International Journal of Advanced Scientific Research
www.allscientificjournal.com
ISSN: 2456-0421
Received: 02-08-2025, Accepted: 01-09-2025, Published: 17-09-2025
Volume 10, Issue 3, 2025, Page No. 211-216

Therapeutic role of ketogenic diet in neurological disorders: Epilepsy to Alzheimer's

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Abstract
The ketogenic diet (KD)—a high-fat, very-low-carbohydrate dietary therapy that induces nutritional ketosis—has re-emerged as an evidence-based intervention for drug-resistant epilepsy and is increasingly investigated across neurological disorders including migraine, traumatic brain injury, autism spectrum disorder, Parkinson's disease, and Alzheimer's disease. Proposed mechanisms span neuronal excitability modulation via altered neurotransmission, improvements in mitochondrial bioenergetics and oxidative stress, anti-inflammatory signaling, epigenetic effects, and enhanced cerebral energetics through ketone bodies (β-hydroxybutyrate and acetoacetate). Robust pediatric data support efficacy for refractory epilepsy and specific metabolic epilepsies (e.g., GLUT1 deficiency), while adult epilepsy studies show growing but smaller evidence bases. For Alzheimer's disease and mild cognitive impairment, early trials of ketogenic or medium-chain triglyceride (MCT)–supplemented diets suggest cognitive benefits, particularly in APOE ε4–negative individuals, though results are mixed and adherence challenges remain. Safety considerations include gastrointestinal intolerance, dyslipidemia, renal stones, micronutrient insufficiency, and rare complications; careful screening, monitoring, and multidisciplinary implementation mitigate risk. This review synthesizes mechanistic rationales, clinical evidence, protocols, and knowledge gaps, outlining priorities for rigorous trials, biomarkers of response, and patient-tailored approaches.

Keywords: Ketogenic diet, neurological disorders, epilepsy, alzheimer, dyslipidemia, human health

Introduction

Originally introduced in the 1920s to emulate the anticonvulsant effects of fasting, the ketogenic diet (KD) restricts carbohydrates sufficiently to shift metabolism from glucose to fatty acid oxidation, producing ketone bodies as alternative cerebral fuels (Wheless, 2008) [53]. After a mid-century decline due to antiepileptic drugs, the KD was revitalized in the 1990s for refractory pediatric epilepsy and has since diversified into protocols such as the classic long-chain triglyceride KD (typically 4:1 fat:protein+carbohydrate), medium-chain triglyceride (MCT) KD, Modified Atkins Diet (MAD), and Low Glycemic Index Treatment (LGIT) (Kossoff *et al*., 2009; Neal *et al*., 2008) [31, 32, 38]. Beyond seizure control, ketosis exerts pleiotropic effects relevant to neurodegeneration and neuroinflammation, prompting investigation in multiple neurological conditions (Masino & Rho, 2012; Paoli *et al*., 2014) [35, 40].

The role of diet in disease prevention and management has gained substantial recognition in recent decades, particularly within the field of neurological disorders where conventional pharmacological therapies often show limitations in efficacy and tolerability. Among dietary interventions, the ketogenic diet (KD)—a high-fat, moderate-protein, and very low-carbohydrate nutritional regimen—has emerged as a therapeutic strategy for neurological conditions ranging from epilepsy to neurodegenerative diseases such as Alzheimer's disease (AD). Originally developed in the 1920s as a treatment for drug-resistant epilepsy, the ketogenic diet induces a state of nutritional ketosis, whereby ketone bodies such as β-hydroxybutyrate (BHB), acetoacetate, and acetone become the primary energy substrates for the brain, replacing glucose as the predominant fuel source (Neal *et al*., 2008; Paoli *et al*., 2014) [38, 40]. This metabolic shift confers multiple neuroprotective effects, including enhanced mitochondrial efficiency, reduced oxidative stress, modulation of neurotransmitter balance, and attenuation of neuroinflammation, thereby offering therapeutic potential beyond epilepsy (Masino & Rho, 2019).

The rising global burden of neurological disorders further underscores the urgency of exploring effective dietary interventions. According to the World Health Organization (WHO), neurological diseases constitute a leading cause of disability-adjusted life years (DALYs) worldwide, with epilepsy affecting approximately 50 million individuals, and dementia—including Alzheimer's disease—impacting over 55 million people globally (WHO, 2021). Despite advancements in pharmacotherapy, many patients exhibit incomplete responses to standard treatments, such as antiseizure drugs in epilepsy or cholinesterase inhibitors in Alzheimer's disease, with adverse side effects often compounding the disease burden (Wirrell, 2016; Cummings *et al*., 2019). Consequently, there is a growing emphasis on adjunctive and non-pharmacological therapies, with the ketogenic diet gaining renewed interest due to its multifaceted mechanisms of action in the brain.

Epilepsy remains the most well-established indication for ketogenic dietary therapy. Numerous clinical and preclinical studies have demonstrated that the KD significantly reduces seizure frequency in patients with drug-resistant epilepsy, with approximately 30–50% of patients achieving at least a

50% reduction in seizures (Neal *et al*., 2008; Kossoff & Wang, 2013) [30, 38]. Proposed mechanisms include stabilization of neuronal excitability through modulation of GABAergic and glutamatergic transmission, improvement in mitochondrial bioenergetics, and direct anticonvulsant effects of ketone bodies (Rho, 2017). In particular, the enhanced synthesis of gamma-aminobutyric acid (GABA), the brain's primary inhibitory neurotransmitter, and the reduction of excitatory glutamate levels help restore the excitatory-inhibitory balance crucial for seizure control (Bough & Rho, 2007) [4]. These mechanisms suggest a broader therapeutic utility of KD in other neurological disorders characterized by excitotoxicity and energy metabolism impairments.

Beyond epilepsy, accumulating evidence suggests that the ketogenic diet may confer neuroprotective effects in a spectrum of neurological disorders, particularly Alzheimer's disease, Parkinson's disease, multiple sclerosis, traumatic brain injury, and amyotrophic lateral sclerosis (Gasior *et al*., 2006; Paoli *et al*., 2014) [21, 40]. In Alzheimer's disease, impaired glucose metabolism in the brain—often termed "type 3 diabetes"—is a hallmark feature that precedes clinical symptom onset (Cunnane *et al*., 2016) [12]. Ketone bodies can bypass this glucose hypometabolism, serving as an alternative energy substrate for neurons, thereby preserving cognitive function and reducing neurodegeneration (Krikorian *et al*., 2012). Clinical studies have reported improvements in memory performance and overall cognition in mild cognitive impairment and early AD patients supplemented with medium-chain triglyceride (MCT)-based ketogenic interventions (Reger *et al*., 2004; Henderson *et al*., 2009) [24, 25, 44]. Mechanistically, the KD reduces amyloid-β accumulation, enhances synaptic plasticity, and suppresses neuroinflammation, which are central processes in AD pathology (Kashiwaya *et al*., 2013) [28].

Furthermore, the diet's ability to modulate mitochondrial function and oxidative stress has broad implications for neuroprotection. Mitochondrial dysfunction is a common denominator across various neurological disorders, including Parkinson's disease and amyotrophic lateral sclerosis, where energy failure and free radical damage exacerbate neuronal death (Zhou *et al*., 2012). Ketone bodies improve mitochondrial efficiency, increase ATP production, and activate signaling pathways such as peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), which regulates mitochondrial biogenesis and antioxidant defenses (Bough *et al*., 2006). These adaptations may slow disease progression and enhance neuronal resilience in chronic neurodegenerative states.

Another emerging mechanism underlying the therapeutic efficacy of the KD is its anti-inflammatory potential. Neuroinflammation, mediated by microglial activation and cytokine dysregulation, is a key pathogenic feature in disorders such as epilepsy, Alzheimer's disease, and multiple sclerosis (Heneka *et al*., 2015). Ketone bodies, particularly BHB, inhibit the NLRP3 inflammasome, a critical mediator of innate immune activation, thereby reducing neuroinflammatory cascades (Youm *et al*., 2015). This immunomodulatory effect highlights the potential of the KD to attenuate progressive neuronal damage driven by chronic inflammation.

The gut-brain axis also represents a novel avenue through which the ketogenic diet may exert therapeutic effects. Dysbiosis and alterations in gut microbiota composition have been implicated in epilepsy and neurodegenerative disorders, influencing neuroinflammation and neurotransmitter metabolism (Sharon *et al*., 2016). Recent studies suggest that the KD alters gut microbiota diversity and composition, promoting beneficial bacterial strains that enhance GABA production and reduce seizure susceptibility (Olson *et al*., 2018). In Alzheimer's disease, modulation of gut microbiota by KD may attenuate systemic inflammation and improve cognitive outcomes, although this area requires further clinical validation.

Despite its promising benefits, the ketogenic diet also presents challenges and limitations in clinical practice. Adherence to the diet can be difficult due to its restrictive nature, and long-term use may result in side effects such as dyslipidemia, nephrolithiasis, micronutrient deficiencies, and gastrointestinal disturbances (Kossoff & Wang, 2013) [30]. Moreover, the variability in patient response underscores the need for personalized approaches that account for genetic, metabolic, and disease-specific factors. Modified versions of KD, such as the medium-chain triglyceride diet, modified Atkins diet, and low glycemic index treatment, have been developed to improve tolerability and compliance while retaining therapeutic efficacy (Kossoff *et al*., 2009) [31, 32].

In light of these considerations, the ketogenic diet represents a unique metabolic therapy with broad therapeutic implications for neurological disorders. Its historical success in epilepsy has catalyzed research into its potential role in neurodegenerative diseases such as Alzheimer's, where conventional therapies remain limited. The convergence of mechanisms involving energy metabolism, mitochondrial function, neurotransmitter regulation, neuroinflammation, and gut microbiota highlights the KD as a multifaceted intervention that targets fundamental pathophysiological processes in the brain. However, further large-scale randomized controlled trials are necessary to establish standardized protocols, evaluate long-term safety, and delineate patient populations most likely to benefit from ketogenic therapies.

Thus, this review seeks to provide a comprehensive synthesis of the therapeutic role of the ketogenic diet in neurological disorders, beginning with its established application in epilepsy and extending to its emerging role in Alzheimer's disease and beyond. By bridging clinical evidence with mechanistic insights, the review underscores the potential of ketogenic interventions as adjunctive or alternative therapies for neurological health.

Mechanisms of Action: From Ion Channels to Inflammation

Neurotransmission and network excitability. Ketosis increases GABAergic tone and reduces glutamatergic excitation, potentially through altered Krebs cycle intermediates, adenosine signaling, and modulation of vesicular glutamate transport (Yudkoff *et al*., 2007; Masino *et al*., 2011) [36, 54]. Mitochondrial bioenergetics. Ketones enhance mitochondrial efficiency, increase ATP per oxygen, reduce reactive oxygen species, and upregulate antioxidant defenses (Veech, 2004; Bough & Rho, 2007) [4, 52]. Ion channels and metabolic sensors. KD influences ATP-sensitive potassium channels and dampens neuronal hyperexcitability (Ma *et al*., 2007) [34]. Inflammation and redox. β-Hydroxybutyrate inhibits the NLRP3 inflammasome and acts as a class I histone deacetylase (HDAC) inhibitor, linking ketosis to anti-inflammatory and epigenetic effects (Youm *et al*., 2015; Shimazu *et al*., 2013) [46]. Cerebral energetics. In conditions with impaired glucose utilization (e.g., Alzheimer's disease, post-traumatic states), ketones provide an efficient alternative fuel that may normalize regional energy deficits (Cunnane *et al*., 2016; Courchesne-Loyer *et al*., 2013) [11, 12].

Epilepsy: Evidence Base and Clinical Use

Pediatric drug-resistant epilepsy. Multiple controlled and observational studies demonstrate significant seizure reduction with KD. A randomized controlled trial (RCT) showed a median 38% seizure reduction vs. 6% in controls at 3 months, with 38% achieving ≥50% reduction (Neal *et al*., 2008) [38]. Long-term cohorts report sustained benefits and some seizure freedom, especially in epileptic encephalopathies (Krylova *et al*., 2017; Freeman *et al*., 2006) [19, 33]. Metabolic epilepsies. The KD is first-line therapy for GLUT1 deficiency and pyruvate dehydrogenase complex deficiency, where it replaces missing cerebral fuel (Klepper & Leiendecker, 2007) [29]. Adult epilepsy. Trials of KD and MAD show responder rates of ~30–50% at 3–6 months, albeit with higher attrition due to tolerability and lifestyle constraints (Cervenka *et al*., 2016) [8].

Protocols and selection. Classic KD or MCT-based KD may be chosen by lipid tolerance and caloric needs; MAD and LGIT offer greater flexibility with somewhat lower efficacy but improved adherence (Kossoff *et al*., 2009) [31, 32]. Adverse effects and monitoring. Early GI intolerance, constipation, dyslipidemia, kidney stones, micronutrient deficits, and growth concerns (pediatrics) require supplementation (vitamins/minerals, citrate), hydration, and periodic labs (Kossoff *et al*., 2009; Kang *et al*., 2004) [27, 31, 32].

Beyond Epilepsy: Expanding Neurological Indications

1. Migraine

Small trials and case series suggest reduced migraine frequency and weight-independent benefits of KD and very-low-calorie ketogenic diets, possibly via cortical excitability and CGRP/energy metabolism pathways (Di Lorenzo *et al*., 2015; Ripa *et al*., 2021) [13, 14, 45]. Evidence remains preliminary, and pragmatic protocols often use short induction phases.

2. Traumatic Brain Injury (TBI)

Preclinical studies indicate that ketones improve cerebral energy metabolism and reduce edema and oxidative stress after TBI (Prins, 2008) [43]. Early clinical feasibility studies in ICU patients show safety and target ketosis achievement, but robust outcome data are pending (Ardelt *et al*., 2016) [1].

3. Autism Spectrum Disorder (ASD)

Open-label studies and small controlled trials suggest improvements in seizure burden and some behavioral domains with KD or modified KD in children with comorbid epilepsy/ASD (Evangeliou *et al*., 2003; Napoli *et al*., 2014) [16, 17, 37]. Heterogeneity and adherence limit generalizability.

4. Parkinson's Disease (PD)

Pilot studies have reported improvements in Unified Parkinson's Disease Rating Scale (UPDRS) motor and non-motor scores with KD, potentially through mitochondrial and dopaminergic support and reduced neuroinflammation (VanItallie *et al*., 2005; Phillips *et al*., 2018) [41, 42, 51]. Comparative trials vs. low-fat diets suggest symptom benefits but require larger RCTs.

5. Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS)

Animal models show reduced demyelination and inflammation with ketosis; small human studies in MS demonstrate weight loss, improved fatigue, and quality-of-life indices (Brenton *et al*., 2019) [5, 6]. ALS data are limited and mixed, with concerns about weight loss (Zhou *et al*., 2010) [56].

Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI)

Rationale. AD features early cerebral glucose hypometabolism; ketones can supply up to 60% of brain energy needs when elevated, potentially bypassing metabolic bottlenecks (Cunnane *et al*., 2016) [12]. β-Hydroxybutyrate also exerts signaling effects relevant to amyloid/tau, oxidative stress, and inflammation (Kashiwaya *et al*., 2013; Newman & Verdin, 2017) [28, 39].

Clinical evidence

- **MCT and ketone esters:** Trials of MCT emulsions (producing modest ketosis) showed cognitive improvements in memory and attention tests in MCI/AD, especially among APOE ε4–negative individuals (Reger *et al*., 2004; Henderson *et al*., 2009) [24, 25, 44].
- **Whole-diet KD:** Small RCTs and pilot studies show improved memory scores, daily function, and cerebrospinal fluid biomarkers with higher ketone levels, though adherence and GI tolerance are variable (Taylor *et al*., 2018; Fortier *et al*., 2020) [18, 48, 49].
- **Heterogeneity:** APOE genotype, baseline insulin resistance, and dietary adherence moderate responses; long-term disease-modifying effects remain unproven (Cunnane *et al*., 2016) [12].

Practical considerations: Mediterranean-ketogenic hybrids and food-first MCT strategies can improve acceptability while maintaining ketosis (Phillips *et al*., 2021). Cognitive outcomes appear related to achieved ketone levels and duration of adherence (Fortier *et al*., 2020) [18].

Implementation: Diet Variants, Monitoring, and Safety

Dietary variants.

- **Classic KD (4:1 or 3:1):** Highest ketosis; used in pediatrics and refractory epilepsy.
- **MCT KD:** Replaces part of long-chain fats with MCT to allow more carbohydrate/protein at similar ketosis (Huttenlocher, 1976) [26].
- **Modified Atkins (10–20 g net carbs/day) and LGIT (40–60 g/day, GI ≤50):** Greater flexibility for

adolescents/adults and non-epilepsy indications (Kossoff *et al*., 2009) [31, 32].

Screening and Monitoring: Baseline labs (complete metabolic panel, lipids, carnitine in selected cases), renal ultrasound history, growth (children), medications (carbonic anhydrase inhibitors raise stone risk), and diet education are essential. Follow-up includes lipids, micronutrients (selenium, zinc, vitamin D), acid–base status, and urinary citrate; potassium citrate prophylaxis reduces nephrolithiasis (Kang *et al*., 2004) [27].

Adverse effects: Short-term: nausea, constipation, hypoglycemia, fatigue; longer-term: dyslipidemia, kidney stones, micronutrient insufficiency, menstrual irregularities, and in rare cases cardiomyopathy with selenium deficiency (Kossoff *et al*., 2009; Bergqvist *et al*., 2003) [3, 31, 32]. Contraindications include disorders of fatty-acid oxidation, primary carnitine deficiency, porphyria, pancreatitis, significant hepatic failure, and unstable cardiac disease (Kossoff *et al*., 2009) [31, 32].

Knowledge Gaps and Future Directions

Key needs include (i) large, genotype- and phenotype-stratified RCTs in AD, PD, migraine, and TBI; (ii) standardized definitions of dietary adherence and target ketone ranges; (iii) identification of biomarkers (e.g., brain ketone uptake via PET, CSF metabolites) to predict responders; (iv) long-term safety data in adults with comorbidities; and (v) comparative effectiveness vs. pharmacotherapy or combined approaches (diet + exercise + cognitive training). Precision nutrition frameworks that integrate metabolic profiles (insulin resistance, APOE status), microbiome data, and patient preferences may optimize benefit–risk (Cunnane *et al*., 2016; Newman & Verdin, 2017) [12, 39].

Table 1: Therapeutic Role of Ketogenic Diet in Neurological Disorders

Neurological Disorder	Mechanism of Action of Ketogenic Diet	Observed Therapeutic Role	Key Findings / Evidence	References
Epilepsy	Enhances GABAergic activity, reduces neuronal excitability, stabilizes brain energy metabolism	Reduces seizure frequency, particularly in drug-resistant epilepsy	Clinical trials show ~50% seizure reduction in children and adults resistant to anti-epileptic drugs	Freeman *et al*., 2007 [20]; Kossoff & Wang, 2013 [30]
Autism Spectrum Disorder (ASD)	Improves mitochondrial function, modulates neurotransmitters, reduces oxidative stress	Potential improvement in behaviour, cognition, and social interaction	Animal models and pilot studies suggest improvements in core symptoms	Evangeliou *et al*., 2003 [16, 17]; Napoli *et al*., 2014 [37]
Parkinson's Disease	Enhances mitochondrial efficiency, reduces oxidative damage, increases ATP production	May improve motor symptoms and protect dopaminergic neurons	Preclinical studies and limited clinical data indicate motor function improvements	VanItallie *et al*., 2005 [51]; Phillips *et al*., 2018 [41, 42]
Alzheimer's Disease	Provides ketones as alternative energy source to glucose-deficient neurons; reduces amyloid-beta toxicity	Enhances cognition, delays progression, improves memory and daily function	Clinical trials report improved cognitive performance and memory recall	Henderson *et al*., 2009 [24, 25]; Taylor *et al*., 2018 [48, 49]
Multiple Sclerosis (MS)	Anti-inflammatory, improves mitochondrial activity, reduces neurodegeneration	Reduces fatigue, improves motor functions, may slow progression	Animal studies and small human studies support neuroprotective benefits	Choi *et al*., 2016 [10]; Brenton *et al*., 2019 [5, 6]
Amyotrophic Lateral Sclerosis (ALS)	Enhances energy metabolism, reduces excitotoxicity, provides neuroprotection	May slow disease progression and improve muscle function	Animal studies show prolonged survival; human evidence still limited	Zhao *et al*., 2006 [55]; Dorst *et al*., 2013 [15]
Migraine	Stabilizes neuronal hyperexcitability, modulates brain energy metabolism	Reduction in migraine frequency and severity	Preliminary clinical evidence suggests benefit in chronic migraine patients	Di Lorenzo *et al*., 2015 [13, 14]; Barbanti *et al*., 2017 [2]

Conclusion

The ketogenic diet is an established therapy for refractory epilepsy and GLUT1 deficiency and a promising, biologically plausible intervention across a spectrum of neurological disorders. While mechanistic rationales are compelling—combining improved cerebral energetics, anti-inflammatory signaling, and modulation of excitability—clinical efficacy outside epilepsy is not yet definitive. Carefully selected patients, diet variants tailored for adherence, and structured monitoring enable safe implementation. Ongoing rigorous trials should clarify which patients benefit most, optimal ketogenic "dose," and durability of effects, especially in Alzheimer's disease and other neurodegenerative conditions.

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