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The Impact of Intermittent Fasting on Alzheimer's Disease Risk: A Literature Review

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Abstract:
Introduction and purpose: In the face of an aging population, the increasing number of elderly individuals raises the incidence of age-related conditions, including Alzheimer's disease (AD), which is a leading cause of global disability and a significant burden on society. The lack of effective treatments for AD underscores the importance of prevention. Recent reports suggest that intermittent fasting (IF) may counteract the disease processes associated with AD and serve as a potential preventive strategy. This review aims to outline the impact of IF on the risk of developing Alzheimer's disease.
Materials and methods: A literature search was conducted using the medical databases PubMed and Google Scholar. Articles were retrieved in English, employing the keywords: "Alzheimer's disease", "dementia", "intermittent fasting", "ketone bodies", "cognition".
State of knowledge: IF is a dietary regimen involving cyclic restriction of food intake, practiced in many cultures and religions. The interest in IF has increased due to its numerous health benefits, and recent studies indicate its potential in delaying and preventing pathological processes associated with AD, such as β-amyloid accumulation, neuroinflammation, and vascular damage, making IF a potentially protective intervention against neurodegeneration.
Summary: IF is a promising strategy for improving cognitive function and brain health. Due to the limited number of studies conducted on humans, further research is needed to confirm its effectiveness in preventing AD.
Keywords: Alzheimer's disease; dementia; intermittent fasting; ketone bodies; cognition

INTRODUCTION AND PURPOSE

In recent years, the demographic situation in highly developed countries has been trending towards an aging society, and the rapid pace of global population aging represents one of the greatest challenges of our time [1]. It is estimated that the elderly population (≥ 65 years) will reach 1 billion by 2030 and increase to 1.6 billion by 2050. The increasing proportion of elderly individuals in society contributes to the continuous rise in the incidence of age-related conditions, including dementia and Alzheimer's disease (AD). The dominant strategy aimed at mitigating the impact of an aging population on healthcare is the extension of healthspan, which focuses on increasing the years of healthy life and delaying the onset of chronic diseases and disabilities [2,3].

AD is a leading cause of global disability and poses a significant burden on patients, their families, caregivers, and society as a whole. Despite being known for over 100 years, there are still no effective treatments for the disease, and research on disease-modifying drugs has yielded disappointing results, highlighting the need for effective primary prevention [4,5,6]. Excessive food intake combined with low physical activity promotes the development of neurodegenerative diseases and cognitive function disorders. Currently, the most common dietary pattern in society involves eating meals at least three times a day. Recent reports suggest that intermittent fasting (IF) is a dietary pattern that positively influences many health markers and may counteract the disease processes underlying AD, serving as a preventive strategy against its development [7]. The purpose of this review is to outline the impact of intermittent fasting on the risk of developing Alzheimer's disease.

Materials and methods

A comprehensive review of the literature was performed by searching through databases such as PubMed and Google Scholar. Articles were retrieved employing the keywords: “Alzheimer’s disease”, “dementia”, “intermittent fasting”, “ketone bodies”, “cognition”. The search included articles published from 2014 to 2024. Frequently cited publications published earlier were also included. Only publications in the English language were considered for inclusion.

STATE OF KNOWLEDGE

1. Alzheimer's Disease

2. Alzheimer's disease (AD) is the most common cause of dementia worldwide, accounting for more than two-thirds of dementia cases in individuals over the age of 65, and is also the most prevalent neurodegenerative disease. Its incidence continues to rise due to the global aging population, and currently, approximately 55 million people suffer from AD globally. Moreover, projections indicate that by 2050, the number of AD patients will increase to about 152 million. According to data, 1 in 10 individuals over the age of 65 shows early-stage symptoms of the disease, and more than one-third of people aged 85 and older may exhibit advanced AD symptoms. European population studies have shown an increase in the percentage of AD patients from 0.6% in the 65-69 age group to 22.2% in patients over 90 years old, further confirming global trends in AD incidence [1,8,9,10].
AD is characterized by a chronic and progressive course, accompanied by the gradual loss of neurons and synapses, resulting in decreased neuroplasticity of the brain [11]. This process begins with changes in the central nervous system (CNS) occurring many years before the onset of clinical symptoms. These pathologies include the accumulation of senile plaques formed from toxic forms of amyloid-β (Aβ), neurofibrillary tangles of hyperphosphorylated tau protein, apolipoprotein E (ApoE), and presenilin. The molecular mechanisms of neurodegeneration involve apoptosis, oxidative stress, inflammation, and immune activation [12,13]. Neuroinflammation plays an important role in the pathogenesis of AD. It is hypothesized that uncontrolled activation of microglia in the brain leads to the release of neurotoxins and inflammatory factors, which trigger local and systemic inflammatory responses, promoting neuronal loss [11,12,14].

3. It is widely believed that misfolded proteins are key factors causing AD. Large aggregates of Aβ are formed as a byproduct of the proteolytic processing of amyloid precursor protein (APP), and Aβ fragments exhibit cytotoxic properties towards neurons and promote the formation of harmful reactive oxygen species. The accumulation of neurofibrillary tangles is the result of hyperphosphorylation of tau protein, whose neurotoxicity leads to the destabilization of microtubules and neuronal apoptosis [1,15].

4. The blood-brain barrier (BBB) is formed by endothelial cells (EC) lining the brain microvessels and controls the exchange of molecules between the CNS and the blood, thus maintaining homeostasis. The transport of glucose and ketone bodies from the blood to the brain is facilitated by glucose transporter 1 (GLUT1) and monocarboxylate transporter 1 (MCT1). The passage of soluble Aβ across the BBB is regulated by the low-density lipoprotein receptor-related protein 1 (LRP1), which is responsible for removing Aβ from the

brain. Additionally, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) limit the influx of Aβ into the brain. In AD, decreased expression of LRP1 and P-gp is one of the key disturbances, leading to the accumulation of Aβ due to reduced clearance of this protein from the brain [16].

5. Vascular pathologies are one of the elements of AD pathogenesis. It is estimated that vascular changes occur in 50% of patients with clinically diagnosed AD, and cerebral atherosclerosis is considered a typical pathological feature of this disease. Neuroimaging studies have shown a 20% lower blood flow through the brain in patients with Alzheimer's dementia compared to those without dementia. The deposition of amyloid in the walls of cerebral arteries and capillaries leads to the development of cerebral amyloid angiopathy (CAA), which occurs in 85-95% of AD patients. Due to impaired Aβ clearance, its deposits accumulate in arteries and capillaries, leading to the degeneration of vascular cells over time. Consequently, this results in the weakening of vessel walls, decreased cerebral blood flow (CBF), reduced cerebrovascular reactivity, and disruption of BBB integrity, potentially leading to microinfarcts and microbleeds, contributing to cognitive decline. BBB permeability is regulated by EC and other cells of the neurovascular unit, such as pericytes, astrocytes, and perivascular cells. In AD, BBB dysfunction is associated with the degeneration of EC, pericytes, astrocytic end-feet, and changes in the basement membrane, which disrupts the process of Aβ clearance [17,18].

6. In AD patients, the most noticeable feature is the progressive degradation of functional networks in the cerebral cortex and hippocampus, with initial damage to neurons in brain areas responsible for memory, language, and thinking. The massive death of malfunctioning neurons hinders the formation of new memory traces. In the early stages of the disease, there are usually no symptoms. As it progresses, more neurons become damaged, affecting increasingly larger areas of the brain. Patients may present a spectrum of clinical symptoms ranging from mild memory impairments to severe, debilitating loss of memory and cognitive functions [12,15,19].

7. AD is a multifactorial disorder, with major risk factors including older age, genetic predisposition, and a positive family history. The risk of developing AD doubles every 5 years after the age of 65 [19,20]. It is estimated that genetic factors play a significant role in about 70% of AD cases. For most patients, the disease manifests in later life and these cases are sporadic. Studies indicate the existence of several genetic factors that increase the risk of AD, the most significant of which is the presence of the ε4 allele in the apolipoprotein E

(ApoE) gene. This allele significantly raises the risk of developing late-onset AD and is present in approximately 16% of the population. A small percentage of AD cases are associated with early onset, resulting from dominant genetic mutations in one of three genes encoding proteins: APP (amyloid precursor protein), PSEN1 (presenilin 1), and PSEN2 (presenilin 2). In these cases, symptoms appear before the age of 65 [5,21]. It is estimated that up to 40% of AD cases can be attributed to modifiable risk factors, such as hypertension, diabetes, hypercholesterolemia, smoking, alcohol consumption, low physical activity, obesity, unhealthy diet, low educational level, lack of adequate rest, and low social engagement. Additionally, the risk of AD increases with a history of brain injury and stroke, depression, sleep disorders, exposure to environmental factors (heavy metals and trace elements), chronic CNS infections, low socioeconomic status, social isolation, and lack of cognitive activity [19,21,22,23]. Recent reports suggest that gut microbiota play a significant role in the pathogenesis of AD [24]. These data underscore the importance of prevention through interventions targeting modifiable risk factors, which can significantly reduce the incidence of AD [25].

8. Dementia, including AD, is the leading cause of disability and dependency among the elderly, burdening patients, their families, caregivers, society, and healthcare systems. It is estimated that the average time for the disease to progress from mild to severe is six years. The advanced stage of AD, accompanied by extensive neuronal damage, leads to extreme cognitive impairment and prevents patients from meeting their basic needs, requiring long-term and round-the-clock care [19,21]. According to global reports, the costs associated with the treatment and care of AD patients amounted to approximately 305 billion dollars in 2020, and projections indicate that these expenses may exceed 1 trillion dollars by 2050 [1]. Effective treatments for dementia-related diseases have not yet been developed, highlighting the importance of prevention. The best preventive effects are achieved when interventions are implemented before the first symptoms of dementia appear, around the age of 50. Scientific studies indicate that amyloid deposition begins approximately 15-20 years before the onset of cognitive impairment. During this period the number of synapses, cognitive functions, and neuropathological changes in the nervous system compensate for each other, increasing the chances of maintaining long-term health [10,20]. Recent scientific reports confirm the importance of lifestyle-related factors, which can open new avenues for preventing brain diseases. It has been shown that several diets, including the Mediterranean, DASH, and MIND diets, support brain health. Calorie-restricted diets have also demonstrated a positive

impact on cognitive functions. Despite these benefits, maintaining these diets and caloric restrictions long-term can be challenging. In recent years, an increasing body of evidence from animal and human studies suggests that fasting periods without calorie reduction may have a similar impact on cognitive health and prevent the development of AD. Consequently, interest has grown in eating patterns that regulate the timing and frequency of meals, with particular attention to intermittent fasting (IF) [26].

2. Intermittent Fasting

Intermittent fasting (IF) is a dietary regimen characterized by cyclic, complete breaks from eating alternating with periods of normal eating [18]. Various models of IF are described in the literature, including:

- TRE/TRF (time-restricted eating/feeding): A feeding window lasting 6-12 hours during the day;
- ADF (alternate day fasting): Complete fasting every other day, alternating with an ad libitum (unrestricted) diet;
- MADF (modified ADF): A modification of ADF, involving consuming less than 25% of the individual's daily caloric requirement during fasting periods;
- IF 5:2: Cyclic fasting for two non-consecutive days per week, which can be complete or partial fasting with energy intake restricted to 400-600 kcal/day.

Additionally, to differentiate studies on short-term, frequent fasting periods from those with less frequent but longer fasting intervals, researchers use the term "periodic fasting" (PF). PF lasts from 2 to 21 days (typically 2-7 days) and is repeated once a month or less frequently. A subtype of PF is the fasting mimicking diet (FMD), which involves temporarily reducing caloric intake to 30-50% of the daily requirement, mimicking the biological effects of food abstinence [7,18,26,27,28,29].

IF is not a new concept but rather harkens back to the dietary habits of our Paleolithic ancestors, who led a nomadic lifestyle. Procuring food through hunting, fishing, and gathering edible plants necessitated irregular meal consumption due to the variable availability of food. This eating pattern was the norm, forcing the body to adapt by storing energy as fat, which allowed survival during periods of food scarcity. During times of food absence, the body could utilize energy reserves by switching from glucose to stored lipids, resulting in a series of metabolic changes. These changes not only involved a shift in the primary energy source but also brought numerous health benefits, which form the basis of current research on animal models and humans [26,30].

Fasting is also practiced in many cultures and religions worldwide. Muslims abstain from eating and drinking from dawn to dusk during the month of Ramadan, which usually lasts 28 days and corresponds to TRE due to the feeding window lasting from 5 to 12 hours daily. Various fasting protocols are also practiced in other religions, such as Buddhism and Judaism. It is important to note that fasting differs from calorie restriction (CR), where daily caloric intake is chronically reduced by 20-40% with regular meal consumption. Fasting should also not be confused with starvation, which is characterized by a chronic deficiency of nutrients and leads to adverse health effects [28,31].

2.1. Biology of Intermittent Fasting

Due to the numerous variants of IF, their overall impact on metabolic functions varies. A common feature of each subtype is the occurrence of the "metabolic switch" phenomenon approximately 12-36 hours after the onset of fasting [26,32]. The consequence of this process is a change in the energy source, initially through glycogenolysis, followed by lipolysis, which involves the breakdown of lipids from adipose tissue into free fatty acids (FFA). These FFAs are then converted into acetyl-CoA through β-oxidation, leading to the synthesis of ketones: β-hydroxybutyrate (BHB) and acetoacetate (AcAc) [33].

The primary energy source for the brain is glucose, and unlike other organs that can metabolize free fatty acids (FFA) when glucose is scarce, the brain uses ketone bodies as an alternative energy source. In individuals with AD, there is regional cerebral hypometabolism of glucose, interpreted as a consequence of neuronal dysfunction and death. Studies have shown that reduced glucose metabolism in certain brain areas may occur even before the onset of cognitive impairment and may not only be a consequence but also a possible cause of AD. Cunnane et al. demonstrated that in individuals in the early stages of AD, global glucose uptake in PET scans is lower compared to healthy individuals, particularly in the parietal cortex, posterior cingulate, and thalamus. These abnormalities were not observed in AcAc uptake, suggesting that neurons in individuals with AD retain functional ketone uptake and metabolism, unlike glucose [34].

Beyond their energy function, ketones play a signaling role and regulate the expression and activity of transcription factors such as peroxisome proliferator-activated receptor γ (PPAR γ) coactivator 1α (PGC-1α), sirtuins (SIRTs), and poly (ADP-ribose) polymerase 1 (PARP1). During fasting, there is an increase in AMP-activated protein kinase (AMPK) activity, which leads to the activation of sirtuins (especially SIRT1 and SIRT3) and inhibition of the mTOR pathway, as well as the creation of mild oxidative stress that activates antioxidant and

cytoprotective enzymes, including superoxide dismutase (SOD), catalase, and peroxidase. Metabolic switching during fasting also affects protein metabolism in neurons by reducing mTOR pathway activity, leading to global inhibition of protein synthesis, increased autophagy resulting in the removal of damaged organelles, and recycling of endogenous proteins. This also reduces oxidative stress and supports DNA repair processes [26,35,36]. Ketones stimulate neurons to express brain-derived neurotrophic factor (BDNF), which promotes mitochondrial biogenesis, synaptic plasticity, and resistance to cellular stress. Increased levels of BDNF have been observed in humans during fasting [33,37]. IF also increases the levels of sirtuins, which slow down the aging process by stimulating autophagy, repairing DNA damage, and inhibiting cell apoptosis. They also modulate T lymphocyte activity, reducing the immune response [38]. IF can benefit the brain by improving insulin sensitivity, which naturally decreases with age. Reducing food intake lowers circulating insulin levels and increases insulin receptor sensitivity, contributing to reduced insulin resistance [35]. During fasting, blood levels of adiponectin also increase, which has anti-atherosclerotic and anti-inflammatory effects by inhibiting monocyte adhesion to EC [39]. It is worth noting that returning to normal eating after practicing IF and metabolic switching from ketones to glucose can bring additional health benefits. Reactivation of the mTOR pathway leads to increased protein synthesis and mitochondrial biogenesis, as well as reduced autophagy. During the refeeding phase, processes related to cell growth and plasticity occur, increasing the number of mesenchymal and progenitor cells, which promotes tissue regeneration [26].

3. Intermittent Fasting and Alzheimer's Disease - Research Evidence

IF has recently gained popularity due to its numerous health benefits, and recent studies indicate its promising protection against neurodegeneration, including AD. The metabolic switch to ketones and the adaptive responses of the nervous system to fasting play an important role in enhancing performance and mitigating the effects of diseases. Despite the various IF regimens, all induce the fundamental metabolic changes characteristic of the fasting period. It is worth noting that despite similarities, IF and CR may lead to different biological outcomes. The primary difference is that IF does not necessarily involve a reduction in energy intake, unlike CR. However, an overall reduction in caloric intake is often observed during IF due to the narrow feeding window. In the literature, some researchers have analyzed IF models or isocaloric diets relative to IF as CR, hence some studies on CR are also discussed [7,40].

4. **3.1. Effects of Intermittent Fasting on Cognitive Health in Human Research**

In the literature, the number of studies assessing the impact of IF on cognitive health in humans is limited. Ooi et al. examined the effects of IF on cognitive functions among 99 elderly individuals with mild cognitive impairment (MCI). Participants were divided into three cohorts: regularly practicing IF (r-IF), irregularly practicing IF (i-IF), and non-fasters (n-IF). After a 3-year follow-up, the successful aging rate was 24.3% in the r-IF group, compared to 14.2% in the i-IF group and 3.7% in the n-IF group ($p<0.05$). Additionally, the r-IF group showed significant reductions in body weight, BMI, mean systolic and diastolic blood pressure (SBP and DBP), fasting insulin and glucose levels, and CRP (C-reactive protein). Molecular studies revealed fewer DNA damages and increased SOD activity in the r-IF group compared to the other groups [41].

5. In the brain tissue of healthy individuals, the HOMER 1 gene exhibits high expression and plays a key role in maintaining synaptic plasticity, learning, and memory. Studies have shown that mRNA expression of the HOMER 1 gene is altered in certain brain regions of individuals with AD, and reduced mRNA expression of HOMER 1 has also been observed in transgenic mice with an AD model. Mindikoglu et al. conducted a study among 14 healthy individuals who practiced a 14-hour daily fast without calorie restriction for 30 days. The results showed a 25-fold increase in HOMER 1 protein levels ($p=0.0443$) by the end of the 4-week IF period compared to the baseline value before fasting. Additionally, there was a significant reduction in the levels of APP ($p=0.0026$) and ARPP-21 (cAMP-regulated phosphoprotein 21) ($p=0.0410$), which are associated with the development of AD. Based on these findings, the authors concluded that a 30-day IF regimen may improve cognitive functions and prevent the development of AD [42,43,44].

6. In one study, a significant increase in verbal memory scores (average increase of 20%; $p<0.001$) was observed after 3 months of a calorie-restricted diet by 30% in healthy individuals, which was correlated with decreased insulin and CRP levels [45]. Similar results were obtained by Leclerc et al., who demonstrated greater improvement in working memory among healthy individuals following a 25% calorie-restricted diet for 2 years compared to the control group on an ad libitum diet [46]. Reger et al. showed that hyperketonemia induced by oral intake of medium-chain triglycerides improved cognitive functions in individuals with AD and MCI. Neurobiological evidence suggests that ketone bodies are an effective alternative energy source for the brain, and raising plasma ketone levels may improve cognitive functioning in older individuals with memory impairments [47].

3.2. Effects of Intermittent Fasting on Cognitive Health in Animal Models

Laboratory studies on rodents have shown that long-term IF improves health indicators and counteracts diseases such as diabetes, vascular diseases, cancer, and AD. In animal studies, the IF group is usually compared with a control group fed ad libitum, and depending on the study design, CR regimens are also included. The main IF protocols used in rodents are ADF and TRF [7,48]. Singh et al., in an experiment on 24-month-old rats subjected to ADF for 3 months, observed better motor coordination and spatial memory compared to the control group [49]. Similar results were obtained in 15-month-old rats subjected to ADF for 12 weeks, noting improvements in motor coordination, learning ability, and reduced oxidative damage to proteins [50]. Talani et al., using a 3-week restriction of food intake to 2 hours per day (TRF) in rats, observed improved long-term spatial memory compared to the control group [51]. Cyclic administration of a 4-day FMD in mice promoted hippocampal neurogenesis, improved cognitive performance and short- and long-term memory, and reduced inflammation, supporting the hypothesis that IF in rodents promotes protection against neurodegeneration [52]. Using ADF in wild-type mice resulted in better learning performance and memory compared to mice fed a high-fat and ad libitum diet, and the improvement in cognitive functions was associated with the thickening of the pyramidal cell layer in the CA1 region of the hippocampus [53].

7. 3.3. Impact of Intermittent Fasting on the Pathogenesis of Alzheimer's Disease

Versele et al. in a study on a human BBB model, noted an increase in P-gp protein levels in the presence of AcAc and LRP1 protein levels in the presence of BHB, suggesting that ketone bodies aid in the removal of Aβ from the brain [16]. Similarly, Zhang et al. found that IF prevents Aβ deposition by restoring the polarization of aquaporin-4 (AQP-4) [54]. The beneficial effect of IF and ketone bodies on reducing Aβ accumulation has also been confirmed in other studies on transgenic rodents [55,56,57,58]. In a study on 3xTgAD mice subjected to an ADF or CR diet from 5 months of age, cognitive impairments did not develop, unlike in 3xTgAD mice on an ad libitum diet. Moreover, Aβ and phosphorylated tau protein levels in the hippocampus did not differ between the study and control groups, which may suggest that alleviating age-related cognitive deficits can occur independently of Aβ and tau-related pathology [59]. Studies in humans indicate that IF positively impacts the function and integrity of the vascular endothelium, reducing markers of vascular damage and promoting the maintenance of vascular homeostasis [60,61,62]. In rodents following an episode of cerebral ischemia, prolonged PF favored angiogenesis dependent on endothelial progenitor

cells (EPC) and reduced ischemic damage [63]. IF and CR alleviate neuroinflammation by reducing the accumulation of pathogenic monocytes in the CNS, thereby decreasing the severity of inflammation and autoimmunization [27,64,65]. Additionally, fasting during Ramadan in healthy adults resulted in a significant reduction in pro-inflammatory cytokine levels, including tumor necrosis factor α (TNF-α) ($p<0.05$), and a decrease in the number of immune cells [66]. A study conducted on monkeys showed that long-term CR reduced the levels of pro-inflammatory IL-6, which is associated with neuronal loss and brain atrophy [67]. Not all studies confirm these results. Lazic et al. observed a significant increase in pro-inflammatory cytokine levels in the cerebral cortex, reduced levels of synaptic plasticity proteins, and neuronal damage in 5XFAD transgenic mice fed an ADF regimen for 4 months [68]. Studies indicate that IF affects mitochondria in neurons of the hippocampus and other brain regions by increasing their biogenesis and resistance to excitotoxic stress, and these processes are regulated by BDNF, PGC-1α, and SIRT3 [7][69][70]. Additionally, by inducing BDNF expression, IF can promote neuronal survival and plasticity. In heterozygous mice with a knocked-out BDNF gene on an ad libitum diet, reduced neurogenesis was observed compared to mice on a 3-month ADF diet, suggesting that ADF supports the survival of newly generated neural stem cells [27].

3.4. Impact of Intermittent Fasting on Alzheimer's Disease Risk Factors

Increasing scientific evidence suggests that a chronic positive energy balance resulting from excessive calorie intake and a sedentary lifestyle may increase the risk of developing AD [55]. The medical literature highlights the beneficial impact of IF on metabolic indicators such as body weight, glucose metabolism, lipid profiles, insulin sensitivity, and blood pressure (BP). IF improves insulin sensitivity and reduces insulin resistance, which contributes to the development of atherosclerosis and vascular diseases. Additionally, it positively affects lipid profiles and BP, thereby maintaining vascular health. These data suggest that IF can modify known risk factors for AD, indicating its potential in reducing the risk of developing this disease [18].

Domaszewski et al. evaluated the effectiveness of IF in reducing body fat and lowering the body mass index in 45 overweight women over 60 years old. The intervention in the study group involved complete abstinence from eating for 16 hours daily for 6 weeks. The results showed a difference in body weight (about 2 kg) in favor of the study group compared to the control group, which continued their usual eating habits. The weight loss was mainly due to a reduction in body fat, while muscle mass remained unchanged [71]. Many studies indicate IF

as a promising strategy for weight reduction and combating obesity, as well as improving muscle endurance, with results showing weight loss ranging from 0.8% to 13.0% of initial body weight without severe side effects [72,73]. In studies on mice fed an ADF regimen, their body weight was comparable to rodents fed ad libitum, but they exhibited significantly better glucose metabolism (lower fasting glucose and insulin levels) and increased fatty acid mobilization (higher BHB levels) [7]. Improved insulin sensitivity and glucose tolerance resulting from IF in mice were also confirmed by Gotthardt et al. [74]. Another study demonstrated improved glycemic control in patients with type 2 diabetes who practiced IF with at least a 16-hour fasting period, presenting significantly lower fasting glucose levels compared to the CR group [72,75].

Some studies do not confirm the described conclusions. It has been reported that IF worsened metabolic indicators in mice with genetic hypercholesterolemia, causing obesity, diabetes, insulin resistance, and tripling the risk of atherosclerosis, as well as worsening glucose tolerance in rats fed an ADF regimen for 8 months [76,77].

IF affects circulating hormone levels. In rodents fed an ADF diet, elevated corticosterone levels were noted, which did not negatively impact the neurons of the animals, unlike uncontrolled, chronic stress. Chronic stress reduces the expression of the mineralocorticoid receptor (MR) while maintaining glucocorticoid receptor (GR) levels in hippocampal neurons, increasing the susceptibility of nerve cells to oxidative and metabolic stress. IF reduces GR expression while maintaining MR levels, which promotes improved synaptic plasticity and neuron resilience to stress [7].

High BP values can be positively affected by IF. Sutton et al. demonstrated a reduction in SBP by 11 ± 4 mmHg ($p=0.03$) and DBP by 10 ± 4 mmHg ($p=0.03$) in men with prediabetes who consumed meals within a 6-hour feeding window for 5 weeks, with no change in their body weight. The effectiveness of this intervention was compared to the effectiveness of antihypertensive drugs such as angiotensin-converting enzyme inhibitors (ACEI). They also noted a reduction in insulin resistance ($p=0.005$) and a decrease in the oxidative stress marker 8-isoprostane ($p=0.05$) [78]. The neuroprotective effect of IF has been demonstrated in animal models of traumatic brain injury and ischemic stroke, where its application limited the ischemic lesion and post-infarct neuronal loss, improved neurobehavioral deficits, and reduced stroke-related mortality risk [79,80].

In small observational studies among healthy, obese, and dyslipidemic individuals, IF has shown a significant positive impact on lipid profile improvement by reducing total cholesterol,

LDL, and triglyceride levels while increasing HDL levels in plasma. However, evaluating the effectiveness of this intervention requires further studies on larger populations [81,82]. Mindikoglu et al. noted a significant increase in tropomyosin 3 (TPM3) and tropomyosin 4 (TPM4) levels in healthy individuals after 30 days of practicing a 14-hour IF. These proteins are crucial for stabilizing the actin cytoskeleton, and their dysfunction can lead to the development of hypertension. Additionally, they observed increased expression of the PLIN4 gene, regulated by PPAR-γ, which leads to reduced insulin resistance and improved lipid metabolism, as well as the expression of CFL1 and PKM2 genes, which play key roles in glucose uptake and mitochondrial protection. These results suggest that a 30-day IF regimen may be significant in preventing metabolic syndrome, which contributes to the development of AD [42].

3.5. Intermittent Fasting, Gut Microbiome and Alzheimer's Disease

Recent studies highlight the significant role of gut microbiota in the pathogenesis of AD, positioning it as a factor that increases susceptibility to the disease. The composition of the gut microbiome influences brain health through neural, endocrine, and immune pathways, collectively defined as the microbiota-gut-brain axis (MGBA). In AD, specific changes in the gut microbiome composition are observed, leading to increased gut barrier permeability and activation of immune cells, promoting neuroinflammation, neuronal damage, and loss. Additionally, studies suggest that gut dysbiosis may promote Aβ aggregation, oxidative stress, and insulin resistance [24,83,84].

Various factors influence the diversity and modulation of the gut microbiome, with diet being the most significant. Through its role in metabolism, circadian rhythms, and immune system functioning, the microbiota can mediate the effects of IF on brain health and cognitive functions. IF has been shown to restructure the gut microbiome, enriching its composition and altering the profile of microbial metabolites. In one study, such changes improved cognitive functions and spatial memory in diabetic mice, and TRE in healthy adult men enhanced diurnal oscillations related to microbiota modulation, enriching its composition and increasing the expression of circadian genes, likely through the activation of SIRT1 [26,85,86].

4. Adverse Effects of Intermittent Fasting

IF is considered a safe health intervention, though it can cause side effects such as headaches, lack of energy, reduced concentration and mood, constipation, cold sensations, and bad breath. Currently, there is a lack of evidence on the safety of IF in individuals with type 1 and type 2 diabetes. Due to daily fluctuations in insulin and blood glucose levels in this group, glycemic

monitoring is necessary to enable safe breaking of the fast. Most studies have shown that IF supports neuronal health, but in individuals with ALS (amyotrophic lateral sclerosis), it may promote neurodegeneration and disease progression. IF is not recommended in advanced dementia due to the risk of malnutrition, which worsens the prognosis of the disease. It is also not recommended for individuals with anorexia nervosa due to the potential for excessive weight loss [18]. Animal studies have shown that chronic ADF can lead to diastolic dysfunction and negatively affect reproduction in young animals [87].
A 2024 meta-analysis of 15 clinical trials involving 1,365 overweight or obese individuals did not show an increased incidence of fatigue or headaches. However, it did note a higher risk of dizziness in IF groups with unrestricted early morning food consumption [88]. Despite potential health benefits, the use of IF requires caution, especially in individuals with certain medical conditions. Further research is needed to fully understand its long-term safety and side effects.

CONCLUSION

The use of IF appears to be a promising approach in delaying or preventing pathological processes in Alzheimer's disease. Although IF has been a well-known dietary regimen for years, it represents a new strategy as an intervention to improve cognitive functions and brain health in humans. Due to the limited number of studies conducted on humans, further research is needed to better understand its impact on cognitive health and AD prevention.

Disclosure

Authors’contribution:

Conceptualization: NS, JS, KS, SS, MKS; Methodology: NS, JS; Software: SS, JS; Check: KS, NS; Formal Analysis: MKS, JS; Investigation: MKS, NS, JS; Resources: KS, SS;
Data Curation: MKS, JS; Writing-Rough Preparation: NS, JS; Writing-Review and Editing: MKS, JS, NS, KS, SS; Visualization: SS, JS; Supervision: KS, SS; Project Administration: MKS, NS, JS

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