Essentials of Frontline Medicine Journal ISSN: 3062-1704 Volume: 2 Issue: 2 (2025)

Targeting Autophagy in Alzheimer's Disease: The Emerging Role of Intermittent Fasting and Caloric Restriction

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Received: August 22 2025. **Accepted:** August 31, 2025. **Published:** August 31, 2025. **DOI: 10.5281/zenodo.17013828**

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Cite This Article as: Kösedağ M. Targeting Autophagy in Alzheimer's Disease: The Emerging Role of Intermittent Fasting and Caloric Restriction. Essentials Frontline Med J. 2025:2(2); 13-18.

Externally Peer-Reviewed.

ABSTRACT

Alzheimer's disease (AD), first described by Alois Alzheimer in 1906, is the most prevalent cause of dementia and a significant public health concern. As global life expectancy increases, so does the burden of AD, with no definitive cure currently available. Existing pharmacological treatments are limited by high costs and adverse side effects, highlighting the urgent need for natural, accessible, and sustainable prevention and management strategies. Among these, conscious dietary patterns are gaining prominence. Recent research suggests that dietary models that induce autophagy, such as intermittent fasting and caloric restriction, may mitigate neurodegeneration by preventing the accumulation of amyloid-beta (Aβ) and the formation of neurofibrillary tau plaques in the brain. Given the rising prevalence and chronic course of AD, family physicians and public health authorities must prioritize comprehensive patient care that extends beyond pharmacological interventions to include diet and lifestyle. This review aims to consolidate current literature on dietary strategies that support autophagy, specifically intermittent fasting and caloric restriction, to inform the management of patients with or at risk for AD. By emphasizing the role of these nutritional interventions, this review seeks to provide a framework for a more sustainable and effective approach to disease prevention and progression.

Keywords: Alzheimer's Disease, autophagy, caloric restriction, diet, intermittent fasting, neurodegenerative diseases, nutrition

INTRODUCTION

In 1906, German psychiatrist and neuropathologist Alois Alzheimer published the findings from a case study of a 51-year-old patient, Auguste Deter, who had suffered from progressive dementia characterized by severe memory loss, behavioral disturbances, and paranoia. A post-mortem microscopic examination of her brain tissue revealed significant pathological changes, including dense amyloid plaques and neurofibrillary tangles. Following this groundbreaking work, Alzheimer's mentor, Emil Kraepelin, formally designated this clinico-pathological condition as "Alzheimer's disease" (AD) in recognition of the discovery (1-4).

Alzheimer's disease is now recognized as the most common cause of dementia, yet its pathogenesis remains incompletely understood. It is a neurodegenerative disorder classified within the group of proteopathies, primarily characterized by the accumulation of abnormally folded amyloid-beta (Aβ) protein in the brain (5, 6). Beyond Aβ deposits, AD is associated with a range of characteristic histopathological, molecular, and biochemical abnormalities. These include widespread neuronal loss, neurofibrillary tangles, dystrophic neurites, increased activation of pro-death signaling pathways, impaired energy metabolism, mitochondrial dysfunction, chronic oxidative stress, and DNA damage (7).

Many of these core abnormalities reflect the effects of brain insulin resistance and insulin deficiency, with the resulting biochemical consequences resembling those of type 1 and type 2 diabetes. This pivotal role of insulin resistance and impaired glucose metabolism has led some recent research to propose a reclassification of AD as "type 3 diabetes" (8, 9).

As a progressive neurodegenerative disorder, AD currently has no definitive cure, and existing treatments are limited by various side effects (10). Consequently, there is an increasing emphasis on nutritional strategies that can support autophagy, a crucial cellular process for waste clearance. Natural dietary approaches, such as

intermittent fasting and caloric restriction, are thought to slow the course of the disease and improve quality of life by exerting beneficial effects on metabolic balance and cellular waste removal (11, 12).

The objective of this review is to bridge the gap between preclinical research and clinical practice by consolidating the evidence on how dietary patterns, such as intermittent fasting and caloric restriction, influence the cellular mechanisms underlying AD. It was aimed to inform healthcare professionals, particularly family physicians, about the potential of these nutritional strategies to activate autophagy and thereby mitigate neurodegeneration. This review provides a practical guide for clinicians to counsel patients on dietary and lifestyle modifications as a complementary approach to current AD therapies.

METHODS

A literature review was conducted to search current evidence on the role of nutritional strategies, specifically intermittent fasting (IF) and caloric restriction (CR), in supporting autophagy within the context of Alzheimer's disease (AD). A comprehensive search was performed using major electronic databases, including PubMed and Google Scholar. The search queries combined terms related to the dietary interventions and key biological processes. Keywords included: "Alzheimer's disease," "intermittent fasting," "caloric restriction," "autophagy," "neurodegeneration," "amyloid-beta," and "tau."

To ensure the relevance and quality of the included literature, studies were selected based on the following criteria:

Inclusion Criteria: Studies published in English from peer-reviewed journals, including experimental studies on animal models and clinical trials involving human subjects, as well as review articles and case reports that discussed the relationship between CR, IF, autophagy, and AD pathophysiology.

Exclusion Criteria: Editorials, opinion pieces, and studies not directly related to the specified keywords or the central theme of the review were excluded.

The extracted data were qualitatively analyzed to identify key themes and synthesize findings on how CR and IF activate autophagy and their subsequent effects on Aβ and tau pathology, neuroinflammation, and cognitive function. The purpose of this qualitative synthesis was to provide a comprehensive overview of the current state of research and to identify areas for future investigation.

THE ROLE OF AUTOPHAGY IN ALZHEIMER'S DISEASE PATHOGENESIS

The pivotal role of cellular self-cleaning and renewal was formally recognized in 2016 when Japanese cell biologist Yoshinori Ohsumi was awarded the Nobel Prize in Physiology or Medicine for his groundbreaking work on autophagy (13). Autophagy, meaning "self-eating," is a fundamental catabolic process by which cells degrade and recycle their own components, including misfolded proteins, dysfunctional organelles, and other cellular waste products. This mechanism is critical for maintaining cellular homeostasis, regulating energy balance, and, in particular, preserving neuronal health (14).

Under normal physiological conditions, the autophagic pathway is essential for maintaining protein quality and preventing the accumulation of intracellular toxic waste. This process is broadly classified into three main subtypes:

Macroautophagy: The most well-known type, which involves the formation of a double-membraned vesicle called an autophagosome that engulfs cellular components and fuses with a lysosome for degradation.

Chaperone-Mediated Autophagy (CMA): A highly selective process that uses a specific chaperone protein to directly transport targeted proteins across the lysosomal membrane.

Mitophagy: A specialized form of autophagy that selectively clears damaged or dysfunctional mitochondria.

The integrity of these pathways is crucial for neuronal function. In neurodegenerative diseases like AD, these processes become dysfunctional, leading to the accumulation of toxic protein aggregates (Table 1).

Table 1. Types of Autophagy and Their Relationship with Alzheimer's Disease

Type of Autophagy	Definition and Mechanism	Relationship with Alzheimer's Disease
Macro autophagy	Double-membraned autophagosomes engulf cytoplasmic contents (damaged organelles, protein aggregates) and fuse with lysosomes. The contents are enzymatically degraded and recycled (15).	Plays a critical role in the clearance of amyloid beta (Aβ) and tau aggregates in AD; impairment of this process may accelerate disease progression (16).
Mitophagy	The selective degradation of damaged or dysfunctional mitochondria through their sequestration into autophagosomes and subsequent delivery to lysosomes for breakdown (17).	Essential for maintaining neuronal energy homeostasis; targeted reduction of mitochondrial dysfunction in AD may be achieved through mitophagy (18).
Chaperone-Mediated Autophagy (CMA)	Proteins containing a KFERQ-like motif are recognized by the HSC70 chaperone and the LAMP-2A receptor, which facilitates their direct translocation across the lysosomal membrane for degradation (19).	Exhibits high selectivity; involved in the degradation of pathological proteins such as tau in AD (20).

Given its critical role in cellular protein and organelle metabolism, functional impairments in autophagy are believed to contribute significantly to the progression of AD. Indeed, a growing body of evidence indicates that disruptions in the autophagic-lysosomal pathway occur in the early stages of the disease (21). While the initiation of macroautophagy may increase in the early phases of AD, defects in the subsequent lysosomal degradation stage lead to the accumulation of autophagosomes, preventing the complete clearance of misfolded proteins like Aβ and tau (22).

Studies have consistently demonstrated the importance of functional autophagy for neuronal survival. Autophagic dysfunction has been linked to the accumulation of polyubiquitinated proteins in aging neurons, a condition that predisposes to the development of neurodegenerative diseases (23). The development of Aβ pathology in the brain, for instance, is associated with synaptic dysfunction, which is linked to decreased mitochondrial function and impaired autophagy (24). A recent experimental study further demonstrated that synaptic autophagy is crucial for maintaining protein homeostasis and that its reduction disrupts normal cognitive function. This work proposed that impaired autophagic activity may directly contribute to the cognitive decline seen in AD (25).

The close relationship between autophagy and AD pathology has led to the proposal that autophagy activation is a promising therapeutic strategy for the disease. Investigating cellular pathways that can enhance both autophagy and lysosomal proteolytic activity in neurons is therefore of paramount importance for developing effective treatments for AD (16).

NUTRITIONAL INDUCTION OF AUTOPHAGY: THE ROLES OF CALORIC RESTRICTION AND INTERMITTENT FASTING

The lack of definitive treatments for a range of neurodegenerative diseases, including AD, Parkinson's disease, and multiple sclerosis, has directed recent research toward the therapeutic potential of daily dietary habits (26). The role of nutritional interventions, particularly caloric restriction (CR) and intermittent fasting (IF), has gained prominence as a means to address the rising prevalence of these conditions (27). Both CR and IF are recognized as potent dietary strategies for inducing autophagy, a process that is closely linked to the pathogenesis and progression of AD.

Caloric Restriction

Caloric restriction is a dietary approach that involves a consistent reduction in caloric intake without compromising the consumption of essential nutrients. It is widely considered the gold standard for delaying aging and extending a healthy lifespan (29, 30). The therapeutic use of CR and other forms of reduced food intake dates back to ancient times, particularly in the management of epilepsy (31, 32).

Recent studies on the effects of CR on AD have provided valuable insights. Experimental and clinical research demonstrate that CR can modulate insulin signaling pathways, enhance the production of antioxidant and anti-apoptotic proteins, promote DNA repair,

increase histone deacetylase activity, and reduce amyloid-beta (Aβ) plaque accumulation (33). Animal models have further shown that long-term CR can inhibit the development of AD by gradually altering the gut microbiota, leading to the depletion of microbes that trigger Aβ plaque formation (34).

In a prospective clinical study of healthy elderly individuals, a three-month period of 30% CR resulted in a 20% improvement in verbal memory performance. This cognitive enhancement was strongly correlated with significant reductions in insulin and high-sensitivity C-reactive protein (CRP) levels, suggesting that the benefits of CR are mediated through improved insulin sensitivity and reduced inflammation (35). Furthermore, a randomized controlled trial in obese postmenopausal women on a 12-week low-calorie diet demonstrated improvements in recognition memory, an increase in gray matter volume in the inferior frontal gyrus and hippocampus, and enhanced hippocampal functional connectivity. These findings indicate that CR may represent a viable dietary strategy to slow AD progression, particularly during the active weight loss phase (36).

Intermittent Fasting

Intermittent fasting, characterized by extended periods of food abstinence, induces an energy deficit that activates cellular stress response mechanisms, including autophagy (37, 38). This mechanism is believed to slow the progression of AD and other neurodegenerative diseases by reducing neuroinflammation, improving insulin resistance, regulating the gut microbiota, and clearing pathological protein aggregates like Aβ and tau (37).

In animal models, fasting regimens have been shown to improve AD-related processes and functional outcomes, protect cells from DNA damage, and promote the apoptosis of damaged cells (39). A key study suggested that intermittent fasting provides a simple, safe, and inexpensive method to promote a therapeutic neuronal response by inducing neuronal autophagy (40).

A recent study showed that a 30-day period of intermittent fasting from dawn to dusk modulated protective serum proteins against cancer, metabolic syndrome, and AD in healthy individuals, independent of caloric restriction or weight loss. This regimen also activated key regulatory proteins involved in DNA repair, circadian rhythm, immune function, and cognitive processes, underscoring its potential as a protective and therapeutic strategy (41).

Moreover, in a 36-month prospective study of elderly individuals with mild cognitive impairment, those who regularly practiced intermittent fasting had a significantly higher rate of successful aging without cognitive decline (24.3%) compared to those who did not. This group also exhibited reductions in oxidative stress and inflammatory markers and improved metabolic parameters, further supporting the beneficial role of IF on cognitive health and AD prevention (42).

LIMITATIONS

This review, while providing a valuable synthesis of the current literature, is subject to several limitations. First, the included studies exhibit significant heterogeneity in their methodologies. Animal studies vary widely in species, models of AD, and dietary protocols (e.g., fasting duration, caloric reduction percentage). Similarly, human clinical trials differ in sample size, dietary regimens, and patient populations, which complicates a direct comparison of their findings.

Second, many of the promising findings on the effects of CR and IF on autophagy and AD pathology are derived from preclinical animal models. While these studies provide mechanistic insights, their results may not be directly translatable to human subjects due to differences in metabolism, genetics, and disease progression.

Finally, the reviewed literature includes both randomized controlled trials and observational studies. This variability in study design, particularly the lack of large-scale, long-term clinical trials on nutritional interventions for AD, presents a significant limitation. It makes it challenging to definitively establish the long-term efficacy and clinical feasibility of CR and IF as standard therapeutic strategies for AD patients. These limitations highlight the need for future research to focus on standardized, large-scale, and long-term human clinical trials to validate the promising findings from preclinical studies.

CONCLUSION

Alzheimer's disease (AD) is a major public health concern, characterized by its increasing global prevalence and irreversible neurodegenerative progression. The evidence reviewed here indicates that beyond pharmacological interventions, conscious dietary and lifestyle modifications can play a pivotal role in managing the disease. Specifically, autophagy induced by intermittent fasting and caloric restriction contributes to the clearance of abnormal protein aggregates, preserves mitochondrial function, and reduces neuroinflammation, thereby offering a potential protective and disease-slowing effect in AD pathophysiology.

Family physicians, as primary healthcare providers, are uniquely positioned to integrate these nutritional and lifestyle modifications into the long-term management of patients. Incorporating these approaches into the treatment plans for individuals at risk for or diagnosed with AD promotes a more holistic and sustainable strategy alongside pharmacological therapy.

This review underscores the preventive and therapeutic potential of autophagy-activating dietary strategies in AD. It emphasizes the importance of nutrition-focused approaches from both a clinical and public health perspective. To definitively establish the efficacy and feasibility of these interventions, future research must focus on large-scale, well-designed clinical trials.

DECLARATIONS

Ethical Consideration: This study, being a comprehensive review of published literature, did not require ethical approval from an institutional review board (IRB) or equivalent ethics committee. The data analyzed were entirely sourced from publicly available, peer-reviewed articles, and did not involve direct interaction with human subjects, collection of primary data, or any form of intervention. Therefore, the principles governing research ethics, such as informed consent and protection of participant privacy, are not applicable to this study.

Contributions: This study was conducted by a single author.

Financial Support: No financial funding was received from any institution or organization for this study.

Conflict of Interest Statement: There are no potential conflicts of interest to declare.

Data Availability Statement: This review has searched the online literature and is included in the references.

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