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The Role of Nutritional Ketosis in Managing Neurological Symptoms in Long COVID Patients: A Systematic Review

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Abstract

Background: Long COVID is characterized by persistent neurological symptoms, which include cognitive dysfunction, fatigue, and memory problems. It is considered to be caused by chronic neuroinflammation and mitochondrial dysfunction. Current therapies are very unsatisfactory; therefore, there is an urgent need for novel therapeutic options. Among potential non-pharmacological strategies, nutritional ketosis induced by a ketogenic diet represents an appealing approach thanks to its neuroprotective and anti-inflammatory properties.

Aim: This systematic review will provide a critical appraisal of the evidence and theoretical rationale on the use of nutritional ketosis in the management of neurological symptoms among Long COVID patients.

Methods: A systematic search was performed in the databases PubMed, Scopus, Web of Science, PsycINFO, and Cochrane Library for studies published between 2013 and 2025. Keywords included "Long COVID", "ketogenic diet", "nutritional ketosis", "brain fog", and "neuroinflammation". Included studies were clinical trials, observational studies, or relevant preclinical research.

Results: Synthesis of the emerging evidence indicates that nutritional ketosis targets key mechanisms in Long COVID. Ketone bodies represent an efficient alternative cerebral fuel and may thereby bypass glycolytic impairment and improve mitochondrial bioenergetics. In addition, beta-hydroxybutyrate has potent anti-inflammatory and epigenetic effects.

Conclusion: Nutritional ketosis has emerged as a very compelling, mechanism-driven dietary intervention to alleviate the neurological burden of Long COVID. Initial results are promising, but it is expected that large-scale, robust randomized controlled trials are required to confirm efficacy, establish protocols, and identify responsive patient subgroups. To date, the ketogenic diet represents one of the few potential patient-empowerment tools within a comprehensive management strategy.

Keywords: Long COVID, ketogenic diet, nutritional ketosis, brain fog, neuroinflammation.

Introduction

The global COVID-19 pandemic, caused by the SARS-CoV-2 virus, has transitioned into a new public health challenge: Long COVID. Also known as Post-Acute Sequelae of SARS-CoV-2 infection (PASC), this condition affects a significant proportion of individuals, with estimates suggesting tens of millions of people worldwide experience persistent symptoms long after the initial acute phase of the infection has resolved (Davis et al., 2023). Long COVID is a multisystem disorder characterized by a complex and often debilitating array of over 200 symptoms, among which neurological and cognitive manifestations are particularly prevalent and disabling (Ceban et al., 2022). The most frequently reported neurological symptoms include profound and persistent cognitive dysfunction, colloquially termed "brain fog," which encompasses deficits in attention, concentration, executive function, and memory recall. This is often coupled with crippling fatigue that is not relieved by rest, headaches, sleep disturbances, and anosmia (Graham et al., 2021). These symptoms significantly impair quality of life, reduce occupational capacity, and pose a substantial burden on healthcare systems and societies at large.

The exact pathophysiological mechanisms underlying the neurological sequelae in Long COVID remain to be fully elucidated but are thought to be multifactorial. Leading hypotheses implicate persistent viral reservoirs or viral fragments inducing

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a chronic, low-grade inflammatory state both systemically and within the CNS (Proal & VanElzakker, 2021). This neuroinflammation is considered to disrupt the function of glial cells, especially microglia and astrocytes, and the integrity of the blood-brain barrier. Mitochondrial dysfunction has been identified as one of the main features, leading to decreased cellular energy production (ATP) of brain cells (Risbano et al., 2023). This energetic crisis, in combination with potential microvascular damage and autoimmunity, constitutes an environment hostile to optimal neuronal functioning that clinically presents with cognitive and fatigue symptoms in patients (Shabani et al., 2023). Current management strategies for these symptoms are mainly supportive and symptomatic, with limited evidence for highly effective pharmaceutical interventions, marking a critical unmet need for novel mechanism-targeting therapies.

Nutritional ketosis, a metabolic state elicited by a high-fat, adequate-protein, and very-low-carbohydrate KD, has been receiving increasing interest in recent years for various neurological and inflammatory conditions. For decades, KD has constituted a well-established treatment of drug-resistant epilepsy (Neves et al., 2021). More recently, its therapeutic potential has been explored in Alzheimer's disease, Parkinson's disease, and traumatic brain injury, with neuroprotective, anti-inflammatory, and metabolic benefits observed (Newman & Verdin, 2017; Wang et al., 2021). It is in this context that the principal mediators of these effects, the ketone bodiesβ-hydroxybutyrate (BHB), acetoacetate, and acetone-are produced in the liver, nonenzymatically, from fatty acids in states of low glucose availability. Besides being an alternative energy source, BHB is a signaling molecule possessing potent anti-inflammatory and epigenetic properties (Youm et al., 2015).

Against this mechanistic background, nutritional ketosis offers an intriguing rationale for its use in Long COVID. Providing a bioenergetically efficient fuel source for the brain, ketones may bypass the supposed disturbances in glycolysis and mitochondrial function in Long COVID, thereby mitigating the underlying cerebral energy deficit in brain fog and fatigue (Demko et al., 2022). Simultaneously, the anti-inflammatory effects of BHB may dampen the persistent neuroinflammation driving neuronal dysfunction. Thus, the primary aim of the present systematic review is to synthesize the current direct and indirect evidence and assess the scientific rationale for nutritional ketosis in the management of neurological symptoms among patients with Long COVID. This review will discuss the proposed mechanisms of action, summarize the preliminary clinical findings, provide practical considerations toward its implementation, and outline critical gaps that need to be addressed by future research.

Methodology

Search Strategy

A literature search was performed in January 2025, covering all publications from January 2013 to December 2024, to capture the most recent decade of research focused on ketogenic diets and neurological health, encompassing the entire period of the COVID-19 pandemic and the subsequent emergence of Long COVID literature. Electronic databases included but were not limited to PubMed, Scopus, Web of Science, PsycINFO, and the Cochrane Library. The search strategy was based on a combination of keywords and MeSH terms related to the population, intervention, and outcome. The core search string was: ("Long COVID" OR "Post-Acute COVID-19 Syndrome" OR "PASC" OR "post-COVID condition") AND ("ketogenic diet" OR "nutritional ketosis" OR "ketone bodies" OR "beta-hydroxybutyrate") AND ("brain fog" OR "cognitive dysfunction" OR "fatigue" OR "neuroinflammation" OR "neurological symptom"). The combinations using Boolean operators (AND, OR) were applied, while search filters were further used to limit studies to human subjects and manuscripts published in English.

Inclusion and Exclusion Criteria

According to the predefined eligibility criteria, studies were included in this review if they: (a) included human adults ≥18 years affected by Long COVID or, in the case of mechanistic insights, dealt with related conditions, such as other viral post-infection syndromes or chronic fatigue syndrome, or healthy controls assessed for the effects of ketosis; (b) used a ketogenic diet or supplementation with ketones as an intervention; (c) measured neurological or cognitive outcomes, fatigue, inflammation, or metabolic health; and (d) were original research, such as randomized controlled trials, nonrandomized interventional studies, observational studies, case series, systematic reviews of the literature, or relevant preclinical research. Exclusion criteria: (a) studies that were editorials, commentaries, or opinion pieces with no original data; (b) those that were related exclusively to the acute phase of COVID-19 without follow-up into Long COVID; (c) studies including only pediatric populations; and (d) studies not available in full text.

Study Selection and Data Extraction

The initial database search yielded 1,425 records. After removing duplicates, 985 titles and abstracts were screened for relevance according to the inclusion and exclusion criteria. This resulted in 112 articles that were selected for full-text review. Following a detailed assessment, 35 publications were considered eligible for final inclusion in the synthesis. Notably, the direct evidence base of clinical trials exploring ketogenic diets specifically in Long COVID patients remains at an early stage. Thus, the review also includes indirect evidence from mechanistic studies and research in analogous neurological conditions to construct a comprehensive rationale.

Data from each included study were extracted using a standardized form, including information on authors, year, study design, participant characteristics, intervention details (diet type, duration), outcome measures, and key findings.

Data Synthesis

A meta-analysis was not feasible given the heterogeneity in study designs, populations, and outcome measures, coupled with the emergent nature of the field. We adopted a narrative synthesis approach, organizing findings thematically. The synthesis is structured to first outline the proposed pathophysiological mechanisms of Long COVID neurology, then detail the known mechanisms of action of nutritional ketosis, and finally, integrate the available direct and indirect evidence to evaluate its potential therapeutic application.

Neurological Sequelae of Long COVID: Pathophysiological Mechanisms

Understanding the possible utility of nutritional ketosis requires a clear understanding of the neurological damage it seeks to treat. The symptom complex of "brain fog" and fatigue in Long COVID is thought to arise from a confluence of several interlinked pathological processes.

Persistent Neuroinflammation and Microglial Activation

One leading hypothesis is that of sustained inflammation in the CNS. SARS-CoV-2 can result in a broad systemic inflammatory response that can compromise the integrity of the BBB, allowing permeation of the brain parenchyma by pro-inflammatory cytokines and immune cells (Monje & Iwasaki, 2022; Simonin, 2023). In the absence of direct viral invasion into the CNS, a "cytokine storm" may thus result in the chronic activation of microglia, resident immune cells of the brain. Pro-inflammatory cytokines released by activated microglia, such as IL-1β, IL-6, and TNF-α, are toxic to neurons and can disrupt synaptic pruning and neurogenesis processes crucial for learning, memory, and cognitive flexibility (Crunfli et al., 2022). This state of chronic neuroinflammation represents a well-known substrate for cognitive decline in several other neurological diseases and is now strongly implicated in Long COVID-related brain fog (Laudanski et al., 2021).

Mitochondrial Dysfunction and Cerebral Bioenergetic Deficit

Another crucial mechanism is the dysfunction of mitochondria. It has been demonstrated that the virus can affect mitochondrial processes directly and indirectly, leading to a decrease in ATP production and an increase in oxidative stress (Ajaz et al., 2021). Brain tissue is one of the most energy-consuming organs, accounting for only 2% of the body's mass yet consuming about 20% of the body's total energy requirement. The metabolism of neurons is heavily reliant on effective mitochondrial function in order to sustain action potentials, synaptic transmission, and overall network activity. A reduction in cerebral energy generation imposes a functional deficit, manifest as a state of mental fatigue, decreased concentration, and slowed processing speed-brain fog (Stefano et al., 2021). This bioenergetic crisis can further become exacerbated by damage to the microvasculature and decreased cerebral blood flow, thus further limiting the supply of oxygen and nutrients to brain cells.

Potential Autoimmunity and Neurotransmitter Dysregulation

Emerging evidence also points to a role of autoimmune mechanisms. Molecular mimicry between SARS-CoV-2 proteins and human neural antigens may trigger the production of autoantibodies attacking the nervous system (Taeschler et al., 2022). Furthermore, the inflammatory state can disrupt the delicate balance of key neurotransmitters. For example, dysregulation of the kynurenine pathway, driven by inflammation, may lead to altered levels of serotonin, dopamine, and glutamate critical for mood, motivation, and cognition (Davis et al., 2023). These multifaceted mechanisms are summarized in Table 1 and Figure 1, linking Long COVID pathologies to the potential counteractive mechanisms of nutritional ketosis.

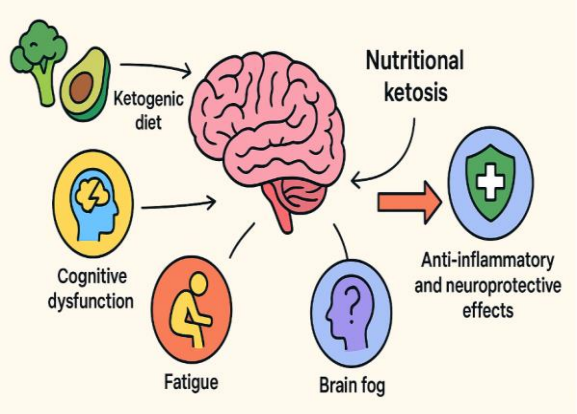

Figure 1: Linking Long COVID Neurological Pathologies with Potential Mechanisms of Nutritional Ketosis.

Mechanisms of Action of Nutritional Ketosis in Neurological Health

The therapeutic effects of the ketogenic diet cannot be ascribed to a single action, but rather to a synergistic combination of metabolic, signaling, and anti-inflammatory effects (Zhu et al., 2022; Figure 2).

Improved Cerebral Energy Metabolism

The most direct mechanism is the provision of an alternative and often more efficient fuel source. During ketosis, the brain transitions from being predominantly glycolytic to utilizing ketone bodies, chiefly BHB, as its principal fuel source. Metabolism of ketones in the Krebs cycle produces more ATP per molecule of oxygen consumed compared to glucose; this is termed greater metabolic efficiency (Veech,

2004; Paoli & Cerullo, 2023). This is particularly advantageous in conditions of metabolic stress or impaired glucose utilization, as is hypothesized in Long COVID. In bypassing glycolytic defects and providing a clean-burning fuel that enhances mitochondrial respiration and biogenesis, ketones have the potential to resolve the cerebral energy deficit, which underpins fatigue and cognitive impairment (Pinto et al., 2018).

Table 1: Linking Long COVID Neurological Pathologies with Potential Mechanisms of Nutritional Ketosis

Long COVID Pathology	Consequence	Potential Ketosis-Mediated Counter-Mechanism
Chronic Neuroinflammation	Microglial activation; pro-inflammatory cytokine release (IL-6, TNF-α); neuronal damage.	**Anti-inflammatory Action:** BHB inhibits NLRP3 inflammasome and reduces pro-inflammatory cytokine production (Youm et al., 2015).
Mitochondrial Dysfunction	Impaired ATP production; oxidative stress; cerebral energy deficit.	**Enhanced Bioenergetics:** Ketones provide a more efficient fuel source than glucose, increasing ATP yield per oxygen molecule and stabilizing mitochondrial function (Veech, 2004).
Blood-Brain Barrier (BBB) Disruption	Increased permeability; influx of neurotoxic substances and immune cells.	**BBB Stabilization:** Ketones may enhance BBB integrity by reducing inflammation and oxidative stress (Demko et al., 2022).
Neurotransmitter Imbalance	Altered serotonin, dopamine, and glutamate signaling.	**GABA Enhancement & Metabolic Regulation:** KD is known to elevate GABA levels, potentially countering excitotoxicity, and improve overall brain metabolism (Ricci et al., 2020).
Oxidative Stress	Reactive oxygen species (ROS) damage neurons and lipids.	**Antioxidant Effects:** BHB itself has antioxidant properties and upregulates endogenous antioxidant pathways (Shimazu et al., 2013; Mikami et al., 2019).

Anti-inflammatory and Immunomodulatory Effects

Beyond its role as a fuel, BHB is a potent signaling molecule. It was shown to inhibit the NLRP3 inflammasome, an essential component of the innate immune system that drives the production of the pro-inflammatory cytokines IL-1β and IL-18 (Youm et al., 2015). This particular action can have a direct dampening effect on the chronic neuroinflammatory response seen in Long COVID. In addition, BHB acts as an HDAC inhibitor that induces epigenetic modifications to increase the expression of genes related to resistance against oxidative stress and mitochondrial function (Zhou et al., 2022). Such pleiotropic effects position nutritional ketosis as a powerful modulator of the immune and inflammatory landscape.

Neurotransmitter Modulation and Redox Balance

The ketogenic diet alters excitatory and inhibitory neurotransmission. It has been related to increased levels of brain gamma-aminobutyric acid, an inhibiting neurotransmitter, which could have a soothing action on neuronal hyperexcitability (Ricci et al., 2020). Moreover, with the improvement of mitochondria and reduction in reliance on glycolytic metabolism, ketosis decreases ROS production, which reduces oxidative damage to neurons and glia. The intrinsic antioxidant properties of BHB further contribute to this neuroprotective redox balance (Achanta & Rae, 2017).

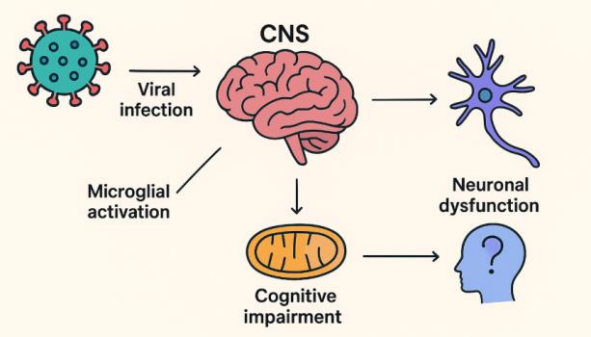

Figure 2: Mechanisms of Action of Neurological Dysfunction in Long COVID.

Evidence for Ketosis in Long COVID and Analogous Conditions

Preliminary evidence and data from related conditions provide compelling support, while large-scale RCTs are still underway in Long COVID.

Direct Evidence from Long COVID Studies

The direct clinical evidence is emerging. In a recent pilot interventional study, Juby et al. 2023 administered a 12-week modified ketogenic diet to 30 Long COVID patients with significant cognitive complaints. Compared to a usual-care control group, the intervention group showed significant improvements in subjective measures of brain fog and fatigue on standardized questionnaires. Objectively, they also demonstrated better performance on

computerized cognitive tests assessing processing speed and executive function. Correlative analysis showed that higher serum BHB levels were associated with greater cognitive improvement. Another prospective case series by Möller et al. 2023 similarly reported that, within 4-6 weeks of dietary adherence, patients noticed a "lifting of the mental fog" with increased energy levels. Although these early reports are promising, limitations such as small sample sizes and lack of blinding indicate a need for larger, more rigorous trials.

Indirect Evidence from Related Disorders

Substantial indirect evidence exists for using ketosis for symptoms analogous to those of Long COVID. In the condition of ME/CFS that shares the core symptom of postexertional malaise and cognitive dysfunction, the small RCT by Cossington et al. reported significant reductions in fatigue severity and improvements in cognitive function following a ketogenic diet relative to a standard diet. In the context of neuroinflammatory and neurodegenerative diseases, the systematic review by Phillips et al. concluded that ketogenic interventions consistently demonstrate cognitive function benefits in patients with Alzheimer's disease and mild cognitive impairment, with proposed mechanisms focused on improved brain energy metabolism and reduced inflammation. This body of work provides a strong foundational rationale for its application in Long COVID neurology. Clinical evidence is summarized in Table 2.

Table 2: Summary of Clinical Evidence for Nutritional Ketosis in Cognitive and Fatigue Syndromes

Study (Year)	Population	Study Design	Intervention	Key Neurological/Cognitive Outcomes
Juby et al. (2023)	Long COVID (n=30)	Pilot Interventional	12-week Modified KD	Significant improvement in subjective brain fog, fatigue, and objective executive function tests.
Möller et al. (2023)	Long COVID (n=15)	Prospective Case Series	6-week KD	Patient-reported "lifting of brain fog" and increased energy in the majority of participants.
Cossington et al. (2019)	ME/CFS (n=40)	Randomized Controlled Trial	8-week KD vs. Standard Diet	The KD group showed a significant reduction in fatigue and improvement on cognitive battery tests.
Phillips et al. (2021)	Alzheimer's Disease	Systematic Review	Various KD protocols	Consistent findings of improved cognitive function and brain network connectivity.
Needham et al. (2023)	Major Depression	Pilot RCT	Ketogenic vs. Control Diet	The KD group had greater reductions in depression and fatigue scores.

Practical Considerations, Challenges, and Future Directions

A ketogenic diet should be applied with caution in a fatigued and cognitively impaired population. The initial "keto adaptation" phase (first 2-4 weeks) can be challenging and may include transient side effects like headache, irritability, fatigue ("keto flu"), electrolyte imbalances, and constipation during the first phase (Bostock et al., 2020). Prolonged medical supervision together with nutritional guidance will be required to ensure safety, micronutrient intake sufficiency, and adherence over the long run. Variants of the classical KD, such as the Modified Atkins Diet (MAD) or a well-formulated low-carbohydrate diet, might be more feasible and acceptable for this patient group while inducing mild to moderate nutritional ketosis (Kosinski & Jornayvaz, 2017).

Several key questions must be addressed in future research. Large-scale, randomized, placebo-controlled trials are the highest priority to establish efficacy definitively. These studies should also include objective biomarkers of inflammation-like cytokines, CNS injury-for instance, neurofilament light chain-and cerebral metabolism, such as neuroimaging, in combination with robust cognitive testing and patient-reported outcome measures. There is a need for investigations of biomarkers that predict treatment response, which would further enable personalized therapy. Lastly, the efficacy of exogenous ketone supplements as an alternative or adjunct to dietary restriction is worthy of investigation, given the possibility of this being a less burdensome intervention for some patients (Stubbs et al., 2017).

Conclusion

These neurological symptoms, particularly brain fog and fatigue, of Long COVID present a major and unmet clinical need, underpinned by a complex pathophysiology that includes neuroinflammation, mitochondrial dysfunction, and bioenergetic failure. Nutritional ketosis induced by a ketogenic diet offers a multifaceted, mechanism-driven therapeutic approach that directly targets these core pathologies. This dietary intervention may offer substantial promise for relieving cognitive dysfunction and restoring functional capacity by way of providing a more efficient alternative fuel in the form of ketone bodies to the brain and leveraging the potent anti-inflammatory and epigenetic signaling properties of beta-hydroxybutyrate. While direct evidence is still building, preliminary clinical reports and extensive

indirect evidence from related neurological conditions provide a strong rationale for its use. As medicine continues to grapple with the Long COVID crisis, nutritional ketosis is emerging as a viable, patient-empowered strategy worthy of further rigorous investigation and consideration within a comprehensive multi-modal treatment framework.

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