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Editorial Open access

Amelioration of Symptoms and Biomarkers of Alzheimers Disease by Physical Exercise

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Abstract

Physical exercise advantages have been manifested in several neurodegenerative and/or neuropsychiatric disorders implying that these, largely non-invasive, non-pharmacologic interventions, ought to be examined closely in the Alzheimer's disease (AD) and other dementias context. Thus, according to the tenets of an increasingly broad consensus, preventative and interventional agents for AD and dementia conditions should include physical activity, proper and appropriate lifestyle ingredients, cognitive-affective and intellectual stimulation and the management of conditions such as hypertension, diabetes and obesity.

Keywords: AD; Cardiovascular disorders; Exercise; Cognition; Biomarkers; Prevention; Intervention

Editorial

The economic, logistic and caregiver burdens of worldwide Alzheimer's disease (AD), and in dementia of other causes also, is fasting approaching epic and insurmountable proportions, and among individuals motivation to improve 'brain health' through new information and/or their own efforts is markedly limited [1]. Healthy nutritional habits, including drinking plenty of water and maintaining hydration, are fundamental components for sustaining life, health and wellbeing with dietary patterns and lifestyles involved intimately in delaying the progression of the ageing process and reducing the risk of AD. Nutritional factors and physical exercise benefits have been manifested in other neurodegenerative disorders [2], implying that these, largely non-invasive interventions, ought to be examined closely in the AD context. In a large meta-analysis of putative protective factors for the disorder [3], grade I evidence for four medical treatments (oestrogen, statin, antihypertensive medications and non-steroidal anti-inflammatory drugs therapy) and four dietary interventions (folate, vitamin E/C and coffee) was obtained. Epidemiological, biomarker, metabolic, neurocognitive and neuroimaging studies have furnished markedly copious evidence indicating the presence of indolent prodromal AD neuropathology long in advance of symptomatic onset with mechanistic links existing possibly between epigenomic status, DNA damage, and chronically unhealthy/dysfunctional body systems in the expression of disorder. For example, Hishikawa et al. [4] showed that greater cognitive and affective decline occurred in patients presenting AD with metabolic syndrome than those patients, with marked insulin resistance and vascular endothelial dysfunction observed in the former together with pathological brain white matter alterations. Dietary supplements aimed at reducing pro-inflammatory cytokine availability may also retard AD progression under conditions of exacerbated immunosenescence. The consensus seems to warrant individual-based combinations of early, multi-component nutritional approaches (a Mediterranean-style diet, multivitamins and key combinatorial supplements, etc), together with particular lifestyle modifications, such as social activities merged with intellectual and physical exercise. Assessment-based, tailored nutritional guidance implemented with a personal and positive approach may inspire and empower AD families to make positive changes in their diets, leading them to improved nutrition and quality of life [5]. Early disclosure of the presence of an amyloid burden from PET-scan analysis appears to engender the decision to alter lifestyle through appropriate diet and physical exercise adherence [6]. This approach is becoming increasingly more attractive in view of the questions raised concerning the efficacy and cost-benefit dilemmas arising from the use/misuse of cognition-enhancing drugs [7].

Exercise for AD

In order to meet the challenges posed by AD, dementia and related disorders, prior knowledge of common, reliable risk factors and their effectors seems essential. Behavioral traits/attributes that include low education, smoking, poor/inappropriate diet, neglect of oral health, lack of exercise/sedentary habit, apathy and hypertension are some of the risk factors that are shared commonly among these conditions. Furthermore, common genetic susceptibility traits, such as the apolipoprotein E gene, together with an individual's unhealthy lifestyle may influence also the development of complicating co-morbidities, e.g. periodontitis, atherosclerosis/stroke, diabetes, that are combined with AD [8]. Physical exercise endowers protective effects against the cognitive decline in ageing and AD [2] by delaying the neurodegenerative trajectory of normal ageing through the modification of vascular, neuroimmune and metabolic risk factors and/or consistently augments brain function by inducing structural and neurochemical changes in the hippocampus and related medial temporal lobe circuitry-brain areas that are important for cognitive performance [9]. The major focus of studies to ascertain the functional capacity of the aged/elderly aged ought to be the investigation of the effects of exercise programs, compared to a social/recreational intervention, upon the ability of people with dementia living in nursing homes to perform activities of daily living. Among the secondary objectives, linked with the cost-effectiveness of the interventions, and

the effects of the interventions on patients' physical function, neuropsychiatric symptoms, pain, nutritional status, and the incidence of falls and fractures should be the continual monitoring of quality-of-life variables. Neuroinflammation presents a critical, aggravating and pathological feature of AD and neurodegenerative conditions by contributing to the observed cognitive decline, and recent evidence demonstrates that it also affects negatively hippocampal neurogenesis. Physical exercise offers a potent, non-pharmacological inducer of hippocampal neurogenesis, with manifestations of positive beneficial effects of exercise on cognitive function documented regularly due to its pro-neurogenic effects. Nevertheless, the interplay between exercise- and neuroinflammatory-induced changes in hippocampal neurogenesis and associated cognitive function remains to be unfolded [10]. In a randomized controlled trial with supervised moderate-to-high intensity exercise levels in patients presenting mild AD, observed that the exercise intervention reduced neuropsychiatric symptoms in mild AD patients with possible additional benefits involving preserved cognition in a subgroup of patients exercising with high attendance and greater intensity. AD causes a gradual decline in cognition, limitations of dual-tasking and physical function leading to total dependence, and regular exercise improves cognitive function through beneficial adaptations in vascular physiology and improved neurovascular coupling [11], showed that exercise intervention improved the speed of responses during the "Go-no-Go" cognitive task without any accompanying increase in errors in patients presenting mild cognitive impairment, that was improved by a cognitive enrichment program. In a meta-analysis of 802 patients in 18 randomized controlled studies found that the physical exercise interventions were equally beneficial in patients with AD and in patients with AD or a non-AD dementia diagnosis. Combined (i.e. aerobic and non-aerobic) exercise interventions and aerobic-only exercise interventions induced positive effects on cognition, while this association was absent for non-aerobic exercise interventions with both high frequency and low frequency interventions producing a positive effect on cognitive performance. Finally, Hoffmann et al. obtained a dose-response relationship between moderate-to-high intensity exercise and cognitive performance, using a Symbol Digit Modalities Test, in a randomized controlled trial on AD patients.

Animal laboratory observations using aged/transgenic/lesioned, or combinations thereof, rodents in invariably confirm the beneficial effects of exercise/activity in disorder models. A range of epidemiological studies accentuate the relevance of regular exercise interventions for the enhancement or maintenance of neurocognitive functioning and integrity over different types of subjects presenting cognitive impairments. Following a long periods of strength-resistance training, the expressions of oxidative stress can be reduced, the brain-derived neurotrophic factor (BDNF) and insulin-like growth factor I (IGF1) serum concentrations enhanced, and several parameters of cognitive performance improved [12]. For example, to study the effects of long-term treadmill running exercise upon the spatial memory parameters of AD mice and the possible role of β-amyloid, BDNF and microglia in this connection, male APPswe/PS1dE9 AD-type mice, aged four months, were given access to treadmill exercise for five months with 6 sessions per week that incorporated a gradually increased load [13]. They found that the 5-month treadmill exercise decreased markedly the escape latencies in the circular water maze and improved the spatial memory of the AD mice in the water maze test. Concurrently, treadmill exercise significantly increased the number of BDNF-positive cells and decreased the ratios of activated microglia in both the cerebral cortex and the hippocampus. Nevertheless, treadmill exercise did not significantly alleviate the accumulation of β-amyloid in either the cerebral cortex or the hippocampus of the AD mice, utilized three months of low (15 m/min on a level treadmill) and high (32 m/min at a 10% grade) intensity exercise training to analyse effects upon soluble Aβ40 and Aβ42 levels in extracellular enriched fractions from the cortex and hippocampus of young Tg2576 mice, a transgenic mouse model that produces brain amyloids and although memory is normal as juveniles, as they grow older they accumulate amyloids and lose their memory capacity [14]. Soleus muscle citrate synthase activity was increased by 39% in the LOW group relative to SED, and by 71% in the HI group relative to LOW, indicating an exercise training effect in these mice [15]. Soluble Aβ40 concentrations were decreased significantly in an exercise intensity training dose-dependent manner in the cortex. In the hippocampus, and concentrations were decreased significantly in the high intensity group relative to the low intensity and sedentary groups. Soluble Aβ42 levels also decreased significantly in an exercise intensity training dose-dependent manner in both the cortex and hippocampus. Five proteins involved in Aβ clearance (neprilysin, IDE, MMP9, LRP1 and HSP70) were elevated by exercise training with intensity of exercise an important parameter in each case. In a study in which APP/PSEN1 'double-transgenic' and wild-type mice were allowed unlimited voluntary exercise for seven months, the wheel-running improved cognition in these animals [16]. Mean daily distance run was strongly correlated with spatial memory in the water maze in the wild-type mice ($r(2) = 0.959$), but was uncorrelated in the transgenics ($r(2) = 0.013$). Proteomic analyses demonstrated that the sedentary transgenic mice differed significantly from the sedentary wild-types in the context of those proteins involved in synaptic transmission, cytoskeletal regulation, and neurogenesis. When these mice were allowed to exercise, the transgenic mouse deficiencies in cytoskeletal regulation and neurogenesis became normalized to a large extent yet the abnormal synaptic proteins did not change. Contrastingly, exercise enhanced the proteins associated with cytoskeletal regulation, oxidative phosphorylation, and synaptic transmission in the wild-type mice. Soluble and insoluble Aβ40 and Aβ42 levels were decreased significantly in both the cortex and hippocampus of active, exercising transgenic mice, implying that this intervention may have exerted an influence upon the cognitive improvement in the APP/PSEN1 mice. β-secretase was significantly reduced in the exercised APP/PSEN1 mice compared to sedentary controls, suggesting a mechanism for reduced Aβ. Voluntary wheel running for 10 weeks by the double transgenic APPswe/PS1ΔE9 decreased Aβ burden, Thioflavin-S-positive plaques and Aβ oligomers in the hippocampus [17]. Exercising APPswe/PS1ΔE9 mice displayed fewer phosphorylated tau protein and decreased astrogliosis as evidenced by lower staining of GFAP. Further, runner APPswe/PS1ΔE9 mice showed increased number of neurons in the hippocampus and exhibited increased cell proliferation and generation of cells positive for the immature neuronal protein doublecortin, indicating that running increased neurogenesis. These exercising APPswe/PS1ΔE9 mice showed improved spatial memory performance in the Morris water maze.

Early-onset familial Alzheimer's disease and late-onset sporadic AD both follow a similar pathological and biochemical course that includes: neuron and synapse loss and dysfunction, microvascular damage, microgliosis, extracellular amyloid-β deposition, tau phosphorylation, formation of intracellular neurofibrillary tangles, endoreduplication and related cell cycle events in affected brain regions. Cell cycle abnormalities debut early in the disease process, prior to the appearance of plaques and tangles, and explain the

biochemical (e.g. tau phosphorylation), neuropathological (e.g. neuron hypertrophy; polypoidy) and cognitive changes. The neuroprotective mechanisms induced by physical exercise are linked to an elevated production of superoxide dismutase, endothelial nitric oxide synthase, BDNF, nerve growth factor, insulin-like growth factor, and vascular endothelial growth factor, and a reduction in the production of free radicals in brain regions, such as the hippocampus, known to be implicated in cognition, particularly involved in memory performance, compared four groups of healthy older adults (65-() years), based on the presence or absence of an APOE-ε4 allele (High Risk; Low Risk) and self-reported frequency and intensity of leisure time physical activity. As the authors had predicted, greater levels of physical activity were associated with greater fractional anisotropy and lower radial diffusivity in healthy older adults who did not possess the APOE-ε4 allele. Nevertheless, the effects of physical activity were reversed in older adults who were at increased genetic risk for AD, resulting in significant interactions between physical activity and genetic risk in several white matter tracts. In the High Risk-Low physical activity participants, who had exhibited episodic memory decline over the previous 18-months, radial diffusivity was lower and fractional anisotropy was higher, compared to the High Risk-High physical activity participants. In white matter tracts that contribute learning and memory processes, radial diffusivity was negatively correlated with episodic memory performance in physically inactive APOE-ε4 carriers, whereas radial diffusivity was correlated positively with episodic memory performance in physically active APOE-ε4 carriers and the two Low Risk groups. In 6-month-old male APP/PS1 transgenic mice, dentate gyrus volume, the myelinated fiber length and volume in the dentate gyrus, and the myelin sheath volume and thickness in the dentate gyrus were all significantly increased in the running-exercised group of mice compared with the sedentary group of mice [18]. Thus, running exercise was effective in preventing dentate gyrus atrophy and delay the progression of the myelinated fiber loss and the demyelination of the myelin sheaths in the dentate gyrus in an AD APP/PS1 mouse model.

AD affects multiple cell types within the neurovascular unit, including brain vascular cells (endothelial cells, pericytes, and vascular smooth muscle cells), glial cells (astrocytes and microglia), and neurons thus necessitating the identification and integration of biomarkers of the neurovascular unit cell-specific responses and injury. Avoidance of toxins, reduction of stress, prevention of somatic diseases, implementation of mental and physical exercises, as well as the use of dietary compounds like antioxidants and supplements can be protective against mild cognitive impairment [19]. Progressive resistance training, whether endurance-aerobic or resistance-strength, together with adequate dietary proteins and other nutrient-rich constituents contribute to the maintenance of muscle health and function in older adults with both factors promoting brain function and prevention of cognitive decline via several pathways, including the regulation of various growth and neurotrophic factors BDNF and IGF-1, and/or the modulation of systemic inflammation. Advisedly, the combination of dietary and exercise intervention ought to provide optimal results in AD: In a large study to assess a multi-domain approach to prevent cognitive decline in at-risk elderly people from the general population, improved or maintained adequate cognitive functioning in at-risk elderly people. Investigations performed on animal models and human subjects have described robust beneficial effects of regular exercise and intermittent energy restriction/fasting on cognitive function and mood, particularly in the contexts of aging and associated neurodegenerative disorders [20]. Much evidence supports the links between several modifiable risk factors and a reduced risk for cognitive decline, and sufficient observations are available to suggest that some modifiable risk factors may be associated with reduced risk of dementia [21]. Increasingly, cholesterol biochemical pathway modifications are being combined with more-or-less formalized physical exercise programs [22], exercise schedules, statins, and dietaryfruit intake were related to a lower risk for AD mortality [23]. In chronically, unpredicatable stressed mice, Hutton et al. have shown that the combination of dietary supplementation and exercise exerted multiple beneficial effects, as assessed by the number of doublecortin (DCX)-positive immature neurons in the dentate gyrus, the sectional area of the dentate gyrus and hippocampal CA1, as well as increased hippocampal BDNF messenger ribonucleic acid (mRNA) and serum vascular endothelial growth factor (VEGF) levels whereas these benefits were not observed in chronically stressed animals that were exposed to either the dietary supplementation or the exercise intervention alone. According to an increasingly broad consensus, preventative and interventional agents should include physical activity, proper and appropriate dietary ingredients, cognitive-affective and intellectual stimulation and the management of conditions such as hypertension, diabetes and obesity [24].

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