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Time-Restricted Feeding as a Circadian Therapeutic Strategy for Alzheimer's Disease

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Abstract:

Time-Restricted Feeding (TRF), a form of intermittent fasting, has been recognized as a promising non-pharmacological intervention for improving circadian rhythms and metabolic health. Given the critical role of circadian rhythm disruption in Alzheimer's disease (AD) pathogenesis, TRF is gaining increasing attention as a potential strategy for mitigating AD pathology. This review examines the biological mechanisms through which TRF influences AD-related processes, including circadian rhythms, amyloid-β deposition, tau pathology, and neuroinflammation. Animal studies demonstrate that TRF enhances neuronal resistance, improves synaptic plasticity, and modulates AD-associated metabolic pathways. Concurrently, clinical research suggests TRF may improve sleep architecture and cognitive function, though challenges remain regarding adherence and long-term efficacy. By integrating animal and human studies, this review highlights TRF's multiple roles in AD prevention and treatment. Notably, TRF serves not only as a circadian rhythm-based lifestyle intervention but also as a potential significant adjunct strategy in AD therapy. Future directions include conducting long-term clinical trials and developing personalized treatment plans based on individual genotypes and chronotypes to maximize therapeutic benefits.

Keywords: Time-restricted feeding; Circadian rhythm; Alzheimer's disease; Neurodegeneration.

1. Introduction

The number of people that are affected by dementia increased due to population ageing and population growth, Alzheimer's disease (AD) is the most common cause of dementia [1]. Alzheimer's disease is a neurological disease that is characterized by the progressive degeneration of neurons, its symptoms include progressive cognitive decline and visuospatial cognitive impairment. Latest data show that by 2050, the rate of dementia will triple worldwide, if biological (rather than clinical) definitions are used

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to characterize Alzheimer's disease, these would be three times higher [2]. Despite decades of research, the core mechanism of Alzheimer's disease remains unknown. Currently there are multiple treatments for Alzheimer's disease, but these focus on symptom relief rather than curing the disease or delaying its progression. Existing drugs (such as acetylcholinesterase inhibitors and anti-amyloid monoclonal antibodies) only provide modest symptom relief and have limited effects in slowing disease progression. The continuous rise in global Alzheimer's disease cases highlights the importance of exploring new treatment strategies beyond current approaches. These limitations underline the urgent need for lifestyle-based and non-pharmacological strategies that target underlying disease mechanisms rather than only alleviating symptoms.

Evidence indicates that the risk of individuals developing dementia is highly related to multiple genetic factors, but environments and lifestyle factors, such as sleep disruption are also considered as risk factors [3]. Circadian rhythm is a main regulator of almost all behavioral and physiological processes [4]. At the primary stage of Alzheimer's disease, the patients typically show a sleep-wake cycle and circadian disruption, and these symptoms would be a risk factor for accelerating the development of Alzheimer's disease. Animal models also indicate that circadian disruptions that are caused by genes or environment led to an increasing Alzheimer's disease level. Circadian rhythm disruption may contribute to increased β-amyloid (Aβ) accumulation, accelerate hyperphosphorylation of phosphorylated tau (pTau) protein, and impair the clearance function of the brain's lymphatic system and then further lead to the development of Alzheimer's disease [5]. These findings highlight that circadian clocks may be a significant factor of the therapy of Alzheimer's disease.

Based on the associations between circadian disruption and Alzheimer's disease, targeting circadian regulation gives a potential therapeutic pathway. Time-restricted feeding (TRF) and have now gained growing attention. TRF is from circadian rhythm research, a concept that maintains individuals' metabolism, behavior, and physiology in 24-hour under constant light conditions [6]. It requires restricting food intake to fixed daily circadian clock. Studies demonstrate that time-restricted feeding has positive effects on multiple aspects, including neuroinflammation, behavior, and brain-derived neurotrophic factor (BDNF) expression [7]. Based on study [5], In AD mouse models, TRF has been reported to mitigate Aβ pathology, enhance synaptic plasticity, and maintain cognitive function compared to other treatment. These findings suggest the potential possibility of TRF delaying AD-related decline.

Despite showing as a potential treatment pathway for Alzheimer's disease, its mechanisms and application remain incompletely understood. The key research gaps include how to find an individual's optimal feeding time window, and the possibility of long-term use in elderly patients. To address this, this article focuses on: (1) summarize current studies on the impacts of TRF on AD-related pathology and treatment; (2) clarify the underlying biological mechanisms; and (3) propose future directions and the development of a more personalized TRF therapy of AD.

According to research, intermittent fasting (IF) is a broad concept that means regulating the timing of eating by short-term fasts to improve body health. There are many kinds of IF [8]. Time-restricted feeding (TRF) is a protocol that food intake is fixed to a constant daily time, around 6-10 hours, with remaining total caloric intake. It aims to use the feeding-fasting cycle to regulate and fix circadian rhythms. Superchiasmatic nucleus (SCN) is the main control of circadian rhythms, controls multiple secondary clocks in the brain and coordinates peripheral areas and organs, including the gut, liver, and adipose tissue. While there is circadian distribution, which is normal in AD patients, it leads to physiological disruption and neuroplasticity impairment. Light is the determining factor of SCN regulation; however, food intake also can impact the circadian clock in peripheral areas [9]. Based on this, TRF can help to reset and recover the synchronization between circadian clock and external environmental timing and further keep systemic homeostasis. This indicates that TRF may mitigate AD-related pathological symptoms.

2. Mechanisms and Clinical Applications of TRF in AD

2.1 Mechanism and Evidence

TRF plays a significant role in AD mechanisms and mitigates its development from multiple pathways: regulating circadian rhythm genes, improving metabolism, and reducing neuroinflammation. Time-restricted feeding can regulate the biological clock at the genetic level. Disruption of circadian genes has been shown to be associated with multiple homeostasis functions and is one of the key contributing factors to Alzheimer's disease. Based on research [10], multiple studies indicate that time-restricted feeding enhances the expression of the neuron-promoting neuropeptide Y (NPY) gene in neurons when leptin levels are low. Furthermore, TRF restores the rhythmic expression of regulatory factors such as CREB and mTOR, along with their associated downstream metabolic pathways. It also improves the rhythmic expression of core circadian genes like Bmal1 and Clock. Alzheimer's disease

patients exhibit reduced BMAL1 expression. Applying TRF restores circadian clock genes, can further protecting patients from circadian rhythm disruption caused by Alzheimer‘s disease [7]. This gene-level regulation indicates that TRF not only resets circadian rhythms but also directly modulates molecular pathways associated with Alzheimer‘s disease pathology.

TRF also plays a role in improving metabolism and energy resource utilization. Alzheimer‘s disease patients exhibit low levels of brain-derived neurotrophic factor (BDNF). TRF is known to optimize energy utilization through mitochondrial biogenesis and enhanced oxidative phosphorylation efficiency. Furthermore, fasting reduces blood glucose and hepatic glycogen levels by modulating insulin signaling, prompting the body to seek ketone bodies as an alternative energy source. According to research [11], one ketone body—β-hydroxybutyrate (BHB)—can trigger an increase in BDNF levels, a factor crucial for maintaining and enhancing neuronal plasticity. Consequently, TRF may mitigate the progression of Alzheimer‘s disease. This metabolic shift may help strengthen neurons‘ resistance to damage under pathological stress conditions associated with AD.

Although evidence suggests Alzheimer‘s disease (AD) arises from multiple factors, neuroinflammation has been demonstrated to play a central role by accelerating the pathological processes of β-amyloid (Aβ) and tau proteins [12]. Research [13] confirms that intermittent fasting (IF) mitigates moderate neuroinflammation and cognitive decline in Alzheimer‘s disease. Further studies indicate this intervention reduces expression levels of pro-inflammatory genes in critical brain regions such as the cerebral cortex and hippocampus, which are associated with memory and daily functioning [14]. This indicates TRF‘s potential in mitigating chronic neuroinflammation—a key driver of synaptic loss in AD progression. Studies further confirm that TRF significantly enhances memory capacity, reduces Aβ aggregation, and promotes Aβ clearance in AD mouse models by influencing the amyloid precursor protein (APP) [5]. Thus, TRF serves as a multi-dimensional intervention that addresses molecular pathology while regulating systemic physiological functions.

Time-restricted eating can have an impact on Alzheimer’s disease-related pathologies by modulating the neurometabolic environment. Studies have found that TRF can promote the improvement of neuronal autophagy levels, thereby enhancing the ability of cells to clear protein aggregation. In terms of synaptic function, TRF intervention has been shown to increase synaptic protein expression in the hippocampus, improve synaptic plasticity and neural network connectivity efficiency. In addition, TRF regulates the energy metabolism state of the brain microenvironment, improving the energy supply of nerve cells by enhancing mitochondrial function and fatty acid oxidation, while reducing oxidative stress levels. In terms of the immune microenvironment, TRF can affect the active state of microglia and astrocytes, attenuate the release of pro-inflammatory factors, and thus limit inflammation-mediated nerve damage. The synergistic effect of metabolism and immunity may also delay the occurrence of neurodegenerative changes by interfering with the abnormal phosphorylation process of tau protein. Animal experiments have shown that TRF can improve the performance of learning and memory tasks and promote upregulation of nerve growth factor and its receptor expression at the molecular level. These evidence suggest that TRF not only intervenes in the pathological process at the molecular level, but may also provide protective effects at the level of neural networks and system functions, providing a theoretical basis for exploring non-pharmacological intervention strategies for Alzheimer’s disease.

2.2 Clinical Applications and Challenges

Although evidence shows that Time-Restricted Feeding (TRF) in Alzheimer’s Disease is compelling in animal model, translation to human use remain at an early stage. According to the research [7], the study shows that Italian elders whose eating time is restricted to less than 10 h (TRF) were less likely to have cognitive impairment comparing to elders who has no restricted eating time. Concurrently, pilot study in overweight, sedentary older adults [15] also reported an average adherence rate of 84% over four weeks’ Time-Restricted feeding (fast for 16h per day). They also report improvement in weight loss, walking speed, and quality of life with minimal side effects. Moreover, primary intervention in overweight or sedentary older adults points that TRF improves metabolic health improvement in functional capacity, suggesting possibility and safety of non-demented populations [16].

Meta-analyses and current reviews also point that TRF has high potential in influencing AD-related biomarkers. TRF can play a role in reducing Aβ deposition, decreasing pro-inflammatory cytokines, and modulating gut microbiota composition [17]. This indicates that TRF has potential for preventing cognitive decline. However, the application of TRF in Alzheimer‘s disease (AD) remains limited. TRF effectiveness may differ on varied individuals: patients with obesity, metabolic disorders, or circadian disruption may have better benefits compared to other individuals.

Long-term application of TRF protocols in older population, especially those with cognitive impairment, remains concerns. Although pilot data [15] indicates that there is high adherence (around 84%) in short-term treatment,

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challenges remain. Participants misunderstand fasting guidelines or need more initial instructions to guide protocols. Besides, other factors, such as environments, lifestyles, social meals and irregular schedules, may influence long-term TRF treatment. For elderly patients, it is risky to fast without carefully monitored. Moreover, the durability of effects of TRF, for example, improvement in cognition, still requires confirmation.

Personalized TRF protocols may be necessary based on individuals' different chronotype (morning type and evening type). Multiple chronotype has different optimal feeding windows to maximize cognitive and sleep benefits. The stage of Alzheimer's disease also matters, for early AD patients, TRF may benefit more than late-stage patients. In the future, Time-Restricted Feeding (TRF) may need to integrate and cooperate with genes, chronobiology, and Alzheimer's disease progression to maximize its effectiveness. Also, future research may need to combine TRF with neuroimaging or biomarkers to confirm the impacts of it.

Clinical promotion of time-restricted eating faces multiple challenges in the elderly population. Studies have shown that individual adherence can reach a high level in short-term interventions, but the diversity of eating time, social activities, and lifestyles in long-term interventions may lead to actual implementation biases. Individuals with different physiological states respond differently to TRF, with metabolic abnormalities, obesity, or circadian rhythm disorders likely to obtain more significant intervention benefits, while those with more severe cognitive impairment may have limited effects. Elderly patients are at risk of eating or fasting rapidly without monitoring, requiring individualized intervention and ongoing follow-up. The long-term effects of TRF on cognitive function, metabolic health and quality of life have not been systematically verified, and the combined evaluation of biomarkers, brain imaging and behavioral indicators can provide a quantitative basis for the efficacy. The type of circadian rhythm, the duration of the diet window, and the initial stage of intervention may affect the intervention effect, suggesting that personalized programs need to be designed in the future. TRF has potential value in Alzheimer's disease prevention and intervention, but its clinical application still needs to be combined with multidisciplinary approaches, including chronobiology, metabolic regulation, and neuroimaging, to optimize intervention strategies and clarify mechanisms, providing theoretical support and practical basis for large-scale clinical promotion.

3. Conclusion

Time-Restricted Feeding (TRF) demonstrates potential as a circadian rhythm-based intervention for Alzheimer's disease (AD). Multiple studies suggest TRF may restore circadian rhythms, improve sleep quality, enhance neuronal plasticity, and reduce amyloid and tau pathology. These findings indicate that metabolic and circadian regulation are closely linked to the mechanisms underlying neurodegenerative diseases like Alzheimer's. Clinical studies indicate TRF is feasible in elderly populations and may positively impact sleep and metabolic regulation. However, patient compliance and population heterogeneity remain significant challenges, requiring multidimensional validation of efficacy through sleep architecture, cognitive assessments, and lifestyle habits.

Several challenges persist: long-term adherence among patients with cognitive impairment remains unclear, and individual variations (e.g., genetic background and circadian rhythm type) may significantly influence intervention outcomes. Furthermore, existing studies are limited in scale and duration, with few incorporating comprehensive assessments that include neuroimaging or biomarker detection.

Overall, TRF currently represents a potential low-cost non-pharmacological intervention for neurodegenerative diseases such as Alzheimer's disease, matching the multifactorial pathological characteristics of the disease. It shows potential as a complementary approach to drug therapy by acting through multiple mechanisms including metabolic regulation, neuroinflammation, and synaptic plasticity. Future efforts should focus on conducting large-scale, multicenter clinical trials and promoting cross-disciplinary collaboration. To advance personalized intervention strategies centered on TRF, genetic background, circadian rhythm type, and disease stage must be considered collectively. This approach holds promises for redefining treatment options for Alzheimer's disease.

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