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Ketogenic diets and Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by decline in cognitive functions and associated with the neuropathological hallmarks of amyloid β-peptide plaques and neurofibrillary tangles. Cerebral glucose uptake and metabolism deteriorate in AD and this hypometabolism precedes the onset of clinical signs in AD. The early decline in brain glucose metabolism in AD has become a potential target for therapeutic intervention. This has led to investigations assessing the supplementation of the normal glucose supply with ketone bodies which are produced by the body during glucose deprivation and can be metabolized by the brain when glucose utilization is impaired. The present review provides a synopsis of preclinical studies and clinical trials assessing the efficacy of ketogenic diets in the treatment of AD. Both the direct administration of ketone bodies and the use of high-fat, low-carbohydrate ketogenic diets have been shown to be efficacious in animal models of AD and clinical trials with AD patients. The mechanism underlying the efficacy of ketogenic diets remains unclear, but some evidence points to the normalization of aberrant energy metabolism. At present there is only limited evidence of the usefulness of ketogenic diets in AD. However, this dietary approach seems to be promising and deserves further clinical investigations.

Keywords: Alzheimer's disease; Ketone bodies; Ketogenic diet; Therapy

1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease and the most common cause of dementia, accounting for over 50% of individuals affected [1]. This disease is characterized by progressive memory impairment and cognitive decline interfering with daily life activities. The most common early symptom of AD is difficulty remembering recent events. The symptoms of patients with advancing disease can include executive dysfunction, disorientation, problems with language, mood swings, behavioral changes and impaired self-care [2]. Age-standardized prevalence for individuals aged over 60 years varied between 5% and 7% in most world regions [3]. An estimated 35.6 million people lived with dementia worldwide in 2010, with numbers expected to almost double every 20 years [3].

AD has a long preclinical phase of several decades and the most important risk factor for AD is increasing age. Impaired vascular health has been shown to be another major risk factor for cognitive decline and interventions for cardiovascular risk may therefore improve cognitive health at the population level [4,5]. Other lifestyle-related factors, such as obesity, diabetes, smoking, diet, physical and mental inactivity, have been suggested to play a role in dementia, and potential preventive measures related to these risk factors should be investigated [6].

AD is neuropathologically defined by neuronal loss and the accumulation of extracellular amyloid β-peptide (Aβ)-

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containing plaques and intracellular hyperphosphorylated tau protein-containing neurofibrillary tangles in the brain [7]. The accumulation of abnormally folded Aβ and tau proteins in amyloid plaques and neuronal tangles, respectively, appear to be causally associated with the neurodegeneration in AD [8]. However, a linear causality between amyloid and tau and AD seems to be too simplistic an assumption made by the original amyloid hypothesis [9]. The cognitive decline in AD is associated with progressive synaptic dysfunction and neuronal atrophy, mainly in the neocortex, limbic system and subcortical brain areas [7].

The etiology of AD is unknown, but both genetic and environmental risk factors have been suggested to be involved. Genome-wide association studies have shown more than 20 genetic loci to be associated with the risk of AD [10]. The identified AD risk genes are related to lipid and cholesterol processing, inflammatory responses and the immune system. The majority of these genes affect Aβ production and clearance, emphasizing the special role of this pathway in the pathogenesis of AD. Carriers of the presenilin 1 mutation have the highest risk of AD [10]. Another major susceptibility gene is the apolipoprotein E (ApoE) gene which is related to sporadic late-onset AD, the epsilon 4 (E4) variant of ApoE was found to increase the risk for AD [10].

Curative therapies for AD are not available and supportive care plays an important role in the treatment of patients with AD. Symptomatic treatments providing temporary alleviation of the symptoms of AD without modifying the disease progression include drugs such as acetylcholinesterase inhibitors and the glutamate antagonist memantine [1]. Most of these drugs offer at best a moderate symptomatic effect. Other therapeutic strategies focus on anti-amyloid approaches, including active and passive immunization, γ-secretase and β-secretase inhibitors, and antiaggregation drugs [1]. A further understanding of the etiopathogenesis of AD is needed in order to develop disease-modifying therapies which can prevent, delay or treat the symptoms of AD. Type 2 diabetes and insulin resistance are the main lifestyle-related risk factors for AD. Lifestyle-modifying approaches including diet and physical exercise may show beneficial effects in the prevention and early treatment of AD.

The accumulation of Aβ and the development of AD have been proposed to be related to dietary factors. For example, the findings of a Dutch study suggested that diets rich in saturated fat and cholesterol increase the risk of several types of dementia [11]. However, a subsequent 6-year follow-up of the same study population found no correlation between fat consumption and dementia [12]. Another large study of elderly participants found only weak trends between cognitive decline and the intake of saturated fat and cholesterol as assessed using a food questionnaire [13].

The findings of recent investigations have suggested that caloric restriction prevents age-related neuronal damage and may be useful in the prevention and treatment of AD [14]. Hypotheses linking caloric restriction to cognitive capability include anti-inflammatory mechanisms, reduction of neural oxidative stress, promotion of synaptic plasticity as well as induction of various stress and neurotrophic/neuroprotective factors [14]. Caloric restriction may also prevent Aβ neuropathology in AD transgenic animal models [14]. A relative recent dietary approach to the treatment of AD is the administration of ketogenic diets.

2. Development of ketogenic diets

During infancy and early childhood, ketone bodies play an important role beside glucose as oxidizable substrates and energy source for the brain [15] since their blood plasma concentrations are high and an abundance of monocarboxylic acid transporters render the blood–brain barrier greatly permeable to ketone bodies [16]. In adult humans, high ketone body concentrations are found during fasting and on a high-fat diet. In addition, the permeability of the blood–brain barrier increases with fasting [16]. Ketone bodies when present at sufficient concentrations to saturate metabolism can support most, if not all, basal (non-signaling) neuronal energy needs and up to approximately half of the activity-dependent oxidative needs of neurons [17].

When food was scarce, ketosis may have been a survival mechanism during human evolution [18]. Foods containing large amounts of carbohydrates have relatively recently become a part of the human diet and may be more evolutionarily discordant than high fat diets [19]. High carbohydrate diets stimulate insulin signaling and lead to a suppression of lipid metabolism and ketogenesis [20]. The evolutionary switch to diets high in carbohydrates (ketodeficient diet) has been hypothesized to play a role in the development of AD [21].

It has long been known that fasting has anticonvulsant properties. The ketogenic diet was developed in the 1920s to mimic the physiological alterations observed in prolonged fasting [22] when energy is mainly derived from the utilization of body fat or dietary fat. This diet was successfully used as a therapeutic approach for seizures [23]. Due to the availability of antiepileptic drugs the ketogenic diet was not in use for decades, but was in favor again in the 1990s, particularly in the therapy of pharmacoresistant epilepsy. The ketogenic diet is very high in fat and low in carbohydrates and is believed to simulate the effects of starvation by primarily metabolizing fat as energy supply [24]. While fasting the organism metabolizes stored body fat via lipolysis and the ensuing β-oxidation of fatty acids leads to the production of acetoacetate, β-hydroxybutyrate and acetone which can easily cross the blood–brain barrier. These ketone bodies can be used as precursors for the generation of adenosine triphosphate (ATP).

The ketogenic diet has now become an established and effective nonpharmacological treatment for epilepsy [25–27]. A number of patients with intractable epilepsy have been shown to become seizure-free or to have a significant reduction in seizure frequency during the administration of a ketogenic diet and even following the discontinuation of the diet, suggesting disease-modifying effects in some patients with epilepsy [27]. Several mechanisms underlying the anticonvulsive effects of ketone bodies have been proposed [27], including changes in ATP production, altered brain pH affecting neuronal excitability, direct inhibitory effects of ketone bodies or fatty acids on ion

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