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# Searching the Linkage between High Fat Diet and Alzheimer's Disease: A Debatable Proof Stand for Ketogenic Diet to Alleviate Symptoms of Alzheimer's Patient with APOE ε4 Allele

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## Abstract

Alzheimer's disease (AD) is an incurable neurodegenerative form of dementia affecting millions of individuals worldwide. A hallmark of AD is the deregulation of the level of ß-amyloid (Aß) that leads to the appearance of the senile plaques that contain Aß derived from the cleavage of the amyloid precursor protein. Among numerous risk factors for AD, genetic risk factor such as possession of ε4 allele of apolipoprotein E (ApoE4) is considered as a crucial risk factor. Moreover, dietary fat composition has also been concerned as an important factor for AD since cholesterol and blood-brain barrier functions are linked with AD. The primary genetic risk factor is ApoE ε4 allele that encodes one of several proteins responsible for cholesterol transport and it is considered as foremost cholesterol transport proteins in the brain. For the progression of AD high level of serum/plasma cholesterol has been recommended as a causative factor. But this statement is debatable meanwhile brain cholesterol levels of AD patients are highly variable and cholesterol levels in serum/plasma and brain of AD patients do not consider cholesterol as a risk factor in AD. Indeed, APOE ε4 is neither essential nor enough for the development of *AD*, it only serves as a synergistic and increases the risk of AD. Another prominent feature of AD is region-specific declines in brain glucose metabolism. The brain cells are totally different from other cells of the body, the brain cells cannot competently metabolize fats, therefore completely depends on glucose as an energy substrate. Consequently, inhibition of glucose metabolism can have intense effects on the brain functions. As a result hypo-metabolism observed in AD has just attained considerable attention as a probable target for interference in the disease progression. One propitious way is to maintain the regular glucose supply to the brain with ketone bodies from ketogenic diet represents a potent therapeutic for AD. Therefore the objective of this study was to analyze the relationship of the high dietary fat composition to the risk of developing AD by considering the impact of ApoE genotype.

**Keywords:** Alzheimer's disease; Amyloid-ß; High fat diet; Ketogenic diet; Ketone bodies; APOE ε4

**Abbreviations** AD: Alzheimer's Disease; Aß: ß-Amyloid; APP: Amyloid Precursor Protein; BACE1: ß-site APP-Cleaving Enzyme 1; PSEN1: Presenilin 1; PSEN2: Presenilin 2; APOE: Apolipoprotein E; AHRQ: Agency for Healthcare Research and Quality; KD: Ketogenic Diets; BBB: Blood-Brain Barrier; CSF: Cerebrospinal Fluid; CNS: Central Nervous System; LDL: Low Density Lipoprotein; SFA: Saturated Fatty Acids; TFA: Trans Fatty Acids, MUFA: Monounsaturated Fatty Acids; PUFA: Polyunsaturated Fatty Acids; GC: Global Cognitive; MCI: Mild Cognitive Impairment ; MMSE: Mini Mental State Examination; VD: Vascular Dementia; ATP: Adenosine Triphosphate; ß-OHB: ß-Hydroxybutyrate; MCTG: Medium Chain Triglycerides; ε4+: Subjects with Apoε4; ε4−: Subjects without Apoε4; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-CGIC: Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; ITT: Intention-To-Treat; PP: Per Protocol; DC: Dosage Compliant; CDR: Clinical Dementia Rating, TMT: Trail Making Test; V-PAL: Verbal Paired Associate Learning; GDS: Geriatric Depression Scale; CO: Coconut Oil; MCFA: Medium-Chain Fatty Acids; MCT: Medium-Chain Triglyceride; ADLs: Activities of Daily Living; MRI: Magnetic Resonance Imaging; KME: Ketone Monoester

## Introduction

Alzheimer's disease (AD) is an irreversible, neurodegenerative disorders and the most common cause of dementia account for 60 to 70% of cases, mostly affecting people older than 65 years of age [1]. Worldwide AD affects approximately 35.6 million people. This will increase with aging owing to the baby boomers generation becoming older and will probably affect nearly 106.8 million people by 2050 [2,3]. This progressive brain disorder is characterized by accumulation of extracellular senile plaques, dystrophic neurites and intracellular

neurofibrillar tangles [4,5]. The plaques mainly consist of the ß-amyloid (Aß) peptide which is derived from the cleavage of the amyloid precursor protein (APP) [6]. APP is a transmembrane protein that is vital for the growth, survival and repair of post-injury of neuron [7,8]. Proteolysis of APP is occurred by α-, ß- and γ-secretases [9]. In the brain, ß-secretase such as ß-site APP-cleaving enzyme 1 (BACE1) is the major enzyme responsible for cleavage of APP to form C99 fragment and soluble APPß [10]. This generated C99 is cleaved by γ-secrets to produce several isoforms of neurotoxic Aß [11-13]. The most common isoforms are Aß40 and Aß42. Among these, two isoforms Aß40 form is common and Aß42 is the more fibrillogenic consequently linked to disease states [14].

Moreover, both presenilin 1 (PSEN1) and 2 (PSEN2) control the proteolytic function of γ-secretase and mutations in these proteins can change the activity of γ-secretase and increase the ratio of Aß in early-onset forms of AD [15]. Aß is a complex peptide of 36–43 amino acids which combines with various types of receptors and or generates insoluble agglomeration and eventually non-physiological aggregation of Aß alternate with the normal neuronal functions [16]. Although the exact role of Aß in the etiology of AD remains unclear, it is clear that Aß is a key risk factor and has a central role in the onset and progression of AD [17].

Early-onset and late-onset both forms of AD have a genetic component [18]. Early-onset AD occurs in people age 30 to 60 years and represents less than 5% of all people with Alzheimer's [19]. A number of different single-gene mutations on chromosomes 21, 14 and 1 are responsible for early-onset AD by the formation of abnormal proteins [20]. Mutations on chromosome 21 are responsible for the formation of abnormal APP [21]. A mutation on chromosome 14 causes the formation of abnormal PSEN1 as well as mutation on chromosome 1 leads to the formation of abnormal PSEN2 [22]. Aforementioned mutations play a vital role in the breakdown of APP. In fact, most of the Alzheimer's patients have the late-onset form and symptoms appear in the mid-60s and later [23]. The influence of a specific gene in late-onset AD is not yet completely understood. However, one genetic risk factor, i.e., having one form of the apolipoprotein E (APOE) gene on chromosome 19, does increase a person's risk [24]. There are various forms of APOE (i.e., ε2, ε3 and ε4). APOE ε2 is relatively rare and may provide little protective action against the disease. Generally, if AD occurs in a person with this allele, it develops later in life than it would in someone with the APOE ε4 gene. APOE ε3 is the most common allele that plays a neutral role in the Alzheimer's [25-27]. On the other hand APOE ε4 is responsible for increasing the risk for AD and is also related to an earlier age of disease onset. A person has zero, one or two APOE ε4 alleles. Having more APOE ε4 alleles increases the risk of developing Alzheimer's, that's why APOE ε4 is called a risk-factor gene. Several studies stated that between 40 and 80% of people with AD hold at least one APOE ε4 allele [28]. The APOE ε4 allele increases the risk of the disease by three times in heterozygotes and by 15 times in homozygotes [29]. However, inheriting an APOE ε4 allele does not mean that a person will absolutely develop Alzheimer's. Some people with an APOE ε4 allele never get the disease and others who develop Alzheimer's do not have any APOE ε4 alleles [30,31].

Dietary factors are integrally linked with the development and propagation of AD [32]. A number of laboratory research and epidemiological studies have explored the associations between high fat diets and AD [33]. Using transgenic mouse models of AD, researchers have reported that high fat diets or diets with added cholesterol increased the levels and deposition of the Aß peptide [34-38]. A number of studies suggested that high intake of saturated fats and trans fats is associated with the risk of AD [39-41]. In addition, few studies suggested that diets rich in omega-3 fatty acids may reduce the risk of AD. In addition, the Mediterranean diet is also associated with the reduced Alzheimer's risk [42]. Some have suggested that the regular consumption of fatty fish intake (i.e., more than twice per week) may be associated with lower risk for AD in individuals without the APOE ε4 allele [43]. However, a systematic review by the Agency for Healthcare Research and Quality (AHRQ) concluded that data are inadequate to justify conclusions. Elevated cholesterol levels are associated with increased risk for AD, even after controlling for the presence of the APOE ε4 allele [44].

The brain's principal energy substrate is glucose. Alzheimer's patients are unable to use glucose properly owing to lack of brain functions, but neurobiological evidence suggests that ketone bodies are an effective alternative energy substrate for the brain [45]. Diets that contain very low carbohydrate and high fat content are well known to induce the hepatic production of ketone bodies (i.e., ß-hydroxybutyrate, acetoacetate and acetone) and are often referred to as ketogenic diets (KD) [46]. The neuroprotective effects of KD have been confirmed by several studies. Researchers confirmed that KDs can enhance cognitive function in pathophysiological as well as normal, healthy experimental animal systems [47,48]. Actually, most of the benefit of KB can be credited with their ability to increase mitochondrial efficiency and supplement the brain's normal reliance on glucose. Inquiry to examine the therapeutic potentiality of KB and ketosis represents a favorable new area of AD research [49,50].

The effect of high fat diet on AD is well known, but the relationship with ApoE is not well understood. Therefore the purpose of this study was to analyze the linkage between high fat diet and AD by envisaging ApoE.

## Lipids in the pathophysiology of Alzheimer's disease

Lipids are vital for proper neuronal development associated with brain and brain functions [51]. The brain is the organ with highest lipid level that constitute 50–60% of the brain's dry weight and represents 25% of the total body cholesterol [52,53]. About 60–70% of the brain cholesterols are in myelin and another pool is neurons and glial cells [54]. Cholesterol is the functional component of all cell membranes, as well as structural support for the neural network. It is important in the formation and functioning of synapses, also serves as a brain antioxidant and an electrical insulator in order to avoid ion leakage [55].

In the development of AD, cholesterol may play a vital role [56]. Exactly, the core of the neuritic plaques that characterize AD is consisted of by cholesterol and neuritic plaques are thought that a crucial role of the APP is to clear excess cholesterol from the brain [56]. The most established genetic risk factor for AD is the ApoE ε4 allele, which has been associated with nearly a doubling in the risk of developing AD [57]. ApoE ε4 allele encodes one of several proteins involved in cholesterol transport and it is considered as chief cholesterol transport proteins in the brain. Several cohort studies also suggested that hypercholesterolemia increase the chance of developing dementia [58-61].

However, there are huge conflicts about the role of elevated cholesterol levels as a risk factor for AD. The study of Popp et al. suggested that plasma cholesterol levels were approximately 10%

higher in AD patients as compared to the control subjects and statistically significant [62]. But in another previous study of the same research team reported that plasma cholesterol levels of AD and control individuals were not statistically significant [63]. In another longitudinal study in case of the first exam, cholesterol levels were significantly higher in AD patients with respect to control subjects, but were not statistically significant at the second exam [64]. According to the study of the Whitmer et al. high cholesterol levels at mid-life were connected with the risk of developing late-life dementia. The outcome of this study recommended that out of 2844 subjects with cholesterol levels above 240 mg/dL only 266 were identified with dementia. A number of the Cox proportional hazards model, also suggested cholesterol levels as risk factors of developing AD [65]. But a previous meta-analysis of 10 studies published between 1986 and 1999 suggested opposite consequence [66]. This study endorsed that the cholesterol level of the AD patients was significantly lower than normal subjects [66]. In addition, Honolulu-Asia aging and Framingham studies found that serum cholesterol levels at mid-life were not associated with late-life dementia or AD [67]. Statistics suggest that in the USA, 98.9 million people have cholesterol levels of 200 mg/dL and higher and 31.9 million have cholesterol levels of 240 mg/dL and higher but only 4.7 million people have AD [68,69].

Another matter is that serum and plasma cholesterol levels are not in equilibrium with the brain cholesterol levels [70]. Usually, alteration of serum and plasma cholesterol does not affect brain cholesterol homeostasis [70]. The study of Kirsch et al. also suggested similar concern [71]. In fact, Erickson and Banks proposed that blood-brain barrier (BBB) may be dysfunctional in AD that could alter brain cholesterol homeostasis [70]. However, analysis of different brain regions and the cerebrospinal fluid (CSF) suggests reduced cholesterol levels, increased cholesterol levels and no changes in cholesterol levels in AD patients versus control subjects. As told by the study of Mason et al. cholesterol levels were lower in the temporal gyrus of autopsied brains of AD patients than control subjects [72]. Sparks found that cholesterol levels in the frontal cortex gray matter of AD patients were modestly but significantly higher with the APOE ε4 genotype related to APOE ε4 control subjects [73].

According to the study of Heverin et al. cholesterol levels were analogous in the cerebral cortex of AD and control subjects [74]. The same researcher also noted an increase in cholesterol levels in the basal ganglia of AD patients with respect to control subjects [74]. In accordance with the study of Eckert et al. cholesterol levels did not differ in hippocampal tissue of AD patients compared to control subjects [75]. Previous studies have confirmed that subjects with dementia and depression had considerably lower serum cholesterol levels than the control subjects [76]. Brain cholesterol levels of AD patients are highly variable consequence elevated total serum cholesterol levels in either mid-life or later do not have a major role in the development of AD.

## Role of ApoE in the development and progression of Alzheimer's disease

ApoE is a 299 amino acid glycoprotein and the major apolipoprotein in the brain [77]. In the central nervous system (CNS), ApoE is mainly produced by astrocytes [27]. ApoE transports cholesterol to neurons via ApoE receptors, which are members of the low density lipoprotein (LDL) receptor gene family [78,79].

ApoE is polymorphic, there are three common alleles of the APOE gene: Apoε2 (Cys112, Cys158), Apoε3 (Cys112, Arg158) and Apoε4 (Arg112, Arg158) [80,81]. Apoε2 has an allele frequency of approximately 7% and Apoε3 has an allele frequency of approximately 79% [82]. There is also confirmation that the Apoε2 allele may exert a protective role in AD as stated earlier [83]. Apoε4 has an allele frequency of approximately 14% and present in at least one copy in approximately 25% of the population [56,82]. A number of studies confirmed that Apoε4 allele is the most prevalent genetic risk factor for AD [84]. Studies suggested that about 2% subjects that are homozygous for APOE ε4 alleles are eight times more likely to develop AD than subjects that are homozygotes for APOE ε3 [56]. In fact, APOE ε4 is not a determinant of the AD its neither necessary nor sufficient to cause AD, it just increases the chance of AD [27].

| Frequency | ApoE (%) | | |
|---|---|---|---|
| | ε2 | ε3 | ε4 |
| General people | 8.4 | 77.9 | 13.7 |
| AD patients | 3.9 | 59.4 | 36.7 |

**Table 1:** Worldwide projected human allele frequencies of ApoE [85].

Studies showed that subjects with the APOE ε4 allele tend to have high serum LDL [44]. In addition, previous study recommended that a high cholesterol level is positively connected with long life of people over 85 years old and in some cases has been shown to be associated with better memory function and reduced dementia [86]. But here is also confusion, since a study showed that although APOE ε4 has been found to double the odds of AD, high cholesterol can nearly triple the threat of AD [59].

## Dietary fats and the risk of Alzheimer's disease

Dietary fat composition is an important factor in the neuropathology of AD [64,87]. The main classes of dietary fatty acids are saturated fatty acids (SFA), trans fatty acids (TFA), monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) [88]. Two essential fatty acids for human are α-linoleic acid (18:2, n-6) and α-linolenic acid (18:3, n-3). In addition, dietary fatty acids are also essential for the sufficient absorption of the lipid soluble vitamins (Vitamin A, D, E and K) [64].

Most of the studies based on laboratory research, animal as well as epidemiologic studies showed that consumptions of high saturated and trans fatty acid increase the chance of dementia and lower risk with the consumptions of high unsaturated fatty acid [64,89] Grimm et al. in the cell culture experiments reported that TFA increased amyloidogenic APP and decreased non-amyloidogenic APP with respect to cis forms of oleic and PUFA [90]. Further, their study found that the TFA also increased Aβ aggregation [90]. Oksman et al. in the study of transgenic mice found that administration of the westernized diet of 40% SFA for the period of 4 months increased the concentration of Aß in the brain with respect to soy oil based diet [91].

However, another study of aged dogs found that diets high in SFA and low in MUFA increased learning faults and decreased cognitive functions [92]. But, another study of Winocur and Greenwood in transgenic mice found diets high in SFA causes learning and memory dysfunction by impairing glucose regulation resulting in reduced glucose uptake in the hippocampus [93].

Several studies recommend that intake of saturated fat increases the risk of AD or cognitive impairment and intake of monounsaturated and polyunsaturated fats has protective effects [93]. Numerous prospective dietary studies also reported similar outcomes. Morris et al. has shown that intakes of saturated fat and trans-unsaturated fat were positively associated with the risk of AD, whereas intakes of ω-6 polyunsaturated fat and monounsaturated fat were inversely associated [94]. They examined that high intake of saturated fats doubled the risk of Alzheimer's and even moderate intake of trans fat increased the risk by 2 to 3 times in Chicago [94].

The study of Luchsinger et al. in New York found a greater risk of AD for those with higher intakes of total fat and saturated fat, but no evidence of an association with the intake of polyunsaturated fats [95]. Researchers of the Rotterdam study also found an increased risk of disease with higher intakes of total fat, saturated fat and cholesterol after 2 years of follow-up, but none of the dietary fat was associated with AD after 6 years of follow-up [40].

A number of prospective epidemiologic studies have investigated the relationship of dietary fatty acid composition to the risk of developing cognitive dysfunction [global cognitive (GC), mild cognitive impairment (MCI), mini mental state examination (MMSE)] and dementia [AD, vascular dementia (VD)] represented in Table 2.

| Name of the Study | N | Follow-up (y) | SFA | TFA | MUFA | PUFA | Result |
|---|---|---|---|---|---|---|---|
| Beydoun et al. [96] | 2251 | 6 | I | – | – | D | GC |
| Devore et al. [97] | 1486 | 1.8 | I | I | d | – | GC |
| Engelhart et al. [98] | 5395 | 6 | D | D | – | – | AD |
| | | | – | – | – | – | Dementia |
| Eskelinen et al. [99] | 1449 | 21 | I | – | – | d | MCI |
| | | | I | – | – | – | GC |
| Heude et al. [100] | 246 | 4.4 | I | – | – | I | MMSE |
| Kalmijn et al. [40] | 5395 | 2 | – | – | – | – | AD |
| | | | i | – | – | – | VD |
| Laitinen et al. [101] | 1449 | 21 | i | – | d | d | AD |
| Luchsinger et al. [95] | 980 | 4 | i | – | – | – | AD |
| Morris et al. [94] | 815 | 3.9 | I | I | d | d | AD |
| Morris et al. [102] | 2560 | 6 | I | I | d | d | GC |
| Naqvi et al. [103] | 482 | 3 | – | – | D | – | GC |
| Okereke et al. [104] | 6183 | 9 | I | – | D | – | GC |
| Roberts et al. [105] | 937 | 3.7 | – | – | – | d | MCI |
| Ronnemaa et al. [106] | 838 | 35 | D | – | – | I | AD |
| Samieri et al. [107] | 1214 | 4 | – | – | – | – | GC |
| Solfrizzi et al. [108] | 704 | 8.5 | – | – | d | d | MMSE |
| Vercambre et al. [109] | 2551 | 8.9 | – | – | d | d | GC |

**Table 2:** Prospective epidemiologic studies of dietary fats and the risk of cognitive dysfunction and dementia [100-116]. [Where, I=Statistically significant increased risk; D=Statistically significant decreased risk; i=Marginally statistically significant increased risk; d=Marginally statistically significant decreased risk].

## Ketogenic diets as a therapeutic target for Alzheimer's disease

KD is a high-fat, medium-protein and low-carbohydrate diet [110]. The KD is so-termed, as maintenance of this diet induces and sustains a ketosis state in the body [111]. The ability of KB to increase mitochondrial efficiency and supplement of glucose makes them attractive compounds to treat AD and other neurological disorders [112]. The KD has demonstrated potential in treating several neurological disorders given in Table 3.

| Name of the Study | Species | Disease Model | Result |
|---|---|---|---|
| Dardzinsk et al. [113] | Rats | Hypoxia ischemia | Neuroprotection |
| Imamura et al. [114] | Cell culture | Parkinson' disease | Increased cell survival |
| Kashiway et al. [115] | Cell culture | Alzheimer's disease | Increased cell survival |
| Klepper et al. [116] | Human | GLUT1 haploinsufficiency | Decrease seizure frequency |
| Maalouf et al. [117] | Cell culture | Glutamate toxicity | Increased mitochondrial efficiency |
| Massieu et al. [118] | Rat cell culture | Glutamate toxicity | Neuroprotection |
| Masuda et al. [119] | Cell culture | Hypoxia | Increased cell survival |
| Mejia-Toiber et al. [120] | Rats | Glutamate toxicity | Neuroprotection and reduced lipid peroxidation |
| Noh et al. [121] | Mice | Kainic acid-induced seizures | Increased cell survival |
| Noh et al. [122] | Cell culture | Glutamate toxicity | Increased cell survival |
| Prins et al. [123] | Rats | Traumatic brain injury | Reduced contusion volume |
| Prins et al. [124] | Rats | Traumatic brain injury | Restored ATP levels after controlled cortical impact |
| Suzuki et al. [125] | Mice | Hypoxia | Maintained ATP and low lactate |
| Suzuki et al. [126] | Mice | Ischemia | Reduced cerebral infarct area |
| Tieu et al. [127] | Mice | Parkinson's disease | Improved neuronal survival, improved mitochondrial efficiency |
| Vanitallie et al. [128] | Human | Parkinson's disease | Improved motor function |
| Van der Auwera et al. [129] | Mice | Alzheimer's disease | Reduced Aβ levels |
| Zhao et al. [130] | Mice | Amyotrophic lateral sclerosis | Increased motor neuron counts |

**Table 3:** Neuroprotective effect of ketogenic diets against various neurological disease models [113-130].

In the study of effects of ß-hydroxybutyrate (ß-HB) on cognition in memory-impaired adults by Reger et al. reported that ketone levels were positively correlated with memory performance [131]. In this study, 20 subjects with AD and or MCI consumed a drink containing emulsified medium chain triglycerides (MCT) or placebo on separate days. When cognitive tests were performed after 90 min, marked ($P$=0.007) increases in levels of the ketone body, ß-HB was observed. APOE genotype moderated ß-HB rises. It was found that subjects with Apoε4 ($\varepsilon$4+), ß-HB levels gradually rise between the 90 and 120 min blood draws in the treatment condition, but for subjects without Apoε4 ($\varepsilon$4−), ß-HB levels remained constant ($P$<0.009). Contrariwise on cognitive testing, MCT treatment aided performance on the AD Assessment Scale-Cognitive Subscale (ADAS-cog) for $\varepsilon$4− subjects, but not for $\varepsilon$4+ subjects ($P$=0.04). In all subjects, higher ketone levels corresponded with greater memory improvements (paragraph recall) with MCT treatment relative to placebo ($P$=0.02) [131].

These preliminary, short-term findings were followed up later by Henderson et al. among 152 subjects with mild to moderate AD [132]. In this study a ketogenic compound was administered to subjects for 90 days and cognitive performance was determined by using ADAS-Cog, MMSE and AD Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) [132]. In this study an oral ketogenic compound was compared with respect to placebo in several subject groups, including: intention-to-treat (ITT), per protocol (PP) and dosage compliant (DC) groups. In each of the subject groups, a significant difference was found between ketogenic compound and placebo in mean change from baseline in ADAS-Cog score among subjects who did not carry the Apoε4 allele on 45$^{th}$ and 90$^{th}$ day. In the ITT subjects, ε4− subjects (N=55) administered ketogenic compound had a significant of 4.77 point difference in mean change from baseline in ADAS-Cog scores at 45$^{th}$ day (P=0.0005) and a 3.36 point difference at 90$^{th}$ day (P=0.0148) compared to placebo. In the PP subjects, ε4− subjects receiving ketogenic compound (N=37) differed from placebo by 5.73 points at 45$^{th}$ day (P=0.0027) and by 4.39 points on 90$^{th}$ day (P=0.0143). In the DC subjects, ε4− subjects receiving ketogenic compound differed from placebo by 6.26 points at 45$^{th}$ day (P=0.0011, N=38) and 5.33 points on 90$^{th}$ day (P=0.0063, N=35). Furthermore, it was found that after 2 h of administration of ketogenic compound, noticeable rises in a serum ketone body especially ß-HB was reported with respect to placebo [132].

Lane-Donovan et al. investigate the effect of diet on ApoE levels by feeding wildtype, ApoE3, and ApoE4 targeted replacement (TR) mice with chow, high-fat, or ketogenic diets [133]. This study found that a high-fat diet reduced hippocampal ApoE levels in mice expressing human ApoE3, but not ApoE4 or murine ApoE, and this effect was not observed after a similar amount of time on a ketogenic diet. Moreover, while a high-fat diet increased steady state plasma ApoE levels in all genotypes, a KD only increased plasma ApoE levels in human ApoE4

TR mice. The KD had no effect on hippocampal ApoE. Together, these results suggest that dietary composition alters ApoE protein levels in an isoform-specific manner. Researchers suggest that the use of dietary interventions to slow the progression AD should take ApoE genotype into consideration [133].

These auspicious primary outcomes of ketogenic compounds presented optimism that dietary interferences might likewise benefit brain health. Krikorian et al. examined the effect of carbohydrate diet on memory of 23 older subjects with MCI by using clinical dementia rating (CDR), trail making test (TMT) part B, verbal paired associate learning test (V-PAL) and geriatric depression scale (GDS) [134]. This study found improved verbal memory performance in the low carbohydrate subjects ($P$=0.01) compared to those on a high-carbohydrate diet after six-week intervention period. However, for low carbohydrate subjects, reductions in weight ($P$<0.0001), waist circumference ($P$<0.0001), fasting glucose ($P$=0.009) and fasting insulin ($P$=0.005) were also observed. Ketone levels were positively correlated with memory performance ($P$=0.04). These findings indicate that very low carbohydrate consumption, even in the short-term, can improve memory function in older adults with an increased the risk for Alzheimer's. The researcher conclude, although this effect may be attributable in part to correction of hyperinsulinemia, other mechanisms associated with ketosis such as reduced inflammation and enhanced energy metabolism also may have contributed to improved neurocognitive function [134].

The therapeutic potentiality of the ketosis hasn't been strictly tested in a formal clinical trial, but current a case study of Newport et al. delivers an astonishing therapeutic target for controlling AD [135]. In this study a 63 year old man with younger-onset, sporadic AD for 12 years began consuming 35 ml of coconut oil (CO) once daily [CO contains ~15% ketogenic medium-chain fatty acids (MCFA)]. After several months, medium-chain triglyceride (MCTG) was added and increased gradually to a 4:3 mixture with CO, eventually reaching 165 ml/day divided into 3 to 4 servings. Use of the MCTG/CO mixtures as dietary supplements was associated with rapid improvement of score of MMSE from 12 to 20, after 2.5 months. Later that additional gradual improvement occurred in gait, social participation, word finding and recall of recent events. Thus, during MCFG treatment for twenty months, the ADAS-Cog score of the patient rose to 6 points and activities of daily living (ADLs) rose 14 points, followed by stabilization. The magnetic resonance imaging (MRI) of the patient showed no further brain atrophy. After that, ketone monoester (KME) was incorporated in the diet of the patient. As a result, the living functions, behavior as well as cognitive ability of the patient were improved. After six to eight weeks of taking 28.7 g of the KME thrice daily, the patient began to exhibit improvement in memory retrieval, spontaneously discussing events that occurred up to a week earlier. In addition, plasma ß-HB levels were measured before and during KME treatment to assess KME-plasma ß-HB dose-response relationships. The only noteworthy changes were in certain plasma lipids. Over 20 months, total cholesterol fell from a pre-KME mean (n=2) of 244 to 163 mg/dL. HDL cholesterol fell from 85 to 68 mg/dL and LDL cholesterol from 145 to 81 mg/dL. Notably, this man carried the Apoε4 gene, thus researchers resolved that ketosis does appear to be highly beneficial for Apoε4 carriers, even if prior studies indicate it's even *more* helpful for those without this risk factor [135].

## Conclusion

Still now Alzheimer's is incurable, but the current treatment strategy can improve the quality of life of the patients by slowing the worsening of the symptoms of dementia. For the efficacious treatment of AD if ketosis is to become affirmed, additional investigation is essential to ascertain the proper mode of administration, since high-fat diets, MCFA, MCT supplements or ketogenic compounds may be discretely efficient. In addition, patient compliance could also represent challenges owing to administering strict diet or supplements. However, it is very inevitable to mark out the minimum and maximum effective dose that will aid to fix the treatment regimen. In spite of these existing questions, the therapeutic potentiality of ketogenic diet suggests a powerful weapon in the fight against the development and progression of AD.

## Author's Contribution

This work was carried out in collaboration between all authors. Author MSU designed the study, wrote the protocol, managed the analyses of the study and prepared the draft of the manuscript. Authors AAM, MAI, MTK, RKR and MMB managed the literature searches under supervision of author MSU. Author AH reviewed the scientific contents of the manuscript. All the authors read and approved the final manuscript.

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## Competing Interests

The authors proclaim that they have no competing interests.

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