



Review Article

## Ketone Bodies as Alternative Brain Fuel: Impact on Cognitive Function in Alzheimer's Disease

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### ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia worldwide and is characterized by progressive cognitive decline, memory impairment, and neurodegeneration. A growing body of evidence suggests that cerebral glucose hypometabolism is an early and significant feature of AD, occurring years before the onset of clinical symptoms. As neuronal glucose utilization becomes impaired, alternative energy substrates such as ketone bodies may provide a viable metabolic strategy to support brain function. Ketone bodies, including  $\beta$ -hydroxybutyrate (BHB), acetoacetate (AcAc) and acetone, are produced primarily in the liver during periods of fasting, carbohydrate restriction, prolonged exercise, or ketogenic dietary interventions. Unlike glucose metabolism, ketone uptake and utilization remain relatively preserved in the Alzheimer's brain. Recent studies have demonstrated that ketogenic diets, medium-chain triglyceride (MCT) supplementation, and exogenous ketone administration may improve cognitive performance, memory, mitochondrial function, and neuronal survival in patients with AD. Ketone bodies also exert neuroprotective effects through reduction of oxidative stress, modulation of neuroinflammation, enhancement of mitochondrial efficiency, and regulation of amyloid-beta and tau pathology. This review examines the pathophysiological basis of impaired cerebral glucose metabolism in AD, the mechanisms by which ketone bodies serve as alternative brain fuels, current clinical evidence supporting ketogenic therapies, and future directions for integrating metabolic interventions into Alzheimer's disease management.

**Keywords:** Alzheimer's disease, Ketone bodies, Ketogenic diet, Cognitive function,  $\beta$ -hydroxybutyrate, Brain metabolism, Neurodegeneration.

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### INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by deterioration of memory, cognition, behavior, and functional independence. It accounts for approximately 60–80% of all dementia cases globally and represents a major public health challenge due to increasing life expectancy and population aging [1]. Histopathologically, AD is characterized by extracellular amyloid-beta ( $A\beta$ ) plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, synaptic dysfunction, neuronal loss, and cerebral atrophy [2].

Recent advances in neuroimaging and molecular neuroscience have revealed that cerebral glucose hypometabolism is among the earliest detectable abnormalities in AD, preceding significant neuronal loss and clinical symptoms by decades [3]. Positron emission tomography (PET) studies consistently demonstrate reduced glucose uptake in the temporal, parietal, and posterior cingulate cortices of individuals with mild cognitive impairment (MCI) and AD [4]. These findings have led researchers to describe Alzheimer's disease as a "metabolic brain disorder" or even "Type 3 diabetes" because of impaired insulin signaling and reduced neuronal glucose utilization [5].

The adult human brain accounts for approximately 20% of total body energy consumption despite constituting only 2% of body weight [6]. Under normal physiological conditions, glucose serves as the primary fuel source for neuronal metabolism. However, during prolonged fasting, starvation, carbohydrate restriction, or ketogenic dietary interventions, the liver produces ketone bodies from fatty acid oxidation. These ketone bodies can supply up to 60–70% of the brain's energy requirements [7].

Ketone bodies include  $\beta$ -hydroxybutyrate (BHB), acetoacetate (AcAc), and acetone. Unlike glucose metabolism, ketone uptake through monocarboxylate transporters remains largely preserved in aging and Alzheimer's disease [8]. Consequently, ketone bodies may compensate for impaired glucose metabolism and provide an alternative source of energy to metabolically compromised neurons [9].

In addition to their energetic role, ketone bodies function as signaling molecules capable of influencing gene expression, reducing oxidative stress, improving mitochondrial function, suppressing neuroinflammation, and enhancing neuronal resilience [10]. Emerging evidence indicates that ketogenic diets, MCT supplementation, and exogenous ketone administration may improve cognitive performance and delay disease progression in selected AD patients [11].

The concept of targeting brain energy metabolism represents a novel therapeutic paradigm that complements existing amyloid- and tau-focused approaches. Understanding the relationship between ketone metabolism and cognitive function may provide valuable insights into developing effective interventions for Alzheimer's disease [12].

#### Pathophysiology of Brain Energy Dysfunction in Alzheimer's Disease

Brain glucose metabolism is significantly impaired in Alzheimer's disease. Reduced expression of glucose transporters GLUT1 and GLUT3 decreases neuronal glucose uptake [13]. Mitochondrial dysfunction further compromises ATP generation, leading to energy deficits that impair synaptic transmission and neuronal survival [14].

Insulin resistance within the brain contributes substantially to AD pathogenesis. Defective insulin signaling affects neuronal growth, synaptic plasticity, neurotransmitter synthesis, and memory formation [15]. Impaired insulin receptor activation promotes amyloid-beta accumulation and tau hyperphosphorylation, accelerating neurodegeneration [16].

Neuroinflammation mediated by activated microglia and astrocytes exacerbates metabolic dysfunction through the production of pro-inflammatory cytokines and reactive oxygen species [17]. Chronic inflammation damages mitochondrial DNA and impairs oxidative phosphorylation, further reducing neuronal energy availability [18].

Because neuronal energy deficiency develops early in AD, interventions that bypass impaired glucose metabolism have attracted considerable research interest [19].

#### **Ketone Bodies: Production and Metabolism**

Ketone bodies are synthesized in hepatic mitochondria during conditions of low carbohydrate availability [20]. Fatty acids undergo  $\beta$ -oxidation to generate acetyl-CoA, which is subsequently converted into acetoacetate and  $\beta$ -hydroxybutyrate. Acetone is produced through spontaneous decarboxylation of acetoacetate [21].

#### **The major ketone bodies are:**

1.  $\beta$ -Hydroxybutyrate (BHB)
2. Acetoacetate (AcAc)
3. Acetone

After entering circulation, ketone bodies cross the blood-brain barrier via monocarboxylate transporters (MCT1 and MCT2) [22]. Within neurons and astrocytes, ketones are converted into acetyl-CoA and enter the tricarboxylic acid (TCA) cycle for ATP production [23].

Importantly, ketone metabolism remains relatively intact even when glucose metabolism is severely compromised in Alzheimer's disease [24].

#### **Mechanisms by Which Ketone Bodies Improve Cognitive Function**

##### 1. Alternative Energy Supply

Ketone bodies bypass defective glucose metabolism and provide efficient ATP production. Studies demonstrate that ketone oxidation can restore cerebral energy deficits and improve neuronal function in AD models [25].

##### 2. Enhancement of Mitochondrial Function

BHB improves mitochondrial respiration, increases ATP generation, and stimulates mitochondrial biogenesis through activation of PGC-1 $\alpha$  signaling pathways [26].

### 3. Reduction of Oxidative Stress

Ketone metabolism generates fewer reactive oxygen species compared to glucose metabolism. BHB enhances antioxidant defenses by increasing expression of superoxide dismutase, catalase, and glutathione-related enzymes [27].

### 4. Anti-inflammatory Effects

BHB inhibits activation of the NLRP3 inflammasome, reducing production of inflammatory cytokines such as IL-1 $\beta$  and IL-18 [28].

### 5. Amyloid-Beta Reduction

Experimental studies suggest ketogenic interventions decrease amyloid-beta accumulation and improve amyloid clearance mechanisms [29].

### 6. Tau Protein Regulation

Ketone metabolism may reduce tau hyperphosphorylation by modulating kinase activity and improving cellular energy homeostasis [30].

### 7. Epigenetic Regulation

BHB functions as a histone deacetylase (HDAC) inhibitor, promoting expression of genes involved in neuroprotection, synaptic plasticity, and cognitive function [31].

## Clinical Evidence

### Medium-Chain Triglyceride Supplementation

Several randomized clinical trials have demonstrated that MCT supplementation increases circulating ketone levels and improves memory performance in patients with mild cognitive impairment and mild AD [32].

### Ketogenic Diets

Ketogenic diets produce sustained nutritional ketosis and have shown improvements in attention, executive function, and memory in pilot studies [33].

### Exogenous Ketone Supplements

Ketone esters and ketone salts rapidly elevate plasma ketone concentrations and may provide cognitive benefits without strict dietary restrictions [34].

### Mild Cognitive Impairment

Patients with MCI often demonstrate greater responsiveness to ketogenic therapies compared with those with advanced AD, suggesting early intervention may be critical [35].

### Potential Limitations of Ketogenic Therapy

Despite promising findings, several challenges remain:

- Long-term adherence to ketogenic diets can be difficult.
- Gastrointestinal adverse effects may occur.
- Nutritional deficiencies may develop without proper supervision.
- Individual responses vary according to genetic factors, including APOE genotype.
- Large multicenter trials are still limited [36].

## MATERIALS AND METHODS

### Materials and Methods

#### Study Design

This review article was conducted to comprehensively evaluate the role of ketone bodies as alternative brain fuels and their impact on cognitive function in patients with Alzheimer's disease (AD). The review summarizes evidence regarding the pathophysiological basis of cerebral glucose hypometabolism, ketone metabolism, ketogenic interventions, neuroprotective mechanisms, and clinical outcomes associated with ketone-based therapies in AD.

#### Literature Search Strategy

A systematic and extensive literature search was performed to identify relevant studies published between January 2000 and June 2026. Electronic databases including PubMed/MEDLINE, Scopus, Embase, Web of Science, Cochrane Library, Google Scholar, ScienceDirect, and SpringerLink were searched. Additional articles were identified through manual screening of reference lists from eligible studies and relevant review articles.

The search strategy incorporated combinations of Medical Subject Headings (MeSH) terms and keywords including:

- Alzheimer's disease

- Dementia
- Mild cognitive impairment
- Brain glucose metabolism
- Cerebral hypometabolism
- Ketone bodies
- $\beta$ -hydroxybutyrate
- Acetoacetate
- Ketogenic diet
- Medium-chain triglycerides
- Exogenous ketones
- Neuroprotection
- Cognitive function
- Brain energy metabolism
- Mitochondrial dysfunction
- Neuroinflammation
- Oxidative stress
- Alternative brain fuel
- Metabolic therapy

Boolean operators ("AND", "OR") were applied to optimize search sensitivity and specificity.

### ***Eligibility Criteria***

#### **Inclusion Criteria**

##### **Studies were included if they:**

1. Investigated ketone body metabolism in Alzheimer's disease or cognitive impairment.
2. Evaluated ketogenic diets, medium-chain triglycerides (MCTs), ketone esters, or exogenous ketone supplementation.
3. Assessed cognitive outcomes, memory performance, executive function, or neurological parameters.
4. Included human clinical trials, observational studies, cohort studies, randomized controlled trials, systematic reviews, meta-analyses, and experimental animal studies.
5. Were published in peer-reviewed journals.
6. Were available in the English language.
7. Provided data related to brain energy metabolism or neuroprotective mechanisms.

#### **Exclusion Criteria**

##### **Studies were excluded if they:**

1. Were conference abstracts without full-text availability.
2. Included insufficient methodological information.
3. Focused exclusively on epilepsy, Parkinson's disease, or other neurological disorders without Alzheimer's disease data.
4. Were duplicate publications.
5. Had incomplete outcome reporting.
6. Were non-English publications lacking reliable translation.
7. Were editorials, commentaries, expert opinions, or letters without original data.

### ***Study Selection Process***

All identified articles were screened independently based on titles and abstracts. Potentially eligible studies underwent full-text review. Duplicates were removed prior to screening. Disagreements regarding study eligibility were resolved through consensus after detailed evaluation of methodological quality and relevance.

### ***Data Extraction***

Relevant information was extracted from each selected study, including:

- Author and year of publication
- Study design
- Sample size
- Participant characteristics
- Intervention type
- Duration of intervention
- Cognitive assessment tools
- Brain imaging findings
- Metabolic biomarkers

- Primary and secondary outcomes
- Major conclusions

Data were organized into evidence tables to facilitate comparison among studies.

### **Quality Assessment**

Methodological quality was assessed according to study design. Randomized controlled trials were evaluated using established risk-of-bias criteria. Observational studies were assessed for participant selection, outcome measurement, confounding variables, and statistical analysis. Systematic reviews and meta-analyses were evaluated based on comprehensiveness of search strategy, study selection methods, and quality appraisal procedures.

### **Outcome Measures**

The primary outcomes included:

- Changes in cognitive performance
- Memory improvement
- Executive function enhancement
- Attention and processing speed
- Neuropsychological assessment scores

### **Secondary outcomes included:**

- Brain glucose metabolism
- Ketone utilization
- Mitochondrial function
- Oxidative stress markers
- Neuroinflammatory biomarkers
- Amyloid-beta pathology
- Tau protein alterations
- Quality of life measures

### **Data Synthesis**

A narrative synthesis approach was employed because of heterogeneity among study populations, intervention methods, outcome measures, and follow-up durations. Evidence was categorized according to mechanistic studies, animal experiments, observational investigations, randomized controlled trials, and systematic reviews. Findings were integrated to provide a comprehensive understanding of the therapeutic role of ketone bodies in Alzheimer's disease.

### **Reporting Guidelines**

The preparation of this review followed recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, reproducibility, and methodological rigor in evidence synthesis.

## **RESULTS**

The evidence from both preclinical and clinical studies consistently demonstrates that ketone bodies provide a viable alternative energy substrate for the brain, particularly under conditions of impaired glucose metabolism such as in Alzheimer's disease (AD) [3,8,9]. Animal models of AD have shown that ketogenic interventions, including high-fat ketogenic diets and exogenous ketone supplementation, significantly increase circulating levels of  $\beta$ -hydroxybutyrate and acetoacetate, which are efficiently transported across the blood-brain barrier via monocarboxylate transporters and utilized for neuronal ATP production [22,23,25]. These metabolic shifts were associated with improved mitochondrial function, enhanced synaptic activity, and reduced oxidative stress markers in hippocampal and cortical neurons [14,26,27,31]. Specifically, ketone-fed transgenic AD mice exhibited lower reactive oxygen species accumulation and upregulated expression of endogenous antioxidant enzymes, such as superoxide dismutase and catalase, compared with controls [27,31]. Moreover, ketone interventions were shown to attenuate neuroinflammatory signaling by suppressing NLRP3 inflammasome activation and reducing pro-inflammatory cytokines, including IL-1 $\beta$  and IL-18, in both rodent and in vitro models [28,52,53].

Evidence also indicates that ketone metabolism can influence classical AD pathology. Several preclinical studies demonstrated that ketogenic diets or ketone ester supplementation reduce amyloid-beta accumulation and deposition in the hippocampus and cortex, likely through enhanced mitochondrial bioenergetics and activation of autophagic clearance pathways [29,45–47]. Additional findings suggest that tau hyperphosphorylation, a hallmark of neurofibrillary tangle formation, is mitigated in the presence of sustained ketone availability, potentially via modulation of kinase activity and improved energy homeostasis in neurons [30,48]. Collectively, these mechanistic findings support the hypothesis that ketone bodies confer multifaceted neuroprotective effects beyond simple energy provision.

Clinical trials have further corroborated these preclinical observations. In patients with mild cognitive impairment (MCI) or early-stage AD, ketogenic diets, medium-chain triglyceride (MCT) supplementation, and exogenous ketone esters were shown to elevate circulating ketone levels, which corresponded with measurable improvements in cognitive domains including memory, attention, and executive function [32,33,34,37,55,56]. Notably, studies indicated that APOE genotype may modulate responsiveness, with APOE ε4 non-carriers generally experiencing more pronounced cognitive benefits [57]. Medium-chain triglyceride supplementation induced mild ketosis and demonstrated improved performance on standardized memory tests over intervention periods ranging from 6 weeks to 3 months [32,55,56]. Similarly, administration of ketone esters in cognitively impaired adults resulted in significant enhancements in working memory and processing speed compared to placebo [61,62].

Neuroimaging studies provided complementary evidence of functional brain benefits. Positron emission tomography (PET) analyses revealed that ketone-based interventions increased cerebral uptake of ketone bodies while partially compensating for glucose hypometabolism in temporoparietal and posterior cingulate cortices, regions critically involved in learning and memory [3,40,41,44]. Furthermore, longitudinal data suggest that sustained ketone availability may support synaptic integrity and slow functional decline in MCI and early AD populations, although the magnitude of effect appears greatest in individuals with preserved neuronal networks and earlier disease stages [35,64,65]. Across studies, ketone interventions were generally well tolerated, with gastrointestinal discomfort being the most commonly reported adverse event, and no serious safety concerns were consistently observed [69,70].

Overall, the collective evidence underscores that ketone bodies can serve as an effective alternative cerebral fuel in conditions of impaired glucose metabolism, simultaneously exerting antioxidant, anti-inflammatory, and disease-modifying effects, while translating into measurable cognitive improvements in both preclinical models and human studies [8–10,24,27–31,37,55–57,61–65].

## DISCUSSION

Alzheimer's disease (AD) remains one of the most challenging neurodegenerative disorders worldwide and is characterized by progressive deterioration of memory, cognition, behavior, and functional independence. Despite decades of research focused on amyloid-beta plaques and neurofibrillary tau tangles, therapeutic success has been limited, highlighting the need for alternative approaches that target additional pathological mechanisms. Increasing evidence suggests that cerebral energy failure represents a fundamental feature of Alzheimer's disease and may occur years before clinical symptoms become apparent [3,4,13]. The findings summarized in this review indicate that ketone bodies possess significant potential to compensate for impaired glucose metabolism and may serve as an effective metabolic therapy for preserving cognitive function in individuals with Alzheimer's disease [8,9].

One of the most important observations emerging from recent research is that cerebral glucose hypometabolism is among the earliest detectable abnormalities in Alzheimer's disease. Neuroimaging studies consistently demonstrate reduced glucose uptake within brain regions responsible for learning, memory, and executive function, including the temporal cortex, parietal cortex, hippocampus, and posterior cingulate gyrus [3,4,41,42]. These metabolic deficits may precede the development of amyloid pathology and clinical manifestations by several years. Such findings have led investigators to propose that impaired energy metabolism is not merely a consequence of neurodegeneration but may actively contribute to disease progression [5,13]. In this context, the ability of ketone bodies to provide an alternative energy substrate becomes particularly important because ketone utilization remains relatively preserved even in individuals with advanced Alzheimer's disease [8,24,43,44].

The concept of utilizing ketone bodies as alternative brain fuel is supported by well-established physiological principles. Under normal conditions, glucose serves as the primary energy source for the brain; however, during fasting, starvation, prolonged exercise, or carbohydrate restriction, ketone bodies can provide up to two-thirds of cerebral energy requirements [7]. β-Hydroxybutyrate and acetoacetate readily cross the blood-brain barrier through monocarboxylate transporters and enter neuronal mitochondria where they are converted into acetyl-CoA for ATP production [22,23]. Unlike glucose metabolism, which is impaired in Alzheimer's disease due to insulin resistance and decreased glucose transporter expression, ketone metabolism remains functional, allowing neurons to access energy despite defects in glucose utilization [13,15,22]. This unique metabolic characteristic forms the biological basis for ketogenic interventions in neurodegenerative disorders [8,24].

The present review found substantial evidence supporting the beneficial effects of ketone bodies on mitochondrial function. Mitochondrial dysfunction is recognized as a central component of Alzheimer's pathology and contributes significantly to neuronal energy failure, oxidative stress, and apoptosis [14,18]. Several experimental studies have demonstrated that ketone bodies improve mitochondrial respiration, increase ATP generation, and enhance mitochondrial biogenesis through activation of regulatory pathways such as PGC-1α [26,49,50]. Improved mitochondrial efficiency results in greater energy availability for synaptic transmission, neuronal repair, and maintenance of cognitive processes. These findings are

consistent with previous reports indicating that mitochondrial dysfunction contributes directly to memory impairment and neurodegeneration in Alzheimer's disease [14,18,50].

Another important finding highlighted in this review is the role of ketone bodies in reducing oxidative stress. Oxidative damage is widely recognized as a major contributor to neuronal injury in Alzheimer's disease [27,51]. Excessive production of reactive oxygen species damages cellular proteins, lipids, and nucleic acids, ultimately leading to synaptic dysfunction and neuronal death. Ketone metabolism produces fewer reactive oxygen species than glucose metabolism and simultaneously enhances endogenous antioxidant defense mechanisms [27].  $\beta$ -Hydroxybutyrate has been shown to increase expression of antioxidant enzymes including superoxide dismutase, catalase, and glutathione peroxidase, thereby protecting neurons against oxidative injury [27,31,51]. The reduction in oxidative stress observed in ketogenic interventions may therefore represent an important mechanism underlying cognitive improvement in Alzheimer's disease. Neuroinflammation represents another critical pathological process targeted by ketone bodies. Chronic activation of microglia and astrocytes contributes to progressive neuronal injury through sustained production of inflammatory cytokines and neurotoxic mediators [17,52]. Studies included in this review demonstrated that  $\beta$ -hydroxybutyrate inhibits activation of the NLRP3 inflammasome, resulting in decreased secretion of pro-inflammatory cytokines such as IL-1 $\beta$  and IL-18 [28,52]. Reduced neuroinflammation has been associated with improved synaptic function, enhanced neuronal survival, and attenuation of disease progression [17,53,54]. These anti-inflammatory properties distinguish ketone bodies from conventional symptomatic therapies and support their potential role as disease-modifying interventions.

An important aspect of ketone metabolism that has gained increasing attention is its influence on amyloid-beta pathology. Accumulation of amyloid-beta plaques remains one of the defining pathological features of Alzheimer's disease and contributes to synaptic dysfunction and neuronal loss [2]. Experimental studies reviewed herein demonstrated reductions in amyloid-beta deposition among animals receiving ketogenic diets or ketone supplementation [29,45–47]. Several mechanisms have been proposed to explain these observations, including improved mitochondrial function, enhanced autophagic clearance, reduced oxidative stress, and modulation of amyloid precursor protein processing [29,46]. Although the exact mechanisms require further investigation, available evidence suggests that ketone bodies may influence fundamental pathological pathways involved in Alzheimer's disease development.

Similarly, the potential effects of ketone bodies on tau pathology deserve consideration. Hyperphosphorylated tau proteins form neurofibrillary tangles that correlate strongly with cognitive decline and disease severity [2]. Emerging evidence indicates that ketone metabolism may reduce tau phosphorylation through modulation of cellular signaling pathways and improvement of neuronal energy homeostasis [30,48]. By maintaining adequate ATP production and reducing oxidative stress, ketone bodies may limit activation of kinases involved in tau phosphorylation. Although human data remain limited, preclinical findings suggest that ketogenic interventions may influence both major pathological hallmarks of Alzheimer's disease [30,48].

The role of ketone bodies as signaling molecules extends beyond their function as metabolic substrates.  $\beta$ -Hydroxybutyrate has been shown to act as a histone deacetylase inhibitor, thereby regulating gene expression associated with neuroprotection, stress resistance, and synaptic plasticity [31]. This epigenetic activity may contribute to enhanced neuronal resilience and improved cognitive performance. Such findings indicate that ketone bodies possess pleiotropic biological effects that extend beyond simple energy replacement. Consequently, ketogenic therapies may simultaneously target multiple pathological processes involved in Alzheimer's disease progression [10,31].

Clinical evidence evaluating ketogenic interventions has expanded considerably during the past decade. Medium-chain triglyceride supplementation has emerged as one of the most practical approaches for inducing mild nutritional ketosis without requiring strict dietary restriction [32,55,56]. Multiple clinical trials have reported improvements in memory, attention, executive function, and overall cognitive performance following MCT administration [32,55]. These benefits are thought to result from rapid hepatic conversion of medium-chain fatty acids into ketone bodies, leading to increased cerebral ketone availability [20,21,55]. The favorable cognitive outcomes observed in these studies support the translational potential of metabolic therapies for Alzheimer's disease management.

Ketogenic diets have also demonstrated promising clinical results. Studies involving patients with mild cognitive impairment and early Alzheimer's disease have reported improvements in verbal memory, processing speed, executive functioning, and activities of daily living following ketogenic dietary interventions [11,33,58,59]. Increased plasma ketone concentrations correlated positively with cognitive improvements, suggesting a direct relationship between ketosis and enhanced brain function [58,59]. These observations support the hypothesis that restoring cerebral energy metabolism can positively influence cognitive outcomes in neurodegenerative disorders.

Interestingly, several studies reported that individuals with mild cognitive impairment derived greater benefit from ketogenic interventions than patients with advanced Alzheimer's disease [35,64,65]. This finding may reflect the greater preservation of neuronal networks during earlier disease stages. Once extensive neuronal loss has occurred, restoration of

energy metabolism alone may be insufficient to reverse cognitive deficits. Therefore, early implementation of metabolic therapies may provide the greatest therapeutic benefit. This concept is consistent with current understanding that interventions targeting disease mechanisms are generally more effective before irreversible neurodegeneration develops [35,64].

Genetic factors may also influence responsiveness to ketogenic therapies. Several studies have reported differential responses according to APOE genotype, with non-carriers of the APOE  $\epsilon$ 4 allele often exhibiting greater cognitive improvement following ketone supplementation [57]. The biological basis for this observation remains incompletely understood but may involve differences in lipid metabolism, mitochondrial function, and cerebral energy utilization. Future studies should further investigate personalized approaches to ketogenic therapy based on genetic and metabolic characteristics [57].

Exogenous ketone supplementation has emerged as an attractive alternative to traditional ketogenic diets because it can rapidly increase circulating ketone concentrations without substantial dietary modification [34,61,62]. Clinical studies have demonstrated improvements in working memory, attention, and cognitive processing following administration of ketone esters and ketone salts [61,62]. Exogenous ketones may therefore provide a practical therapeutic option for patients who find long-term adherence to ketogenic diets challenging. However, additional long-term studies are needed to establish optimal dosing regimens, safety profiles, and sustained cognitive benefits [34,62].

Despite encouraging findings, several limitations remain. Many clinical studies have involved relatively small sample sizes, short intervention periods, and heterogeneous methodologies [36,66,67]. Differences in dietary protocols, ketone formulations, participant characteristics, cognitive assessment tools, and outcome measures complicate direct comparison across studies. Furthermore, long-term adherence to ketogenic diets can be difficult, particularly among elderly individuals with cognitive impairment [36,69]. Gastrointestinal discomfort, nutritional deficiencies, and dietary compliance issues remain important considerations when implementing ketogenic therapies in clinical practice [69,70].

Another limitation is the lack of large multicenter randomized controlled trials evaluating long-term clinical outcomes. Although available studies generally report favorable cognitive effects, definitive conclusions regarding disease modification, progression delay, and survival benefits require further investigation [36,66–68]. Future research should focus on standardized intervention protocols, longer follow-up durations, biomarker-guided patient selection, and integration of neuroimaging techniques to better characterize therapeutic responses [37,67].

Overall, the evidence reviewed strongly supports the concept that ketone bodies represent a promising therapeutic strategy for addressing cerebral energy deficits in Alzheimer's disease. By providing an alternative fuel source, enhancing mitochondrial function, reducing oxidative stress, suppressing neuroinflammation, and potentially influencing amyloid-beta and tau pathology, ketone bodies target multiple mechanisms involved in neurodegeneration [8–10,24,27–31]. The convergence of experimental, mechanistic, and clinical findings suggests that metabolic therapy may complement existing pharmacological approaches and contribute to a more comprehensive management strategy for Alzheimer's disease. As research continues to evolve, ketone-based interventions may become an increasingly important component of precision medicine approaches aimed at preserving cognitive function and improving quality of life in individuals affected by this devastating disorder [37,68,71–75].

## CONCLUSION

Alzheimer's disease is increasingly recognized as a disorder characterized not only by amyloid-beta and tau pathology but also by profound disturbances in cerebral energy metabolism. Accumulating evidence indicates that impaired glucose utilization is an early and significant feature of the disease, contributing to neuronal dysfunction and cognitive decline. Ketone bodies, particularly  $\beta$ -hydroxybutyrate and acetoacetate, provide an effective alternative energy substrate for the brain and can bypass defects in glucose metabolism that occur during Alzheimer's disease progression.

The findings reviewed in this article demonstrate that ketone-based interventions, including ketogenic diets, medium-chain triglyceride supplementation, and exogenous ketone administration, may improve cognitive performance, enhance mitochondrial function, reduce oxidative stress, suppress neuroinflammation, and potentially influence amyloid-beta and tau pathology. Clinical studies have reported improvements in memory, attention, executive function, and overall cognitive outcomes, particularly in individuals with mild cognitive impairment and early-stage Alzheimer's disease.

Beyond their role as metabolic fuels, ketone bodies act as important signaling molecules that regulate gene expression, cellular stress responses, and neuroprotective pathways. These multifaceted actions make ketone-based therapies a promising adjunctive approach in the management of Alzheimer's disease. Although further large-scale randomized controlled trials are needed to establish long-term efficacy and optimal treatment protocols, current evidence supports the growing potential of metabolic therapy as an innovative strategy for preserving cognitive function and improving quality of life in patients with Alzheimer's disease.

## Future Perspectives

Future research should focus on:

- Personalized ketogenic interventions based on metabolic profiling.
- Combination therapies involving ketones and anti-amyloid drugs.
- Long-term safety studies.
- Optimization of exogenous ketone formulations.
- Identification of biomarkers predicting therapeutic response.
- Integration of metabolic imaging techniques into treatment monitoring [37].

## Limitations

- Most studies had small sample sizes.
- Considerable heterogeneity existed in study design and intervention protocols.
- Long-term efficacy and safety data remain limited.
- Adherence to ketogenic diets may be challenging in elderly patients.
- Many studies had short follow-up durations.
- Large multicenter randomized controlled trials are still needed.

## DECLARATIONS:

**Conflicts of interest:** There is no any conflict of interest associated with this study

**Consent to participate:** There is consent to participate.

**Consent for publication:** There is consent for the publication of this paper.

**Authors' contributions:** Author equally contributed the work.

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