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Physical Activity and Alzheimer's Disease- A Short Review

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Abstract:

Alzheimer's disease (AD) is a progressive neurodegenerative disease which is the most common type of dementia and inevitable in aging individuals, it impairs memory loss and cognitive function. Physical activity (PA) has been long related to mental health and has been extensively investigated. The effectiveness of medication in AD so far has no preventive cure, exercise is being recognized as an alternative for treating AD patients. Physical exercise may be a potential treatment for neuro-disorders and cognitive impairment. A sedentary lifestyle is one of the risk factors contributing to AD. Moderate bout of exercise has been found to be effective in the improvement of movement, memory, and learning. Several biochemical factors released during exercise have shown positive alteration in brain function. This review discusses the beneficial effect of exercise on mental health and exercise as a therapeutic measure to treat regressive brain function in AD.

Keywords **—Physical activity, Alzheimer's Disease, Mental health, Exercise.**

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I. INTRODUCTION

Alzheimer's disease is one of the most prevalent type of neurodegenerative disease characterized by dementia, progressive functional cognitive loss, neuropathological intracellular neurofibrillary tangles (NFT) and senile plaques constituting about 90% of elderly population. The plaques are a result of amyloid protein deposition. It features loss of neuronal synapses and pyramidal neurons accompanying irreversible cognitive neurodegenerationFrancis, Palmer, Snape, Wilcock [1]. Senile plaques are a result of insoluble amyloid β (Aβ) protein, the isoform $A\beta_{42}$ is known to be the main isoform as it is formed due to enzymatic cleavage from amyloid precursor protein (APP)[2]. On the other hand, the hyperphosphorylation of tau protein causes NFT, Tau protein plays an important role in stabilizing microtubules in order to form a connection with neuronal cytoskeleton system [3]. Symptoms may vary to rise among individuals at a

different rate and with the death of neurons in parts of the brain, other symptoms such as word finding, language difficulties, problem solving, or even visual spatial relationships may occur. Although, the major risk factor for AD has been the age, familial history and susceptibility genes, however, environmental factors, diet and physical health constitute an important influencing factor as well. The existing diagnosis of AD mainly involves doctoral care and routine lab for assessments based on their phenotypic features, however, other tests including MRI and serological examinations for recognizing biomarkers is also a potential form. Biomarkers are presently isolated from the cerebral spinal fluid (CSF) providing 90% accuracy rate[4]. From a pharmacological prospect acetylcholinesterase in hibitors (AChEIs) are used as in order to enhance the cholinergic neurotransmission by inhibiting AChEs enzymes, therefore U.S. FDA approved drugs such as tacrine, donepezil, rivastigmine, and galantamine are used to treat AD[5, 6]. However, these drugs are only capable delaying the progression of AD and unable to provide a permanent cure.

The benefits of physical activity (PA) has long been recognized and has proven to reduce many health risks. Physical activity is bodily movement involving skeletal muscles at the cost of energy and exercise is a planned subset of PA. A meta-analytical evidence has proven that PA has beneficial effects on hippocampus[7]. PA is gaining interest as a non-pharmacological therapy for maintenance of physical and mental health status.

II. Physical Activity and Neurophysiology

A recent study found that physical activity improves the memory loss in middle aged groups and also slows the progression of neurodegeneration compared to sedentary group[8]. Physical inactivity adds 6% to 10% of majority of the non-communicable diseases and contributes more than 5 million deaths in a year[9]. Exercise shows predominant effectiveness in three areas of the brain mostly, these are vascular physiology, hippocampal volumes and neurogenesis[10]. The hippocampus tends to contract in later age, leading to memory loss and dementia. Hippocampal volumes are comparatively larger in fit adults and are also related with cardiovascular fitness[11]. In a study conducted in 2011, it was found that 1 year of moderate to regular exercise is sufficient for enhancing the hippocampal volume which in turn translates to increased memory function and high level of Brain derived neurotropic factor BDNF serum, a mediator of neurogenesis[12]. Neurogenesis determination is impartially problematic to study in humans, but has shown positive effects of exercise in rats[13]. Brain plasticity is the brain's capacity to adapt changes, in which neurons are able to modify the strength and composition of their connections in

response external and internal stimuli. Neuronal function is regulated through synapse to nucleus signalling[14]. The signals are thought to be produced via different mechanisms such as calcium waves, retrograde transport of proteins and microtubule dependent trafficking[15]. Regulation of synapse to nucleus signalling, specific gene expression of some proteins shows to be necessary for learning and memory. Elevating the physical activity may increase their function and enhance brain plasticity.

Clinical trials have addressed the hypothesis that practicing PA in daily life could potentially decrease the incidence of AD. A recent meta - analysis in 2019 conducted on 673 patients diagnosed with AD demonstrated statistically significant enhancement in cognition concluding that PA and exercise also plays a key role in order to improve cognition in older age groups[16].A three year exercise study on motor performance and cognitive processing on older women participating three times per week significantly improved their ability on motion and cognition compared to the group who were only given care, indicating sedentary lifestyle can be a risk factor to a rapid progression of age related motor performances and cognition[17]. Resistance exercises have been gaining insights widely in recent years, a 2020 meta-analysis of 24 studies on the effect of resistance exercise on cognitive outcomes revealed beneficial effects on cognition but lacked effect on working memory[18]. To elucidate whether aerobic exercise have any role in enhancing cognitive function a study including twelve trails with 754 participants was conducted, unfortunately the study showed no benefit of aerobic exercise on cognitive performance but only the improvement of cardiorespiratory fitness was resulted[19]. Another follow up that contradicts the study is six-month evaluation of aerobic exercise program to examine memory function, where they reported that cardiorespiratory fitness is associated with improved memory and enhances hippocampal volume. [20].

III. BIOLOGICAL FACTORS IN AD

PA is beneficial for overall health and is not limited to skeletal muscles. Exercise induces changes at various levels in the brain and alter physiological phenomena such as neurogenesis, synaptogenesis, neurotrophic factor stimulation and angiogenesis which altogether are responsible for brain functionality and plasticity[21-23]. Regular exercise generates reactive oxygen species (ROS), this exercise induced ROS production induces antioxidants , DNA repair and reduces oxidative stress- related diseases[24]. Circulation of proinflammatory cytokines enhances as a result of exercise induced stress response[25].

BDNF-

BDNF is a neurotrophin whose function has been extensively studied in accordance with physical activity and cognitive performances. They exert important function in growth and regulation of neurons, synaptic plasticity and hippocampal neurogenesis[26, 27]. Brain contributes about 80% of BDNF in circulation at rest or during exercise, however there was a decline after an hour of termination of exercise. This suggests that brain is not solely responsible for production of circulating BDNF[28]. BDNF is also produced by skeletal muscles and is involved in autocrine and paracrine signalling while being regulated by exercise, and exerts retrograde signalling in spinal cord[29]. AD patients constitute about three-fold of reduced BDNF levels suggesting a high level of BDNF in aging individuals is necessary[30]. Long term exercises upregulate BDNF levels enhancing cognitive functions.[31]. Aerobic exercise training increases BDNF levels in blood and reverses the effect of hippocampal volume loss[12].

Cytokines-

Cytokines are proteins secreted by various cell types and they also play a role in regulating sleep, long term memory and neurodegenerative diseases. Cytokines such as IL-6, IL-8 and IL-15 is also released by contracted muscles. Interleukins are able to play a role in brain as it can cross blood brain barrier. IL-6 plays a significant role in physiological neuronal functions and serves in neuroinflammatory pathways [32]. Neuroinflammation is recognized as pathological progression in AD, physical exercises have significant positive effect on inflammatory markers. IL-6 blood levels are comparatively higher in AD and is adhesive to senile plaques. Exercise induces acute response such as trauma and therefore in healthy individuals IL-6 is produced in high levels followed by a rapid decline. A 16 weeks of PA showed effective modulation on IL-6[33]. A study conducted with 6 months of moderate aerobic exercises in elderly resulted in improvement of immune function and induced T-cell proliferative response[34]. Thus, exercise modulates inflammatory responses on CNS and minimizes the risk of neuroinflammation.

Lactate-

Lactate is released by active muscles and used by heart and brains as a fuel after oxidation. In oxygen shortage conditions lactate is used through anaerobic mechanism. Lactate is able to cross the blood brain barrier (BBB) with the help of monocarboxylate carriers which are transmembrane proteins. Lactate is found to be important substrate for neuronal metabolism and LTP regulation[35]. Lactate plays a significant role of angiogenesis and hippocampal neurogenesis. Lactate levels in AD

patients have been found to be high[36]. A lactate receptor, hydrocarboxylic acid receptor (HCAR1) enhances angiogenesis. High intensity workouts increase blood lactate levels and increases vascular endothelial growth factor A (VEGFA) proteins. In recent times, anaerobic exercise that promotes lactate production is showing positive effects on neurodegenerative disease. Thus, both aerobic and anaerobic exercises show improved impact on brain health and functioning (Figure 1).

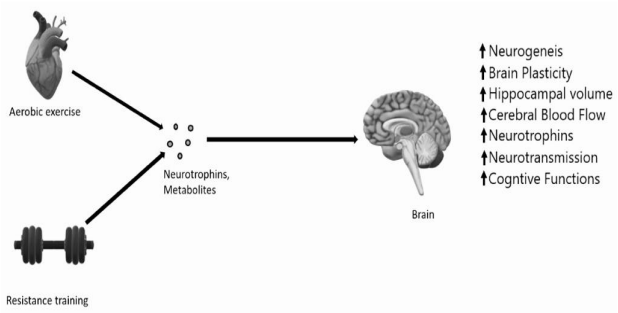

Figure 1. A hypothetical illustration of how cardiovascular training and resistance training can positively impact the functioning of the brain through neurotrophins and metabolites released by the muscles while exercising.

IV. EXERCISE AS A THERAPY FOR AD

There have been very few mega studies on patients with AD. AD affects the activity of daily life in elderly, a study was conducted by involving aerobic exercises, flexibility training and strength exercise for one hour with two times in a week over a one year period, the study found significant differences attributing towards daily life activities in the exercising group compared to the sedentary groups living in a nursing home than routine medical care.[37]. A randomized controlled trail used both drugs and exercise diagnosis for AD. Drugs showed small effects on cognition in AD, however, exercise had slightly strong effects on cognition. They concluded that, exercise showed slow onset of neurodegeneration and improved physical mobility[38]. The cerebral blood flow is sensitive depending on differences in lifestyles. A study with a 16 weeks of moderate to high intensity aerobic exercise program did not improve the concentration of tau or Aβ in Cerebral blood flow (CBF) [39], this suggests that changes in neuronal functions requires several parameters to be taken care of including span, intensity and type of exercises. A 12 weeks randomised trial with supervised aerobic exercise for 1 hour and 3 session per week showed higher resting CBF in the anterior cingulate region suggesting that even shorter exercises programs can facilitate neuroplasticity[40]. These kinds of studies are needed to be performed in AD patients in order to differentiate the cognitive function compared to merely aging people.

V. CONCLUSION

Changes in lifestyle from early adulthood are necessary to delay the onset such neurodegenerative diseases. People with sedentary lifestyle not only are prone to suffer cognitive disfunction but also regresses the mobility and balance of the body. As

AD is one of the major neurodegeneration diseases it is must be understood that the apart from heavy dose of medication, exercise should be compulsory involved in everyday life. Exercise lengthens the body adaptability to stress, increases neurotrophins, metabolites and improves CBF. The exercise programs may differ from individuals and recommended PA for AD might difficult. It is suggested that early treatment of AD must include moderate to high intensity exercises.

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