ABSTRACT
Vascular dementia is the most common neuropsychiatric syndrome and is characterized by synaptic dysfunction, neuroinflammation, and cognitive dysfunction. Vascular dementia is associated with various environmental, genetic, and lifestyle risk factors. Recent research has focused on the association between vascular dementia and dietary patterns, suggesting that dietary regulation leads to better control of energy metabolism, improvements in brain insulin resistance, and the suppression of neuroinflammation. Intermittent fasting is a calorie-restriction method known to be more effective in promoting fat loss and regulating the impairment of glucose metabolism as compared with other dietary restriction regimens. Herein, the authors review the effects of intermittent fasting with regard to vascular dementia based on recent evidence and propose that intermittent fasting could be a therapeutic approach for ameliorating vascular dementia pathology and preventing its onset.

Keywords: Intermittent fasting; Vascular dementia; Cognitive function

INTRODUCTION
Dementia is a highly prevalent chronic neuropsychiatric syndrome globally and is accompanied by memory deficit and cognitive dysfunction, which ultimately result in disability or limitations in the activities of daily living. The population with dementia is rapidly increasing compared to those having other diseases and, based on a clinical report, the number of individuals with dementia is projected to reach approximately 66 million by 2030. Dementia can be commonly classified into 2 types: Alzheimer’s disease (AD) and vascular dementia (VaD). AD is characterized by an onset with a progressive course with memory loss and visuospatial functions that leads to global cognitive impairment, whereas VaD is markedly characterized by vascular changes and its onset is described as being a less gradual progression compared to AD, which involves a step-by-step cognitive decline. The neuropathologic features of these diseases include neuronal loss, atrophy of the frontal and temporal lobes, severe memory loss, and language impairments. AD is degenerative and incurable, while VaD is reversible or temporary. AD patients mainly have difficulty recalling recent events or new information and have more severe troubles with memory loss and communication than do individuals with VaD. VaD occurs as a result of a lack of adequate oxygen transfer to the brain.
and ultimately leads to neuronal cell death. One study demonstrated that VaD patients are more impaired than AD patients in the areas of attention and visual construction tasks.\(^7\) Also, several studies have suggested that memory function and temporal lobe function are mainly impaired in AD, whereas frontal lobe function impairment is predominant in VaD.\(^8\) AD accounts for more than 60% of cases of dementia in older individuals and is characterized by the deposition of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau proteins, representing the most frequent type of dementia worldwide.\(^9\) The excessive accumulation of senile plaques composed of Aβ peptide and the hyperphosphorylation of tau proteins trigger neuroinflammation, blood–brain barrier (BBB) dysfunction, and cognitive decline.\(^10\) VaD is accompanied by cognitive impairment, is the second most prevalent type of dementia, and is attributable to cerebrovascular pathology.\(^11\) Cognitive impairment in VaD is directly correlated with the suppression of cerebral blood pressure (BP) and cardiovascular complications,\(^12\) leading to an increase of BBB permeability from neurotoxic substances and the increase of amyloid deposition.\(^13\) The impairment of cerebrovascular function triggers excessive Aβ deposition and the early opening of the BBB.\(^14\)

According to previous studies, dementia is also related to metabolic diseases such as hypertension and type 2 diabetes\(^15\) as a result of various risk factors related to cognitive decline. With respect to the relationship between dietary pattern(s) and the onset of dementia, many studies to date have investigated therapeutic approaches for preventing dementia using dietary regulation to support diet’s positive role in mitigating memory decline in patients with dementia.\(^16\) Calorie restriction achieved by altering dietary patterns results in weight loss and ultimately improves metabolic and cognitive function by regulating lipid metabolism and improving glucose metabolism, inflammation, and insulin resistance.\(^17\) Previous studies have reported that caloric restriction has demonstrated neuroprotective effects on neuroinflammation and cognitive function.\(^18\) In particular, intermittent fasting as a method of dietary caloric restriction has been shown to more effective in reducing weight and fat mass versus continuous calorie restriction.\(^19\)

Intermittent fasting is not a type of diet but instead is a pattern of eating. Its success more so relies on when one eats rather than what one eats. There are several different methods of intermittent fasting: for example, well-known methods include the Leangains protocol, which involves eating for eight hours and fasting for 16 hours between feedings; the eat-stop-eat protocol, which involves fasting for 24 hours, once a week; and the 5:2 diet, which involves consuming only 500 calories on 2 nonconsecutive days of the week and then normally eating on the other 5 days.\(^20\) Intermittent fasting has been highlighted as a promising method of calorie restriction, in that modulation of the circadian cycle can more effectively regulate the function of the hypothalamus, which controls appetite, energy metabolism, and the inflammatory response.\(^21\) In addition, intermittent fasting has demonstrated neuroprotective effects, a reduction of neuroinflammation, and an improvement in redox status and promotes an increase in the production of neurotrophic factors, leading to increased neurogenesis and improvement in mitochondrial function.\(^22\) Furthermore, intermittent fasting improves cognitive dysfunction and the dysregulation of energy metabolism and dyslipidemia in patients with AD.\(^23\) Another study reported that intermittent fasting protected against brain damage by restoring aquaporin-4 polarity in AD,\(^24\) while a recent investigation indicated that intermittent fasting leads to increases in ketone body levels in the blood and continuously supports neuroprotective effects by regulating the activity of β-hydroxybutyrate in AD.\(^25\) Herein, we review recent evidence regarding the effects of intermittent fasting on dementia and discuss the therapeutic potential of intermittent fasting to prevent the onset of dementia and attenuate neuropathology.
THE EFFECTS OF INTERMITTENT FASTING IN DEMENTIA

1. Intermittent fasting: focus on neuroinflammation
A previous study demonstrated that caloric restriction reduces the production of reactive oxygen species and promotes antioxidant responses such as nuclear factor-erythroid 2 signaling. Additionally, calorie restriction reduces DNA damage by attenuating telomere erosion through regulating nuclear factor kappa B in inflammatory signaling and the production of proinflammatory mediator C-reactive proteins. In particular, intermittent fasting reduces the levels of proinflammatory cytokines including interleukin (IL)-1β and IL-18 in the brain. One study reported that intermittent fasting decreases the production of IL-1α, IL-1β, and tumor necrosis factor-α under lipopolysaccharide-induced inflammatory conditions and increases the production of brain-derived neurotrophic factor in the hippocampus. Furthermore, intermittent fasting has been reported to improve cognitive decline by downregulating inflammatory responses. Intermittent fasting controls inflammatory pathways and contributes to hippocampal neuronal function, relating to memory, and inhibits neuronal cell apoptosis by controlling autophagic flux.

2. Intermittent fasting: focus on neurotransmitters and synaptic plasticity
Neurotransmitters, including glutamate, are involved in synaptic plasticity and contribute to neuronal circuitry. Fasting may activate cAMP responsive element binding signaling in hippocampal and entorhinal cortical neurons involved in synaptic function and memory formation. In particular, intermittent fasting boosts hippocampal plasticity and mitochondrial function via calcium signaling. Intermittent fasting also contributes to neuronal synaptic plasticity by controlling the secretion of neurotransmitters including serotonin, noradrenaline, and dopamine. Intermittent fasting additionally improves the impairment of synaptic plasticity in hippocampal neurons and enhances autonomic synaptic plasticity, subsequently rescuing cognitive impairment.

3. Intermittent fasting: focus on vascular function
Cerebrovascular dysfunction is commonly exhibited in patients with dementia. It leads to neuroinflammation and oxidative stress in the brain and causes neuronal damage; provokes BBB breakdown; and triggers amyloid plaque production by boosting the amyloid precursor protein (APP) cleavage enzyme, beta-secretase, and tau protein phosphorylation. A recent study demonstrated that arterial stiffness (or high-pulse wave velocity) could promote the increase of amyloid beta deposition and exacerbate cognitive decline. Additionally, neurovascular coupling is impaired in AD, and abnormal blood flow leads to an imbalance between neural activity and glucose metabolism in the brain. Calorie restriction has been reported to decrease the risk for atherosclerosis and reduce BP and triglyceride levels in blood vessels. Previous research has demonstrated that intermittent fasting improves endothelial dysfunction and attenuates the risk for cardiovascular diseases. Intermittent fasting has been found to improve endothelial vasorelaxation and stabilize high BP. A few studies have reported dramatic decreases in BP values after intermittent fasting as well as improvement in vascular function.

4. Intermittent fasting: focus on insulin resistance and neurogenesis
Intermittent fasting leads to a decrease in insulin-like growth factor 1 expression and a consequent reduction in glucose levels. Additionally, intermittent fasting enhances insulin sensitivity in neurons and ameliorates dysfunction in glucose metabolism. Neurogenesis describes the process where new neurons are generated to replace injured neurons in the brain.
subventricular and subgranular zones of the hippocampus.\(^4\) In dementia, the process of neurogenesis is impaired and, consequently, cognitive impairment occurs.\(^4\) In AD, the excessive accumulation of APP triggers a decrease in neurogenesis in both the dentate gyrus and subventricular zone.\(^5\) Intermittent fasting enhances hippocampal neurogenesis\(^6\) and reduces brain damage by generating new neurons in response to oxidative stress.\(^7\)

**CONCLUSIONS**

We reviewed the effects of intermittent fasting on dementia based on previous significant findings. We focused on the therapeutic potential of intermittent fasting in view of known risk factors for dementia, including neuroinflammation, synaptic dysfunction, cerebrovascular inflammation, brain insulin resistance, and impaired neurogenesis (Fig. 1). A previous study has reported that chronic intermittent fasting improves cognitive dysfunction.\(^5\) Another recent study demonstrated that intermittent fasting inhibits hippocampal neuronal damage against oxidative stress and, ultimately, suppresses memory deficits.\(^8\) A separate investigation suggested that intermittent fasting ameliorates memory deficits by controlling inflammatory responses.\(^9\) However, although there is much evidence available to support the positive effect of intermittent fasting on cognitive decline in dementia, the mechanisms involved in the fasting process and occurrence of memory deficit remains unclear. We reviewed related mechanisms regarding the therapeutic potential of intermittent fasting in dementia. We suggest that the application of intermittent fasting may be an effective dietary therapy for preventing the onset and/or suppressing the development of dementia.

**REFERENCES**

1. Livingston G, Sommerlad A, Orgeta V, Costaferda SG, Huntley I, Ames D, et al. Dementia prevention, intervention, and care. Lancet 2017;390:2673-2734. [PUBMED] [CROSSREF]
2. Wortmann M. Dementia: a global health priority - highlights from an ADI and World Health Organization report. Alzheimers Res Ther 2012;4:40. [PUBMED] [CROSSREF]
3. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer’s disease. Nat Rev Dis Primers 2015;1:15056. [PUBMED] [CROSSREF]
4. Cummings JL. Alzheimer's disease. N Engl J Med 2004;351:56-67.

5. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kasschau CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263-269.

6. Warren JD, Rohrer JD, Rossor MN. Clinical review. Frontotemporal dementia. BMJ 2013;347:f4827.

7. Dong Y, Gan DZ, Tay SZ, Koay WL, Collinson SL, Hilal S, et al. Patterns of neuropsychological impairment in Alzheimer's disease and mixed dementia. J Neurol Sci 2013;333:5-8.

8. Busse C, Anselmi P, Pompanin S, Zorzi G, Frugiacci F, Camporese G, et al. Specific verbal memory measures may distinguish Alzheimer's disease from dementia with Lewy bodies. J Alzheimers Dis 2017;59:1009-1015.

9. Scheltens P, Blennow K, Breteker MM, de Strooper B, Frisoni GB, Salloway S, et al. Alzheimer's disease. Lancet 2016;388:505-517.

10. Bhaskar K, Konerth M, Kokiko-Cochran ON, Cardona A, Ransohoff RM, Lamb BT. Regulation of tau pathology by the microglial fractalkine receptor. Neuron 2010;68:19-31.

11. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:2672-2713.

12. Bell RD, Winkler EA, Sagare AP, Singh I, LaRue B, Deane R, et al. Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. Neuron 2010;68:409-427.

13. Gupta A, Reis SR, Beiser A, Devine S, Hankee L, Seshadri S, et al. Mid-life cardiovascular risk impacts memory function: the Framingham Offspring study. Alzheimer Dis Assoc Disord 2015;29:117-123.

14. Sun MK, Alkon DL. Links between Alzheimer's disease and diabetes. Timely Top Med Cardiovasc Dis 2006;10:E24.

15. Aridi YS, Walker JL, Wright OR. The association between the Mediterranean dietary pattern and cognitive health: a systematic review. Nutrients 2017;9:E674.

16. Bordone L, Guarente L. Calorie restriction, SIRT1 and metabolism: understanding longevity. Nat Rev Mol Cell Biol 2005;6:298-305.

17. Seimon RV, Roekenes JA, Zibellini J, Zhu B, Gibson AA, Hills AP, et al. Do intermittent diets provide physiological benefits over continuous diets for weight loss? A systematic review of clinical trials. Mol Cell Endocrinol 2015;418:153-172.

18. Davis CS, Clarke RE, Coulter SN, Rounsefell KN, Walker RE, Rauch CE, et al. Intermittent energy restriction and weight loss: a systematic review. Eur J Clin Nutr 2016;70:292-299.

19. Ganesan K, Habboush Y, Sultan S. Intermittent fasting: the choice for a healthier lifestyle. Cureus 2018;10:e2947.

20. Puttonen S, Vitasalo K, Härmä M. Effect of shiftwork on systemic markers of inflammation. Chronobiol Int 2011;28:528-535.

21. Schafer MJ, Dolgalev I, Alldred MJ, Heguy A, Ginsberg SD. Calorie restriction suppresses age-dependent hippocampal transcriptional signatures. PLoS One 2015;10:e013923.
23. Shin BK, Kang S, Kim DS, Park S. Intermittent fasting protects against the deterioration of cognitive function, energy metabolism and dyslipidemia in Alzheimer’s disease-induced estrogen deficient rats. Exp Biol Med (Maywood) 2018;243:334-343.

24. Zhang J, Zhan Z, Li X, Xing A, Jiang C, Chen Y, et al. Intermittent fasting protects against Alzheimer’s disease possible through restoring aquaporin-4 polarity. Front Mol Neurosci 2017;10:395.

25. Wang X, Liu Q, Zhou J, Wu X, Zhu Q, B hydroxybutyrate levels in serum and cerebrospinal fluid under ketone body metabolism in rats. Exp Anim 2017;66:177-182.

26. Vera E, Bernardes de Jesus B, Foronda M, Flores JM, Blasco MA. Telomerase reverse transcriptase synergizes with calorie restriction to increase health span and extend mouse longevity. PLoS One 2013;8:e53760.

27. Fann DY, Santro T, Manzanero S, Widiapradja A, Cheng YL, Lee SY, et al. Intermittent fasting attenuates inflammasome activity in ischemic stroke. Exp Neurol 2014;257:114-119.

28. Vasconcelos AR, Yshii LM, Viel TA, Buck HS, Mattson MP, Scavone C, et al. Intermittent fasting attenuates lipopolysaccharide-induced neuroinflammation and memory impairment. J Neuroinflammation 2014;11:85.

29. Shojaie M, Ghanbari F, Shojaie N. Intermittent fasting could ameliorate cognitive function against distress by regulation of inflammatory response pathway. I Adv Res 2017;8:697-701.

30. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. Cell Metab 2014;19:181-192.

31. Jeong JH, Yu KS, Bak DH, Lee JH, Lee NS, Jeong YG, et al. Intermittent fasting is neuroprotective in focal cerebral ischemia by minimizing autophagic flux disturbance and inhibiting apoptosis. Exp Ther Med 2016;12:3021-3028.

32. Cohen SM, Li B, Tsien RW, Ma H. Evolutionary and functional perspectives on signaling from neuronal surface to nucleus. Biochem Biophys Res Commun 2015;460:88-99.

33. Hirano Y, Masuda T, Naganos S, Matsumo M, Ueno K, Miyashita T, et al. Fasting launches CRTC to facilitate long-term memory formation in Drosophila. Science 2013;339:443-446.

34. Fusco S, Ripoli C, Podd MV, Ranieri SC, Leone L, Toietta G, et al. A role for neuronal cAMP responsive-element binding (CREB)-1 in brain responses to calorie restriction. Proc Natl Acad Sci U S A 2012;109:6201-6206.

35. Kondo M, Nakamura Y, Ishida Y, Shimada S. The 5-HT3 receptor is essential for exercise-induced hippocampal neurogenesis and antidepressant effects. Mol Psychiatry 2015;20:1428-1437.

36. Dasgupta A, Kim J, Manakkadan A, Arumugam TV, Sajikumar S. Intermittent fasting promotes prolonged associative interactions during synaptic tagging/capture by altering the metaplastic properties of the CA1 hippocampal neurons. Neurobiol Learn Mem 2018;154:70-77.

37. Wang M, Wang Q, Whim MD. Fasting induces a form of autonomic synaptic plasticity that prevents hypoglycemia. Proc Natl Acad Sci U S A 2016;113:E3029-E3038.

38. Cabral-Costa JV, Andreotti DZ, Mello NP, Scavone C, Camandola S, Kawamoto EM. Intermittent fasting uncovers and rescues cognitive phenotypes in PTEN neuronal haploinsufficient mice. Sci Rep 2018;8:6595.

39. Gao YZ, Zhang JJ, Liu H, Wu GY, Xiong L, Shu M. Regional cerebral blood flow and cerebrovascular reactivity in Alzheimer’s disease and vascular dementia assessed by arterial spinlabeling magnetic resonance imaging. Curr Neurovasc Res 2013;10:49-53.

40. Iadecola C. The pathobiology of vascular dementia. Neuron 2013;80:844-866.
41. Hughes TM, Wagenknecht LE, Craft S, Mintz A, Heiss G, Palta P, et al. Arterial stiffness and dementia pathology: Atherosclerosis Risk in Communities (ARIC)-PET Study. Neurology 2018;90:e1248-e1256.

42. Tarantini S, Tran CH, Gordon GR, Ungvari Z, Csiszar A. Impaired neurovascular coupling in aging and Alzheimer’s disease: contribution of astrocyte dysfunction and endothelial impairment to cognitive decline. Exp Gerontol 2017;94:52-58.

43. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc Natl Acad Sci U S A 2004;101:6659-6663.

44. Headland ML, Clifton PM, Keogh JB. Effect of intermittent energy restriction on flow mediated dilatation, a measure of endothelial function: a short report. Int J Environ Res Public Health 2018;15:E1166.

45. Erdem Y, Özkan G, Ulusoy Ş, Arıcı M, Derici Ü, Şengül Ş, et al. The effect of intermittent fasting on blood pressure variability in patients with newly diagnosed hypertension or prehypertension. J Am Soc Hypertens 2018;12:42-49.

46. Nematy M, Alinezhad-Namaghi M, Rashed MM, Mozhdahifard M, Sajjadi SS, Akhlaghi S, et al. Effects of Ramadan fasting on cardiovascular risk factors: a prospective observational study. Nutr J 2012;11:69.

47. Antoni R, Johnston KL, Collins AL, Robertson MD. Investigation into the acute effects of total and partial energy restriction on postprandial metabolism among overweight/obese participants. Br J Nutr 2016;115:951-959.

48. Anson RM, Guo Z, de Cabo R, Iyun T, Rios M, Hagepanos A, et al. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. Proc Natl Acad Sci U S A 2003;100:6216-6220.

49. Thompson PM, Hayashi KM, Dutton RA, Chiang MC, Leow AD, Sowell ER, et al. Tracking Alzheimer's disease. Ann N Y Acad Sci 2007;1097:183-214.

50. Wolf SA, Kronenberg G, Lehmann K, Blankenship A, Overall R, Staufenbiel M, et al. Cognitive and physical activity differently modulate disease progression in the amyloid precursor protein (APP)-23 model of Alzheimer’s disease. Biol Psychiatry 2006;60:1314-1323.

51. Wang Z, Andrade N, Torp M, Wattananit S, Arvidsson A, Kokaia Z, et al. Meteorin is a chemokinetic factor in neuroblast migration and promotes stroke-induced striatal neurogenesis. J Cereb Blood Flow Metab 2012;32:387-398.

52. Garza JC, Guo M, Zhang W, Lu XY. Leptin increases adult hippocampal neurogenesis in vivo and in vitro. J Biol Chem 2008;283:18238-18247.

53. Hu Y, Yang Y, Zhang M, Deng M, Zhang JJ. Intermittent fasting pretreatment prevents cognitive impairment in a rat model of chronic cerebral hypoperfusion. J Nutr 2017;147:1437-1445.

54. Hu Y, Zhang M, Chen Y, Yang Y, Zhang JJ. Postoperative intermittent fasting prevents hippocampal oxidative stress and memory deficits in a rat model of chronic cerebral hypoperfusion. Eur J Nutr 2019;58:423-432.

55. Singh R, Manchanda S, Kaur T, Kumar S, Lakhpanal D, Lakhman SS, et al. Middle age onset short-term intermittent fasting dietary restriction prevents brain function impairments in male Wistar rats. Biogerontology 2015;16:775-788.