International Journal of Physical Education, Sports and Health 2016; 3(4): 249-254

P-ISSN: 2394-1685
E-ISSN: 2394-1693
Impact Factor (ISRA): 5.38
IJPESH 2016; 3(4): 249-254

www.kheljournal.com
Received: 16-05-2016
Accepted: 17-06-2016

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Effects of combined exercise on blood lipids, estradiol, and cognitive function in the elderly women with mild cognitive loss

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Abstract
The purpose of the present study was to determine the changes of blood lipids, estradiol, and cognitive function by combined exercise (CEx) in elderly women with mild cognitive loss. Sixteen elderly women with mild cognitive loss (71.9 ± 4.6 years) were randomly divided into two groups: exercise (EG) (n=9) and control groups (CG) (n=7). The CEx was composed of aerobic and resistance exercises (50-60 min, 3 times/week, 12 weeks). The data were analyzed using 2 x 2 repeated measures ANOVA with the SPSS package. Total cholesterol and triglyceride were significantly decreased, while high-density lipoprotein cholesterol was significantly increased in the EG ($p<0.05$). Estradiol concentration and cognitive function test score were not significantly changed. These findings suggest that CEx may be able to regulate blood lipids. However, the CEx program in this study was insufficient to improve cognitive function in the elderly women with mild cognitive loss.

Keywords: Combined exercise, lipids, estradiol, cognitive function, elderly women

1. Introduction

The older population has been increasing dramatically around the world. Aging is associated with cognitive loss as well as functional, hemodynamic, psychological, and physical changes [1]. In old age, it is essential to manage the vascular function and the blood components in order to maintain the brain health such as cognitive function. That's because glucose and oxygen delivery from the vasculature has an important role between energy demand and supply on the cellular aspects of brain energy metabolism [2]. Alagiakrishnan *et al*. [3] reported that there were increasing numbers of people who was identified to be at risk of cognitive impairment, with the rising prevalence of vascular disease. Previous research showed that serum lipids levels were important indicators as a vascular function, and associated with a blood flow as well as a vascular resistance [4]. Specifically, high-density lipoprotein cholesterol (HDL-C) is concerned with vascular dementia. Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are also reported to be associated with Alzheimer's dementia. Kussisto *et al*. [5] reported from the 980 elderly subjects, serum TC was significantly associated with dementia. Hence, management of blood lipids level is important to prevent the vascular problems such as blockages, and to reduce risks of dementia.

The age related estrogen decline is associated with cognitive loss in elderly women. Estradiol is the major human estrogen. In previous studies, some aspect of learning and memory was altered by ovarian hormone such as estrogen and estradiol. In vivo and vitro studies, it indicated that estradiol level regulates memory [6, 7]. Bean *et al* [7] (2014) reported that the ability of estradiol for improving cognition declined with advanced age along with decreased expression of estrogen receptors. Hence, many studies investigated the association between estrogen concentration and cognitive performance. Thus, effective intervention for controlling blood lipids and estrogen concentration is expected to perform a positive role in the maintenance and improvement in the brain function.

Many studies have attempted to reveal the predictive variables of cognitive impairment, and several mediations for remedies have been proposed. It has been recommended to change of the lifestyle and to participate in activities which can improve or stimulate cognitive function.

In particular, physical activity is known as an effective mediation to reduce morbidity related to the cognitive impairment, whereas sedentary or low level physical activity have revealed as great risk factor of dementia in the elderly [8, 9]. Many researchers suggest that regular exercise might not only delay onset of dementia [10] but also improve cerebral blood flow and oxygen delivery [11]. More recent evidences suggest that physical activities increase angiogenesis, synaptogenesis and neurogenesis [12]. The role of central factor including brain derived neurotrophic factor and peripheral factors such as estrogens, growth hormone, IGF-1, corticosteroids in mediation of the effects of physical exercise on brain functions, has been promoted [13].

In several studies showed that elderly people experienced an enhancement in oxygen demand and oxygen transfer capability after aerobic exercises, and furthermore regular aerobic exercises contribute to reduce the vascular risk factors as well as to regulate the serum lipids level. Another cross-sectional study of elderly subjects showed that physically fit seniors had a sensitive connection and activation on the cerebral cortex better than unfit seniors. Similarly, in a study by Erickson *et al*. [13] suggested that the cardiorespiratory fitness had a positive correlation with the hippocampal volume. Similarly, Colcombe & Kramer [14] reported that the aerobic exercises influence on attention, memory function, and cognitive control ability of the elderly. Presumably, an aerobic exercise is contributing to improve of the vascular function by reducing vascular resistance in the elderly.

Resistance exercise has been considered hazardous because of frailty in elderly. However, recently evidence shows that resistance exercise can be beneficial in order to maximize the effect of physical activity [15]. In particular, the results in recent studies have found that resistance exercise has a positive effect on cognitive function in the elderly [16, 17]. Even though the previous researches of the brain functions were focused on an aerobic exercise, resistance exercise is expected to have a positive impact on the cognitive abilities of the elderly by contributing to oxygen transfer efficiency. However, combined exercise intervention studies for cognitive function were not sufficient. A literature review by Tambalis *et al*. [18] reported that aerobic with resistance exercise tended to improve blood lipids level and cognitive function. Therefore, we want to investigate the effect of combined exercise on blood Lipids, estradiol, and cognitive function in elderly with cognitive loss.

In summary, it is considered that participation in combined exercise will be effective not only regulating blood lipids and estradiol concentration but also improving cognitive function in elderly. However, little is known about the effects of combined exercise training with the physiological variables related to cognitive function in the elderly with mild cognitive loss. The purpose of this study was to investigate the effects of combined exercise on serum lipids, estradiol, and cognitive function in the elderly women with mild cognitive loss.

2. Materials and methods

2.1 Subjects

This was a clinical trial. Figure 1 illustrates the study flow diagram of participants in this study. The subjects of this study were sixteen elderly women (71.9 ± 4.6 years) who have had low cognitive function. They were randomly divided into exercise group (EG, n=9) and control group (CG, n=7). The subjects were recruited by flyer posted on the local health center and website advertisements. The inclusion of criteria consisted of state of lower than normal range of cognitive functions but non-diagnosed with dementia using Korean version of Mini-Mental State Examination (MMES-K). Exclusion criteria consisted of: (1) suspected to the dementia, (2) have nerve disorder, and (3) have experience of regular exercise for past three months. Informed consent was completed by all participants and their legal guardians prior to the study procedures. Ethical approval was obtained from the University's Institutional Review Board. The specific characteristics of the subjects are as below (Table 1).

Table 1: Characteristics of subjects

	Exercise group (n=9)	Control group (n=7)	*p*
Age (yrs)	71.2 ± 5.7	70.6 ± 3.7	.798
Height (cm)	152.7 ± 3.9	155.1 ± 4.9	.281
Weight (kg)	58.7 ± 6.2	59.3 ± 4.5	.827
BMI (kg/m^2)	25.8 ± 2.1	24.6 ± 2.4	.319
Body fat (%)	34.9 ± 4.8	33.9 ± 6.9	.743
SBP (mmHg)	128.1 ± 11.9	124.0 ± 12.7	.540
DBP (mmHg)	81.2 ± 8.6	78.3 ± 11.3	.582
RBC (10^6/$\mu\ell$)	4.3 ± 0.4	4.0 ± 0.4	.117
WBC (10^3/$\mu\ell$)	6.9 ± 3.1	6.9 ± 1.8	.969
Hb (g/dL)	12.8 ± 0.8	12.3 ± 1.0	.319
MMSE-K (point)	22.3 ± 1.2	22.1 ± 1.1	.749
Education (yrs)	6.2 ± 2.5	7.0 ± 3.2	.593

Mean ± Standard deviation, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, RBC: red blood cells, WBC: white blood cells, Hb: hemoglobin, MMSE-K: mini mental state examination in Korean version

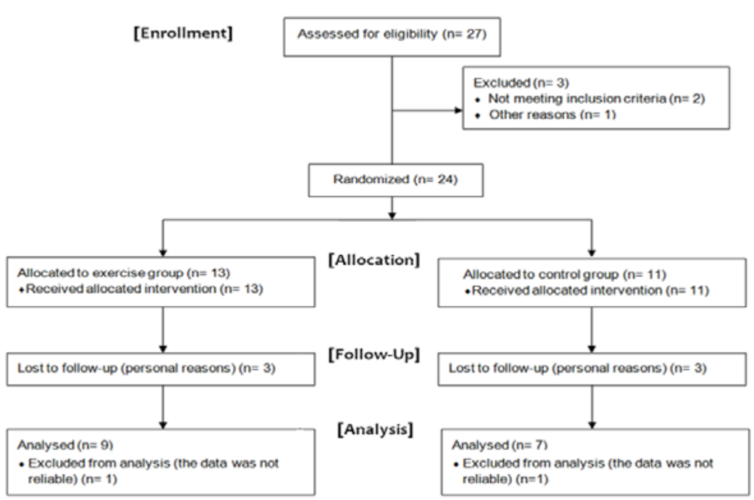

Fig 1: The study flow diagram of participants throughout the study

2.2 Combined exercise program

The subjects in the exercise group participated in combined exercise program composed of aerobic and resistance exercise (50-60 min, 3 times/week, 12 weeks) (Table 2). An aerobic exercise in a combined exercise program included basic aerobic steps and used an elastic band for resistance exercise. The resistance exercise was consisted of sessions which were upper, lower, and core body. Intensity of exercise in this study was set up 40-70% HRR and 12-15 RPE with gradual enhancement. The participants wore a heart rate monitor (Polar, Finland) during each exercise session to verify exercise intensity. The subjects in control group had been maintaining their lives as usual.

Table 2: Combined exercise program

Stage (weeks)		Duration (min)	Type	Intensity (%HRR /RPE)	Frequency (session /week)
	Warm-Up	15	Free gymnastics, Stretching, Basic walking		
1 (1-4)	Main Exercise	25-30	Aerobic exercise: Rhythmic exercise Resistance exercise: overhead pull-down/shoulder press/front raise/biceps curl/side band/hip flexion (1 set, 8 repetitions)	40-50 /12-13	3
2 (5-8)		30-35	Aerobic exercise: Rhythmic exercise Resistance exercise: overhead pull-down/shoulder press/front raise/side lateral raise/biceps curl/ triceps extension side band/abdominal curl/hip flexion/hip extension/squat/calf raise (1-2 sets, 9-10 repetitions)	50-60 /13-14	3
3 (9-12)		35-40	Aerobic exercise: Rhythmic exercise Resistance exercise: overhead pull-down/shoulder press/front raise/side lateral raise/triceps extension/abdominal curl/hip flexion/hip extension/squat/calf raise/leg extension (2 sets, 11-12 repetitions)	60-70 /14-15	3
	Cool-Down	10	Free gymnastics, Stretching		

2.3 Assessment of variables

2.3.1 Cognitive function

The Mini-Mental Status Examination (MMSE) is the most widely used screening instrument for dementia [19, 20]. Assessment of cognitive function was measured with the MMSE-K which was verified measurements for Korean elderly overall cognitive abilities. The MMSE-K contains 19 items and the maximum score is 30 points (10 points for orientation, 6 for verbal memory, 5 for concentration and calculation, 5 for language, 3 for praxis, 1 for visuospatial construction). All subjects were asked to complete the MMSE-K by clinical experts of neuropsychiatry who works at the Yongsan-Gu Center for Dementia. The subjects were selected by MMSE-K score between 20 and 24 based on previous studies [21, 22] (Figure 2). All subjects were tested MMSE-K at initial score, then again after 12 weeks.

Interpretation	Score
Normal	Over 25
Borderline	20 - 24
Mild impairment	15 - 19
Moderate impairment	10 - 14
High impairment	Below 9

Fig 2: Staging of disease by MMSE-K

2.3.2 Biological analysis

Venous blood samples were drawn in the morning after minimum 8 h fasting and resting for 20 min. Subjects abstained from tobacco smoking during fasting. Subjects were instructed to avoid heavy physical activity 36 h prior to blood sampling. Fasting blood samples were collected in EDTA or SST tubes. Samples were stored at -20 °C in separate portions for subsequent analyses after isolate plasma by centrifugation (3000 times g for 10 min). TC, triglyceride (TG), HDL-C, and LDL-C were quantified by enzymatic colorimetric procedures (Modular analytics PE Analyzer; Roche, Germany) and commercially available kits (CHOL; TG; HDL-C plus 3rd generation; and LDL-C plus 2nd generation, Roche, Germany). Assay for estradiol was implemented by ECLIA procedures (Modular Analytics E170 Analyzer, Roche, Germany) and kit (Estradiol II, Roche, Germany).

2.4 Statistical analysis

SPSS 12.0 program was used for the statistical analysis. Kolmogrov-Smirnov test (K-S test) was utilized to assess the normality of distribution for tested variables. Normal distribution was observed for variables. All data are expressed as mean and standard deviation. 2 x 2 repeated measures ANOVA was used to compare between two groups. When significant interaction was shown, main effects analyzing (Sidak) was applied. Statistical significance was assumed for values less than 0.05.

3. Results

The data from the total 16 subjects were recorded in this study. Each variable was normally distributed (K-S test). The two groups (EG vs. CG) were similar regarding age (EG: 71.22 ± 5.70 years, CG: 70.59 ± 3.74 years), and cognitive function by MMSE-K (EG: 22.33 ± 1.22, CG: 22.14 ± 1.07).

3.1 Blood variables

Table 3. shows the intervention-to-treat changes in blood lipids by group. TC, TG, and HDL-C had significant interaction effect between groups and time points respectively. Results for analyzing main effect, HDL-C ($p<.05$) was significantly increased, and TG ($p<.05$) was significantly decreased after 12 weeks in the exercise group. However, there were no significant Group x Time interaction on LDL-C and estradiol levels between two groups.

3.2 Cognitive function

Table 4. Shows the intervention-to-treat changes in cognitive function by group. MMSE-K score was no significant Group x Time interaction between two groups.

Table 3: Results on blood lipids and estradiol before and after 12 weeks of intervention in the control group and the exercise group

Variables	Group	Pre	Post	t (*p*)	F	Interaction (*p*)
TC (mg/dL)	EG	216.7±26.7	204.1±17.5	2.126(0.066)	G:2.643 T:0.824 G x T:5.247*	*p*<.05 (.038)
	CG	186.1±32.1	191.6±33.4	1.182(0.282)		
	t(*p*)	2.078(.057)	0.902(.392)			
TG (mg/dL)	EG	111.9±12.0	91.4±20.8	2.520*(0.036)	G:2.063 T:0.852 G x T:5.637*	*p*<.05 (.032)
	CG	85.6±28.1	94.6±18.6	-0.954(0.377)		
	t(*p*)	2.317(.050)	-0.312(.759)			
HDL-C (mg/dL)	EG	48.3±7.6	55.1±9.7	-2.599*(0.032)	G:0.985 T:2.113 G x T:5.433*	*P*<.05 (.035)
	CG	57.1±11.5	55.6±11.2	0.690(0.516)		
	t(*p*)	-1.846(.086)	-0.088(.931)			
LDL-C (mg/dL)	EG	135.3±16.8	133.9±12.3	-	G:3.326 T:0.578 G x T:1.412	*p*>.05 (.254)
	CG	111.7±26.9	118.3±32.1	-		
	t(*p*)	-	-			
Estradiol (pg/mL)	EG	5.7±1.5	8.1±4.2	-	G:0.006 T:11.448** G x T:0.355	*p*>.05 (.561)
	CG	5.1±0.2	8.53±4.2	-		
	t(*p*)	-	-			

$^{*}p<.05$, $^{**}p<.01$, CG: control group, EG: exercise group, G: group, T: time, G x T: interaction between group and time

Table 4: Result on cognitive function before and after 12 weeks of intervention in the control group and the exercise group

Variables	Group	Pre	Post	t(*p*)	F	Interaction (*p*)
MMSE-K (point)	EG	22.3±1.2	23.7±1.3	-	G:0.022 T:13.796** G x T:0.093	P>.05 (.765)
	CG	22.1±1.1	23.7±1.3	-		
	t(*p*)	-	-			

$^{*}p<.05$, $^{**}p<.01$, CG: control group, EG: exercise group, G: group, T: time, G x T: interaction between group and time

4. Discussion

Many longitudinal studies reported that blood lipids level is related to a vascular function and cognitive function. TC level is related to cognitive function such as memory in previous studies [23]. Moreover Lower serum LDL level is also associated with better cognitive performance [24]. Romas *et al.* [25] reported that Alzheimer's disease was associated with TC levels. Furthermore, High TC and LDL-C levels may influence the risk of cognitive impairment by increasing subclinical vascular disease [26]. Concretely, high level of TG and LDL-C as well as low HDL-C level is causative of enhancing blood pressure, thickening of blood vessel walls, and decreasing blood circulation.

There were reported that increased exercise and physical activity level affect blood lipids positively, whereas decreased physical activity were strong predictors of dementia particularly. Boardley *et al*. [27] had 131 elderly subjects participated in 16 weeks of physical exercise training (aerobic, resistance, combined exercise groups, and control group). As a result, TC, TG, and LDL-C were dropped significantly for all exercise groups (aerobic, resistance, combined exercise groups) compared with control group. Tambalis *et al*. [18] have reviewed 84 studies investigated for changes of blood lipids level following different types of exercise (aerobic, resistance, and combined aerobic with resistance). They were most commonly obtained as a result that 12 weeks of exercise increased HDL-C, meanwhile, decreased TG and LDL-C.

In the current study, TC and TG levels were reduced, whereas HDL-C level was significantly increased by 12 weeks combined exercise. We assume that a combined exercise including aerobic and resistance exercise is expected to have effects on blood vessel function, and brain blood flow positively.

Estrogen was known that affect of the central nervous system (CNS). A neurotransmitter is related strongly with cognitive function, estrogen is playing an important role in the concentration of choline acetyltransferase, the synthetic enzyme for acetylcholine [28]. Hence, Sherwin [29] reported that estrogen's numerous neurotrophic effects might explain how this hormone could protect against declines in cognition with aging. Moreover, alteration of estrogen concentration has a serious effect on a blood lipids level. Estrogen serves to balance between LDL-C and HDL-C. Thus, estrogen decreases will result in a negative impact on the function of the blood vessel, leading to elevate blood pressure, and fat accumulating in the blood vessel. In many previous studies, they focused on the effects of the estrogen hormone replacement therapy on blood lipids levels and cardiovascular disease risk [30]. However, the results were not consistence whether estrogen related with blood lipids and cognitive function or not.

In the current study, we analyzed estradiol which is a steroid and estrogen sex hormone, and the primary female sex hormone. As a result, blood estradiol concentration was not changed after 12 weeks exercise in the elderly with low cognition. The results of the previous studies revealed changes of estradiol concentration by exercise or physical activity [31, 32]. In connection with the different result in this study versus previous studies, there is a possibility that may be different depending on the duration of exercise intervention. The subjects in the exercise group participated combined exercise during 3 month in this study, while a duration of exercise in previous studies that have alteration on the estradiol level conducted at least 6 month or more. With our subjects consisted of elderly with low cognition, maybe we should apply longer intervention duration than 3 month in future study.

The most previous researches have reported that the physical exercise might be improved by cognition that is attributable from improved blood flow. Ozkaya *et al*. [16] and Peig-Chiello *et al*. [17] reported that the resistance training have positive effect on both the vascular system and cognitive performance in the elderly. In addition, both endurance training and strength training are observed in improving cognitive function with no statistically differences between aerobic and resistance in elderly subjects significantly. Based upon these previous studies, combined exercise training in this study can contribute to supply more oxygen to the brain by increasing red blood cells (RBCs) and hemoglobin (Hb) levels in plasma. In addition, enhanced oxygen-carrying capacity also can help to increase exercise duration and reducing recovery time by giving more supply of the oxygen demand during exercise. Furthermore that is considered to be helpful for improving neurotransmitters such as beta-endorphin, dopamine, and serotonin which is released during exercise, thereby enhancing the level of arousal of the brain.

In the current study, however, there was no significant alteration on cognitive function following combined exercise. Gates *et al*. [33] reported by a meta-analysis of randomized controlled trials that there was very limited evidence that exercise improves cognitive function in individuals with mild cognitive impairment (MCI). Verghese *et al*. [34] also showed non-significant association between physical activity and risk of cognitive impairment. These studies support the results of this study. However, several studies have reported that physical exercise can decrease the risk of cognitive decline. We suggest that exercise duration is one of the reasons that revealed conflicting results on cognitive function. The most researches which had positive effect of exercise on cognitive function were applied over 12 months. Long term exercise duration is considered important factor for encouraging stimuli on the cognition in case of elderly with low cognition. The researches by Weuve *et al*. [35], and Suzuki *et al*. [36] supported importance regarding exercise duration on cognitive function.

Our findings in this study should be interpreted within the context of the following limitations. As in many other observational studies, we assessed cognitive function by MMSE-K without coadjutant tests. Therefore, it was difficult to define the term of MCI in this study. Hence, the subjects in this study defined as elderly with mild cognitive loss. In addition, current study did not address mechanisms of action. Based on the previous studies, we assumed why these results occurred in this study.

In summary, combined exercise during three months have positive effect partially, the concentration of TC, TG, and HDL-C, but not estradiol and cognitive function. Therefore, we can speculate regarding these results, combined exercise may be able to affect cerebral blood flow positively via regulation of blood lipids levels. However, there is insufficient evidence to establish the beneficial relationship between combined exercise and cognition. It is recommended that future studies designed long-term exercise period at least over 6 month to elucidate exercise mechanisms on cognitive function in elderly with low cognition.

5. Conclusions

Our findings suggest that combined exercise during 3 month was not effect on estradiol level and cognitive function in the elderly with mild cognitive loss. However, it is possible for assisting cognitive enhancement potentially by improved blood lipids levels.

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