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Alzheimer's Disease and Habitual Exercise: Relationship Mediated and Fostered by Vascular Risk Profiles?

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Alzheimer's disease, the most frequent form of dementia that accounts for 50-70% of all cases, impairs memory and learning, precludes independent living, and poses psychological and financial strain on caregivers and the healthcare system [1]. Since the first discovery from a patient of Alois Alzheimerin 1906, a century of vigorous research has established key pathological features, including the conspicuous neuro degeneration that preferentially target shippo campus and the deposition of cerebral amyloid plaques and neurofibrillary tangles. However, there have been no established strategies to treat Alzheimer's disease, and the currently-identified risk factors for Alzheimer's disease (i.e., aging and ApoEε4 allele) are non-modifiable [2]. As a large number of baby boomers will be facing elevated risks of developing Alzheimer's disease in the near future, there is an ever increasing need to search for modifiable risk factors and to identify intervention strategies to attenuate and prevent the disease development [3]. Emerging evidence indicates that vascular dysfunction and risk factors for vascular disease may be mechanistically linked with an elevated risk of dementia and that regular physical activity may improve cognitive function presumably through the improvement of vascular function.

The chronic exposure to risk factors for vascular disease accelerates structural brain aging and cognitive decline. For example, hypertension, diabetes, smoking, and obesity in midlife are all associated with an increased progression of vascular brain injury (e.g., white matter hyperintensity), global and hippocampal atrophy, and decline in executive function [4]. All of these vascular risk factors could also develop into cerebral atherosclerosis, a prominent characteristic of Alzheimer's disease, and compromises the normal cerebral perfusion leading to cerebral hypoxia that stimulates the production of cerebral amyloid [5,6]. Indeed, Framingham atherosclerotic risk scores are correlated with the level of cerebral amyloid deposition [7]. Taken together, these pathological findings support the notion that chronic exposure to vascular risk factors can contribute to the pathogenesis of Alzheimer's disease at the preclinical stage.

Vascular function and risk factors for vascular disease are largely modifiable and may pave a way in identifying an effective intervention against Alzheimer's disease. For example, regular aerobic exercise is widely regarded as an effective strategy to improve vascular function and increasingly recognized in terms of its benefit on cognitive function [8,9]. In particular, regular aerobic exercise ameliorates vascular endothelial function and central artery stiffness [8]. Cerebrovascular endothelium composes blood-brain barrier and strictly regulates the molecular trafficking between the brain and blood. One of the most important molecules that need clearance from the brain parenchyma is amyloid-β [10]. In this context, regular aerobic exercise is associated with preserved cerebrovascular endothelial function and the lower level of cerebral amyloid deposition [11,12]. Arterial stiffness is also an important feature that influences the cerebrovascular and cognitive function. With stiffening of cardiothoracic artery, pulsatile pressure energy can penetrate into the distal capillaries and increases the risk of end-organ damage [13]. Central artery stiffness also impairs baroreflex sensitivity and may elevate the risk of cerebral hypo- and hyperperfusion in response to transient blood pressure changes [14]. In fact, arterial stiffness is associated with lower cerebral perfusion, higher prevalence of subcortical infact, and accelerated cognitive decline [15,16]. It is reasonable to hypothesize that the favorable effect of regular aerobic exercise on vascular function, particularly endothelial function and arterial stiffness, may translate into a better cognitive function.

Although vascular function and risk factors for vascular disease appear to be a promising mediator for the exercise-related improvement in cognitive function, regular aerobic exercise may benefit cognitive function directly via stimulating the release of neurotrophic factor. Voluntary wheel running in rodents promoted neurogenesis and enhanced long-term potentiation in dentate gyrus of hippocampus [17,18]. The exercise-related enlargement of hippocampal volume in animals was associated with an elevated local cerebral perfusion resulting from angiogenesis and brain-derived neurotrophic factor [19]. In humans, a1-year aerobic exercise training intervention, which primarily consisted of walking, improved memory function and increased the hippocampal volume [20].

The evidence supporting the benefit of regular exercise in attenuating the risk of dementia is accumulating. However, there are many important questions that remain to be addressed regarding the mechanistic interaction among vascular risk, regular aerobic exercise, and cognitive function. Does the exercise-related improvement in vascular riskbenefit cognitive function independent from aging and genetic risk factor (i.e., ApoEε4 allele)? Does the improvement of cerebrovascular function from regular aerobic exercise promote the neurogenesis of hippocampus? What is the key component of vascular function that mediates the relation between regular aerobic exercise and better cognitive function? What are the optimal mode, intensity, volume, and frequency of physical activity inorder to attenuate the risk of cognitive decline and impairment? As we likely encounter an exponential increase in the prevalence of dementia due to the rapid population aging [1], we are in the immediate need to answer these questions and lower the devastating effect of Alzheimer's disease for the future generations.

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