Master's Thesis of Sports Science

Effects of Exercise on AD7c-NTP (Alzheimer-Associated Neuronal Thread Protein) Levels among Healthy Korean Elderly

운동이 65세 이상 국내 노인들의 소변 AD7c-NTP 단백질량에 미치는 영향

February 2023

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Seoul National University
Exercise Physiology Major

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Submitting a master's thesis of
Physical Education

February 2023

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Confirming the master's thesis written by
Donghyun Kim
February 2023

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Abstract

Alzheimer-associated Neuronal Thread Protein, also known as AD7C-NTP, is a protein found in the long axonal processes that originate from the nerve cell body. It is found in increased concentrations in extracts of brain tissue, cortical neurons, urine and cerebrospinal fluid in early Alzheimer's disease stages and its level is related with dementia severity.

Although relatively long distance from brain to urine, cerebrospinal fluid and urine have similar molecular mass and accuracy of AD7c-NTP. Earlier studies reported that AD7c-NTP is a prospective urinary Alzheimer's disease biomarker and can be utilized to distinguish between healthy people and Alzheimer's disease patients. Also, this protein has been demonstrated to grow with age in healthy population. Therefore, lowering the urinary level of AD7c-NTP is one of the possible mechanism which can prevent the progression to Alzheimer's disease. Earlier studies showed that exercise has benefits on plasma/CSF Alzheimer's disease biomarkers, thus preventing progression to Alzheimer's disease. Nevertheless, there was no earlier study examining the exercise effect on urinary Alzheimer's disease biomarker. This is the first study analyzing the exercise effect on urinary AD7C-NTP levels.

Participants (n=50) were randomly assigned to 3 groups: active control group (CON), combined resistance/aerobic exercise group

(RAG) and aerobic exercise group (AG). Total of 12 weeks of exercise intervention has been implemented. Active control group was asked to do activities of daily living (ADL) and dynamic stretching 2 times/week at home. Combined resistance/aerobic exercise group was asked to perform TheraBand resistance exercise at Gymnasium, Seoul National University, as well as walking exercise according to walking guidelines, suggested by Korean Golden Age Forum. Aerobic exercise group performed walking exercise according to walking guidelines, suggested by Korean Golden Age Forum. At week 0 and 12, AD7C-NTP levels in urine, Korean-Mini-Mental State Examination (K-MMSE) test, Korean-Color Word Stroop test (K-CWST) have been measured to evaluate cognitive function.

Following exercise intervention for 12 weeks, the AD7c-NTP levels in active control group increased while the AD7c-NTP levels in exercise groups decreased. However, no significant difference of AD7C-NTP levels between groups was observed before and after exercise intervention. Furthermore, no significant difference of K-MMSE scores was found between groups before and after exercise intervention. And, no significant difference of Korean-Color Word Stroop test scores was observed between groups before and after exercise intervention.

This study is significant as it is the first study looking at exercise effect on AD7C-NTP levels in urine among Korean healthy elderly. Previous researches have successfully demonstrated the exercise benefits on Alzheimer's disease biomarkers in plasma and

cerebrospinal fluid. However, this study could not demonstrate the exercise benefits on Alzheimer's disease urine biomarker, AD7C-NTP, among Korean healthy elderly.

Therefore, in future study, participants with low cognitive function should be recruited to observe the effect of exercise on AD7c-NTP levels in urine, as participants recruited in this study have high cognitive function. Furthermore, long term of exercise intervention and a large number of sample size are needed to confirm these findings.

Keywords: AD7C-NTP, Urine biomarker, Exercise, Cognitive Function, Alzheimer's disease
Student Number: 2021-23732

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I. Introduction

1.1. Significance of research

While we are confronting with the issues of COVID-19, we are also confronting with the tremendous challenges of an aging population (Zheng & Chen, 2022). In the United Nations report, in 2019, 1 in 11 world population was above the age 65 and this figure will be doubled to 1 in 6 by 2050 (United Nations, 2019). As the population ages globally, the rate of Alzheimer's disease is growing rapidly. The global dementia incidence was 13.5 million in 2000, globally. In 2025, it is reported to increase to 21.2 million and then to 36.7 million by 2050 (Zheng & Chen, 2022). According to statistics, Alzheimer's disease was reported as the sixth and seventh major causes of mortality in 2020 and 2021, respectively (United Nations, 2019). The mortality from stroke, heart disease, and HIV decreased from 2000 to 2019. However, the mortality from Alzheimer's disease increased by greater than 145% (Alzheimer's associations, 2022). However, unfortunately, the Alzheimer's disease pathogenesis is not known (Lerner et al., 2012). What makes the worse situation is in Alzheimer's disease, the symptoms appear 10 to 20 years later, after early degenerative brain alterations, making it difficult to stop the disease progression (Zheng & Chen, 2022).

Acetylcholinesterase (AChE) inhibitors as well as antagonists of

N-methyl D-aspartate (NMDA) receptor are generally used pharmacological treatments of Alzheimer's disease (Geerts & Grossberg, 2006). They delay the Alzheimer's disease progression in later phases and also provide some symptomatic relief, but do not achieve a perfect cure (Cass, 2017). For these reasons, exercise has been represented as a viable means of prevention of Alzheimer's disease due to its relatively safe with few side effects (Cass, 2017).

Physical exercise, defined as purposeful and repetitive physical activity, have been reported to prevent against cognitive reduction and Alzheimer's disease (Pillard et al., 2015). Although currently, there is no agreement regarding the best physical activity protocol for Alzheimer's disease patients, many studies reported that aerobic exercise and resistance training are linked to enhanced cognitive performance (Yaffe, 2010). Aerobic exercise has been reported to increase white and gray matter volume, increases blood flow and improve memory function (Voss et al., 2019). Strength exercise has been known to improve selective attention, associative memory and brain plasticity compared with balance exercises (Nagamatsu et al., 2012)

Brain imaging analysis such as fluorodeoxyglucose (FDG) PET and amyloid PET are used for Alzheimer's disease diagnosis. However, these imaging techniques are very expensive and are not practical for large populations (Erickson et al., 2011). Therefore, biomarkers that measure the effect of exercise on Alzheimer' disease-related outcomes rapidly and at low-cost cost are needed

to announce disease progression and develop the novel therapeutic targets.

Urine biomarker is becoming a significant source for Alzheimer's disease diagnosis. In contrast to cerebrospinal fluid (CSF) and plasma, urine can be collected continuously without pain or trauma on the subjects. Urine collection is simple, safer and less costly than that of blood and cerebrospinal fluid (Jing & Gao, 2018).

However, comparatively few researches have examined urine as a potential Alzheimer's disease biomarker, because of its separation from the brain by the two barriers which are blood-brain barrier and glomerular filtration (Kurbatova et al., 2020).

Alzheimer-associated neuronal thread protein, has been recognized as a significant urinary biomarker (Zhang, 2013). This urinary protein successfully differentiates healthy people and Alzheimer's disease patients (Xu et al., 2022). This protein has been also reported to increase with age in healthy population (Ma et al., 2014). Therefore, lowering this protein is a significant process to prevent Alzheimer's disease progression among older adults. However, it is currently unknown which treatment can lower this protein. Although exercise has proven its effect on preventing from progression to Alzheimer's disease (Paillard et al., 2015), there is no previous study looking at the 'exercise' effect on AD7c-NTP in urine. This study uses 'exercise' as a treatment to lower the AD7c-NTP level in urine and compares the AD7c-NTP levels in urine between groups.

1.2. Purpose of Research

The first purpose of this research is to analyze the effects of 12-week exercise on Alzheimer-associated neuronal thread protein (AD7c-NTP) levels in urine among healthy Korean elderly. The second purpose is to analyze the effects of 12-week exercise on cognitive performance among healthy Korean elderly. The third purpose is to analyze the effects of 12-week exercise on attention/inhibition in frontal lobe among healthy Korean elderly.

1.3 Research Hypothesis

The hypotheses of this study were:

1) Combined Resistance/Aerobic exercise group and Aerobic exercise group will have a significantly lower levels of urinary AD7c-NTP than Active Control group following 12 weeks of exercise intervention.

2) Combined Resistance/Aerobic exercise group and Aerobic exercise group will significantly improve cognitive performance than Active Control group following 12 weeks of exercise intervention.

3) Combined Resistance/Aerobic exercise group and Aerobic exercise group will significantly improve attention and inhibition in frontal lobe than Active Control group following 12 weeks of exercise intervention.

II. Background

2.1 Definition of Alzheimer's disease

Alzheimer's disease contributes to 60-80% of dementia. It gradually impairs memory, thinking abilities and finally the capacity to carry out the easy tasks (National Institute on Aging, 2021). It is caused by aberrant protein accumulation surrounding brain cells. These proteins, amyloid and tau, are responsible for cell death (Busche et al., 2020). However, the specific causation of Alzheimer's disease, remains unknown. The memory impairment, difficulty walking, difficulty speaking, personality and behavioral changes are the characterization of this disease (Alzheimer's disease, 2019). The development of Alzheimer's disease consists of 3 stages: the symptomatic stage, the mild cognitive impairment and Alzheimer's disease (Dubois et al., 2007). Currently, there are several medical tests for diagnosing Alzheimer's disease. Brain imaging analyses such as Tau PET imaging and fluorodeoxyglucose (FDG) PET are currently utilized for its diagnosis (Johnson et al., 2012). Also, the paper-based questionnaire including Mini-Mental State Examination (MMSE) as well as Montreal Cognitive Assessment (MoCA) are also generally utilized for diagnosis (Chapman et al., 2016).

2.2 Prevalence of Alzheimer's disease

Globally, approximately 55 million people have Alzheimer disease and other dementias, in which over 60% of this population are from low to middle income countries. As the older population rises, the Alzheimer's disease patients will be anticipated to increase to 78 million in 2030. In 2050, it is reported that around 139 million will suffer from Alzheimer's disease (World Health Organization, 2022). In Korean population aged over 40, the Alzheimer's disease incidence between 2006 and 2015 has raised from 1.83 per 1,000 persons in 2006 to 5.21 per 1,000 persons in 2015. In 2006, the Alzheimer's disease prevalence was 3.17 per 1000 people. However, in 2015, this figure raised to 15.75 per 1000 people (Baek et al., 2022). In 2020, the dementia prevalence was approximately 10.25%, among people aged over 65 years in Korea. As Korea is a rapidly-growing ageing country, by 2050, this figure will rise to approximately 15.91% and the dementia population in Korea is expected to rise to approximately 3.02 million people (Shon & Yoon, 2021).

2.3 Risk factors of Alzheimer's disease

Although the precise causation of Alzheimer's disease remains unknown, earlier researches have reported that age is the most significant risk factor (National Health Service, 2021). Alzheimer's disease mainly occurs at the age above 65. For those 65 and older, the chance of developing Alzheimer's disease becomes twice every five years (National Institute on Aging, 2019). 1 in 6 people over 80 have a dementia which is mostly Alzheimer's disease (National Health Service, 2021). Gender is also an important Alzheimer's disease risk factor. For those of 65 years and older, women have two times higher rates of developing Alzheimer's disease than men (Alzheimer's society, 2022). However, the precise causation of this is not known. In addition, family history is also an Alzheimer's disease risk factor. However, there is a very small percentage that Alzheimer's disease is being genetically transmitted from one generation to the next (Alzheimer's society, 2022). Other risk factors of Alzheimer disease include diabetes, hypertension and obesity (Reitz & Mayeux, 2014).

2.4 Exercise and Alzheimer's disease

Physical exercise is a great instrument for slowing down the physical and cognitive reduction of Alzheimer's disease patients (Yu et al., 2006). Previous longitudinal epidemiological researches have shown that physical activity delays the Alzheimer's disease onset in an older population (Paillard et al., 2015). In 2009, the meta-analysis study proved that the physical activity decreased the chance of developing Alzheimer's disease up to 45% (Hamer et al., 2009). Furthermore, an American study examining 1,740 individuals above 65 years old, reported that the dementia incidence was 13 per 1000 individuals who did exercise for three times per week. In contrast, the dementia incidence was 19.7 per 1000 people who did exercise less than three times per week (Larson et al., 2006). A 10-year longitudinal study in Western European countries found that subjects who reduced their daily physical activity had greater cognitive reduction than subjects who maintained their daily physical activity (Gelder et al., 2004). According to Winchester et al. (2013), the regular walking has an association with improved cognition. In this research, the walking aerobic exercise improves the motor functions of AD patients (Winchester et al., 2013).

Since Alzheimer's disease is related with low muscle mass and strength, many studies reported that muscle strength exercise is a great instrument to improve muscle mass and strength in Alzheimer's disease patients (Scherder et al., 2010; Nagamatsu et al. 2012). Previous study (Scherder et al., 2010) showed that the

strength of quadriceps muscle had an association with an enhancement in working memory and attention. In addition, a longitudinal research of 3.6 years revealed that the probability of developing Alzheimer's disease was lowered by 43% for every unit increase in muscle strength at the onset of cognitive impairment (Boyle et al., 2009). Finally, Nagamatsu et al. (2012) indicated that, relative to 2 times/week balance exercises for 6 months, 6 months of 2 times/week strength training enhanced selective attention, associative memory and brain plasticity.

The benefits of exercise on the Alzheimer's disease prevention has also been established in animal researches. It has been observed that moderate-to-vigorous physical exercise enhances the antioxidant enzymes production, such as eNOS, BDNF and IGF in animal models (Paillard et al., 2015). Physical exercise also increases brain plasticity in animal models. According to Yueda et al. (2009), Alzheimer's disease mice, after running of 1 hour, 5 days/week, 16 weeks, showed a more spacious hippocampus than control. Similarly, the majority of the present understanding of the processes behind the protective effects of physical exercise has come from research on Alzheimer's disease animal models (Paillard et al., 2015).

There have been studies investigating the association between exercise and Alzheimer's disease related biomarkers (Valenzuela et al., 2020). Previous study (Loprinzi & Frith, 2019) found that brain-derived neurotrophic factor (BDNF) enhances synaptic integrity and neuronal survival and is important for memory function

and brain plasticity (Peng et al., 2005). Low BDNF levels were detected in Alzheimer's disease patients' brain (Holsinger et al., 2000). In human studies, both acute and chronic exercise increase peripheral BDNF concentrations, which is related with improved cognitive function (Winter et al., 2007; Griffin et al., 2011). Furthermore, aerobic exercise-induced hippocampus volume enlargement is related with increased BDNF blood levels in cognitively healthy older individuals, and high BDNF serum levels lead to a lower Alzheimer's disease risk (Weinstein et al., 2014). Irisin, an exercise induced myokine, has also been found to improve cognitive function (Kim et al., 2022). FNDC5/Irisin, an exercise-linked hormone, moderates the benefit of exercise in Alzheimer's disease models by promoting synaptic plasticity and memory (Chen & Gan, 2019). In the previous study (Islam et al., 2021), genetic deletion of FNDC5/irisin deteriorates cognitive performance in Alzheimer's disease mouse. However, by administering irisin directly to the dentate gyrus, diminished pattern separation in F5KO mice was rescued. Additionally, the neuropathology and cognitive loss in AD mouse models were improved by peripheral delivery of irisin to the liver (Islam et al., 2021). Furthermore, another research (Lourenco et al., 2019) proved that overexpression of irisin enhances memory of mouse with Alzheimer's disease.

2.5 Plasma and Cerebrospinal fluid (CSF) biomarkers in Alzheimer's disease

A biomarker is an objective measurement of a biological process that assess disease risk and direct clinical diagnosis (Blennow et al., 2010). The extracellular space in the brain comes into direct contact with cerebrospinal fluid (CSF) (Anoop et al., 2010). For these reasons, the CSF is known to be the optimal source of Alzheimer's disease biomarkers (Blennow et al., 2010). The core biomarkers in CSF include total tau, amyloid beta 42 and p-tau 181. These CSF biomarkers have proven its diagnostic accuracy for Alzheimer's disease (Hansson., 2019). However, to collect CSF biomarker, the lumbar puncture should be implemented which the symptoms such as headache and back discomfort can occur (National Health Service, 2021).

Plasma is a complex bodily fluid that contains peptides, proteins, metabolites and lipids in the central nervous system and various organs (Hye et al., 2006). The repeatability of venipuncture, as contrasted to lumbar puncture, makes it appropriate for use in clinical trials. According to prior research (Simren J et al., 2021), plasma concentrations of p-tau181 and glial fibrillary acidic protein (GFAP) are increased in patients with Alzheimer's disease, suggesting that these may act as prospective blood biomarkers. However, for plasma collection, the venipuncture is required which can cause the symptoms of pain and bleeding (Buowari, 2013).

2.6 Urine biomarker in Alzheimer's disease

Compared to plasma and cerebrospinal fluid (CSF), urine is an easily available biological fluid and can be collected continuously without trauma or pain on the subjects (Anoop et al., 2010). Furthermore, urine collection is safer, simple and less costly than that of blood and cerebrospinal fluid (Jing & Gao, 2018). Most importantly, urine has no homeostasis mechanism which makes it a better source of biomarker than other body fluids (Wu & Gao, 2015). With its benefits and effects, many studies have undergone through researches about urine for Alzheimer's disease biomarker (Christopher et al., 2008). Among these studies, urinary AD7c-NTP has been recognized as a significant urinary biomarker (Suzanne et al., 2002; Zhang et al., 2014). There were also other studies that have been researched about urine biomarker in Alzheimer's disease. According to Yao and Hong (2018), Gene Ontology (GO) enrichment analysis was used to analyze 2,754 genes. Among those, three proteins, SPP1, GSN, and IGFBP7 genes, were found to be significantly expressed in the urine of Alzheimer's disease. Another study indicated that the apolipoprotein C3 levels in urine were considerably greater in Alzheimer's disease group, as contrasted to control group, suggesting that this protein can be a prospective urine biomarker (Watanabe et al., 2020). Furthermore, urinary F2-isoprostanes has been significantly elevated in patients with Alzheimer's disease, relative to healthy people, suggesting that

it is also an important urinary biomarker (Montine et al., 2002; Bohnstedt et al., 2003).

Nevertheless, since urinary biomarker has relatively recently investigated compared to plasma and CSF biomarkers, many research is still going on and further research is needed for Alzheimer's disease diagnosis.

2.7 Alzheimer-associated Neuronal Thread Protein (AD7c-NTP)

Alzheimer-associated neuronal thread protein (AD7c-NTP) has a molecular weight of 41-kD, and is existed in the long axonal processes of nerve cell body in the brain. During the processes of proliferation, differentiation and neurodegeneration, the expression of this protein is increased. A researcher, in 1997, separated a new cDNA that contains an Alu sequence and found that it is overexpressed in neurons and brains with Alzheimer's disease (De la monte et al., 1997). Therefore, this is named Alzheimer-associated neuronal thread protein (AD7c-NTP). This protein is related with the pathological alterations of Alzheimer's disease and is elevated in brains of Alzheimer's disease.

According to many in vitro studies, the AD7c-NTP overexpression in transfected neurons promote cell death and neuritic sprouting. These are the two neuroanatomical lesions related with Alzheimer's disease (Ghanbari et al., 1997). This study also identified that the urine and cerebrospinal fluid have the same molecular weight of AD7c-NTP (Ghanbari et al., 1997). This study reported that the CSF and urine testing have the similar diagnostic accuracy for Alzheimer's disease (Ghanbari et al., 1997).

2.8 AD7c-NTP for diagnosis of Alzheimer's disease

In earlier Alzheimer's disease stage, the expression of AD7c-NTP is increased in extracts of brain tissue, cortical neurons, cerebrospinal fluid and urine. The level of AD7c-NTP is correlated positively with dementia severity (Zhang & Shi, 2013).

AD7c-NTP in CSF

Previous study demonstrated that the average AD7c-NTP concentration in AD group was greater, as contrasted to the control group, in postmortem cerebrospinal fluid (CSF) (De la monte et al., 1997). Another research reported that the concentration of AD7c-NTP was elevated in the CSF from probable AD patients, relative to the CSF levels of control subjects (Ghanbari et al., 1997). Furthermore, according to De la monte et al. (2002), the average AD7c-NTP levels in cerebrospinal fluid were almost 3 times higher in AD group, relative to the control group. In this study, it is found that the AD7c-NTP levels in CSF increased above 2 ng/ml in 89% of AD patients while there was only 11% of the age-matched control group (De la monte et al., 2002). Another study reported that the CSF levels of AD7c-NTP have association with dementia severity and CSF phospho-tau concentrations (Kahle et al., 2000). This study showed that AD7c-NTP overexpression is correlated with phopho-tau accumulation in CNS neurons (Kahle et al., 2000).

AD7c-NTP in urine

According to Ghanbari et al. (1998), urine and cerebrospinal fluid have the same molecular weight of AD7c-NTP. This study also reported that both have similar accuracy. In the previous study (Munzar et al., 2002), Alzheimer's disease group has greater levels of AD7c-NTP than non-Alzheimer's disease group, as measured on urine samples. Another study (Ma et al., 2015) reported that the urinary AD7c-NTP concentrations of AD and MCI groups were considerably greater than healthy population. This research indicated that the AD7c-NTP concentrations in urine increased sequentially from healthy to MCI to AD groups and can be used to distinguish between groups. This is further confirmed by other study (Xu et al., 2022). This research proved that urine AD7c-NTP levels declined sequentially from AD to MCI to healthy groups and showed that this protein can be a potential urine biomarker. This study also demonstrated that the urinary AD7c-NTP concentrations have a negative correlation with MMSE scores. Furthermore, another study (Zhang et al., 2020) reported that the AD7c-NTP concentrations in urine were greater in hypertensive older adults. A common chronic disease, hypertension, has an association with cognitive impairment (Bermejo-Pareja et al., 2010). Among 134 hypertensive patients, the AD7c-NTP level in urine was considerably elevated in the lower cognitive function (LCF) group compared to the normal control (NC) group (Zhang et al., 2020). In addition, the urinary AD7c-NTP biomarker can also be used to differentiate amnestic mild cognitive impairment (aMCI)

patients from non-amnestic mild cognitive impairment (naMCI) patients (Ku et al., 2019). In aMCI, the memory impairment predominates and has a greater risk of transformation to Alzheimer's disease. People with naMCI have impairment in other areas than memory and have a greater risk of transformation to other dementia such as Lewy body dementia. This study demonstrated that aMCI group has a higher level of AD7c-NTP and thus greater chance of developing Alzheimer's disease than the naMCI group (Ku et al., 2019). These studies provided the evidence that urinary AD7c-NTP can be a prospective Alzheimer's disease biomarker.

2.9 AD7c-NTP and age

AD7c-NTP is an Alzheimer's disease biomarker with increased cerebrospinal fluid and urine concentrations from Alzheimer's disease patients (Youn et al., 2011). Several studies indicated that the increased AD7c-NTP concentrations can also be observed in healthy population (Ma et al., 2015; Xu et al., 2022). Ma et al (2014) indicated that there is an association between age and urinary AD7c-NTP levels among healthy people. From age 20-29 to 60-69, the urinary AD7c-NTP concentrations increased and the significant difference of AD7c-NTP concentrations between age groups was observed. This is further demonstrated by another study (Jin et al., 2018). This study indicated that the urinary AD7c-NTP concentrations between age 80-89 was considerably greater than other age groups (<60, 60-69 and 70-79). These studies demonstrated that the age is a huge risk factor for determining the AD7c-NTP levels in urine.

III. Methods

3.1 Participants

This study is a randomized control trial with ethical approval granted from Institutional Review Board (IRB) of Seoul National University (SNUIRB No. 2106/002-009). A total of 60 participants aged over 65 years were recruited from Gwanak-gu welfare center. G-power 3.1.0 (effect size: 0.25) was used to calculate the total number. Among 60 participants, 5 participants were dropped out due to healthy issues and 5 participants were dropped out because the AD7c-NTP levels were not in the ELISA Kit's detection range (0.1 ng~1.7 ng/ml). So, a total of 50 participants completed this study.

The inclusion criteria of participants were healthy Korean men and women who were over 65 years old. The exclusion criteria of participants were BMI smaller than 18.5 kg/m^2 or higher than 30 kg/m^2 , alcoholic, smoker, had an experience of surgical operation within 6 months, continuously consumed health functional foods within 1 month after first visit, have a VO_2 max which is in first class or top 50% of second class in the same age and continuously did high-intensity exercise within 3 months after first visit.

The participants were randomly divided into 3 groups:

I) Active Control Group (CG), were asked to continue their

routine daily activities and perform static and dynamic stretching 2 times/week for 1 hour (n=15)

II) Combined Resistance/Aerobic Exercise Group (RAG), were asked to do TheraBand resistance exercise 2 times/week as well as walking according to the guidelines (Korea Golden Age Forum, 2010) (n=16).

III) Aerobic Exercise Group (AG), were asked to walk recommended walking steps according to age, as suggested in the walking guidelines (Korea Golden Age Forum, 2010) (n=19).

3.2 Study Procedure

A schematic study design is presented in Figure 1. On the 1st visit, participants were asked not to eat for 12 hours before the start of the experiment and were requested to come in a fasting state. Prior to the baseline measurement, participants were familiarized of experimental procedures and signed a consent document for participation in the study. The screening was conducted on the 1st visit (pre-test day), followed by 12 weeks of exercise intervention and the 2nd visit (post-test day). On the 1st visit, screening was processed through the questionnaires. After screening, participants who were qualified, were randomized to one of three groups, a) Active Control group, b) Combined Resistance/Aerobic exercise group, c) Aerobic exercise group. After randomization, participants were asked to do pre-test which include Korean-Mini-Mental State Examination (K-MMSE), Korean-Color Word Stroop test (K-CWST) and urine collection. After pre-test, 12 weeks of exercise intervention were conducted. During the 12 weeks of exercise intervention, 5 participants were dropped out due to healthy issues. After 12 weeks of exercise, participants were asked to perform post-test (2nd visit). Also, same with the 1st visit, in the 2nd visit, participants were asked not to eat for 12 hours before start of the experiment. After post-test, urine samples were investigated by Enzyme-Linked Immunosorbent Assay (ELISA). Detailed procedures are shown in Figure 1.

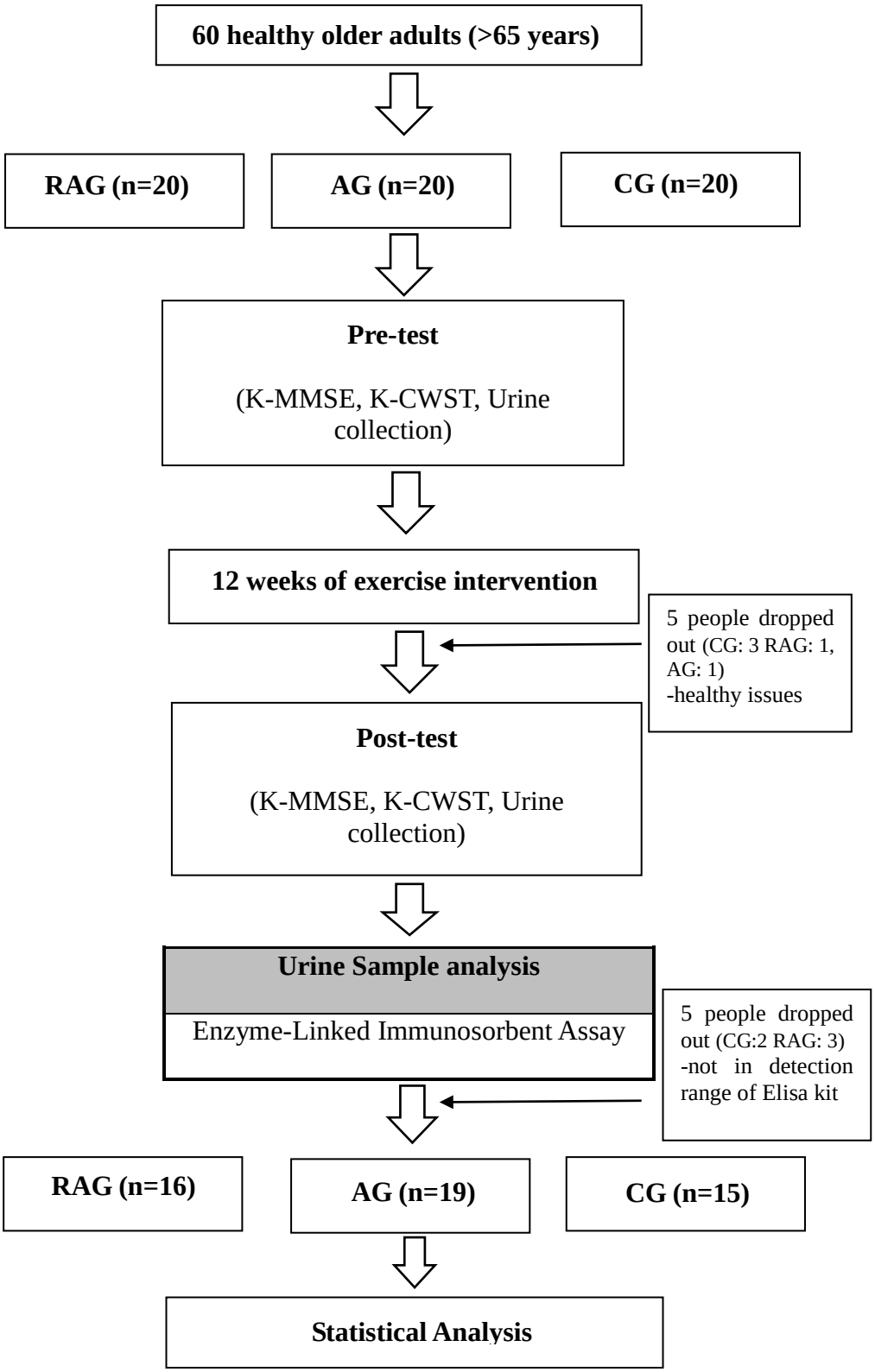


Figure 1. Study design

3.3 Exercise Program

The exercise program used in this study is shown in Table 1.
The active control group was asked to do routine daily activities and dynamic stretching 2 times/week for 1 hour, 12 weeks. The participants in active control group were provided the booklet that contains the protocol of stretching exercises.

The combined resistance/aerobic exercise group was asked to do Theraband resistance exercise 2 times/week as well as walking exercise according to walking guidelines (Korea Golden Age Forum, 2010). The Theraband resistance exercise is composed of upper body (arm, shoulder), core (abdominal, back) and lower body (hamstring, quadriceps) parts. Detailed resistance exercise protocol is shown in Table 2. The Theraband resistance exercise was composed of 3 sessions, which include 10 minutes of warm-up session, 40 minutes of main exercise session and 10 minutes of cool-down session. The Theraband intensity is increased by increasing the repetitions and changing the color of Theraband every 3 weeks based on participants' Rate of Perceived Exertion (RPE) and handgrip strength. Starting with yellow Theraband from 1-3 weeks, the red Theraband (4-6 weeks), green Theraband (7-9 weeks) and blue Theraband(10-12 weeks) were used. Combined resistance/aerobic exercise group also performed aerobic walking exercise according to walking guidelines (Korea Golden Age Forum, 2010). The participants in combined resistance/aerobic exercise group were guided to use smartwatch (Mi Watch Lite; Xiaomi, Pekin,

China) on 1st visit. When they started walking exercise, they turned ‘on’ the smartwatch and turned ‘off’ smartwatch after they finished walking exercise. The number of walking steps were monitored using smartwatch.

The aerobic exercise group was asked to do aerobic walking exercise according to walking guidelines (Korea Golden Age Forum, 2010). The participants in aerobic exercise group were also guided to use smartwatch. Same with combined resistance/aerobic exercise group, the number of walking steps were monitored using smartwatch. The exercise intervention persisted for 12 weeks.

Table 1. Exercise protocol

	Exercise Protocol
Active Control Group	Routine daily activities and dynamic stretching (2 times/week for 1 hour, 12 weeks)
Combined Resistance/Aerobic Exercise Group	TheraBand resistance exercise composed of upper, core, lower (arm curls, chest press, squat, knee extension. etc) (2 times/week, 12 weeks) Aerobic walking exercise according to walking guidelines (Korea Golden Age Forum, 2010) Age 60−69: 35000−50000 steps/week 70−79: 30000−45000 steps/week 80−89: 20000−35000 steps/week
Aerobic Exercise Group	Aerobic walking exercise according to walking guidelines (Korea Golden Age Forum, 2010) Age 60−69:35000−50000 steps/week 70−79: 30000−45000 steps/week 80−89: 20000−35000 steps/week

Table 2. Resistance Exercise Protocol

Exercise Period	Upper Body	Lower body	Core	Repetitions	Intensity
1–3 weeks	Biceps curl Arm horizontal abduction Seated row	Toe & Heel raise Lying leg abduction Bent knee plantar flexion	Torso twist Dead Bug	8	1 (Yellow)
4–6 weeks	Triceps extension Shoulder press Chest Fly	Standing kickback Toe & Heel raise	Monkey Plank	10	2 (Red)
7–9 weeks	Lateral raise Upright row Side bend	Lateral raise Squat Lateral walk	Side Plank	10	3 (Green)
10–12 weeks	Push up (beginner) Front raise Lower abdominal press	Lunge Leg raise One leg circle	Pelvic lift	12	4 (Blue)

3.4 Korean-Mini-Mental State Examination (K-MMSE) test

The Mini-Mental State Examination (MMSE) is a commonly utilized measurement for assessing cognitive performance and diagnosing cognitive impairment (Han et al., 2008). The K-MMSE is a Mini-Mental State Examination (MMSE) that has been translated into Korean (Han et al., 2008). The K-MMSE includes the components of spatial orientation (5 scores), time orientation (5 scores), attention and calculation (5 scores), memory registration (3 scores), memory recall (3 scores), space-time configuration (1 score) and language (8 scores), contributing to 30 scores in total (Park et al., 2021). According to Kwon et al. (1989), K-MMSE score between 24 to 30 is considered normal, score between 20 to 23 is considered mild cognitive impairment (MCI) and score below 20 is considered as dementia. At week 0 and 12, K-MMSE test has been implemented.

3.5 Korean-Color Word Stroop Test (K-CWST)

The Color-Word naming test, also known as the Stroop test, has been frequently utilized since its creation by Stroop in 1935 (Stroop, 1935). The Korean-Color Word Stroop test has been translated from the 1989 version created by Morris and his colleagues (Lee et al., 2002). The Korean-Color Word Stroop test examines the selective attention and inhibition of frontal lobe and also used to diagnose dementia (Kim et al., 2004). The KST consists of word naming (WN), color naming (CN) and interference color naming (ICN). The word naming task is the reading of the words that are printed in 'black'. The color naming task is the reading the colors of the words that are printed in either 'red', 'blue' or 'yellow'. The interference color naming task is the reading the ink color of color words that were mismatched to word meaning (Kim et al. 2004). Participants were given 45 seconds and asked to read 100 words as fast as they can. The number of correct answers and errors were measured. At week 0 and 12, participants completed the Korean-Color Word Stroop Test.

3.6 Urine Collection

Participants were asked to come in a fasting state prior to 12 hours before start of the experiment and a total of 20ml of urine was collected per each participant in the morning at week 0 and 12. After collection, 20ml of urine was immediately kept at −80° C.

3.7 Enzyme−linked immunosorbent Assay (ELISA)

The urinary AD7c−NTP levels were determined by enzyme−linked immunosorbent assay (ELISA). The Human Alzheimer−associated neuronal thread protein ELISA Kit (MyBioSource, Cat#MBS726151, USA) was used for analyzing. The ELISA kit used in this study employs the competitive enzyme immunoassay approach with monoclonal anti−AD7c−NTP antibody and an AD7c−NTP−HRP conjugate. A total of 100 urine samples (RAG: 16, AG: 19, CG: 15) before and after exercise, were analyzed. After urine collection, all 100 urine samples were kept at −80° C freezer and 4° C before the day of the experiment. The 100ul of standards and 100ul of urine samples were transferred to 96 well plates. The 100ul of Phosphate−buffered saline (PBS), pH between 7.0−7.2, was used for blank control well. The 10ul of balance solution and a 50ul of conjugate was put into each well except for blank control well. After adding conjugate, the urine samples were incubated at

the degree of 37° C. The incubation period lasted for 1 hour. After incubation, plates were washed for 5 times with 1 x wash solution. Then, 50ul of substrate A and B were put into each well. After addition of substrate A and B, plates were incubated at 37° C. Then, a 50ul of stop solution which stop the reaction was put into each well. Lastly, the urinary AD7c-NTP level was quantified using microplate reader (Nanoquant infinite m200 Pro, Tecan).

3.8 Statistical analysis

The SPSS version 29.0. (SPSS, IBM Corporation, IL, USA) was utilized for statistical analysis. The data are represented as mean ± standard deviation (SD). The normality at the baseline was evaluated by Shapiro-Wilk test. One-way ANOVA was utilized to compare the difference between three groups. Two-way repeated measures ANOVA was utilized to observe time (before and after exercise) x group (CG vs RAG vs AG) interactions. This was followed by Bonferroni's post hoc test that compares the difference between groups individually. p-value < .05 was regarded as statistically significant.

3.9 Ethical Statements

All procedures processed in this study were approved by the ethics committee of the Seoul National University (IRB approval no. 2106/002-009).

IV. Results

4.1 Baseline characteristics of participants

Table 3 describes participants' baseline characteristics. Total of 50 participants were included in the study. Of these 50 participants, 15 were active control group, 16 were combined resistance/aerobic exercise group and 19 were aerobic exercise group. All participants were normally distributed and there was no significant difference in participants' characteristics (age, height, weight and BMI) between groups at the baseline (Table 3).

Table 3. Baseline characteristics of participants

	Active Control Group (n=15)	**Combined Resistance/Aerobic Exercise Group (n=16)**	**Aerobic Exercise Group (n=19)**	**P-value**
Age (years)	73.5 ± 6.4	74.4 ± 4.7	73.3 ± 4.6	0.338
Height (cm)	153.8 ± 7.4	156.0 ± 6.4	156.1 ± 8.7	0.526
Weight (kg)	55.8 ± 10.3	57.9 ± 6.9	59.4 ± 7.7	0.405
BMI (kg/m^2)	23.4 ± 2.8	23.6 ± 3.1	24.4 ± 2.3	0.302

Data are represented as the mean ± Standard Deviation.

P−value represents difference between groups.

BMI: Body Mass Index.

4.2 Effects of exercise on AD7c-NTP between groups

The AD7c-NTP levels in urine between groups before and after exercise are shown in Table 4 and Figure 2. The AD7c-NTP levels in active control group increased after exercise while AD7c-NTP levels in combined resistance/aerobic exercise and aerobic exercise groups decreased after exercise (Table 4). However, there was no significant difference of AD7c-NTP between groups before and after exercise intervention (p=.151).

4.3 Effects of exercise on K-MMSE scores between groups

The K-MMSE scores between groups before and after 12 weeks of exercise are shown in Table 4 and Figure 3. The K-MMSE scores for all three groups increased after exercise, compared to before exercise (Table 4). However, there was no significant difference between groups before and after exercise intervention (p=.727).

4.4 Effects of exercise on Korean-Color Word Stroop test scores between groups

The Korean-Color Word Stroop test scores between groups before and after 12 weeks of exercise, are represented in Table 4 and Figure 4. In Stroop Words-Naming, Color-Naming and Color-Interference tests, the difference of correct scores between before and after exercise is greater in combined resistance/aerobic exercise than other two groups (Table 4). However, there was no significant difference of Stroop Words-Naming (p=.279), Stroop Color-Naming (p=.815) and Stroop Color-Interference (p=.899) tests between groups before and after exercise intervention.

Table 4. Comparison of cognitive outcomes between groups before and after intervention

Factor	Time	Active Control Group (n=15)	Combined Resistance/Aerobic Exercise group (n=16)	Aerobic Exercise Group (n=19)
AD7c-NTP (ng/ml)	Pre	1.2 ± 0.9	1.0 ± 0.4	1.2 ± 0.6
	Post	1.7 ± 1.2	0.9 ± 0.7	1.1 ± 0.9
K-MMSE (score)	Pre	25.7 ± 3.0	27.2 ± 1.6	26.3 ± 2.7
	Post	26.5 ± 3.3	27.3 ± 1.6	26.6 ± 2.7
Stroop Words Naming	Pre	70.8 ± 15.1	69.8 ± 11.5	68.6 ± 14.6
	Post	71.7 ± 14.4	72.3 ± 12.3	67.0 ± 15.2
Stroop Color Naming	Pre	59.1 ± 9.7	54.3 ± 11.3	53.5 ± 9.9
	Post	59.8 ± 9.2	56.6 ± 9.4	55.2 ± 10.3
Stroop Color Interference	Pre	30.0 ± 11.0	29.9 ± 11.7	31.6 ± 10.2
	Post	31.7 ± 9.8	32.3 ± 11.5	32.7 ± 14.7

Data are represented as the mean ± Standard Deviation.

**P < 0.05 vs. Aerobic Exercise group, #P < 0.05 vs. Control,

*P < 0.05 vs. Combined Resistance/Aerobic Exercise group.

AD7c-NTP: Alzheimer-associated neuronal thread protein.

K-MMSE: Korean-Mini-Mental State Examination.

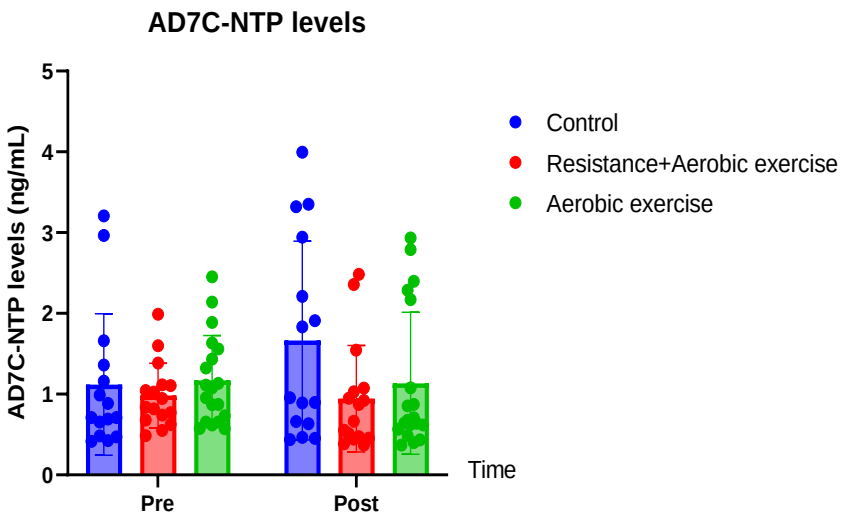


Figure 2. Effects of exercise on urinary AD7c-NTP between groups before and after exercise intervention

The values are shown as the mean ± SD. **P < 0.05 vs. Aerobic Exercise group, #P < 0.05 vs. Control, *P < 0.05 vs. Combined Resistance/Aerobic Exercise group.

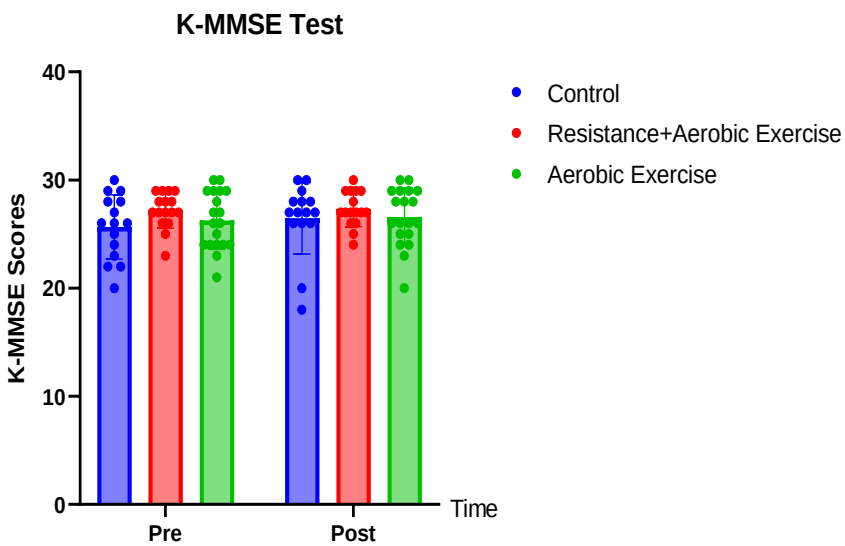
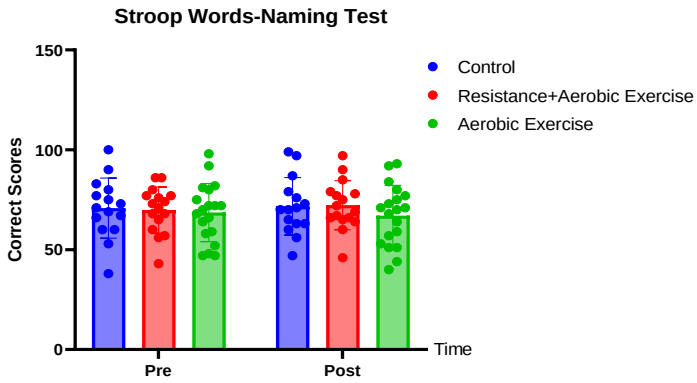


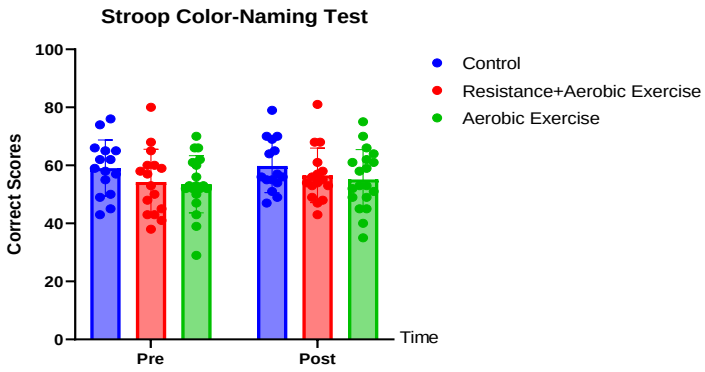
Figure 3. Effects of exercise on K-MMSE scores between groups before and after exercise intervention

The values are shown as the mean ± SD. **P < 0.05 vs. Aerobic Exercise group, #P < 0.05 vs. Control, *P < 0.05 vs. Combined Resistance/Aerobic Exercise group.

A.



B.



C.

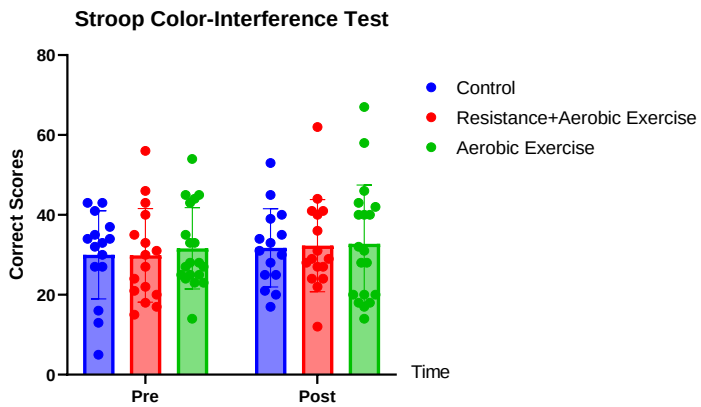


Figure 4. Effects of exercise on Stroop Words-Naming, Color-Naming, Color-Interference test between groups before and after exercise intervention

A) Stroop Words-Naming test B) Stroop Color-Naming test C) Stroop Color-Interference test. The values are shown as the mean ± SD. **P < 0.05 vs. Aerobic Exercise group, #P < 0.05 vs. Control, *P < 0.05 vs. Combined Resistance/Aerobic Exercise group.

V. Discussion

Alzheimer's disease (AD) is a major medical issue of 21st century and the leading cause of dementia (Yiannopoulou et al., 2020). Given our aging population and rising life expectancy, developing new Alzheimer's disease (AD) treatments has gained societal relevance (Thal et al., 2006). Even though the global incidence of Alzheimer's disease is rising rapidly, its early diagnosis remains difficult (Seol et al., 2020). Therefore, biomarkers have become a crucial part of Alzheimer's disease research because of its great dependability and precision (Mayeux, 2004).

Due to its non-invasiveness and repeatability of collection, urine is becoming a crucial source of Alzheimer's disease biomarker (Njoku et al., 2020). Compared to plasma and cerebrospinal fluid, urine can be collected continuously and completely without pain on the subjects (Zhang et al., 2022). It is also simple, safer and less costly than that of blood and cerebrospinal fluid (Jing & Gao, 2018). However, there have been few studies investigating the possibility of urine as an Alzheimer's disease biomarker, due to its relatively long distance from cerebrospinal fluid to urine (Kurbatova et al., 2020).

This study is the first study to see the difference of urinary Alzheimer's disease biomarker, AD7c-NTP between groups with exercise intervention. However, in this study, exercise did not have any effect on lowering urinary AD7c-NTP levels between groups.

Furthermore, there was no difference of Korean-Mini-Mental State Examination (K-MMSE) scores and Korean-Color Word Stroop Test (K-CWST) scores between groups, indicating that exercise did not have a beneficial effect on cognitive performance.

Previous studies have shown the positive relationship between exercise and Alzheimer disease-related biomarkers. Previous study (Rasmussen et al., 2009) showed that aerobic exercise elevates BDNF levels remarkably, compared to resting conditions. This study demonstrated that aerobic treadmill exercise raises the mRNA concentrations of BDNF in the hippocampus of mouse. Furthermore, Coelho et al. (2014) has demonstrated that aerobic exercise elevates plasma BDNF concentrations in patients with Alzheimer's disease, enhancing cognition. These studies support that BDNF levels have an association with physical activity.

Another potent Alzheimer disease-related biomarker, Cathepsin B, which is recently discovered myokine, has been reported to elevate in plasma during exercise in human and animal models (Moon et al., 2016). During exercise, the Cathepsin B crosses the blood-brain barrier (BBB) and contribute to increase in BDNF expression in the hippocampus. In this study, exercise training increased the Cathepsin B levels in mouse, monkey and human plasma. However, exercise did not improve memory and neurogenesis in Cathepsin B knock-out mice (Moon et al., 2016). This study supports that Cathepsin B levels have an association with physical activity (Moon et al., 2016).

Irisin is an essential myokine demonstrated to pass the blood-

brain barrier and increase during exercise (Madhu et al., 2022). It stimulates hippocampal neurogenesis by increasing BDNF expression. According to Islam et al. (2021), exercise raises the irisin levels and the increased level of irisin has benefits on cognitive function. In the previous study (Wrann et al., 2013), running-wheel exercise for 1 month, increased the PGC-1a and FNDC5/Irisin expression in mice, enhancing cognitive function. However, the mice that is deficient in PGC-1a showed lower FNDC5/Irisin expression in the hippocampus.

Likewise, many studies have successfully demonstrated the benefits of exercise on Alzheimer's disease-related biomarkers, thus preventing progression to Alzheimer's disease. Nevertheless, no research has examined the exercise benefits on Alzheimer's disease urine biomarkers.

This study is the first study looking at exercise effect on urinary Alzheimer's disease biomarker. The major finding of this study is that there was no difference of urinary AD7c-NTP concentrations between groups after exercise intervention. This might be because every participant's glomerular filtration rate in the kidney was varied in this study. As the glomerular filtration rate differs for each participant, the AD7c-NTP level excreted in urine can also vary between subjects (Fenton et al., 2018). As the level of AD7c-NTP can be affected by the glomerular filtration rate in the kidney (Polesel et al., 2022), it is important to make sure that all participants' glomerular filtration rate is in the similar range to minimize the variation. Therefore, in the future study, the

measurement of glomerular filtration rate is needed for every participant to minimize the variation between groups. In addition, depending on the diet that participants took during the study, the glomerular filtration rate can be affected, influencing the level of AD7c-NTP in urine. Although there was no previous study investigating the relationship between urinary AD7c-NTP and diet, previous study showed that high-protein diet induced higher glomerular filtration rate than low-protein diet (Wei et al., 2019). Therefore, in the future study, monitoring of the participants' diet is essential to minimize the variation between groups.

Another finding of this study is that there was no difference of K-MMSE scores between groups, indicating that exercise did not have any effect on improving cognitive performance among healthy Korean elderly. Previous researches have demonstrated the benefits of exercise on K-MMSE scores among Korean elderly. In the previous study (Koo & Moon, 2012), three times a week for 9 week of aerobic exercise significantly increase the K-MMSE scores in exercise group while there was no difference of K-MMSE scores in control group. This is supported by another study (Koh et al., 2020). This study showed an association of physical exercise and K-MMSE scores in the Korean elderly without dementia. The K-MMSE scores of elderly, who do not exercise regularly, were comparatively lower than elderly who exercise regularly (Koh et al., 2020). However, the result of the current study is inconsistent with the results of the previous studies. This might be because participants were cognitively healthy in this study. The average K-

MMSE scores for control group was 25.7 ± 3.0, combined resistance/aerobic exercise group was 27.2 ± 1.6, aerobic exercise group was 26.3 ± 2.7 at the baseline. According to Kwon et al. (1989), K-MMSE score between 24 to 30 is considered normal, score between 20-23 is considered mild cognitive impairment (MCI) and score below 20 is considered as dementia. The participants recruited in this study are included in the cognitively 'normal' category. Therefore, exercise might not have benefits on improving cognitive function among cognitively healthy participants.

Furthermore, this study could not demonstrate the positive effect of exercise on Korean-Color Word Stroop test between groups. Since many studies demonstrated that older adults benefit from the Stroop effect, the Stroop test has been used to investigate age-associated declines in attention and inhibition (Kramer et al., 1994). The decline in executive function in Alzheimer's disease patients has been represented in several studies utilizing different versions of the Stroop test (Bondi et al., 2002). Executive function is a complex structure that encompasses the ability to plan, direct and keep focus (Homack & Riccio, 2004). In the previous study (Alves et al., 2012), 42 healthy women were assigned randomly to strength exercise, aerobic exercise or control groups. Both aerobic and strength training groups completed the Stroop "non-color word" and "color word" tests faster than the control group, showing the positive effect of exercise on executive function in the brain (Alves et al., 2012). Liu-Ambrose et al. (2010) also demonstrated

that the once or twice weekly strength training of 12 months significantly enhanced Stroop test performance, compared to balance and tone control group, in cognitively healthy women aged 65–75 years. The result of the current study is inconsistent with previous studies' findings. This might be speculated that exercise could not increase the cerebral blood flow, resulting in no effect on working memory (Pontifex et al., 2009). This is supported by previous study (Pontifex et al., 2009). In this study, an acute bout of aerobic exercise was found to increase performance on a working memory task. However, there was no improvement of working memory after a strength exercise session (Pontifex et al., 2009). The Stroop test measures working memory which is one of the component of executive function (Alves et al., 2012). Pontifex et al. (2009) speculated that strength training could reduce blood flow, resulting in no effect of exercise on working memory (Pontifex et al. 2009; Rowland & Fernhall, 2007). In addition, it might be speculated that the control group's activity levels were high during exercise intervention. Therefore, exercise might be insufficient to show the difference between control and exercise groups. As the exercise intervention period overlapped with COVID–19, there were some difficulties in monitoring the activity levels of individuals in control group.

However, there are several limitations of this study. Firstly, participants' health condition, including cognitive function was generally high in this study. As this study overlapped with the period of COVID–19, participants whose healthy condition were

generally low, could not be recruited as they are more susceptible to Coronavirus disease. According to Wang et al. (2021), patients with dementia are at increased risk for COVID-19, in comparison to patients without dementia. Therefore, participants whose cognitive function were high, were recruited in this study. This might lead to negative effect of exercise on improving cognitive function among cognitively healthy participants.

Secondly, the female participants' proportion in each group was high (CG: 13 Female, 2 Male. RAG: 13 Female, 3 Male. AG: 13 Female, 6 Male). Therefore, the sample in each group can be representative of only 'female' population. In future study, the same number of female and male participants in each group will provide more accurate and reliable results.

Thirdly, each group's sample size might be insufficient to represent the group difference. According to Andrade (2020), a sample which is larger than necessary will better represent the entire population and will therefore produce more accurate results. Therefore, in future study, large number of sample size in each group is needed to produce more accurate and reliable results.

Fourth, relatively short term exercise intervention period (12 weeks) might not be sufficient to have exercise benefits on cognitive function. In future study, longer than 12 weeks of exercise intervention can be applied to observe the difference of cognitive function between groups.

VI. Conclusion

This study is significant as it is the first exercise intervention study that observe Alzheimer's disease biomarker in urine besides plasma and cerebrospinal fluid. This study investigated the effects of exercise on urinary AD7c-NTP levels between groups. 12 weeks of exercise intervention did not have a significant effect on urinary AD7c-NTP levels, K-MMSE test and Korean-Color Word Stroop test among >65 years' healthy Korean elderly. However, since the period conducted in this study overlapped with the period of COVID-19, only participants whose cognitive function were high, were recruited in this study. Therefore, to overcome the limitations of current study and to confirm these findings, future study needs to investigate a large number of participants with lower cognitive function and long-term exercise intervention.

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초 록

알츠하이머 단백질 중 하나인 Alzheimer-associated Neuronal Thread Protein (AD7c-NTP)는 신경세포체로부터 뻗어 나오는 축삭 돌기에 존재하는 약 41kD의 단백질이다. AD7c-NTP는 신경퇴화과정 초기의 피질 뉴런, 뇌조직 추출물, 뇌척수액, 소변 등에서 검출되며, 그 수치는 치매의 심각성과 정비례한다.

뇌에서 소변까지의 거리는 비교적 멀지만, 소변에서 검출되는 AD7c-NTP의 분자량은 뇌척수액에서 검출되는 AD7c-NTP의 분자량과 유사한것으로 보고되었다. 선행연구에서 AD7c-NTP는 알츠하이머병을 진단하는 잠재적인 바이오마커로 증명되었고, 소변에서의 AD7c-NTP 수치를 통해 알츠하이머 환자, 경도인지장애 환자, 일반인들을 명확히 구별할 수 있는 것으로 보고되었다. 또한, AD7c-NTP는 건강한 사람들에게서도 나이가 증가할수록 많아지는 것으로 보고되었다. 따라서, 소변에서의 AD7c-NTP의 수치를 낮추는 것이 알츠하이머병으로의 진행을 막는 하나의 방법이다. 선행연구에서 운동이 혈장 및 뇌척수액 알츠하이머 바이오마커에 긍정적인 영향을 미쳐 알츠하이머병을 지연시킬 수 있다고 보고하였다. 하지만, 운동이 소변 알츠하이머 바이오마커에 어떠한 영향을 미치는지 조사한 선행연구는 없었다. 따라서, 본 연구는 운동을 통해 소변 알츠하이머 바이오마커 중 하나인 AD7c-NTP의 변화를 측정한 첫번째 연구이다.

참가자 (n=50)는 활동적 대조그룹 (CON:15), 유산소운동과 저항성운동을 합친 복합운동그룹 (RAG:16), 유산소운동 그룹 (AG:19), 총 3개의 그룹으로 랜덤하게 배정되었다. 총 12주간 운동을 하였으며, 활동적 대조그룹은 집에서 1주일에 2회 일상생활과 동적 스트레칭을 하였다. 복합운동그룹은 서울대학교 체육관에서 주 2회 세라벤드 운동을 하였고, 이와 동시에 한국골든에이지포럼에서 제시한 보행 지침에 따라 걷기운동을 실시하였다. 유산소운동그룹은 한국골든에이지포럼에서 제시한 보행 지침에 따라 걷기운동을 실시하였다. 총 0주와 12주차에 소변의 AD7c-NTP 수치, 한글판 간이정신상태검사 (K-MMSE), 한글판 색상-단어 검사 (K-CWST)를 측정하여 인지기능을 평가하였다.

운동 12주 후, 활동적 대조그룹은 AD7c-NTP가 증가하고, 운동그룹은 AD7c-NTP가 감소하는 추세를 보였으나, 그룹간의 유의미한 차이가 없었다. 더 나아가, 인지수행능력을 측정하는 K-MMSE와 전두엽의 주의력과 억제 기능을 측정하는 K-CWST에서도 그룹간의 유의미한 차이는 나타나지 않았다.

본 연구는 국내 건강한 노인을 대상으로 운동이 소변 알츠하이머 바이오마커 중 하나인 AD7c-NTP에 미치는 영향을 본 첫번째 연구이므로 의미가 있다. 이전 연구에서 운동이 혈장 및 뇌척수액 알츠하이머 바이오마커에 긍정적인 영향을 미친다는 것이 증명되었지만, 본 연구에서는 운동이 소변 알츠하이머 바이오마커인 AD7c-NTP에 긍정적인 영향을 미친다는 것을 증명하지 못하였다.

따라서, 향후 연구에서는 본 연구에서보다 긴 중재 기간과 인지기능

이 낮은 피험자들을 대상으로 운동이 소변 AD7c-NTP 수치에 미치는 영향을 확인한다면 더욱 더 의미가 있을 것이다.

Keywords: AD7c-NTP, 소변 바이오마커, 운동, 인지기능, 알츠하이머병
Student Number: 2021-23732