Effects of exercise training on stroke risk factors, homocysteine concentration, and cognitive function according the APOE genotype in stroke patients

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INTRODUCTION

Stroke is one of the major causes of dysfunction and death worldwide (Barker and Mullooly, 1997), due to acute cerebrovascular disease that causes paralysis on one side of the body, accompanied by a sudden onset of consciousness due to cerebrovascular bleeding and infarction (Sarti et al., 2000). Factors such as race, age, sex, hypertension, smoking, diabetes, hyperlipidemia, obesity, and physical inactivity have traditionally been reported as risk factors for stroke and recent studies have shown that elevated levels of homocysteine (Hcy) in the blood are associated with the incidence of stroke (Pettigrew et al., 2008).

It is also reported that cognitive impairment, which increases with age, is caused by stroke. Epidemiological studies have shown that patients with stroke have a higher risk of developing dementia than the normal population (Leys et al., 2005; Savva and Stephan, 2010). Within 3 months after stroke, the cognitive function reduces by 23% to 55%, and it reduces by 11% to 31% within 1 year (Tham et al., 2002). Moreover, stroke increases the prevalence of dementia by 4 to 12 times (Leyes et al., 2005). The mechanism behind development of dementia after the onset of stroke has not been clarified yet, but it is suggested that the level of Hcy in protein (HDL)-C increased significantly in the both groups. According to the APOE genotype, systolic blood pressure in the APOE ε4 group decreased, but in the APOE ε3 group increased after exercise training. TC, LDL-C, and TG in the APOE ε4 group decreased more extensively than those in the APOE ε3 group after exercise training. VO₂max (maximal oxygen consumption) and cognition increased significantly in both groups. Folate acid intake also increased significantly in both groups. The APOE genotype affects variations in the risk factors of stroke after exercise training. However, the Hcy and cognitive function did not differ based on the APOE genotype.

Keywords: APOE genotype, Homocysteine, Cognitive function, Exercise training, Stroke patients
blood is related to the risk of stroke (Hogervorst et al., 2002).

Elevated serum Hcy levels induce inflammatory responses, affect the inflammatory function of endothelial cells at the gene expression stage (Roth et al., 2001), and increase oxidative stress (Konukoglu et al., 2005). The highly reactive thiol group of Hcy is readily oxidized to the active form (Loscalzo, 1996), resulting in auto-oxidation and oxidative damage of Hcy, which has been reported to cause cognitive impairment, neurotoxicity (Obeid and Herrmann, 2006), and brain damage (Schäfer et al., 2005).

Physical inactivity and low cardiorespiratory fitness are major risk factors for cardiovascular disease and indicate the prevalence of and mortality from all diseases (LaMonte et al., 2005). Regular exercise increases cardiorespiratory fitness, and decreases cardiovascular disease and cognitive function in elderly individuals (Kemoun et al., 2010). It has been suggested that the risk of recurrent stroke and prevalence of dementia may be lowered by exercise (Kramer and Erickson, 2007).

However, exercise training was reported to decrease or maintain Hcy concentrations (Gaume et al., 2005; Randeva et al., 2002) or even increase them after endurance training (Herrmann et al., 2003). Therefore, the effect of physical activity on Hcy concentration is still unclear.

These results can be explained by the effect of genetic factors and dietary intake on Hcy levels. The lack of coenzyme required for the metabolism of Hcy affects its elevation in the blood. If nutrient intake required for the metabolism of remethylated methionine is insufficient, i.e., in the presence of reduced levels of vitamin B6, vitamin B12 (folic acid), and vitamin B12 or when there is a lack of enzymatic activity required for Hcy metabolism, conversion to cysteine is not achieved, which induces an elevation in the concentration of Hcy in the blood (Brosnan and Brosnan, 2006).

In addition, the apolipoprotein E (APOE) gene has also been suggested to associate with stroke and dementia. APOE plays an important role in metabolism and cholesterol transport (Kuusi et al., 1989). The APOE E4 allele binds to low-density lipoprotein (LDL) receptors but is related to elevations in cholesterol (Mahley and Huang, 1999), which increases the risk of cardiovascular disease, stroke, and dementia (Hamzi et al., 2011). However, the effects of exercise training on dementia according to the APOE genotype are not consistent as reported in the literature. Allard et al. (2017) reported that individuals who lack the APOE E4 allele showed a significant increase in the related brain factors after 6 months of exercise training while individuals with APOE E4 did not. Another study reported that the risk of developing dementia was not significantly different between nonexercisers and exercisers after a 5-year follow-up in individuals with the APOE E4 allele while, the risk was higher in nonexercisers than exercisers among individuals who lack the APOE E4 allele.

Therefore, this study aimed to investigate the effects of combined aerobic and resistance exercise on the risk for stroke, including blood pressure, lipid profiles, Hcy concentrations, and cognitive function, according to the APOE genotype along with dietary intervention.

MATERIALS AND METHODS

Subjects

The study participants were 68 ischemic stroke patients. Informed consent was obtained from all subjects before their participation. A questionnaire assessed the medical history of study subjects. Subjects were excluded based on the following criteria: (1) intake of drugs (folic acid, vitamin B6, and B12, antagonists, etc.) that change plasma Hcy concentration, (2) excess of coffee (>4 cups) and alcohol (>2 cups) consumption, (3) comorbid diseases like coronary artery disease, (4) cigarette smoking, and (5) female sex, because plasma Hcy concentrations are affected by gender.

After explaining the purpose and procedure of the study to the participants, we collected blood samples, which were subjected to APOE genotype analysis. Of the 68 subjects, we identified 0 (0%) stroke patients with the ε2 genotype, 31 (45.58%) with the ε3 genotype (ε2/ε3 and ε3/ε3), and 37 (54.42%) with the ε4 genotype (ε3/ε4 and ε4/ε4) in this study. Results of this screening were used to classify subjects into the ε3 (n = 13) or ε4 (n = 15) genotype groups (Table 1).

Anthropometry measurements

Before and after the exercise training, anthropometric measurements were obtained for all subjects. Height and body weight were also recorded (Tanita, Seoul, Korea) and body mass index (BMI) was calculated from the ratio of weight (kg)/height (m²).

Cognition measurements

To examine the cognitive function in participants, the Mini-Mental State Examination (MMSE) developed by Folstein et al. (1975) was used. To examine the cognition function of Korean elderly people, we used the simplified Korean version of MMSE (MMSE-K). MMSE-K is the most commonly used test method for cognitive function. It has 5 points of commands and orientation, 3 points of recall, 5 points of attention and calculation, 3 points of memory, 7 points of language, and 2 points of judgment.
and understanding. A higher score implies a higher cognitive function. A score below 20 implies cognitive impairment, from 21 to 23 implies cognitive impairment, and 24 or more implies normal status.

**Ascertainment of diet intake**

Diet intake was ascertained by interviewer-mediated 24-hr recall. Three-day diets were completed during the exercise training period, including 2 days on weekdays and 1 day on weekends. Food composition values for folate, vitamin B₆, and other macronutrients were obtained using Can pro professional 3.0 (The Korean Nutrition Society, Seoul, Korea) based on the Korean nutrient data base. Unfortunately, we could not examine vitamin B₁₂ intake, owing to limited data in Can pro professional 3.0. During the exercise-training period, nutrition education was provided to the stroke patients. However, nutritional intervention was not provided in order to verify the effect of exercise training.

**Blood collection and assessment of biomarkers**

Serum aliquots were stored at -80°C until assayed. Total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using an enzymatic colorimetric method and analyzed by the COBAS Integra 800 (Roche Korea, Seoul, Korea). Plasma glucose levels were measured using a commercially available kit. Hcy was determined by FPLC, using a radiometric tyrosine assay.

**Genotyping**

Total blood DNA was extracted and purified from 200 μL of whole blood in anticoagulant tubes with ethylenediaminetetraacetic acid, using the Axogen Blood Mini Kit according to manufacturer’s instructions (Axogen Biosciences, Seoul, Korea). Genotyping of the APOE status was performed using the method described by Hagberg et al. (1999). APOE polymorphism was tested using the polymerase chain reaction amplification and restriction digestion with HindIII to distinguish the mutant and wild-type alleles.

**Preliminary testing**

Before the trials, each subject’s maximal oxygen consumption (VO₂max) was measured to establish the exercise intensity. Subjects were familiarized with cycling and were informed of what was required of them with regard to the experiment. Next, they completed a cycling exercise test to determine each of their VO₂max adhering to the Ramp Protocol. Moreover, one repetition maximum (RM) for each subject according to the American College of Sports Medicine guidelines was measured for resistance training (Berger, 1965).

**Exercise training**

Exercise training was supervised by four experienced physical education instructors and was performed 5 days a week for six months. Each session consisted of 10 min of warming up, aerobic exercise by 45 min of cycling at 60% VO₂R for 3 days a week, resistance training at 60%–75% intensity of individual RM in the form of 3 sets with 12–15 repetitions (the chest, back, shoulder, triceps, biceps, abdomen, and lower-extremity muscle group) each for 2 days a week, and 5 min of cooling down.

**Statistical analysis**

All data are presented as means ± standard deviation. Changes in risk factors before and after exercise training according to the genotype were analyzed using two-way analysis of variance with repeated measures, and within-group comparisons using a paired t-test for post hoc analysis. All statistical analyses were performed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA), and P-values of < 0.05 were considered statistically significant.

**RESULTS**

**The changes in body composition after exercise training according to APOE genotype**

There were no significant differences in baseline values between the genotypes. After exercise training, body weight (P < 0.001), BMI (P < 0.001), percent body fat (P < 0.05) decreased in the both APOE groups. According to the APOE genotype, changes in BMI showed a difference in the interaction between time and group (P < 0.05). The change in BMI in the APOE ε4 group was significantly higher than that in the APO ε3 group (P < 0.01) (Table 2).

**Table 1. Characteristics of participants**

| Variable                  | Genotype               | t     | Sig.  |
|---------------------------|------------------------|-------|-------|
|                           | APOE ε₃ (n = 13)       |       |       |
|                           | APOE ε₄ (n = 15)       |       |       |
| Age (yr)                  | 56.80 ± 10.65          | 56.67 ± 9.19 | 0.037 | 0.971 |
| Region of attack, right:left | 4.9                   | 4.11  | -0.728 | 0.473 |
| Period of stroke (yr)     | 2.27 ± 1.79            | 2.07 ± 1.39 | 0.342 | 0.735 |

Values are presented as mean ± standard deviation.
Table 2. Changes in body composition after exercise training according to the APOE genotype

| Variable                  | Genotype       | F     | Sig.   |
|---------------------------|----------------|-------|--------|
|                          | APOEε3         | APOEε4|        |
| Body weight (kg)          | Pre            | 64.79 ± 7.15 | 63.66 ± 10.52 | Time | 56.134 | 0.000*** |
|                          | Post           | 63.20 ± 7.37 | 61.17 ± 10.66 | Group | 0.228 | 0.637   |
|                          |                | 24.57 ± 2.71 | 24.42 ± 3.52 | T×G | 2.723 | 0.110   |
| BMI (kg/m²)               | Pre            | 24.11 ± 2.88 | 22.63 ± 2.89 | Time | 16.535 | 0.000*** |
|                          | Post           | 42.04 ± 7.28 | 44.37 ± 9.158 | Group | 0.866 | 0.360   |
| Muscle mass (kg)          | Pre            | 41.98 ± 8.28 | 43.54 ± 8.30 | Group | 0.425 | 0.520   |
|                          | Post           | 29.18 ± 7.41 | 24.44 ± 6.45 | Time | 7.330 | 0.011** |
| Percent body fat (%)      | Pre            | 28.00 ± 9.49 | 22.46 ± 6.22 | Group | 3.680 | 0.065   |

Values are presented as mean ± standard deviation. BMI, body mass index.

*P<0.05, **P<0.01.

Table 3. Changes in stroke risk factors after exercise training according to the APOE genotype

| Variable                  | Genotype       | F     | Sig.   |
|---------------------------|----------------|-------|--------|
|                          | APOEε3         | APOEε4|        |
| SBP (mmHg)                | Pre            | 124.20 ± 7.58 | 118.46 ± 11.35 | Time | 0.344 | 0.562   |
|                          | Post           | 119.13 ± 8.97 | 121.33 ± 15.55 | Group | 0.223 | 0.641   |
| DBP (mmHg)                | Pre            | 82.46 ± 8.42  | 79.60 ± 12.47 | Time | 0.056 | 0.914   |
|                          | Post           | 80.13 ± 8.11  | 82.73 ± 7.44 | Group | 0.001 | 0.972   |
| Fasting glucose (mg/L)    | Pre            | 112.13 ± 30.11 | 110.00 ± 23.81 | Time | 2.296 | 0.141   |
|                          | Post           | 105.20 ± 21.53 | 108.26 ± 26.20 | Group | 0.826 | 0.371   |
| TC (mg/dL)                | Pre            | 199.06 ± 40.69 | 192.93 ± 34.91 | Time | 8.434 | 0.007** |
|                          | Post           | 174.20 ± 32.08 | 183.73 ± 32.85 | Group | 0.155 | 0.697   |
| LDL-C (mg/L)              | Pre            | 325.86 ± 40.31 | 302.20 ± 54.47 | Time | 9.471 | 0.005** |
|                          | Post           | 294.26 ± 36.36 | 297.20 ± 48.53 | Group | 0.447 | 0.609   |
| HDL-C (mg/L)              | Pre            | 53.40 ± 14.64  | 55.86 ± 9.76  | Time | 5.552 | 0.026*  |
|                          | Post           | 57.06 ± 15.52  | 57.80 ± 10.68 | Group | 0.123 | 0.728   |
| Triglycerides (mg/L)      | Pre            | 146.60 ± 72.45 | 139.73 ± 94.12 | Time | 6.683 | 0.015*  |
|                          | Post           | 109.86 ± 59.10 | 139.93 ± 82.34 | Group | 0.176 | 0.678   |
| Homocysteine levels (μmol/L) | Pre         | 17.01 ± 6.91   | 13.49 ± 4.41  | Time | 5.936 | 0.021*  |
|                          | Post           | 15.93 ± 5.55   | 12.52 ± 4.46  | Group | 3.203 | 0.084   |

Values are presented as mean ± standard deviation. SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

*P<0.05, **P<0.01.

Table 4. Changes in physical fitness and cognition after exercise training according to the APOE genotype

| Variable                  | Genotype       | F     | Sig.   |
|---------------------------|----------------|-------|--------|
|                          | APOEε3         | APOEε4|        |
| VO_{max} (mL/kg/min)      | Pre            | 22.59 ± 11.61 | 29.73 ± 10.17 | Time | 37.852 | 0.000*** |
|                          | Post           | 32.50 ± 11.88 | 35.47 ± 11.37 | Group | 1.664 | 0.208   |
| Cognition (score)         | Pre            | 25.13 ± 2.92  | 25.00 ± 4.45 | Time | 22.609 | 0.000*** |
|                          | Post           | 27.33 ± 2.71  | 27.60 ± 3.52 | Group | 0.003 | 0.965   |

Values are presented as mean ± standard deviation. ***P<0.001.

Table 5. Changes in body composition after exercise training according to the APOE genotype

| Variable                  | Genotype       | F     | Sig.   |
|---------------------------|----------------|-------|--------|
|                          | APOEε3         | APOEε4|        |
| Vitamin ε1 (mg)           | Pre            | 1.90 ± 0.55  | 1.60 ± 0.43 | Time | 0.686 | 0.418   |
|                          | Post           | 1.86 ± 0.64  | 1.93 ± 0.66 | Group | 0.393 | 0.538   |
| Vitamin ε2 (mg)           | Pre            | 188.42 ± 55.53 | 215.86 ± 62.82 | Time | 6.600 | 0.019   |
|                          | Post           | 275.79 ± 113.77 | 249.49 ± 84.14 | Group | 0.000 | 0.984   |

Values are presented as mean ± standard deviation.

The changes in stroke risk factors after exercise training according to the APOE genotype

There were no significant differences in baseline values between the two genotypes. After exercise training, TC (P<0.01), LDL-C (P<0.01), TG (P<0.05), and plasma Hcy concentrations (P<0.05) decreased and HDL-C increased (P<0.05) in both groups significantly. According to the APOE genotype, systolic blood pressure (SBP), TC, LDL-C, and TG showed a difference in the interaction between time and group (P<0.05). SBP in the APOE ε4 group decreased, but in the APOE ε3 group after exercise training (Table 3).

The changes in cardiorespiratory fitness and cognition after exercise training according to the APOE genotype

There were no significant differences in baseline values between the two genotypes. After exercise training, the VO_{max} and cognition increased in both groups (P<0.001). However, there was no difference in these changes according to the APOE genotype (Table 4).
The changes in vitamin 6 and folate acid intake during exercise training according to the APOE genotype

There were no significant differences in baseline values between the two genotypes. After exercise training, the folate acid intake increased significantly in both groups (P < 0.05) (Table 5). However, there was no difference in these changes according to the APOE genotype.

DISCUSSION

This study showed that lipid levels including TC, LDL-C, and TG decreased and HDL-C increased in both APOE groups after 6 months of exercise training. These results may be explained by the effects of exercise training including, induction favorable changes in blood lipid levels by up-regulation of lipoprotein lipase activity (Thompson et al., 1997), which regulates the release and transportation of free fatty acids from cyehlomicrons and very low-density lipoproteins to peripheral tissues and liver, consequently leading to a reduction in triglyceride levels (Wannamethee et al., 2000).

However, we found different changes in the lipid profiles of two groups including TC, LDL-C, and TG after exercise training. TC, LDL-C, and TG in the APOE ε4 group showed a higher reduction than those in the APOE ε3 group after exercise training.

APOE is a protein that regulates cholesterol, lipid metabolism, and cellular reparative processes in the circulating plasma and central nervous system (Mahley and Huang, 2012). The APOE gene has three isoforms, which account for the different affinities of APOE protein for lipoprotein particles and binding to LDL receptors (Fullerton et al., 2000). The APOE ε4 allele has been established to have an association with higher circulating cholesterol levels and the buildup of atherosclerotic plaque in peripheral arteries, which leads to an increased risk of cardiovascular disease up to 40% (Eichner et al., 2002). Individuals with the APOE ε4 allele have higher TC and LDL-C levels but lower HDL-C levels compared to those with the APOE ε3 allele (Hallman et al., 1991).

However, the effects of exercise training according to the APOE genotype are different. Bernstein et al. (2002) suggested that high-intensity physical activity with a high amount of energy expenditure may counteract the atherogenic effects of the APOE ε4 allele on lipid profiles. Individuals with the APOE ε4 allele who performed high-intensity physical activity with a lot of energy expenditure showed higher HDL-C and lower TG levels compared to individuals with the APOE ε3 allele (Hagberg et al., 1999). Our results showing that long-term exercise training may induce favorable changes in stroke risk factors including lipid profiles by compensating for the APOE ε4 allele in stroke patients are similar to those published in a previous study.

Hyperhomocysteine also has been reported an independent risk factor for ischemic stroke in Asians, including young individuals (Tan et al., 2002). Also, mild elevations in Hcy concentrations occurred in 42% of patients with cerebrovascular disease, and Lehmann et al. (1999) reported that Hcy is an independent predictor of MMES and a risk factor for the development of dementia (Seshadri et al., 2002).

Despite the results of previous studies on the effects of exercise training on Hcy levels being inconsistent, we found that Hcy concentrations decreased with increasing cardiorespiratory fitness and intake of folate acid in both APOE groups after exercise training.

These results are consistent with those of previous studies, which suggested that Hcy concentrations show a negative correlation with cardiorespiratory fitness in men (Kurl et al., 2003; Mennen et al., 2002). However, the effects of increased intake of folate acid on the reduction of Hcy are not clear. Several previous studies have suggested that folate, vitamin B6, and B12 are important enzymes for Hcy metabolism, and a negative correlation exists between folate intake and Hcy concentration. Despite a lot of studies showing these results, meta-analysis of the correlation between folate intake and Hcy levels showed that the evidence was not sufficient to establish the effects of folic acid supplementation on decreasing the Hcy concentration (Lee et al., 2010). The possible favorable effect of folic acid supplementation on Hcy levels is only applicable in early stages of vascular disease, but it is less effective in advanced disease. Our study participants included a chronic stroke patient. Therefore, our results suggest that the lower Hcy concentration after exercise training may be an effect of increase in cardiorespiratory fitness by long-term exercise training.

Prevention and treatment of poststroke dementia involves reducing the risk factors of stroke, and exercise trainings have been conducted for effectively slowing the cognitive decline and improving the risk factors of stroke (Kemoun et al., 2010). However, evidence showing that physical activity or exercise training can prevent or delay cognitive decline remains controversial. Moderate or vigorous physical activity decreases the incidence of cognitive impairment (Ergen et al., 2010) and exercise training even enhances cognitive function in older individuals (Luck et al., 2007). On the other hand, Slooter et al. (1997) could not demonstrate that exercise training prevented or delayed cognitive impairment.
This study showed that cognition increased after 6 months of exercise training but there was no difference between the different APOE genotypes. Individuals with the APOE ε4 allele have a higher risk of developing dementia and increased cognitive decline (Mortensen and Hogh, 2001; Smith, 2002), as the APOE ε4 allele is associated with multiple pathological impacts, including amyloid deposition and synaptogenesis, the increased accumulation and reduced clearance of amyloid β-peptide, which is a marker for extracellular neuritic plaques in the brain (Cedazo-Mínguez, 2007). However, exercise training could improve brain function in individuals with the APOE ε4 allele (Kim et al., 2008); particularly, those who participated in higher energy expenditure exercise showed greater protection against dementia about 20 years later compared with individuals without the APOE ε4 allele. Another study even suggested that the effect of exercise training on reducing risk of cognitive decline was only observed in individuals with the APOE ε4 allele (Woodard et al., 2012).

However, in our study, there was no difference between the two APOE genotypes, despite the reduced risk of stroke, including lipid profiles and Hcy concentrations, and the increase in cardiorespiratory fitness. These inconsistencies in the effects of exercise training on cognition according to the APOE genotype may be because the neuropathology of vascular cognitive impairment is controversial, and also because cerebrovascular lesions are different in size (from small to large cortical infarcts), nature (vessel wall alteration, infarcts, or hemorrhages, etc.), and location (cortex, white matter, basal ganglia, and hippocampus). Various mechanisms that alter the blood flow and oxygen supply, cortical connectivity, or chronic inflammation in cerebrovascular lesions may have an impact on cognition impairment (Iadecola, 2013). Foster et al. (2014) suggested that poststroke dementia, subcortical ischemic dementia combined with Alzheimer disease and vascular dementia are related to cognitive dysfunction, which extends the pathological changes in cerebrovascular lesions and neuronal atrophy.

This study showed that 6 months of exercise training can result in positive changes in body composition, stroke risk factors including Hcy concentrations, and cognition in stroke patients. The changes in lipid levels showed a difference based on the APOE genotype. Lipid levels in the APOE ε4 group showed more favorable changes compared to the APOE ε3 group after exercise training. However, the changes in Hcy levels and cognition showed no difference according to the APOE genotype. Therefore, future studies should more carefully address the precise clinical phenotypes such as size, nature, and location of cerebrovascular lesions in the study participants and enroll a larger population for the analysis of APOE genotype.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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