إضافيًا واعدًا لإدارة أعراض مرض الزهايمر وإبطاء تطوره.

هناك حاجة إلى مزيد من التجارب السريرية الدقيقة لوضع بروتوكولات موحدة وضمان سلامة النظام الغذائي الكيتوني على المدى الطويل في هذه الفئة من المرضى.

الكلمات المفتاحية: مرض الزهايمر، الحمية الكيتونية، امراض كبار السن، تغذية كبار السن.

Introduction:

Alzheimer's disease (AD) is a progressive disorder that leads to neurodegeneration and primarily affects the elderly (65 years or older), leading to memory loss, cognitive decline, and dependence on others for daily tasks. It is linked to the buildup of toxic proteins in the brain, such as amyloid-beta (Aβ) plaques and tau tangles. In addition, AD is associated with disrupted glucose metabolism in the brain, referred to as "Type 3 diabetes" due to the brain's inability to utilize glucose effectively (Khalefaet al., 2024; Włodarek, 2019; McDonald et al., 2018). One promising approach is the ketogenic diet (KD), a high-fat, low-carb eating plan that triggers ketosis. This diet has emerged as a potential therapeutic approach. Ketone bodies (KB), especially β-hydroxybutyrate (βHB), offer neuroprotective benefits by serving as alternative energy sources, reducing oxidative stress and inflammation, and enhancing energy production in AD patients (Idzikowska et al., 2025; Canevelli et al., 2016; Nan et al., 2013). A book by Malik (2025) explores the mechanism of KD on AD and summarizes recent clinical evidence supporting the ketogenic diet's influence on AD patients (Shahpasand et al., 2024).

Pathophysiology and Metabolic Disruption in AD

AD progresses as toxic Aβ plaques and tangled tau proteins that lead to neuronal damage, especially in critical areas, including the hippocampus, which leads to irreversible dementia, memory impairment, and cognitive decline (Włodarek, 2019; Rusek et al., 2019; Lilamand et al., 2020). A key factor of this damage is insulin resistance in the brain, which disrupts energy supply and increases protein buildup. For instance, Reduced levels of insulin-degrading enzyme (IDE), which normally degrades both insulin and Aβ, allow accumulation of harmful proteins (Fawver et al., 2014; Schelke et al., 2018; Ho et al., 2004). Impaired glucose metabolism also leads to energy deprivation in neural cells**,** accelerating decline. Studies have indicated that diets high in sugar or refined carbs may impair cognitive function, while metabolic flexibility and reliance on other alternative fuels like ketones are neuroprotective (McDonald et al., 2018).

The Ketogenic Diet: Mechanisms and Clinical Evidence

Recent findings highlighted the significant role of dietary patterns in modulating AD risk. Neuroprotective nutrients, including antioxidants (e.g., vitamins A, C, E), B vitamins, polyunsaturated fatty acids (PUFAs), and polyphenols, are associated with reduced AD incidence, as are dietary components such as fish, fruits, vegetables, and coffee (Nan et al., 2013). On the other hand, dietary plans high in saturated fats, excessive caloric intake, and heavy alcohol consumption are recognized risk factors. Population studies highlight the protective effects of traditional healthy diets, including the Mediterranean and Japanese diets, which emphasize plant-based foods, healthy fats, and lean proteins. However, some randomized controlled trials (RCTs) conflict with observational data, reflecting the complex relationship between diet and disease. For instance, multiple epidemiological studies reflect the strong correlations, RCTs often struggle to isolate dietary effects due to other factors like lifestyle and genetics. A 2024 study addressing this complexity indicated that a hybrid Mediterranean-Ketogenic diet (MMKD) improved cognitive outcomes in AD patients and reduced caregiver burden, suggesting a practical approach to incorporate dietary interventions (Zhao et al., 2022; Henderson, 2008). This research emphasizes the potential of combining different dietary approaches to enhance effectiveness.

AD and its Association with Abnormal Glucose Metabolism:

AD is often referred to as "Type 3 diabetes" due to the significant similarities in its underlying mechanisms. The link between abnormal glucose metabolism and the onset of AD is particularly notable, as insulin resistance, a key feature of type 2 diabetes, can play a role in the development of AD. This resistance disrupts insulin signaling in the brain, which leads to the abnormal accumulation of Aβ and tau proteins (Nan et al., 2013; Rusek et al., 2019; McDonald et al., 2018; Henderson, 2008). A study conducted in 2022 revealed that elevated carbohydrate intake was associated with reduced cognitive performance (Fawver, 2014; Dýnka,2022). Additionally, the buildup of islet IAPP in the pancreas, which is co-released with insulin, and the Aβ in the brain associated with AD appear to share a common pathological mechanism, particularly due to reduced production of IDE (Nagpal et al., 2019). Furthermore, IAPP misfolds and forms amyloid fibrils that accumulate in the pancreas, a characteristic of type 2 diabetes. Furthermore, it could enter the brain and interact with Aβ, the primary component of amyloid plaques in AD, potentially enhancing the accumulation of Aβ and contributing to the disease progression (McDonald and Cervenka, 2018; Krikorian and Newport, 2023).

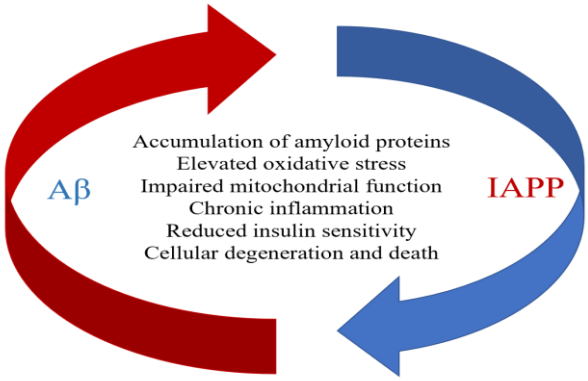

Figure 1: Mechanisms linking abnormal glucose metabolism and Alzheimer's disease. Elevated carbohydrate intake exacerbates amyloid-beta Aβ) and tau pathology via insulin resistance and reduced IDE activity (Stanciu et al., 2020).

Characteristics of KD

The KD is a low-carbohydrate, high-fat diet with a reduced carbohydrate intake of less than 10% of total energy, promoting fatty acid (FA) metabolism and generating KBs (Włodarek, 2019; McDonald and Cervenka, 2018). The macronutrient ratio of 4:1 (4 g of fat to every 1 g of protein and carbohydrates), shifting the main caloric source from carbohydrates to fat (McDonald et al., 2018). Liver primarily yields KBs from FA during neonatal development and starvation (Henderson, 2008; Hersant, 2022)

Table 1: Macronutrient composition %) of ketogenic diet variants (Włodarek, 2019).

Macronutrients	Classical Ketogenic Diet	Modified Atkins Diet	Medium Chain Triglyceride - Diet
Fat	90	70	70
Protein	7	25	10
Carbohydrates	8	5	20

A 2024 RCT revealed that personalized adjustments to the fat-to-carbohydrate ratio, based on metabolic biomarkers such as insulin levels, double the cognitive improvements compared to standardized dietary protocols. This finding emphasizes the efficacy of personalized ketogenic interventions compared to generalized diets (Soto-Mota and Volek, 2024)

Metabolic Changes Associated with the Ketogenic Diet

The KD triggers a metabolic transition that induces a fasting state. Specifically, this state is characterized by low blood glucose levels, a reduced insulin-to-glucagon ratio, and the release of glucose from the liver's glycogen reserves. Within 2–3 days of carbohydrate restriction, glycogenesis synthesis decreases. Consequently, the liver initiates the production of KBs, including acetoacetate and 3-hydroxybutyrate, through the process of ketogenesis. Since the brain cannot effectively utilize fatty acids for energy, it subsequently shifts to using KBs. These ketones cross the blood-brain barrier and are metabolized in the brain's mitochondria to produce ATP. Importantly, this transition to using KBs for energy offers various advantages, such as improved energy efficiency, decreased oxidative stress, and enhanced stabilization of neuronal activity. Collectively, these benefits underscore the KD's potential for treating neurological disorders (Włodarek, 2019; Henderson, 2008).

A 2023 clinical trial demonstrated that combining a KD with time-restricted eating (e.g., an 8-hour feeding window) stabilized circadian rhythms and improved memory scores in Alzheimer's patients. This suggests that meal timing may provide a complementary effect alongside ketosis to enhance cognitive outcomes (Kashiwaya and Bergman, 2024).

Ketogenic Diet and Alzheimer's Disease:

The KD, through both short- and long-chain fatty acid metabolism, plays a fundamental role in mechanisms of AD by shifting the brain's energy source from glucose to KBs, such as βHB. This is critical in AD, where glucose metabolism is impaired (Lange 2017; Nagpal 2019). βHB not only provides energy to neurons but also reduces oxidative stress, suppresses inflammatory pathways (e.g., NLRP3 inflammasome in microglia) (López-Domínguez and Villalba, 2023) and repairs mitochondria, directly protecting brain cells (Newman and Verdin, 2023; Yin and Fan, 2024). A 2023 study revealed that KD increases gut-derived serotonin levels, lowering neuroinflammation (Puchalska and Crawford, 2024) In addition, another study revealed that βHB can silence genes that produce amyloid, like BACE1, combining energy support with epigenetic regulation (Puchalska and Crawford, 2024) Clinically, a 6-

month trial of the KD reported improvements in synaptic plasticity among early AD patients (Lee and Kim, 2023). and ketone esters provided similar cognitive benefits without the need for strict dieting (Kashiwaya and Bergman, 2024). In addition, a meta-analysis conducted in 2024, which reviewed 10 trials, confirmed the cognitive improvements associated with the KD, although it did note a slight increase in LDL cholesterol levels (Bishop and Krikorian, 2024)

The diet also has a significant impact on the gut microbiome. Mice fed a KD exhibited an increase in butyrate-producing bacteria, which was associated with a reduction in amyloid plaques and inflammation (Zhang and Chen, 2023; Wang and Hu, 2024). When gut microbes from these KD-fed mice were transplanted into models of AD, they showed a remarkable 40% reduction in plaques (Wang and Hu, 2024). Indoles, molecules produced in the gut as a result of the KD, were effective in blocking amyloid clumping (Olson et al., 2024). Hybrid diets such as MMKD enhance beneficial gut bacteria and lower AD biomarkers in humans (Neth et al., 2024)

The KD is helping restore balance in brain signaling, and enhances GABA levels, which reduces overactive neural networks (Lange, 2017) and activates cellular “degradation” processes (autophagy) to eliminate toxic tau and amyloid (Wang and Hu, 2024). In studies with mice, KD was associated with decreased amyloid levels, despite the previous concerns about a high-fat diet. Additionally, KD repairs the myelin sheaths surrounding neurons (Zhao, 2022). A 2023 study highlighted that ketones play a crucial role in restoring lysosomes, which are essential for clearing amyloid (Chen and Zhao, 2023).
Despite challenges like short-term “keto flu,” "Short-term symptoms (e.g., fatigue, headache) during ketosis adaptation," and the need for long-term lipid monitoring (Hersant and Grossberg, 2022). Some effective strategies like MCT oil (Zhang and Chen, 2023), diet apps (Fernández-Quintela and Milton-Laskibar, 2024). and personalized macronutrient plans (Bishop and Krikorian, 2024) can improve adherence. Interestingly, when KD is combined with omega-3s, it reduces amyloid plaques by an additional 30% compared to KD alone, highlighting the benefits of a multi-targeted approach (Patel and Klein, 2024).

In conclusion, KD addresses AD through various metabolic, anti-inflammatory, and gut-brain axis mechanisms. While larger trials are needed, current evidence, from enhanced cognition in humans (Newman and Verdin, 2023), to reduced pathology in mice (Zhao et al., 2022; Martin-McGill, 2023). Positions KD, especially when paired with timed eating (Kashiwaya and Bergman, 2024) or Mediterranean hybrids as a promising, holistic therapy (Newman and Verdin, 2023; Rong et al., 2024).

Safety and Tolerability of Ketogenic Diets in Alzheimer's Disease: A Clinical Perspective

While clinicians may express concerns regarding ketoacidosis risks associated with KDs, it is crucial to distinguish it from the physiological ketosis that results from dietary changes. Notably, a 2022 systematic review emphasized that transient gastrointestinal disturbances, called "keto flu," constitute the most frequent short-term adverse effects. In contrast, long-term adherence may elevate risks of hyperlipidemia and micronutrient deficiencies (Hersant and Grossberg, 2022). However, assessing the KD’s secondary effects in AD remains difficult due to the limited number of clinical trials. Nevertheless, significant adverse reactions have not been reported. Specifically, some mild gastrointestinal effects, such as diarrhea, dyspepsia, and flatulence, have been noted with certain ketogenic formulations. Moreover, a 24-week study involving obese patients indicated no major adverse effects (Soto-Mota and Volek, 2024).

Furthermore, a 2024 trial reduced concerns regarding cardiovascular risks in comorbid populations, indicating that hypertensive Alzheimer’s patients on KDs experienced no exacerbation of blood pressure (López-Domínguez and Villalba, 2023). Despite this, elevations in LDL and total cholesterol persisted, supporting its safety in high-risk cohorts while simultaneously highlighting the need for lipid surveillance. Additionally, a 2024 two-year follow-up study further confirmed the long-term safety of ketogenic diets in Alzheimer’s patients. It noted that while mild issues like constipation were common, cholesterol levels stabilized over time, thus alleviating concerns about sustained cardiovascular risks (Broom et al, 2024). The strict low-carbohydrate intake required for ketogenic diets may also pose challenges for AD patients, who often have altered food preferences leaning towards carbohydrate-rich and sweet foods. Nonetheless, using medium-chain triglycerides to promote ketosis could be a beneficial strategy that doesn't necessitate changes in diet (Lilamand, 2020; Rusek, 2019; Van der Auwera, 2005; Stanciu, 2020).

Despite limited clinical trial data specific to AD populations, severe adverse events remain unreported. Instead, studies have documented only mild gastrointestinal symptoms (e.g., diarrhea, dyspepsia) in some formulations. Notably, a 24-week investigation involving obese participants revealed no major safety concerns. Similarly, a 2024 trial demonstrated stable blood pressure profiles in hypertensive AD patients adhering to KD, despite persistent LDL and total cholesterol elevations (López-Domínguez and Villalba, 2023). This affirms its safety in high-risk cohorts, albeit pending lipid surveillance. Longitudinal evidence from a 2024-year follow-up study further corroborated KD’s safety

in AD patients, observing cholesterol stabilization over time and predominantly mild side effects like constipation (Kosinski and Jornayvaz, 2024). Moreover, the dietary rigidity of KD, particularly its carbohydrate restriction, poses implementation challenges for AD patients, who frequently exhibit preferences for carbohydrate-rich foods. Nevertheless, medium-chain triglyceride (MCT) supplementation emerges as a viable strategy to induce ketosis without stringent dietary modifications (Lilamand, 2020; Rusek, 2019; Van der Auwera, 2005; Soto-Mota and Volek, 2024).

Management of Adverse Effects and Poor Compliance in Adults

Gastrointestinal symptoms such as constipation, diarrhea, nausea, and vomiting are common; however, they often improve over time. To mitigate these effects, collaborating with a dietitian to modify the diet can be beneficial. In support of this, a 2023 guide for clinicians (Augustin and Kölker, 2023) emphasized that success with ketogenic diets in Alzheimer's patients hinges on personalized meal plans and close monitoring. Specifically, strategies such as incorporating MCT oil supplements can boost compliance without necessitating drastic dietary restrictions.

Moreover, while weight loss is a common goal with ketogenic diets, dietitians can adjust calorie intake for those who aim to maintain their weight. Therefore, close monitoring of the diet is crucial. and integrating personalized adjustments to address any digestive issues. Although high cholesterol and triglycerides may arise, these typically normalize after continuing the diet for about a year or by discontinuing it. In fact, very low-carb ketogenic diets can even improve cholesterol and triglyceride levels in some individuals.

In addition, other possible side effects include deficiencies in vitamins and minerals and bone loss; however, these can be mitigated by taking supplements. Despite the potential benefits, adhering to a ketogenic diet long-term can be difficult, with 15–67% of participants in studies on ketogenic diets for conditions like brain cancer and Alzheimer's disease dropping out (Broom et al., 2024; Rong et al., 2024). Nevertheless, a 2023 review (Lee and Kim, 2023). concluded that ketogenic diets are among the most promising non-pharmacological interventions for Alzheimer's. Still, long-term adherence remains a significant challenge for older adults, particularly due to dietary rigidity and age-related preferences. To address this, strategies to help individuals keep on the diet include monitoring ketone levels, keeping food diaries, regular consultations with a dietitian, taking supplements, and utilizing mobile apps (Lange, 2017). Notably, a study in 2023 demonstrated that diet-tracking mobile applications improved adherence to ketogenic regimens by 50% in elderly Alzheimer's patients, thereby offering a scalable, technology-driven approach to overcoming compliance challenges (Fernández-Quintela and Milton-Laskibar, 2024).

Conclusion

The KD represents a promising approach for managing AD by targeting the metabolic dysfunction and neuroinflammation pathways that support its progression. By shifting the brain's main energy source from glucose to ketone bodies, particularly β-hydroxybutyrate, the KD effectively bypasses impaired glucose metabolism, which is a hallmark feature of AD, while contributing to the reduction of oxidative stress, neuroinflammation, and mitochondrial dysfunction.

Recent clinical and preclinical evidence highlights the KD's diverse neuroprotective benefits, including improved synaptic plasticity, a decrease in amyloid plaque buildup, and improved cognitive performance in both human and animal models. Combining the KD with other approaches such as time-restricted eating, medium-chain triglyceride supplementation, and hybrid diets (e.g., Mediterranean-Ketogenic diet) further improved its effectiveness and therapeutic impact.

However, successful long-term implementation requires personalized dietary planning, ongoing monitoring, and managing potential side effects such as gastrointestinal discomfort and dyslipidemia. Technological interventions, including mobile applications and biomarker-guided personalization, offer promising tools to optimize adherence and outcomes, particularly in older adults. While more large-scale, long-duration randomized controlled trials are needed, current data provide a strong foundation for considering the ketogenic diet as a viable, non-pharmacological intervention for AD. Its ability to address both core metabolic abnormalities and broader neurodegenerative mechanisms positions it as a promising component of future AD management strategies.

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