Ketone Metabolism: The Link Between the Ketogenic Diet and Alzheimer's Disease

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Abstract. This article presents a comprehensive analysis of the intricate interplay between the ketogenic diet (KD) and Alzheimer's disease (AD). Given that AD is a neurodegenerative condition, and the keto diet is characterized by its low carbohydrate and high fat content, the diet's induction of ketosis offers a novel energy source for optimal brain function. Numerous studies suggest that the KD holds promising potential as a therapeutic avenue for addressing AD. This analysis delves into the metabolic mechanisms underlying this potential relationship, illuminating on how the diet's effects may mitigate, counteract the pathophysiological processes intrinsic to AD. By exploring these connections, this paper contributes to the innovative strategies to address the challenges posed by Alzheimer's disease and promotes a deeper understanding of the therapeutic potential offered by the KD. The shortcomings of Alzheimer's disease and if it can be approved as a treatment for Alzheimer's patients in the future, are pointed out, and predictions are given that healthcare professionals may advance the KD as a medical treatment for AD.

Keywords: Ketone diet, Alzheimer's disease, cognition.

1. Introduction

Alzheimer's disease (AD) primarily afflicts elderly and sometimes middle-aged individuals, making it the most common form of neurodegenerative dementia in the United States today [1]. As its prevalence persists across decades, the imperative to develop effective preventive strategies and treatments has grown stronger. Although currently there are ways to improve the negative symptom that AD patients are struggling with, yet these treatments are complicated unable to meet the need for efficient improvements.

The unwavering endurance of Alzheimer's prevalence over generations has underscored the pressing need for innovative interventions to prevent and alleviate its impact. Within this context, the ketogenic diet (KD) has garnered sustained attention as a potential therapeutic pathway for AD. The KD is a popular dietary pattern in the United States has already been discussed as a potential treatment for AD for several years. Central to its efficacy is the role of ketone bodies that are produced through ketogenic metabolism, ketone bodies play a pivotal role in the treatment process.

This paper discusses the feasibility of the KD as a treatment for AD in terms of the pathogenesis of AD, the main causes that lead to the development of AD, the principle of action of the KD, and the process by which the KD targets and ameliorates the symptoms of AD. The paper also analyzes what shortcomings the KD would have if it were to become one of the treatments for AD and predicts what advances the KD would face if it were to be approved as a treatment for AD.

2. Introduction to AD

AD is a chronic neurodegenerative disease caused by the decline of brain function, which normally comes with the increase of age. The disruption of normal brain function is the result of cytoskeletal change, neuronal dysfunction, and cellular death (Fig. 1). Amyloid-beta peptide (Aβ) in brain tissues and the hyperphosphorylation of microtubule-associated Tau protein are believed as the main factors that are blocking the brain from normal functioning [1, 2]

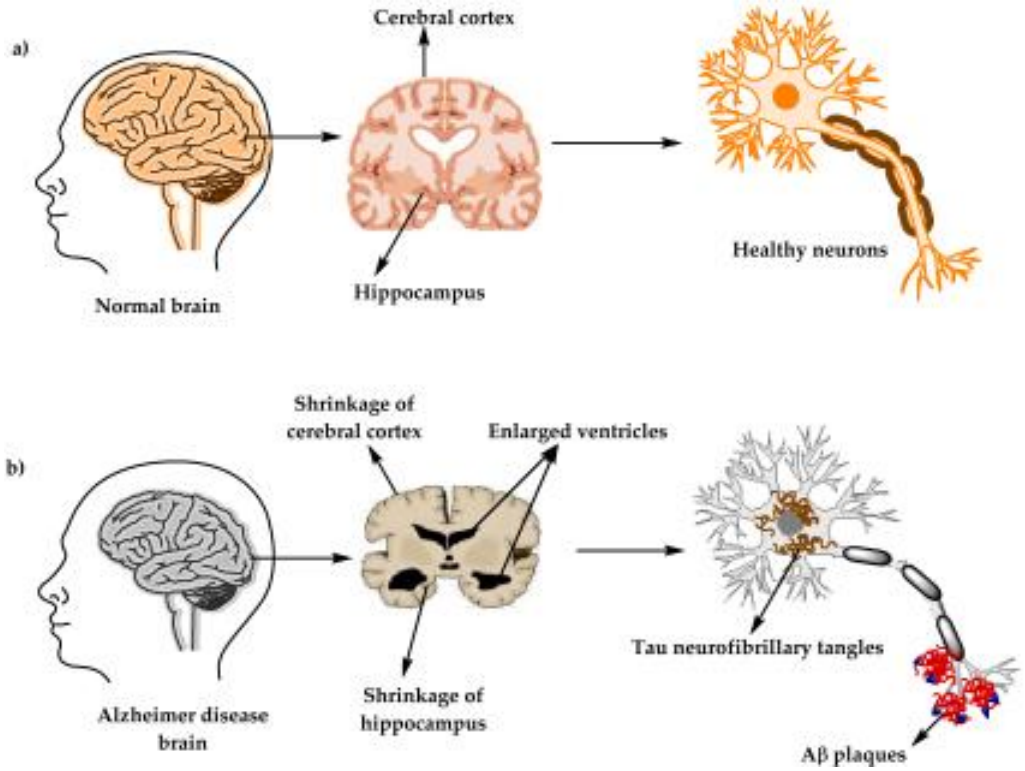


Figure 1. The physiological characteristics of neurons in (a) healthy and (b) AD-affected brains [2].

2.1. The Main Reasons that Caused AD to Form

According to scholarly research, the formation of AD is mainly associated with age, genetics, environmental factors, amyloid protein, and the degeneration of brain cells. There are two main hypotheses recognized by most scholars: While some claim that cholinergic dysfunction is a substantial risk factor for AD, others assert that abnormalities in the production and processing of amyloid proteins are the disease's main underlying cause [2, 3].

2.1.1. The influence of Age on the Formation of AD

The natural process of aging, which results in a decline in biological functioning, is unavoidable. It is one of the key variables contributing to AD; the majority of AD patients were over 65 years old when they received their diagnosis. Early-onset AD (EOAD) is an uncommon type of Alzheimer's that most often results from familial AD cases that manifest in a person's generation. Only 1–6% of all AD cases involve EOAD, which often affects people between the ages of 30-60 or 65. A frequent form of AD that often affects adults over 65 is late-onset AD (LOAD) [3, 4].

2.1.2. The influence of Genetics on the Formation of AD

In recent years, the understanding of the role of genetic factors in shaping the landscape of AD has deepened significantly. These genetic variables have emerged as discernible contributors to the intricate mosaic of AD onset. Specifically, the realm of early-onset AD unveils a hereditary aspect, wherein patients are ensnared by the inheritance of gene defects. This genetic legacy finds its roots in mutations of dominant genes such as APP, PSEN-1, PSEN-2, ApoE, each forging a link to the trajectory of AD. As scholars navigate the genetic tapestry, it becomes evident that approximately 70% of Alzheimer's cases are interwoven with these influential genetic factors, further weaving complexity into the story of this affliction [3].

2.1.3. The influence of Environmental Factors on the Formation of AD

Environmental influences can be dissected into two distinct categories: those that reside within the human immediate realm and those that extend beyond those boundaries. On the outer frontier of environmental impact lie factors like air pollution. The inner environmental factors encompass an

intricate tapestry of elements, encompassing daily dietary patterns, the intake of metals, medications, and susceptibility to infections [3].

2.2. Current Treatments for AD

The global prevalence of AD currently stands at a staggering 24 million cases, a number that continues to escalate with each passing day. This upward trend underscores the urgency to develop effective interventions for this pervasive neurodegenerative affliction. However, the landscape of available treatments remains limited, revolving around just two primary drug classes: cholinesterase enzyme inhibitors and NMDAR antagonists.

Cholinesterase enzyme inhibitors, while addressing a critical aspect of the condition, target the reduction in cholinergic transmission—a hallmark of AD. These inhibitors act as guardians of cognitive function by impeding the breakdown of acetylcholine, a neurotransmitter vital for memory and learning. On a parallel trajectory, NMDAR antagonists intervene to mitigate the damaging consequences of NMDAR overactivation. This excess activation precipitates a cascade leading to cellular demise and synaptic impairment, pivotal elements in the progression of AD pathology. Yet, despite the concerted efforts and advancements in understanding these molecular underpinnings, the landscape remains complex and challenging. The multifaceted nature of AD, characterized by intricate interactions between genetic, environmental, and cellular factors, adds layers of intricacy to its pathogenesis. Moreover, the current therapeutic arsenal, while offering a glimmer of hope, has yet to achieve the desired level of success on the clinical front [3].

3. Introduction to the KD

The KD is a distinctive eating approach marked by its high-fat and low-carbohydrate intake, designed to trigger a metabolic state called ketosis [5]. In this state, the body relies on fat and ketone bodies as its primary energy sources, steering away from the conventional reliance on glucose. The diet typically consists of a fat content of around 70-80%, carbohydrate intake limited to 5-10%, and a moderate protein portion of 10-20% [6]. This shift to ketosis provides an innovative energy alternative for both the brain and body. Widely known for its applications in weight loss and epilepsy control, the KD is also being explored for its potential benefits in conditions like Alzheimer's and Parkinson's diseases. However, its unique composition necessitates meticulous planning to ensure proper nutrient intake and the desired state of ketosis [7]. Consulting a healthcare professional before embracing this diet is highly recommended due to its distinctive nature.

4. Improvements of KD on Brain Function to AD Patients

AD is a type of neurodegenerative diseases. KD causes the body to start producing ketone bodies and go into ketosis, which are aspects of the ketone metabolism. According to studies, KD modulating metabolism, mitochondrial function, inflammation and oxidative stress [5, 8].

4.1. Principle of Ketogenic Metabolism

Ketogenic metabolism results from the body utilising ketone bodies as its primary energy source rather than glucose. When following a diet pattern that is low-carbohydrate and high-fat, ketone bodies are synthesized as the last part of lipid energy metabolism. The liver converts fatty acids into molecules called ketone bodies through a process known as ketogenesis when carbohydrates are scarce (Fig. 2). The ketone bodies produced are released into human body and human brain as energy source [9].

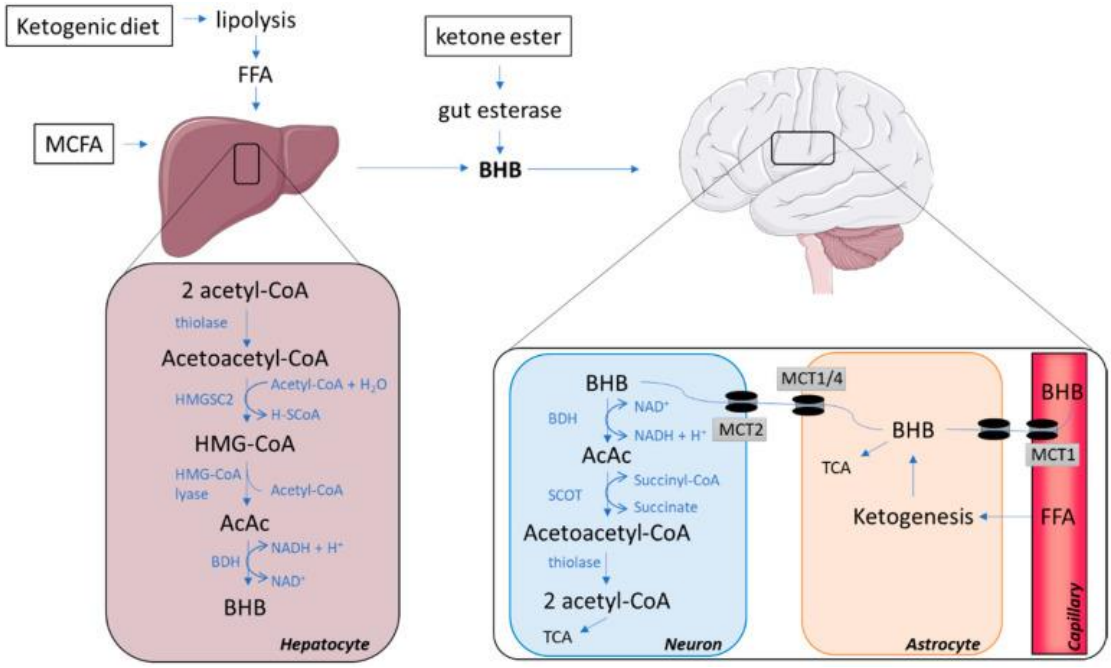


Figure 2. Pathways implicated in ketone body synthesis and catabolism [10].

4.2. Ketone Bodies Serves as Substitute Energy for the Brain

In the context of AD, a pivotal hallmark is the progressive degeneration of brain function [10]. The human brain, with its intricate networks and ceaseless cognitive activities, demands a substantial energy supply to sustain its normal operations. Traditionally, glucose oxidation has been identified as the primary source of this indispensable energy. However, amidst the intricate puzzle of Alzheimer's, ketone bodies emerge as an intriguing player, capable of offering an alternative source of vitality when the usual glucose supply falters. AD is characterized by the impaired metabolism of glucose, a critical substrate for cellular energy production. This metabolic derangement has a cascading effect on brain function, contributing to cognitive decline and other debilitating symptoms [11]. In this context, the potential role of ketone bodies takes center stage. These molecules, produced during states of fasting, low carbohydrate intake, or through interventions like KD. Upon entering the brain, ketone bodies step into a role of utmost significance. They stand poised as substitutes, ready to fill the energy void left by compromised glucose metabolism. This metabolic adaptation is particularly compelling in brain regions that experience the adverse effects of Alzheimer's degeneration. By providing an alternative energy supply, ketone bodies offer a lifeline to regions of the brain that have witnessed decline, potentially helping to sustain their functions and mitigate cognitive decline (Fig. 3) [12].

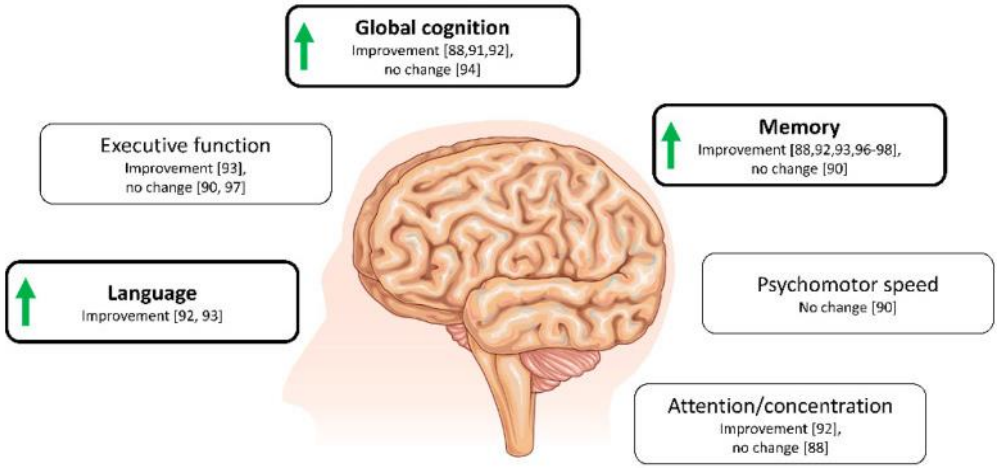


Figure 3. Summary of the cognitive areas impacted by ketogenic therapy [10].

5. The State of Ketosis Ameliorates the Brain Function for AD Patients

5.1. The Enter Principle of Ketosis

The cornerstone of entering the state of ketosis lies in the body's innate ability to pivot from glucose to ketone bodies as an alternative energy source. This transition becomes pronounced when glucose availability diminishes, often stemming from a reduced intake of carbohydrates. This alteration in carbohydrate consumption restricts the influx of fresh glucose required for optimal bodily function. Although the body possesses glycogen stores that temporarily fulfill energy demands, these reserves are finite. As these glycogen stores are gradually depleted, the body undergoes a transformative response—triggering the production of ketone bodies. Distinguished by their capability to traverse cellular membranes unimpeded, ketone bodies offer an agile energy supply to various bodily regions. This transition doesn't exclude the brain, which adjusts its energy preferences in the face of such metabolic changes, ultimately propelling the body into the state of ketosis [6, 9].

5.2. Ketones Implicate Alzheimer's Pathology

According to studies degeneration of brain cells and inflammation are the significant symptoms of AD. With KD as the treatment for AD, these symptoms could be improved with the participation of ketone bodies [13].

5.2.1. Ketone Bodies Have Neuroprotective Impact on Brain Cells

Ketones exert a remarkable neuroprotective impact on brain cells by influencing intricate cellular mechanisms. KD led to the generation of ketone bodies during periods of reduced carbohydrate availability, prompting a series of biochemical changes that contribute to improved mitochondrial function. Mitochondrial dysfunction and oxidative stress are central to neurodegeneration, with both processes resulting in harmful reactive oxygen species (ROS) accumulation. KD appears to counteract this by mitigating ROS production and enhancing mitochondrial respiration, particularly by bypassing complex 1 dysfunction. KD promotes redox processes, mitochondrial biogenesis, and cellular respiration by altering the ratio of NAD+/NADH in its oxidized and reduced forms. Cellular toughness is strengthened by this stability of synaptic activity. This stabilization of synaptic action bolsters cellular resilience. KD-induced gene expression mediated by sirtuin 1 (SIRT1), linked to histone and non-histone target deacetylation, further reinforces protective mechanisms. Activation of Nrf2 via KD elevates the levels of antioxidant enzymes, aiding in oxidative stress management [5].

5.2.2. Ketone Suppress Inflammation

The metabolism of ketone bodies during periods of low carbohydrate availability triggers oxidative stress within mitochondria, which paradoxically leads to a protective, hormetic response in cells. This adaptive mechanism involves activation of cell-protective regulators such as Nrf2, sirtuins, and AMPK. Through this intricate pathway, ketone bodies not only serve as fuel but also exhibit anti-inflammatory effects by upregulating antioxidative activities, enhancing mitochondrial function, promoting DNA repair, and inducing autophagy. This orchestrated response ultimately results in the suppression of inflammation, bolstering the cells' ability to withstand oxidative stress and thrive in conditions of reduced energy availability [6, 7].

6. Shortcomings of the KD as a Treatment

While the KD displays substantial promise as a prospective treatment for AD, it is accompanied by certain limitations. Primarily, the sustainability of this dietary approach poses a formidable challenge. Alzheimer's patients, already grappling with life's complexities, might find it arduous to adhere to such a specific eating regimen. Moreover, the caregiving dynamics become intricate when managing a distinct dietary pattern. Balancing nutrients becomes a concern as the strict high-fat, low-carbohydrate diet narrows down food options, potentially compromising the patients' nutritional intake. Economic and personal factors further complicate matters, as not all individuals can feasibly

maintain well-rounded meals under such stringent guidelines. Lastly, the KD might lead to undesirable side effects, including dizziness and nausea, which could deter its seamless implementation for patients [14].

7. Potential Ways that Advancing the KD

Implementing the KD as a treatment for AD offers room for refinement across various aspects. Enhancements can be introduced to enhance the practicality and adaptability of this approach. Flexibility and convenience are key considerations when tailoring the KD as a treatment. Achieving balanced nutritional intake might necessitate supplementary measures, such as injectable or oral nutrient supplements, ensuring patients receive vital nutrients. Recognizing that the application of the KD in Alzheimer's treatment is still in its developmental stages, the integration of this approach with complementary therapies and personalization strategies holds promise. Future investigations could explore synergistic combinations of the KD with other therapeutic interventions, optimizing outcomes for Alzheimer's patients. Addressing the current limitations, including the scarcity of clinical data, is essential for wider acceptance and understanding [15]. Amplifying the database of clinical experiments and conducting more extensive studies will bolster awareness of the potential benefits of KD treatment for AD, ultimately contributing to improved patient care.

8. Conclusion

The relationship between the KD and AD is intricate, and the KD has great potential as a therapeutic avenue for AD. AD predominantly affects elder and part of middle-aged adults, and the continued prevalence of the disease highlights the need for influential preventative measures and treatment strategies. The KD which is characterized by a unique blend of low-carbohydrate and high-fat, emerges as a promising contender in this narrative, offering new avenues for intervention.

The KD is capable of triggering ketosis, thereby providing an alternative energy source critical to allowing the brains of Alzheimer’s patients to work as normally as possible. This article has scrutinized the effects of mitochondrial activity, oxidative stress, and neuroprotection, revealing both potential advantages and inherent limitations. However, the path to seamless integration of the KD as a therapeutic mechanism is fraught with challenges that include considerations of sustainability, nutritional balance, and individual differences.

In the future, advancing the treatment of AD will require bridging the gap between researchers, healthcare professionals, caregivers, and patients. By doing comprehensive clinical trials, and personalized approaches to fully leverage the benefits of the KD; exploring the connections between metabolism, nutritional science, and neurological health, combining theoretical constructs with practical applications to brighten the outlook for Alzheimer's patients.

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