



Ketogenic diets and Alzheimer's disease

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Received 4 October 2016; accepted 27 October 2016

Available online 24 November 2016

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.

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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 (A β -

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Peer review under responsibility of Beijing Academy of Food Sciences.



containing plaques and intracellular hyperphosphorylated tau protein-containing neurofibrillary tangles in the brain [7]. The accumulation of abnormally folded A β 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 A β 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 A β 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 A β 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

channels, and shifts in amino acid metabolism [28–30]. Since at least some glucose is required for the synthesis of glutamate and the maintenance of homeostasis during glutamatergic activity [31], a ketogenic diet very low in carbohydrates may prevent seizures by compromising the formation of the excitatory neurotransmitter glutamate (for further details see Ref. [32]). This hypothesis is supported by the fact that the replacement of glucose by β -hydroxybutyrate in the medium decreases glutamate availability in cultured neurons [33].

Beside its efficacy in the treatment of refractory epilepsy, the ketogenic diet has been suggested to be useful in the therapy of neurodegenerative and neuromuscular diseases including AD, Parkinson's disease, amyotrophic lateral sclerosis and mitochondrial disorders [34]. The ketogenic diet is likely to have different mechanisms in different diseases [29].

3. Rationale for the use of ketogenic diets in AD

Energy deprivation is harmful to neurons and may contribute to the pathophysiology of AD since brain glucose uptake and metabolism have been shown to be impaired in AD. A decline in cerebral blood flow and mean cerebral oxygen utilization was found to be correlated with increasing severity of dementia [35]. Compared to elderly controls, individuals with senile dementia showed a decrease in regional glucose use in the posterior cingulate, temporal, parietal and prefrontal cortex [36] and this hypometabolism correlated significantly with measures of cognitive functioning [37]. The deficit in brain glucose metabolism is an early feature of AD and could be the consequence of a reduced need for glucose due to synaptic loss and neuronal cell death. However, brain glucose hypometabolism has also been observed in preclinical stages of AD long before the occurrence of cognitive deficits. Clinical studies have reported a decline in cerebral glucose utilization prior to the onset of clinically measurable cognitive decline and the diagnosis of AD [38,39]. Brain hypometabolism preceding the onset of clinical signs of AD may presymptomatically contribute to the risk of AD [40]. Early degeneration of the locus coeruleus, the noradrenergic brain stem nucleus, may be a reason for the compromised glucose metabolism in AD since the locus coeruleus stimulates glucose metabolism, at least in astrocytes (for review see Ref. [41]). Glucose metabolism has also been shown to decrease in healthily aging individuals, but the reduction is more pronounced in ApoE4 carriers than in matched non-carriers [42]. A low regional cerebral metabolic rate of glucose appears to occur early in the AD process long before the onset of clinical signs of dementia or neuronal loss and plaque deposition in the brain [43]. Brain hypometabolism has been suggested to indicate a risk for the future development of dementia [44]. A vicious circle may gradually develop in which latent presymptomatic brain hypometabolism leads to chronic brain energy deprivation, deteriorating neuronal function, further decline in demand for glucose and progression of cognitive impairment [40]. The reason why reduced brain glucose metabolism develops is unknown, but defective brain glucose transport, disrupted glycolysis, or impaired mitochondrial function may be involved (for a detailed account of the consequences of impaired energy

metabolism in AD see Ref. [32]). Mitochondrial DNA is maternally inherited in humans, and it is therefore noteworthy that reduced brain glucose metabolism before the onset of cognitive decline is more pronounced in elderly individuals with a maternal family history of AD than in those with paternal or no family history [45].

The adult human brain represents about 2% of total body weight but requires approximately 20% of the entire body's supply of energy. It relies almost exclusively on glucose as energy substrate and stores only small amounts of glycogen. Fatty acids cannot cross the blood–brain barrier and are not available as energy source in the brain. Although glucose is the brain's major fuel, the ketone bodies β -hydroxybutyrate and acetoacetate produced by the liver from fatty acids can be used as replacement for glucose during starvation, fasting or demanding exercise [18,46]. Fasting or an intake of very small amounts of carbohydrates induces ketosis due to hepatic β -oxidation of long-chain fatty acids. In comparison to glucose, ketone bodies produce a larger amount of energy due to changes in mitochondrial ATP production that they induce [47,48]. Ketone bodies can bypass the block in glycolysis caused by impaired insulin function [49]. While glucose hypometabolism has repeatedly been demonstrated in patients with AD [24], the metabolism of ketone bodies was unchanged, at least in the early disease stages [50]. In a state of brain energy crisis, ketone bodies can be used as an auxiliary and alternative fuel for brain metabolism [16]. Since fuel hypometabolism in the AD brain appears to be specific to glucose, the administration of ketone bodies may overcome the reduction in glucose uptake and metabolism and improve the energy deficit in the brain. Both calorie restriction and consumption of a ketogenic diet reduce carbohydrate intake and lead to a compensatory rise in ketone bodies. This has been shown to improve mitochondrial function, reduce the expression of apoptotic and inflammatory mediators and increase the activity of neurotrophic factors [51]. Dietary carbohydrate reduction appears to have neuroprotective effects [52] and ketone bodies have been demonstrated to protect neurons against multiple types of neuronal injury and to have mitochondrial effects similar to those following calorie restriction or ketogenic diet [51]. In summary, an increase in ketone body supply, provided by a ketogenic diet or by the administration of ketone esters, would be expected to alleviate the impaired brain glucose metabolism preceding the onset of AD.

4. Ketone bodies in a cell culture model of AD

Neuroprotective properties of ketone bodies have been investigated in cell cultures. A proteolytic fragment of the β chain of amyloid precursor protein, A β 1–42, is toxic to hippocampal cells. The exposure of 6-day cultured hippocampal neurons from 18-day-old embryos to 5 μ M A β 1–42 reduced cell number as well as neurite number and length compared to control [53]. When the cells were simultaneously exposed to 4 mM D- β -hydroxybutyrate, the surviving cell number doubled and both cell size and neurite outgrowth increased in comparison with cells exposed to A β 1–42 alone [53]. These findings show that β -hydroxybutyrate may provide neuroprotection from A β 1–42

toxicity. In addition, exposure of cells to ketone bodies for 14 h increased both surviving cell number and neurite number compared to control cells, suggesting that ketone bodies can act as growth factors to neurons in culture [53]. The ability of ketone bodies to protect neurons in culture suggests that defects in mitochondrial energy generation contribute to the pathophysiology of AD and that ketone bodies may have therapeutic potential. This needs to be investigated using *in vivo* studies.

5. Ketogenic diets in animal models of AD

Animal models have provided insight into the underlying mechanisms of AD and have been useful in the preclinical evaluation of potential treatments [54]. Genetically modified animals exhibiting critical aspects of AD neuropathology have helped understand the function of genes associated with AD. Several studies have used genetically modified rodents as AD models in order to assess the therapeutic efficacy of ketogenic diet and ketone bodies in regard to pathological changes and behavioral deficits.

In a transgenic mouse model, the effects of a ketogenic diet composed of very high saturated fat and extremely low carbohydrate content were investigated [55]. These mice exhibit significant levels of soluble A β at three months of age and extensive plaque deposition at age 12–14 months [56]. Two groups of female transgenic mice carrying the “London” APP mutation (APP/V717I) were fed *ad libitum* for 43 days either a standard diet composed of high carbohydrate/low fat chow or a ketogenic diet composed of very low carbohydrate/high saturated fat chow [55]. Animals fed the ketogenic diet showed greatly increased serum ketone body concentrations and significantly reduced brain A β 40 and A β 42 levels while no changes in cognitive performance were found [55]. The finding that A β reduction did not improve cognitive performance may be due to the relatively short intervention. Long-term administration of the ketogenic diet may be required in order to produce behavioral effects.

Another study assessed the effects of a ketogenic diet in two transgenic mouse lines [57]. Five-month-old APP/PS1 mice (model of amyloid deposition) and Tg4510 mice (model of tau deposition) were fed either a ketogenic or a control diet for three months. Behavioral testing during the last two weeks of treatment showed that mice fed the ketogenic diet performed significantly better on a rotarod than those in the control group independent of genotype [57]. In the open field test, both transgenic mouse lines presented increased locomotor activity compared to nontransgenic, age-matched controls, and this effect was not influenced by the ketogenic diet [57]. The radial arm water maze identified learning deficits in both transgenic lines without significant differences between the diets. Tissue measures of amyloid, tau, astroglial and microglial markers in transgenic lines showed no differences between mice fed the ketogenic or control diet [57]. These findings suggest that ketogenic diets may play a role in enhancing motor performance in the two mouse models while not affecting amyloid or tau deposition.

An effect on amyloid or tau deposition may not be necessary in order to achieve improvements in cognitive functions following dietary interventions. In the triple-transgenic mouse model of AD (3xTgAD mice), two different energy restriction regimens (40% calorie restriction and intermittent fasting) were tested in regard to their ability to protect against cognitive decline [58]. Groups of 3xTgAD mice were maintained on calorie restriction, intermittent fasting or an *ad libitum* control diet starting at three months of age. Half of the mice in each diet group were tested using the open field and the Morris swim task at age 10 months and the other half at 17 months [58]. At 10 months 3xTgAD mice on the control diet showed reduced exploratory activity compared to non-transgenic mice and 3xTgAD mice on calorie restriction and intermittent fasting [58]. No significant differences were found in performance in the water maze between genotypes or diets in 10-month-old mice [58]. In 17-month-old 3xTgAD mice, the calorie restriction and intermittent fasting groups exhibited higher levels of exploratory behavior and better performance in the swim task, compared to 3xTgAD mice on the control diet [58]. 3xTgAD mice in the calorie restriction group showed lower levels of A β 1–40, A β 1–42 and phosphorylated tau in the hippocampus compared to the control diet group, while A β and phosphorylated tau levels were not decreased in 3xTgAD mice in the intermittent fasting group [58]. These findings suggest that intermittent fasting, which may increase levels of ketone bodies, can ameliorate age-related cognitive deficits without affecting A β or tau levels.

Medium chain triglycerides are easily converted to ketone bodies. A study assessing the effects of ketosis induced by the administration of medium chain triglycerides was performed in aged dogs, a natural model of amyloidosis [59]. The dogs received a 2 g/kg/day dose of medium chain triglycerides for 2 months. Compared to age-matched controls, markedly improved mitochondrial function was observed in aged dogs receiving medium chain triglycerides [59]. This effect was most prominent in the parietal lobe. In addition, there was a trend towards a decrease in A β levels in the parietal lobe [59]. These results suggest that short-term administration of medium chain triglycerides improves energy metabolism in the aged canine brain.

Mitochondrial bioenergetic deficits have been shown to be closely related to the pathogenesis of AD [60]. These deficits activate a cascade of neurotoxic outcomes, including an increase in oxidative stress and the production of A β , which impair synaptic functions and lead to neuronal death [61]. A decline in mitochondrial bioenergetics has also been demonstrated to precede AD pathology in the female triple-transgenic AD (3xTgAD) mouse model [62]. In the brains of these mice, a temporary increase in the expression of ketogenic markers was also found, indicating a compensatory energy production mechanism [62]. In order to investigate if this alternative energy supply could be preserved, the effects of 2-deoxy-D-glucose (2-DG) administration on brain AD pathology were assessed [63]. 2-DG is known to competitively block glucose metabolism and to induce ketogenesis in the liver, *i.e.* a compensatory production of ketone bodies as alternative energy substrates.

Six-month-old female 3xTgAD mice were fed either a diet containing 0.04% 2-DG or a regular diet (AIN-93G) for seven

weeks. The 2-DG diet markedly increased serum ketone body levels and brain expression of enzymes required for ketone body metabolism. Mice fed the 2-DG diet showed a significant reduction of both amyloid precursor protein (APP) and amyloid beta ($A\beta$) oligomers as well as a significant increase in α -secretase and decrease in γ -secretase expression, indicating that 2-DG induced a shift towards a non-amyloidogenic pathway [63]. In comparison to the control diet, the 7-week dietary 2-DG administration significantly induced ketogenesis, sustained mitochondrial bioenergetic function, and reduced $A\beta$ pathology. In summary, these preclinical findings suggest that the dietary 2-DG intervention can delay the progression of bioenergetic deficits and $A\beta$ production in the brain [63].

The hypothesis that a ketone ester-based diet can ameliorate AD pathogenesis was tested in the 3xTgAD mouse model [64]. Beginning at a presymptomatic age, male 3xTgAD mice were fed either a diet containing a physiological enantiomeric precursor of ketone bodies or an isocaloric carbohydrate diet. The mice fed a precursor of ketone bodies showed reduced $A\beta$ and hyperphosphorylated tau deposition in the hippocampus, amygdala and cortex [64]. In behavioral tests performed at 4 and 7 months following the initiation of the experimental diet, 3xTgAD mice exhibited significant improvements in learning and memory tests as assessed using the Morris water maze [64]. These results demonstrate that long-term feeding of ketone esters reduces $A\beta$ accumulation and hyperphosphorylated tau pathology and improves cognitive functions in a mouse model of AD. The preclinical findings suggest that a ketone ester-containing diet can potentially retard the disease process and improve cognitive functions of patients with AD.

Ketone bodies cannot provide additional citric acid cycle intermediates which limits the anabolic capacity of the cell. The supplementation of ketogenic diet with anaplerotic compounds such as triheptanoin may increase the effects of the diet [65]. The hypothesis that supplementation with triheptanoin can increase the beneficial effects of ketogenic diet was tested in a rodent model of familial AD, the APP/PS1 transgenic mouse. Three-month-old APP/PS1 mice were fed a ketogenic diet plus triheptanoin supplementation for three months. This treatment reduced the memory impairment of the mice at the age of 6 months. $A\beta$ production and deposition were not significantly changed by either ketogenic diet alone or the combination diet [65]. However, mice fed with triheptanoin-rich ketogenic diet demonstrated a reduction in astroglial response in the vicinity of $A\beta$ plaques and a decrease in the expression of the pro-inflammatory cytokine interferon- γ in astrocytes. Ketogenic diets supplemented with anaplerotic compounds may therefore delay cognitive impairment by acting via astrocytes in energy metabolism responses [65]. These results suggest the potential therapeutic utility of triheptanoin-rich ketogenic diets at early stages of AD.

In summary, several reports have indicated neuroprotective properties of ketone bodies in animal models of AD. However, the translational concordance between these preclinical studies and clinical trials in humans needs to be investigated.

6. Clinical trials of ketogenic diets in AD

As shown above, several strategies are available in order to induce ketosis, i.e. the administration of (1) high-fat, low-carbohydrate, low-protein, ketogenic diets, (2) medium chain triglycerides, and (3) ketone bodies. These approaches have been used in a few clinical trials assessing the efficacy of ketone bodies in patients with AD.

Oral administration of medium chain triglycerides has been shown to induce ketosis in humans [66]. Due to their short fatty acid chain lengths, medium chain triglycerides do not underlie the regulation imposed on long chain fatty acids and they undergo obligatory oxidation. When fatty acids are oxidized at high rates, large amounts of acetyl coenzyme A are generated. Following the intake of a sufficiently large amount of medium chain triglycerides, the excess acetyl coenzyme A produced exceeds the capacity of the citric acid cycle and leads to the synthesis of ketone bodies in liver mitochondria [67]. In contrast to the ketogenic diet, medium chain triglycerides are oxidized regardless of the consumption of other nutrients, and a restriction of carbohydrate or protein intake is therefore not necessary.

The effects of an increase in plasma ketone body levels on cognitive functions were investigated in older adults with memory disorders [66]. Elevation of ketone levels was induced using an oral dose of medium chain triglycerides. On separate days, 20 subjects with AD or mild cognitive impairment imbibed a drink containing emulsified medium chain triglycerides or placebo. A significant increase in β -hydroxybutyrate levels was observed 90 min after administration when cognitive testing was performed. The increase in β -hydroxybutyrate was moderated by ApoE genotype [66]. In ApoE4-positive participants, β -hydroxybutyrate levels continued to rise between the 90 and 120-min blood sampling in the treatment condition, while levels in ApoE4-negative subjects remained constant [66]. The administration of medium chain triglycerides facilitated performance on the AD Assessment Scale-Cognitive Subscale in ApoE4-negative participants, but not in ApoE4-positive participants. Higher ketone values were associated with greater improvement in paragraph recall under medium chain triglyceride treatment relative to placebo across all participants [66]. Future studies need to assess the therapeutic benefits of medium chain triglycerides and the mediation by ApoE-4 status in patients with AD.

An oral ketogenic compound, AC-1202, was administered to individuals with probable AD in order to assess if chronic induction of mild ketosis can improve cognitive performance [68,69]. AC-1202 is a form of medium chain triglycerides and elevates serum ketone bodies even in the presence of dietary carbohydrates. Daily administration of AC-1202 over 90 days was evaluated in 152 patients with a diagnosis of mild to moderate AD in a randomized, placebo-controlled, double-blind, parallel-group study. The participants were on a normal diet and continued taking their usual AD medications. Primary cognitive end points were mean change from baseline in the AD Assessment Scale-Cognitive subscale (ADAS-Cog), and global scores in the AD Cooperative Study — Clinical

Global Impression of Change (ADCS-CGIC). AC-1202 was compared to placebo in several population groups, including intention-to-treat (ITT), per protocol, and dosage compliant groups. The results were also stratified by ApoE4 carriage status. AC-1202 significantly increased serum ketone bodies two hours after administration compared to placebo [68,69]. Each population group showed a significant difference between AC-1202 and placebo in mean change from baseline in ADAS-Cog score on days 45 and 90. Effects were most notable in subjects who did not carry the ApoE4 allele, patients with the ApoE4 genotype did not benefit. Adverse events were more frequently observed in participants receiving AC-1202 and concerned mainly transient, mild to moderate gastrointestinal effects [68,69]. In summary, the oral ketogenic compound AC-1202 was found to have memory-enhancing effects after 45 and 90 days of treatment. This medium-chain triglyceride preparation of fractionated coconut oil (caprylic triglyceride) has been approved for the treatment of AD in the USA [70].

In another study, ketosis was induced by a diet very low in carbohydrates [71]. Twenty-three older adults with mild cognitive impairment were randomly assigned to either a high carbohydrate or very low carbohydrate diet. Following the 6-week intervention period, improved verbal memory performance was observed in participants receiving the low carbohydrate diet [71]. Changes in calorie intake, insulin level, and weight were not correlated with memory performance for the entire sample, although a trend toward a moderate relationship between insulin and memory was observed within the low carbohydrate group [71]. Ketone levels were positively correlated with memory performance [71]. These findings indicate that a very low carbohydrate diet can improve memory function in older adults with increased risk for AD. The mechanism of action underlying this cognitive change remains to be established.

A new way to produce therapeutic hyperketonemia has recently been described [72]. In a 63-year-old patient with younger-onset sporadic AD for 12 years and a pretreatment Mini-Mental State Examination score of 12, a first trial was conducted of prolonged oral administration of a potent ketogenic agent, (*R*)-3-hydroxybutyl (*R*)-3-hydroxybutyrate (ketone monoester) [73]. This ketone monoester has been shown to improve cognitive performance and reduce A β and tau deposition in cognition-relevant areas in a mouse model of AD [64]. The compound was administered as a food supplement without changes in the habitual diet. In the 20-month trial, the ketone ester produced repeated diurnal increases in plasma β -hydroxybutyrate levels and improved cognitive performance, mood, affect, behavior and activities of daily living [72]. Plasma ketone levels and the patient's performance seemed to be running parallel, with interaction and conversation improving noticeably at higher levels and declining as ketone concentrations approached baseline. An increase in the patient's self-sufficiency and a reduced need for supervision were also noted [72]. However, properly designed case-control studies need to confirm these observations.

In summary, a moderate improvement in AD symptoms has been found following dietary supplementation with relatively low concentrations of ketone bodies. In individuals with

epilepsy, the highest possible portion of the calorie need may have to be provided in the form of ketone bodies in order to decrease glucose metabolism sufficiently to compromise glutamate production in neurons. By contrast, much lower amounts of ketone bodies can have therapeutic effects in AD probably by different mechanisms. The smaller ketone body doses administered in AD may owe their effect mainly to the support of energy metabolism, but they might also inhibit the release of gliotransmitter glutamate [32].

7. Possible problems with ketogenic diets in AD

Physicians are commonly afraid of ketosis because severe hyperketonemia induced by insulin deficiency may be a life-threatening condition in patients with type 1 diabetes. It is, however, important to distinguish between diabetic ketoacidosis and nutritional ketosis ("physiological ketosis" [74]). Ketoacidosis is a pathological metabolic state characterized by extreme ketosis which cannot be adequately regulated due to a lack of insulin. The resulting pH imbalance may be fatal. However, this kind of metabolic derangement is not possible in ketosis induced by dietary changes.

The evaluation of side effects of ketogenic diets in patients with AD is difficult due to the small number of available clinical trials. Major adverse reactions have not been reported in the literature. Transient, mild to moderate gastrointestinal effects such as diarrhea, dyspepsia, and flatulence were reported in patients receiving a formulation of medium chain triglycerides [68,69]. The administration of a ketogenic diet to 83 obese patients for 24 weeks did not produce any significant adverse effects [75].

Strict adherence to low carbohydrate consumption is needed in ketogenic diets. This may be difficult for AD patients due to their altered food preference toward carbohydrate-rich and sweet foods [76,77]. The administration of medium chain triglycerides in order to induce ketosis may be favorable in AD since there is no need for dietary change.

8. Conclusions and future directions

More than 50% of all dementia cases are caused by AD. There are currently no therapies available to prevent or at least delay the progression of the disease. The early and region-specific 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 toxic effects of A β 1–42 on hippocampal neurons in culture were reversed by D- β -hydroxybutyrate, suggesting that ketone bodies may have neuroprotective efficacy [53]. Some animal studies have shown that high-fat diets are associated with elevated A β loads [78,79] while decreased A β levels were observed following the administration of a ketogenic diet high in saturated fat and very low in carbohydrates [55]. These seemingly conflicting findings can be explained by the fact that, in the earlier studies, fat was added to the diet without a marked reduc-

tion in carbohydrates. Dietary strategies attempting to decrease A β levels should therefore consider the interactions of dietary components and their metabolic outcomes, i.e. total calories, carbohydrate levels and the production of ketone bodies need to be taken into account. The translational relevance of these findings should be confirmed in clinical studies with AD patients.

Data from clinical trials suggest that medium chain triglycerides improve cognition in patients with mild to moderate AD in ApoE4-negative patients [68,69]. In order to establish the role of medium chain triglycerides in the therapy of AD, genetic screening including ApoE4 carriage status would have to be routinely performed in patients. A novel approach to induce therapeutic hyperketonemia is the administration of ketone monoesters [72]. A case report using this method presented promising results. However, case–control studies need to confirm this observation.

Best results of dietary ketogenic approaches in AD may be expected by early presymptomatic treatment [80]. However, a reliable diagnostic identification of individuals with minimal neuropathological alterations would be necessary. It is currently unclear whether or not cognitive decline can be delayed if brain hypometabolism is improved preclinically or early in the course of the disease. Future studies need to demonstrate that the neuroprotective properties of ketone bodies can influence or prevent AD-related impairment of clinically relevant functions such as cognition. In this respect, there is at present only limited evidence of the usefulness of ketogenic diets in AD. However, this novel dietary approach seems to be interesting and deserves further clinical investigations in AD.

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