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Review

Intermittent Metabolic Switching and Vascular Cognitive Impairment

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Intermittent fasting (IF), a dietary pattern alternating between eating and fasting periods within a 24-hour cycle, has garnered recognition for its potential to enhance both healthspan and lifespan in animal models and humans. It also shows promise in alleviating age-related diseases, including neurodegeneration. Vascular cognitive impairment (VCI) spans a severity range from mild cognitive deficits to severe cognitive deficits and loss of function in vascular dementia. Chronic cerebral hypoperfusion has emerged as a significant contributor to VCI, instigating vascular pathologies such as microbleeds, blood-brain barrier dysfunction, neuronal loss, and white matter lesions. Preclinical studies in rodents strongly suggest that IF has the potential to attenuate pathological mechanisms, including excitotoxicity, oxidative stress, inflammation, and cell death pathways in VCI models. Hence, this supports evaluating IF in clinical trials for both existing and at-risk VCI patients. This review compiles existing data supporting IF's potential in treating VCI-related vascular and neuronal pathologies, emphasizing the mechanisms by which IF may mitigate these issues. Hence providing a comprehensive overview of the available data supporting IF's potential in treating VCI by emphasizing the underlying mechanisms that make IF a promising intervention for VCI.

Key words: Intermittent fasting, Dementia, Vascular cognitive impairment, Chronic cerebral hypoperfusion, Inflammation, Neurons, Cell death

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INTRODUCTION

The environment has wielded a substantial influence on the molecular evolution of all living organisms, intricately shaping epigenetic and genetic mechanisms and, in turn, modulating the associated phenotypic responses. Notably, environmental conditions exert a profound impact on the healthspan and lifespan of animals. Among these factors, dietary restriction stands out as a potent catalyst for metabolic shifts, triggering pleiotropic alterations that cascade through biological systems. These changes give rise to observable phenotypic modifications, often associated with substantial health benefits in both animals and humans. A noteworthy method of dietary restriction is intermittent fasting (IF), a specific regimen inducing intermittent metabolic switching. This process is characterized by the depletion of glycogen stores and the simultaneous production of ketone bodies from fatty acids. IF has emerged as a promising dietary intervention with potential applications in mitigating the adverse effects of cardiovascular diseases and neurodegenerative conditions, including vascular cognitive impairment (VCI).

VCI encompasses a spectrum of cognitive alterations attributed to vascular-related factors or burdens associated with cerebrovascular disease (CVD). These factors can give rise to varying degrees of cognitive impairment, ranging from mild cognitive impairment to the severe state of vascular dementia (VaD).[1] With the global population aging, VCI has become a significant concern, placing substantial socioeconomic burdens on healthcare systems. VaD is considered the second most prevalent form of dementia, behind Alzheimer's disease (AD). However, some studies suggest VCI as the most prevalent cause of cognitive impairment and dementia in the elderly, due to potential under-diagnosis. Moreover, it's noteworthy that CVD often coexists with AD pathology, accentuating its clinical relevance, particularly in the context of mixed dementia.[2] This intersection of pathologies raises significant public health concerns, prompting essential discussions regarding the imperative for enhanced treatment modalities and therapies tailored to address the complexities of VCI.

This review endeavors to examine the potential impact of IF on mitigating the risk of VCI and its related pathologies. We achieve this by comprehensively assessing the available evidence regarding the effects of an IF regimen on VCI. Furthermore, we delve into the plausible mechanistic underpinnings of how IF may exert ameliorative effects on the progression and pathological manifestations of VCI.

SEARCH STRATEGY, STUDY SELECTION, AND DATA ACQUISITION

This review was conducted through extensive searches in the United States National Library of Medicine (PubMed), Scopus, and Google Scholar databases. Additionally, a thorough search on www.clinicaltrials.gov was performed to identify any new or ongoing studies. To identify diet interventions, we utilized the following cluster terms (intermittent fasting OR Ramadan OR time-restricted OR alternate OR periodic OR reduced meal frequency OR alternate-day). Subsequently, we combined this cluster (using AND) with terms aimed at determining the outcome of VCI, employing the following cluster terms (vascular cognitive impairment and dementia OR chronic cerebral hypoperfusion). The search had no language restrictions. The inclusion criteria for articles encompassed any animal model or human studies involving various forms of IF regimens in VCI. We excluded studies on AD, mild cognitive impairment without vascular basis, mental health-related cognitive disorders, cancer, and diabetes. Notably, no human studies meeting the criteria were found in the literature. Two vessel occlusion and bilateral common carotid artery stenosis (BCAS) models were introduced in rodents to mimic characteristic features of VaD. IF introduced in these rodents induced both epigenetic and genetic changes, offering protection against white matter (WM) lesions and neuronal cell death, improvement in neurocognitive function, and maintenance of hippocampal neuronal density. IF also demonstrated the preservation of blood-brain barrier (BBB) permeability, reducing the number of leaky microvessels following chronic cerebral hypoperfusion (CCH). Mechanistically, IF was effective in mitigating pathological features in the brain through antioxidative and anti-inflammatory pathways.

INTERMITTENT FASTING AND METABOLIC SWITCHING

IF and calorie restriction (CR) are two distinct paradigms of dietary restriction extensively studied and associated with extensions in both healthspan and lifespan.[3] CR entails a consistent reduction in daily calorie intake, often by a specified percentage (around 20% to 40%) below an individual's usual caloric requirements. The primary objective of CR is to diminish total energy consumption over an extended period, irrespective of meal timing alterations. In contrast, IF centers on alternating between eating and fasting periods. Unlike CR, IF does not entail a daily reduction in calorie intake. Instead, it involves restricting food consumption to specific time windows while allowing unrestricted eating during others. Notably, during the eating periods of IF, calorie intake may align with or slightly dip below that of an ad libitum group. These dietary restriction methods induce intermittent metabolic switching, depleting glycogen stores, and utilizing liver fat as an energy source, accompanied by the production of ketone bodies (β-hydroxybutyrate [βOHB]) (Fig. 1). In the ketotic state, where total serum βOHB significantly increases from baseline, ketones emerge as crucial contributors to energy expenditure and the preferred energy source for the brain.[4,5] Neurons display adaptive responses to ketones as an al-

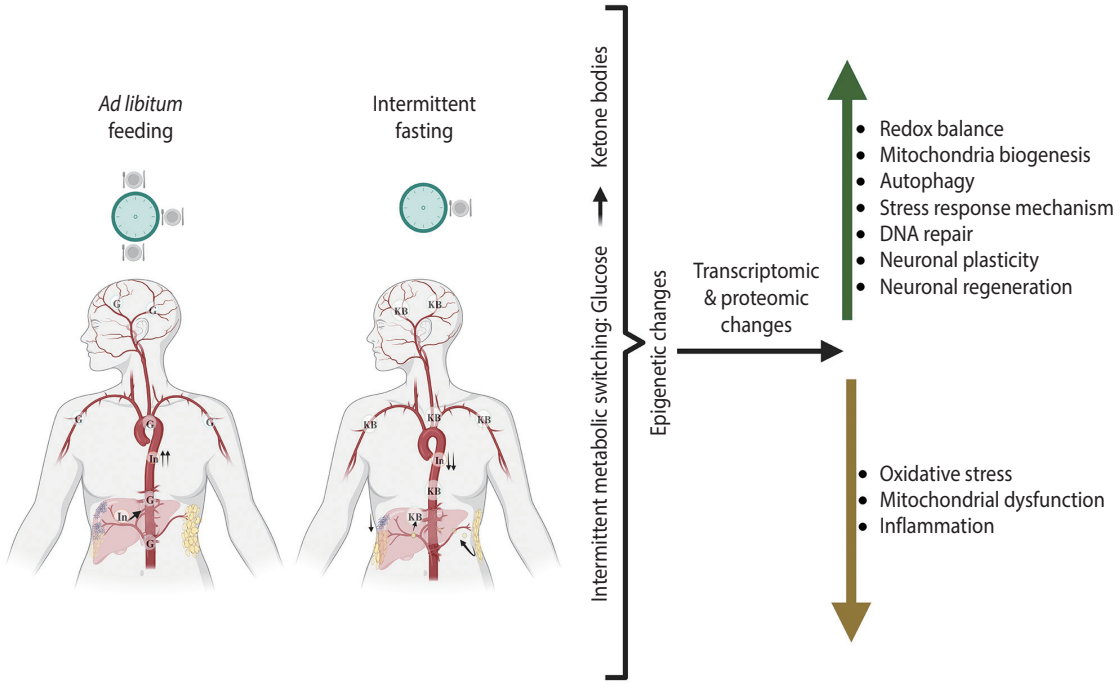

Figure 1. Intermittent fasting (IF) induces intermittent metabolic switching. Following a meal, glucose serves as the primary energy source, with any unused glucose undergoing glycogenesis and being stored in the liver. Conversely, during fasting periods, both liver glycogen and circulating glucose levels decrease, accompanied by a reduction in blood insulin levels. In response to low insulin levels, adipose tissue releases fatty acids, which are converted into ketone bodies (KB) by hepatic cells. During the fasting period, KB become the preferred energy source, marking the transition from glucose to ketones—an event termed intermittent metabolic switching (IMS). IMS triggers epigenetic modifications, leading to transcriptomic, proteomic, and metabolomic changes. These changes contribute to a myriad of beneficial effects associated with IF. IF has been shown to improve redox balance and stress response mechanisms and promote mitochondrial biogenesis, DNA repair, neuronal regeneration, plasticity, and autophagy, while simultaneously reducing inflammation, oxidative stress, and mitochondrial dysfunction.

ternative energy source, characterized by increased expression of brain-derived neurotrophic factor (BDNF) and fibroblast growth factor 2. This metabolic shift also initiates the activation of transcription factors such as cAMP-responsive element-binding protein (CREB) and peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α), leading to the upregulation of genes associated with synaptic plasticity, neurogenesis, and mitochondrial biogenesis. Furthermore, the utilization of ketones stimulates the enhancement of autophagy mechanisms and DNA repair pathways within neuronal networks.[5]

This metabolic shift highlights the adaptability induced by both IF and CR, underscoring the potential benefits of these distinct dietary approaches on brain function and overall health.[5] IF is precisely defined as an eating pattern that cyclically alternates between eating and fasting without altering the total calorie intake. This intervention has garnered significant attention for its potential to promote healthy longevity,[6,7] showcasing positive metabolic and circadian outcomes[8,9] across a spectrum of organisms, ranging from single-cell organisms to multicellular mammals. It is also important to distinguish IF from starvation, the latter representing a state of chronic nutritional insufficiency that may lead to organ failure and eventual death.

IF regimens can be broadly categorized into three types:[10,11] time-restricted feeding, involving the consumption of food during a specific time window each day; every other day fasting, where food is consumed every alternate-day; and periodic fasting (PF), characterized by abstinence from food for 2 days per week while maintaining a normal intake on the remaining 5 days. These distinctive forms of IF exhibit unique metabolic signatures, influencing various cellular and molecular pathways. IF-induced metabolic switching induces robust autophagy, a cellular recycling process associated with numerous health benefits and triggers adaptive responses that enhance cellular resilience. The underlying molecular mechanisms driving the observed healthspan and lifespan extensions re-

main a subject of ongoing research. Investigations into the intricate interactions between nutrient-sensing pathways, epigenetic and genetic mechanisms and cellular stress responses are shedding light on the multiple benefits of IF.[12-15]

IF extends several benefits to the aging brain and under conditions of neurological diseases, potentially influencing cognitive health through a diverse range of biological mechanisms. These encompass the attenuation of excitotoxicity, mitigation of oxidative stress, preservation of mitochondrial function, and dampening of inflammation. IF has further exhibited efficacy in resistance against vascular aging, cognitive decline, and WM injury, offering a promising approach across a spectrum of neurodegenerative diseases.[13-17] Moreover, adherence to an IF diet has been associated with a reduced risk of several chronic conditions, including coronary heart disease,[18] hypertension,[19,20] diabetes,[21] obesity, and metabolic syndromes.[22,23] These interconnected conditions have been implicated in the onset and progression of mild cognitive impairment and dementia. The cumulative evidence underscores the potential of IF not only in promoting cognitive resilience but also in mitigating the risk factors contributing to the development of cognitive disorders. Thus, IF presents a holistic approach to brain health, addressing both cognitive well-being and the interconnected factors influencing cognitive disorders.

CHRONIC CEREBRAL HYPOPERFUSION AS A BASIS OF VCI DEVELOPMENT

VCI encompasses multiple vascular mechanisms and is characterized by CCH.[24-26] CCH can be attributed to multiple vascular factors, including cerebral small vessel disease associated with hypertensive arteriopathy, cerebral microbleeds, lacunar strokes, small vessel occlusion caused by arteriolosclerosis, and small vessel disease related to cerebral amyloid angiopathy, all contributing to the development of VCI.[27,28] It has been well established that CCH precedes cognitive decline in VCI patients with dementia,[29] establishing the role of CCH in VCI progression.

A growing number of studies on VCI have identified CCH as a common vascular factor among the various subtypes of VaD.[26,30,31] CCH has been reported as a major underlying cause that ties together some of the known mechanisms of VCI, such as excitotoxicity, oxidative stress, and inflammation, leading to WM lesions, neurodegeneration, and brain atrophy.[32,33] In animal models of VCI, experimentally inducing CCH in animals has demonstrated the development of VCI features that mimic manifestations in the clinic.

According to the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria, VaD is clinically diagnosed based on a stepwise decline of cognitive impairments, the presence of focal signs during neurological examinations, evidence of a history of cardiovascular disease occurrence such as stroke, and the presence of significant WM disease.[34,35] Structural alterations within the brain during VCI can be characterized into two gross pathologies—(1) vascular and (2) neuronal pathologies which include impairment to cerebrovascular and BBB integrity, damage to the WM, progressive loss of neurons, and brain atrophy. These structural alterations ultimately lead to cognitive deficits and dementia in VCI (Fig. 2).

A central challenge in the prevention and treatment of VCI is predicting and identifying at-risk patients. Given that VCI is a condition with multiple causes and disease progression is unique and dynamic in each individual, there is a need for interventions with pleiotropic molecular mechanisms of action in the brain. IF serves as such a method to treat VCI, as IF is known to have pleiotropic benefits and improve cardiovascular and neurological conditions. In the subsequent sections, we comprehensively examine the impact of IF-induced metabolic switching on vascular and neuronal pathologies in VCI, delving into its scientific underpinnings and potential therapeutic implications.

VASCULAR PATHOLOGIES AND THE EFFECTS OF INTERMITTENT FASTING IN VCI

Vascular pathologies resulting from CCH encompass the development of abnormalities in the BBB and the occurrence of cerebral microbleeds, both of which have been linked to cognitive impairments. This section will explore the potential mitigating effects of IF on these specific vascular pathologies in the context of VCI.

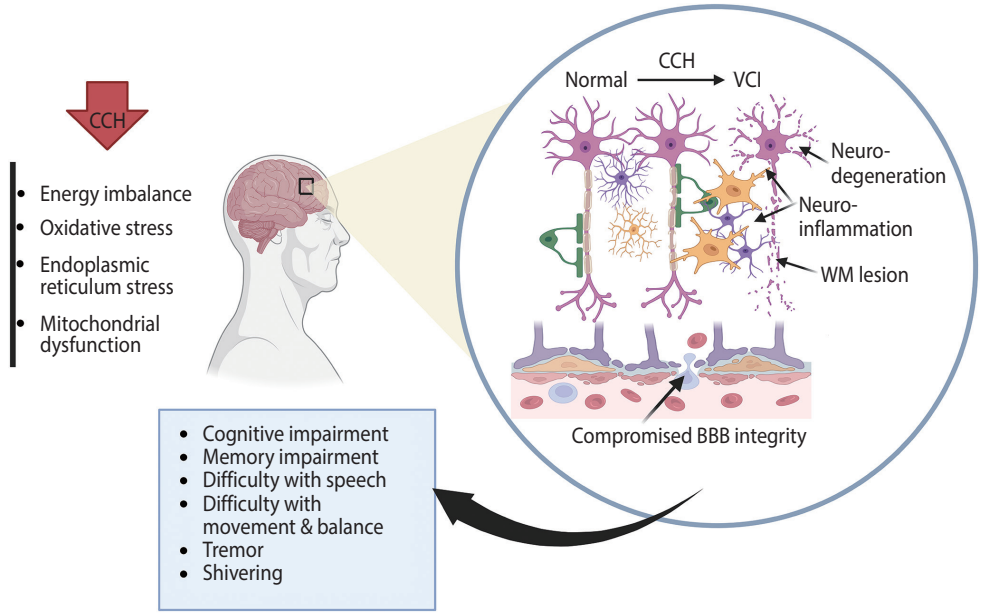

Figure 2. Pathophysiology of vascular cognitive impairment (VCI). Chronic cerebral hypoperfusion (CCH) plays a central role in the complex pathophysiology of VCI, by inducing energy and oxygen deficiency within the brain. CCH causes an energy imbalance, thereby triggering oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction. Together, these pathologies contribute to a compromised blood-brain barrier (BBB) integrity, neuroinflammation, white matter (WM) lesions, and neurodegeneration. Under normal physiological conditions, BBB functions as a selective semipermeable and dynamic interface, crucial for cerebral homeostasis. However, under CCH, its integrity is disrupted, leading to an increased movement of substances between the blood and the brain. The overactivation of glial cells, referred to as neuroinflammation, plays a pivotal role in the pathophysiology of VCI. Additionally, CCH induces damage to the myelin sheath, and the subsequent loss of myelin can impede the propagation of action potentials, eventually resulting in axonal loss and neuronal depletion. These pathological changes culminate in the manifestation of symptoms associated with vascular dementia, including cognitive impairment, memory loss, and other related manifestations.

Effects of intermittent fasting on BBB damage in VCI

The BBB is a dynamic interface crucial for maintaining central nervous system (CNS) homeostasis, thereby ensuring the normal function of the brain. The BBB comprises of endothelial cells lining blood vessels, tight junction (TJ) proteins facilitating molecular control between the blood and brain, pericytes along the vessels, astrocytic end feet, and surrounding basement membranes. Increased permeability of the BBB has been associated with VaD, and extensive research has elucidated the mechanisms underlying BBB breakdown.[36,37] A comprehensive understanding of the mechanisms governing BBB dysregulation and VCI/VaD pathophysiology may offer insights for guiding VCI care decisions and potentially identifying new therapeutic targets at various stages of VCI progression and VaD manifestation.

A common cause of increased BBB permeability is the disruption of the inter-endothelial TJ proteins. Dysregulation of these proteins compromises BBB integrity and molecular passage.[38,39] High brain glucose levels due to dysregulated glucose metabolism during CCH is associated with BBB endothelial dysfunction.[40] Plausibly, high blood glucose induces translocation of TJ protein zonula occludens-1, affecting BBB integrity.[40] IF has been reported to display potent effects on glucose metabolism and insulin signaling.[41,42] IF positively influences glucose metabolism and insulin signaling, increasing the expression of TJ.[43] Taken together, IF may maintain BBB integrity, mitigating vascular pathology post-CCH (Fig. 3).[16]

Endothelial dysfunction, partly due to inflammatory cytokines and decreased autophagy, contributes to cerebrovascular damage. The BBB function becomes compromised under inflammatory conditions.[44] Inflammatory cytokines affect endothelial TJ proteins[45] and induce brain leukocyte infiltration.[46] IF reduces brain inflammation through ketone bodies, which activate anti-inflammatory mechanisms.[47-49] For example, IF may prevent BBB damage by upregulating forkhead transcription factor 1 (FoxO1) and sup-

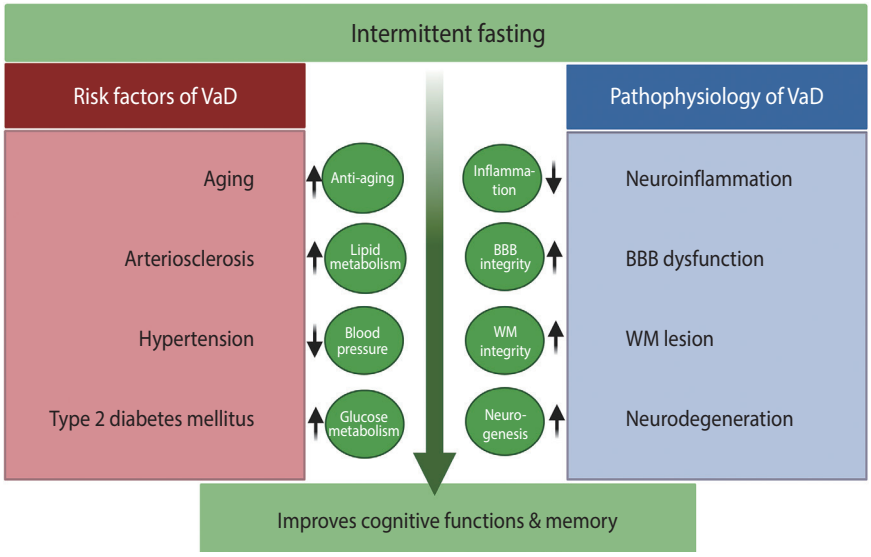

Figure 3. The potential therapeutic effects of intermittent fasting (IF) on vascular dementia (VaD). IF provides multifaceted benefits that can counteract the pathology of VaD. One major risk factor for VaD is aging, and IF is known to slows down this process. The protective effects of IF extend to other risk factors such as arteriosclerosis, hypertension, and type 2 diabetes mellitus by improving lipid metabolism, reducing blood pressure, and improving insulin sensitivity and glucose metabolism, respectively. Moreover, IF reduces inflammation, preserves the blood-brain barrier (BBB) and white matter (WM) integrity, and promotes neurogenesis. These diverse effects collectively place IF as a promising therapeutic approach against VaD.

pressing nuclear factor κB, a potent proinflammatory transcription factor under disease conditions.[50,51] Endothelial dysfunction and inflammatory markers such as intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 decrease after fasting, suggesting reduced leukocyte infiltration.[52,53] Therefore, IF may be able to exert its endothelial protective effects through reduction in inflammatory signals, and hence preserve BBB integrity.

Oxidative stress is intricately linked to inflammation. Ketone bodies produced during IF-induced metabolic switching exhibit antioxidative effects by upregulating the transcription of genes, including antioxidant enzymes (superoxide dismutase [SOD] 1, SOD2, and catalase) and FoxO, which mediate the protective actions of sirtuins (Sirts).[54-57] Robust antioxidant activity, particularly that of manganese SOD, is recognized as essential for maintaining a healthy BBB.[58] FoxO3, diminished in endothelial cells under hypoxia, is implicated in BBB damage.[59] Downstream of FoxO3 lies the Sirt3 axis, known for its pivotal role in cellular resistance and regulation of BBB permeability post-ischemia.[60] Additionally, Sirt3 safeguards against oxidative stress by modulating mitochondrial calcium and biogenesis.[61] While evidence specific to VCI models is lacking, it remains plausible that IF could potentially elevate antioxidant SODs, FoxO3, and Sirt3 levels in endothelial cells, thus contributing to the maintenance of BBB integrity.

IF has been documented to elevate autophagy levels, particularly in hypoxic states.[62] IF also has been reported to enhance endothelial function in metabolic disease states by promoting autophagy.[63] Autophagy plays a crucial role in maintaining endothelial homeostasis within vascular beds, thereby preserving the physiological structure and function of the endothelium within the BBB.[64] Consequently, IF may have the potential to sustain endothelial homeostasis, enhance endothelial function, and thus protect BBB integrity through autophagy mechanisms. The astrocytic end feet surrounding the endothelium contribute significantly to BBB maintenance. They regulate the constriction of microvessels to control blood flow,[65] facilitate the diffusion of solutes between the blood and the brain,[66] and maintain endothelial cell properties. Aquaporin (AQP) proteins are essential channels involved in water transport across the BBB, crucial for maintaining well-regulated water homeostasis in the CNS.[67] IF has demonstrated the ability to restore and maintain AQP levels in the brain.[68] While this restorative effect has been observed in AD, there is potential for this mechanism to contribute to IF's positive effects and reduction of BBB damage in other conditions, including VaD.

Effects of intermittent fasting on cerebral microbleeds in VCI

Cerebral microbleeds are minute chronic brain haemorrhages, likely stemming from structural abnormalities in small blood vessels within the brain, detectable through magnetic resonance imaging (MRI) sequences.[69] Among VaD patients, the frequency of microbleeds in the brain ranges from 65% to 84.9%.[70,71] The location of microbleeds in specific areas of the brain can result in focal damage, disrupting the structural connectivity of neurological tracts and leading to impairment in specific cognitive domains.[72,73] Cerebral microbleeds serve as downstream markers of brain damage caused by vascular pathological mechanisms and are associated with an increased risk of cognitive impairment and dementia in the general population.[74] These microbleeds are directly linked to microvascular leakiness, leading to the extravasation of blood constituents into the brain through vessel walls and *vice versa*. Therefore, microbleed formation plays a pivotal role as a downstream effect of BBB dysfunction and endothelial damage.[75]

Microbleeds are closely associated with hypertensive vasculopathy and VaD, affecting the microvasculature in various brain regions such as the deep gray nuclei, brainstem, cerebellum, and deep WM.[76] The prevalence of microbleeds is linked to chronic hypertension and cognitive decline in the elderly.[77,78] Adherence to an IF diet has shown beneficial effects on lowering blood pressure in both animals and humans.[79,80] Although the exact mechanism is not fully understood, there is speculation that the upregulation of BDNF may be responsible for the observed improvements in blood pressure during fasting. BDNF has been reported to regulate blood pressure by increasing the release of the neurotransmitter acetylcholine from neurons. Acetylcholine, in turn, is responsible for blood vessel dilation through endothelial nitric oxide synthase and prostaglandin production.[81]

In aging patients, microbleeds have been linked to elevated inflammatory markers such as tumor necrosis factor receptor 2 and lipoprotein phospholipase-A2 (a marker of vascular inflammation).[82] Indeed, inflammation-induced models have been developed to simulate and study microbleed development and treatment in animals, highlighting the causal connection between inflammation and microbleed formation.[83] IF has been characterized to ameliorate inflammation activation in the brain, reducing proinflammatory cytokines and immune cell response following ischemia and CCH.[84,85] Therefore, IF may have the potential to decrease the formation of microbleeds in the brain by attenuating proinflammatory mediators. Furthermore, PF has been reported to promote endothelial progenitor cell-mediated revascularization in mice following ischemic conditions in the brain.[86] PF improves endothelial progenitor cell function, thus enhancing repair and vascular maintenance of adult vessels. Further studies required to elucidate the IF mechanisms through which vascular integrity is maintained following CCH, potentially associated with endothelial progenitor cell health,[86] leading to decreased microvascular fragility and a lower incidence of microbleeds.

A dyslipidemic lipid profile in patients has been associated with the formation of cerebral microbleeds.[87] Elevated cholesterol levels in the bloodstream induce pathological structural abnormalities in the vessels, including reduced vasodilatory response, a severe inflammatory phenotype of the vessels, and the accumulation of plaques.[88,89] A lower fraction of healthy lipids, such as high-density lipoprotein (HDL) cholesterol in the serum, has been reported as a risk factor for the formation of cerebral microbleeds.[87] Additionally, abnormal cholesterol metabolism has been linked to an increased risk of VaD in patients.[90] IF has demonstrated the ability to improve lipid profiles in various animal and human studies, increasing serum HDL levels and other lipids, thereby reducing the risk of cardiovascular diseases.[91] While the exact mechanism by which cholesterol influences the vasculature remains incompletely understood, reports suggest heightened expression of angiotensin II type 1 receptors, which are central to mediating the effects of angiotensin II.[89] Angiotensin II induces cerebrovascular remodeling, promotes vascular inflammation and oxidative stress, resulting in impaired regulation of cerebral blood flow.[92] IF has been reported to restore balance in the angiotensin system, thereby reducing angiotensin II-induced vascular pathologies in the brain.[93,94] Furthermore, IF induces lipolysis in fat tissues, mobilizing fatty acid-derived ketones and βOHB, a major component of ketone bodies, into the bloodstream.[95] βOHB can traverse the BBB into the brain parenchyma, facilitating the recovery of stress-induced vascular cell senescence.[96] This mechanism could be instrumental in preserving and maintaining the integrity of the vasculature, potentially preventing microbleed formation in the brain following CCH.

NEURONAL PATHOLOGIES AND THE EFFECTS OF INTERMITTENT FASTING IN VCI

Despite variations among patients, the existing data consistently reveal a distinctive pattern in the development of neuronal pathologies in VCI and VaD. The predominant pattern encompasses the formation of WM lesions, hippocampal and brain atrophy, leading to cognitive impairments—specifically, subcortical dementia with early impairment of frontal lobe function. This section will explore the potential mitigating effects of IF on these specific neuronal pathologies in the context of VCI.

Effects of intermittent fasting on WM damage in VCI

Leukoaraiosis is defined as a spectrum of pathologies involving WM disease observed on MRI sequences of the brain during VCI, depicting the disruption of WM. In affected areas, axons, myelinated fibers, and oligodendrocytes are reduced, and there is an increase in fluid content. This condition represents the earliest and most frequent abnormality during VCI, closely associated with reduced blood flow in the brain—the hallmark feature of VCI.[27,97,98] While WM changes have been postulated to occur as a consequence of BBB breakdown, it is suggested that BBB breakdown may play a pivotal role in the formation of white matter lesions (WMLs).[99]

In other forms of neurological diseases such as multiple sclerosis, myelin damage recruits T cells that traverse the BBB and migrate into the CNS, where they are activated by localized cerebral antigen-presenting cells, promoting further inflammation and damage to the WM.[100,101] This inflammatory response leads to damage to oligodendrocyte precursor cells (OPCs), mature oligodendrocytes, and induces demyelination. Research in multiple sclerosis models has reported that fasting mimicking diet (FMD) increases oligodendrocyte differentiation from precursor cells, while protecting OPCs and mature oligodendrocytes from apoptosis in mice following WM damage.[102] Additionally, IF was found to reduce activated-myelin-induced T cell migration into the CNS following WM damage.[102] Given that OPCs play a role in myelin regeneration, IF may mediate regeneration through the promotion of endogenous glucocorticoid production and the reduction of T cell activation within the lesion area.[102] Furthermore, intermittent caloric restriction using the modified FMD was effective in the treatment of animal model of multiple sclerosis through ameliorating inflammatory response and promoting recovery of the damaged tissue.[103] This underscores the potential of IF in ameliorating and reversing WM damage in mice, even in VCI models. Furthermore, long-term adherence to IF may be suitable for promoting the regeneration and replacement of damaged oligodendrocytes, thereby proving effective in the treatment of chronic diseases such as VCI and VaD (Fig. 3). Indeed, studies from our laboratory employing an animal model of VaD, the BCAS model, have demonstrated that IF protects against WML.[14,16]

Effects of intermittent fasting on brain atrophy in VCI

A reduction in cortical volume has been observed in patients following the manifestation of VCI.[104] Cortical atrophy may be linked to dysregulated apoptosis during VCI, leading to neuronal loss, a decline in synaptic plasticity and hippocampal shrinkage.[33,105] Neuronal loss resulting from apoptosis contributes to cerebral atrophy and the degeneration of neuronal populations in the brain. Apoptotic cell death plays a pivotal role in inflammatory processes, regulating the function of both neuronal and glial cells in VCI. There is evidence suggesting that adult neurogenesis is crucial for the maintenance of hippocampal volume.[106] IF has been reported, under non-pathological conditions, to increase the longevity protein Klotho,[107] Notch signaling,[108] and the BDNF pathway,[85] consequently promoting neurogenesis. Several studies have acknowledged the positive effects of IF in stroke, where it enhanced neuronal cell proliferation and survival in the subventricular zone and hippocampal regions.[15,85,109] Interestingly, chronic stress stimuli have been associated with a reduction in the number and size of glial cells, particularly astrocytes, suggesting a potential contribution to brain volume reduction or atrophy.[110]

Effects of intermittent fasting on cognitive impairments in VCI

Cognitive functions predominantly arise from the complex interplay between cortical and subcortical regions. Vascular lesions, prevalent in VCI, have the potential to disrupt these intricate brain networks, resulting in functional deficits.[111-113] Furthermore, it has become increasingly evident that specific regions of WM are vulnera-

ble and linked to the development of cognitive impairments.[114,115] This insight is supported by findings that indicate the emergence of cognitive impairments following damage and disruption to networks within the WM, especially in critical areas such as the internal capsule[116] and corpus callosum.[117]

Learning and memory impairments have been associated with increased levels of reactive oxygen species (ROS).[118] However, IF demonstrates the ability to attenuate ROS levels through increased ketone levels in the blood[119,120] and has been shown to increase antioxidants, neurotrophic factors, and protein chaperones in the brain.[85] The elevation in antioxidant levels, such as SOD, neurotrophic factors like BDNF, and heat shock proteins has been associated with improved spatial learning, memory-related hippocampal long-term potentiation, and working memory.[85,121,122] Neuroinflammation is another mechanism underlying dementia and cognitive decline in the elderly.[123] IF has been reported to exhibit a reduction in proinflammatory cytokines (interleukin [IL]-1α, IL-1β, tumor necrosis factor-α, IL-6, interferon γ).[85,124] In addition, a decrease in toll-like receptor 4, which plays a role in neuroinflammation in neurological conditions.[51,125,126] IF suppresses neuroinflammation and oxidative stress and preserves cognitive function in VaD.[127]

Finally, the gut microbiome, though primarily having a role in metabolism, also mediates effects on brain health and cognition. The gut microbiota has been implicated in the pathogenesis of various neurodegenerative diseases.[128,129] IF has been reported to show a more enriched gut microbiome composition and metabolites that are linked to improved cognitive functioning in both mice and humans.[43,130,131]

CONCLUSION

The increasing prevalence of VCI is a pressing global public health challenge. Despite the absence of clinical trials specifically conducted on VCI cohorts to validate the efficacy of IF, the promising outcomes observed in animal models underscore its potential in improving VCI prognosis. While the precise molecular and cellular mechanisms underlying IF's impact remain to be fully elucidated, its positive influence on various cardiovascular, metabolic, and neurodegenerative conditions suggests a broad spectrum of benefits. This review provides an exploration of IF's role in managing VCI, aiming to offer a novel perspective on how it might attenuate the pathologies associated with this condition.

Upon comprehensive scrutiny of the existing literature, a compelling case emerges for the therapeutic application of IF in VCI and VaD. These findings should serve as a catalyst for future investigations, spanning both animal models and clinical settings, to refine our understanding of the myriad mechanisms underlying IF's potential in mitigating VCI pathogenesis. Prospective, longitudinal trials hold the promise of uncovering sustained improvements, not only in preventing pathological manifestations but also in ameliorating the degree and rate of cognitive decline. This, in turn, could yield substantial benefits for individuals at risk of VCI on a global scale. As research in the field advances, the insights gained provide a solid foundation for designing and implementing further trials, as well as offering new avenues for therapeutic interventions in the realm of VCI.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Study concept and design: VR, NIT, and TVA; acquisition of data: VR and NIT; analysis and interpretation of data: VR; drafting of the manuscript: VR, DYF, and TVA; critical revision of the man-

uscript: VR, NIT, DYF, CPC, MKPL, and TVA; obtained funding: TVA; administrative, technical, or material support: NIT; and study supervision: TVA.

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