The role of nutritional ketosis in the cognitive function of aging populations: A narrative review

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ABSTRACT

Introduction: Cognitive decline is a hallmark of aging and a major contributor to conditions such as Alzheimer's disease (AD) and Parkinson's disease (PD). These disorders share common pathological features, including neuroinflammation, oxidative stress, and mitochondrial dysfunction. Nutritional ketosis, a metabolic state characterized by elevated ketone bodies, most commonly serum β-hydroxybutyrate (BHB), induced by a ketogenic diet, is typically defined by concentrations ranging from 0.5 to 9.0 mmol/L without acidosis, distinguishing it from pathological ketoacidosis. Ketone bodies serve as alternative energy substrates to glucose and exhibit anti-inflammatory and neuroprotective effects. This narrative review evaluates current evidence on the role of nutritional ketosis in mitigating cognitive dysfunction in elderly individuals, focusing on a range of neurodegenerative and cognitive disorders. **Materials and Methods:** A literature search was conducted using PubMed, Cochrane, and ResearchGate databases. Search strategies used appropriate terminology related to cognitive function, aging populations and nutritional ketosis. The review focused on studies involving participants aged 60 years and older. Eligible study designs included randomized controlled trials, cohort studies, cross-sectional studies, systematic reviews, and narrative reviews. **Results:** Ketone bodies such as BHB provide an efficient energy substrate to the aging brain, particularly when glucose metabolism is compromised, as seen in epilepsy, AD and PD. In AD and dementias, research demonstrates that cerebral glucose metabolism deteriorates early in disease progression, while ketone uptake remains intact. Ketogenic interventions may therefore compensate for this diminished glucose metabolism, potentially improving cognitive performance by supporting neuronal ATP production. Clinical trials have shown that both ketogenic diets and exogenous ketone supplementation enhance memory and executive function in older adults with mild cognitive impairment and early-stage AD. In PD, mitochondrial dysfunction, oxidative stress, and neuroinflammation leads to the degeneration of dopaminergic neurons. BHB has been shown to enhance mitochondrial respiration, reduce reactive oxygen species, and modulate the NOD-like receptor protein 3 (NLRP3) inflammasome, potentially protecting neurons in PD. Through improved mitochondrial bioenergetics, modulation of excitatory and inhibitory neurotransmitters, activation of ATP-sensitive potassium channels, reduction of neuroinflammation and oxidative stress, and variation of the gut microbiota, the ketogenic diet has also been shown to have anti-seizure effects on drug-resistant epilepsy in adults. In addition to AD and PD, animal models show that ketone metabolism enhances neurotrophic signalling, decreases amyloid and tau pathology by preventing mitochondrial dysfunction, stimulating autophagy-degrading hyperphosphorylated tau and reducing kinase activity. Histone deacetylase (HDAC) inhibition is one of BHB's effects that may improve cognitive function and neuroprotection. Additionally, usage of exogenous ketone esters can temporarily raise BHB levels and provide only short-term benefits. Current challenges in include diet adherence, gastrointestinal effects, and safety in frail elderly patients. **Conclusion:** Nutritional ketosis holds potential as a non-pharmacological intervention to enhance cognitive function and slow neurodegeneration in elderly individuals. Its ability to bypass impaired glucose metabolism, reduce inflammation, and support mitochondrial health positions it as a potential adjunct therapy in AD, PD, and other forms of dementia. Future research should focus on randomized controlled trials to confirm effectiveness, examine long-term safety, and create tailored protocols for older individuals with cognitive dysfunction.

Keywords: Nutritional ketosis, cognitive function, Alzheimer's disease, Parkinson's disease, aging population