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A community-based approach to trials of aerobic exercise in aging and Alzheimer's disease

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ABSTRACT

The benefits of exercise for aging have received considerable attention in both the popular and academic press. The putative benefits of exercise for maximizing cognitive function and supporting brain health have great potential for combating Alzheimer's disease (AD). Aerobic exercise offers a low-cost, low-risk intervention that is widely available and may have disease modifying effects. Demonstrating that aerobic exercise alters the AD process would have enormous public health implications. The purpose of this paper is to report the protocol of a current, community-based pilot study of aerobic exercise for AD to guide future investigation. This manuscript provides 1) an overview of possible benefits of exercise in those with dementia, 2) a rationale and recommendations for implementation of a community-based approach, 3) recommendation for implementation of similar study protocols, and 4) unique challenges in conducting an exercise trial in AD.

1. Introduction

Americans are living longer than ever before. Six percent of the population is 75 years or older and this age group is expected to increase by 80% in the next decade [1,2]. Aging brings an increased incidence of cognitive and physical decline, especially in those in the eighth decade and beyond [3]. One in 8 individuals over 65 is now living with Alzheimer's disease (AD), [4] and the annual treatment costs of AD are estimated at $183 billion in the US. Spending on dementia care is expected to increase 600% over the next 40 years [4]. Delaying the onset or slowing the progression of AD would significantly reduce annual health care costs in the US [5]. However, there are currently no established and accepted disease modifying or preventive treatments for AD.

A wealth of animal research data suggests that exercise positively impacts brain health. Increased physical activity may have a trophic effect on the brain, particularly the hippocampus. For instance, exercise increases brain-derived neurotrophic factor (BDNF) [6] and other important neurochemicals [7] supporting brain growth and survival. Exercise appears to stimulate neurogenesis [8], enhance neuronal survival [9], increase resistance to brain insults [10,11] and increase synaptic

Abbreviations: ADEPT, Alzheimer's Disease Exercise Program Trial;CDR, Clinical Dementia Rating;MCI, mild cognitive impairment;AD, Alzheimer's disease;the Y, YMCA of Greater Kansas City;THR, target heart rate;KU ADC, University of Kansas Alzheimer's Disease Center;CPT, certified personal trainer;CTSU, Clinical and Translational Science Unit.

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plasticity [12]. Exercise promotes brain vascularization [13,14], mobilizes gene expression profiles predicted to benefit brain plasticity [15], and maintains cognitive function [16]. Additionally, exercise effects on the brain may reduce vascular risk factors (heart disease [17], atherosclerosis [18], stroke [19], and diabetes [20–24]) that are believed to place an individual at risk for dementia, vascular dementia, and AD [25].

Further, there is limited but compelling animal data suggesting that exercise may have disease-modifying benefits in AD. For instance, increased physical activity in mouse models of AD reduces neuropathological burden [26] and may promote hippocampal neurogenesis [27]. The reduction of β-amyloid in the exercising mice was evident in both cortical and hippocampal regions of the brain suggesting that voluntary exercise may mediate the amyloid cascade in favor of reduced production of β-amyloid [26]. Despite the evidence that aerobic exercise may be disease modifying in animals, there is a paucity of rigorous trials of aerobic exercise effects on cognitive function in the earliest stages of AD in humans [28]. The lack of well-designed, randomized controlled trials (RCT) that have investigated exercise effects on cognition has led to scientific position statements [29] and prominent public media editorials [30] on the insufficiency of evidence for addressing cognitive decline. Studies of exercise in dementia are significantly limited by poorly-defined samples and insufficient outcome measures and exercise regimens. Many of these studies include poorly characterized participants or use insensitive cognitive and physical outcome measures. For example, one meta-analysis of older studies suggested physical exercise can benefit physical and cognitive performance [31] but the results are derived from a mix of exercise modalities and dementia states [32–53]. Often these mixed studies include institutionalized elderly patients in nursing homes or psychiatric hospitals with poorly characterized cognitive impairment. Few focus on diagnosing AD [40,54] and fewer examine individuals with early stage AD [55]. Exercise interventions are variable and usually involve resistance (sit-to-stand exercises, strength training, isometric exercises in sitting positions) [41,42,45,47,56,57] and endurance training [53,58,59]. Outcome variables vary widely and include mobility and balance, strength, reaction time, and functional measures [31]. Endurance measures are generally the distance walked over a set time (i.e., modified 6-minute walk). To our knowledge, few studies include standard measures of exercise adaptation such as insulin sensitivity, body composition, lipids, and VO_2 peak in people with well-characterized early stage dementia.

There is promising evidence that aerobic exercise benefits brain health and cognitive function in AD. Cross-sectional evidence from our center has found that peak oxygen consumption (VO_2 peak, a consensually valid measure of aerobic fitness and standard outcome measure of aerobic exercise interventions) in early-stage AD is associated with whole brain volume measures, with higher VO_2 peak associated with less brain atrophy and slower dementia progression [60–62]. In one recent randomized controlled trial (RCT) for individuals with MCI, aerobic exercise improved executive cognitive function, especially in women [55]. Importantly, this study demonstrated that a similar, community-based approach was feasible and has the potential to modify cognitive measures. Exercise may also improve mood and functional capacity [40]. Ongoing RCTs of home-based programs will shed further light on the role of exercise for managing AD, but there is a need for more research among community-dwelling adults in the earliest stages of AD.

While it is common for clinicians to recommend a physically active lifestyle to those with AD, the benefits of exercise in AD are not well-defined and evidence to develop guidelines for the prescription of exercise in AD is lacking [29,63]. Though physical activity typically declines with cognitive impairment [64], a meta-analysis demonstrated physical activity interventions to be successful for improving physical and functional performance as well as cognition [31] suggesting that improving exercise habits is feasible for this population. Although there is consensus that current recommendations (~30 min of exercise most days of the week) provide general health benefits to older adults [65], there remains a need for well-designed RCTs to test the long-term benefits of exercise for preventing cognitive and functional decline. Rigorous RCTs are challenging for a number of reasons including but not limited to their expense, need for control interventions, and recruitment of a cohort of sufficient size. These challenges are magnified by the unique needs of those with AD and their caregivers.

Aerobic exercise offers a low-cost, low-risk intervention that is widely-available and may have disease modifying effects. Demonstrating aerobic exercise alters the AD process would have enormous public health implications. The protocol outlined in this report builds on the strengths from prior programs [40,55] and capitalizes on existing and well recognized community resources. Additionally, it uses publically endorsed exercise recommendations, while providing information on cognitive, functional and physiologic measures that may be sensitive to aerobic exercise training in individuals in the earliest stages of AD.

2. Methods

The University of Kansas Alzheimer's Disease Center (KU ADC) is currently supporting a trial of aerobic exercise for cognition; the Alzheimer's Disease Exercise Program Trial (ADEPT) for adults over 55 in the earliest stages of AD. Personalized aerobic exercise programs are carried out at the Young Men's Christian Association of Greater Kansas City (the Y) locations.

2.1. Study design and specific aims

ADEPT is a 26 week RCT of aerobic exercise vs. non-aerobic activities in individuals 55 years of age and older in the earliest stages of AD. Participants are randomized to a control arm (non-aerobic activities) or treatment arm of 150 min per week of aerobic exercise, typically treadmill walking. All measures are assessed at baseline. Cognitive testing is repeated at Week 13 and all measures are repeated after Week 26.

This study is designed to generate efficacy data to inform a larger multi-site trial on our theories regarding the potential positive benefits of aerobic fitness with respect to cognition (Aim 1), and physical functioning and mental well being (Aim 2). It also seeks to explore potential disease-modifying benefits and potential mechanisms relating aerobic fitness with brain health. Aim 1 uses co-primary outcome