THE EFFECT OF COMBINED EXERCISE TRAINING ON CAROTID ARTERY STRUCTURE AND FUNCTION, AND VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) IN OBESE OLDER WOMEN

JINKEE PARK1, YOSHIHI NAKAMURA1, YOCHAN KWON2, HYUN TAE PARK3, EUN HEE KIM2 and SANGKAB PARK2

Abstract

The purpose of this study was to examine the influence of 12-week combined exercise program on carotid artery structure and function, and vascular endothelial growth factor (VEGF) in obese older women. All subjects were sixty years or older (66.90±4.2 years) who performed the combined exercise training during 12-week consisting of aerobic exercise, band exercise, and yoga exercise for 70 minutes 3 times a week under the supervision of exercise specialist. Despite no statistically significant change in control group, percent body fat mass (3.26 %, p<.01) systolic blood pressure (6.2 mmHg, p<.05), diastolic blood pressure (5.6 mmHg, p<.001), and 10 m maximal walking time (0.56 sec, p<.05) TC (20.5 mg/dl, p<.05) and LDL-C (22.16 mg/dl, p<.05) were significantly decreased respectively after 12-week combined exercise in exercise group. In addition, sit-and-reach (3.6 cm, p<.01) oxygen uptake per weight (3.27 ml/kg/min, p<.05) VEGF (17.85 pg/dl, p<.001) and carotid artery LD (0.4 cm, p<.01) PFV (10.06 cm/sec, p<.05) EFV (6.04 cm/sec, p<.05) were significantly increased in the exercise group than in the control group. The VEGF had the significant correlation with LD (r=.839, p<.01) PFV (r=.427, p<.01) EFV (r=.364, p<.05). In conclusion, 12-week combined exercise program is effective to improve and/or physical function and body composition. And also, exercise can improve serum lipid metabolism, VEGF regulation, and carotid artery function and structure.

key word: combined exercise training, obese, carotid artery structure and function, vascular endothelial growth factor

I. INTRODUCTION

Not only the level of overweight and/or obese, but also physiological degeneration associated with aging accelerates the progression of arteriosclerosis1,2). In particular, age-relate increases of carotid artery intima-media thickness(IMT), an independent risk factor for stroke3), and arteriovascular structural/functional changes such as the decrease of flow velocity(FV3) in obese older adults are closely linked to the early occur of cardiovascular5) and cerebrovascular diseases6).

In recent studies reported that IMT was improved by exercise7) and artery blood velocity underwent improvements8). In this manner, the exercise affects carotid artery structural and/or functional improvement.

However, Olson et al. (2006)9) and Ballaz et al. (2008)10) reported that there were no training-associated significant changes in arteriovascular structure and function. Therefore, the effect of exercise on arteriovascular structure and function was not clearly revealed and related studies are immediately needed.

Meanwhile, vascular endothelial growth factor (VEGF) has been reported as a key mediate factor of angiogenesis11) but the mechanisms between exercise and physiological angiogenesis are unclear. However,
only a few studies reported the effect of exercise on VEGF, such as acute and single bout short-term exercise, on changes and/or up-regulating of VEGF in healthy men\textsuperscript{12} acute exercise on angiogenesis growth factor in healthy young adults\textsuperscript{13,14} among the studies on up-regulating of VEGF during exercise.

Therefore, we examined the influence of 12-week well-designed combined exercise program on carotid artery structure, function, and VEGF in obese older women. In addition, this study was performed to investigated the between this exercise program and body composition, body function, and serum lipid parameters.

II . MATERIALS and METHODS

A . Subjects

All subjects who aged over sixty (66.90 ± 4.2 years) have participated the recreational program in the community center (Busan, Korea).

Criteria of recruitment were willingness to participate, attendance at an annual medical examination, the absence of chronic conditions (particularly severe disease or pain that could limit physical activity) no history of cardiovascular diseases, hyperlipidemia, and high blood pressure or received no medication, known to affect arteriosclerosis, and no current regular exercise habits (at least three days per week). Subjects gave written informed consent to participation in this institutionally approved study, after the protocol, stresses, and possible risks had been fully explained to them, and we were randomly divided into two groups: exercise group (n=10) and control group (n=10). Written informed consent was obtained from all subjects in accordance with the requirements by the ethics committee of Dong-A University. The anthropometric characteristics of subjects are listed in Table 1.

B . Methods

1. Body composition measurements

Weight, height, BMI, body fat ( % ) were measured by bio-electrical impedance analysis using body composition analyzer (VENUS-5.5, Jawon Medical, Seoul, Korea) and waist to hip ratio ( WHR ) was measured with waist/hip circumference. In blood pressure, brachial artery blood pressure was measured with mercury sphygmomanometer after the subjects had been seated at rest for 10 minutes.

2. Exercise load test

Exercise load test was administered before and after 12 weeks using Balke treadmill protocol and \textsuperscript{15} \textsubscript{VO}_2\textsubscript{CO}_2 ( Qurak b2, Cosmed Srl, Roma, Italy ) and blood pressure ( Tango, Sun Tech Medical, North Car, USA ) were assessed constantly during testing.

Maximal exercise was determined by ACSM's\textsuperscript{15} guidelines.

3. Physical function measurements

The assessment of body function was measured using sit-and-reach measurements. Subjects performed the normal and maximal test along a straight line of 20 m, measurements for the 10 m walking speed were taken

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n=10)</th>
<th>Exercise group (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.7±5.2</td>
<td>66.1±3.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>154.0±5.5</td>
<td>155.1±4.3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>58.6±3.2</td>
<td>58.2±4.2</td>
</tr>
<tr>
<td>Body fat mass (%)</td>
<td>32.06±1.87</td>
<td>32.29±1.99</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137.50±4.25</td>
<td>138.10±3.28</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82.00±3.16</td>
<td>83.00±3.59</td>
</tr>
</tbody>
</table>
according to the time taken to walk 10 m excluding 5 m at the acceleration and deceleration zone, respectively.16

4. Combined exercise program

All subjects performed the combined exercise training during 12-week; aerobic, band, and yoga exercise for 70 minutes 3 times a week under the supervision of exercise specialist.

We made the subjects perceive their walking speed equivalent to the individual ratings of perceived exertion (RPE) through several preliminary tests.

Aerobic exercise was conducted by indoor walking for 40 minutes (1 to 6 week: 10~11 RPE, 7 to 12 week: 12~13 RPE)

Band exercise was performed with 10 positions (1 to 6 week: 8~11 repetitions, 7 to 12 week: 12~15 repetitions) for 15 minutes using elastic green band (Thera-Band, Ohio, USA)

Yoga was composed by 12 positions was performed for 15 minutes without a pain until the joint worked maximally. Exercise program is represented in Table 2.

5. Blood tests

   All subjects collected 10ml blood from an antecubital vein in the fasting state for 12 hours before and after 12 weeks, and then total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were analyzed using automatic chemical analyzer (Hitachi 7600-110/7170 analyzer, Tokyo, Japan).

   For vascular endothelial growth factor (VEGF), peripheral blood was centrifuged at 700×g (4 °C for 5 min) immediately after blood collection and then was analyzed using human enzyme-linked immuno-sorbent assay kit including monoclonal anti-VEGF antibodies (ELISA R&D systems, Minnesota, USA).

6. Ultrasound image measure

   Carotid artery Intima-media thickness (IMT), luminal diameter (LD), peak-systolic flow velocity (PFV) and end-diastolic flow velocity (EFV) were measured using B-mode ultrasound and 10MHz probe (LOGIQ 3, GE Healthcare, Wisconsin, USA).

   In the measures of the carotid arteries, the subjects lying on their back turned their head to 45 degrees and fully exposed to the carotid arteries in a darkroom after they relaxed for minimum 10 minutes and left

<table>
<thead>
<tr>
<th>Items</th>
<th>Contents</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm up</td>
<td>Gymnastics, Stretching</td>
<td>10min</td>
</tr>
<tr>
<td>Aerobic exercise</td>
<td>Walking</td>
<td>40min</td>
</tr>
<tr>
<td></td>
<td>1<del>6 week, 10</del>11RPE, 7<del>12week, 12</del>13RPE, 3 days a week</td>
<td></td>
</tr>
<tr>
<td>Elastic-band exercise</td>
<td>Chest press, Seated rows, Shoulder press, Biceps curl, Triceps extension, Trunk extension, Abdominal Crunch, Squats, Leg press, Calf raise</td>
<td>15min</td>
</tr>
<tr>
<td></td>
<td>1<del>6 week, 8</del>11frequency, 7<del>12week, 12</del>15frequency, 1set, 3 days a weeks</td>
<td>70min</td>
</tr>
<tr>
<td>Yoga</td>
<td>Maha Mudra, Parivrtta Janu Sirsa, Upavistha Kona, Ardha Matsyendr, Baddha Kona, Gomukha, Shashank, Sphinx, Malsy, Kandhar, Shava Udarakarshan, Supta Pawanmukt</td>
<td>15min</td>
</tr>
<tr>
<td>Cooling down</td>
<td>Gymnastics, Stretching</td>
<td>10min</td>
</tr>
</tbody>
</table>
carotid artery was measured by ultrasound.

Carotid artery IMT was defined as the straight distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall and LD was defined as the straight distance between the inner membrane of near wall and the inner membrane of far wall. IMT was measured in 1 cm proximal region from the bulb of the internal and external carotid artery and on the same region of interest LD, PFV, and EFV were measured.

C. Statistical analysis

All data were expressed as means and standard deviations. Analysis of difference for body composition, body function, serum lipid, VEGF, and carotid artery parameters were conducted using ANOVA and if there are significant differences among variances, we performed the post-hoc test by Tukey method.

After adjusted body fat percentage, blood pressure, maximal oxygen uptake, and serum lipid, partial correlation coefficient and linear regression coefficient were calculated to examine the connection between the change of VEGF and the carotid artery by exercise. Statistical significance level was p < .05.

III. RESULTS

In exercise group, body fat mass percentage (from 32.29 ± 1.99 % to 29.03 ± 1.88 %; p < .01), systolic blood pressure (from 138.10 ± 3.38 mmHg to 131.90 ± 5.84 mmHg; p < .05), diastolic blood pressure (from 83.00 ± 3.59 mmHg to 77.40 ± 3.06 mmHg; p < .001), and 10 m maximal walking time (from 5.80 ± 0.64 sec to 5.24 ± 0.38 sec; p < .05), TC (from 195.30 ± 12.10 mg/dl to 174.80 ± 16.22 mg/dl; p < .05), and LDL-C (from 113.98 ± 15.69 mg/dl to 91.82 ± 20.85 mg/dl; p < .05) were significantly decreased respectively after 12-week combined exercise. Also, sit-and-reach (from 12.88 ± 1.53 cm to 16.48 ± 1.98 cm; p < .01), oxygen uptake per weight (from 30.65 ± 2.52 ml/kg/min to 33.92 ± 2.82 ml/kg/min; p < .05), VEGF (from 10.78 ± 5.26 pg/dl to 28.63 ± 7.17 pg/dl; p < .001), and carotid artery LD (from 0.68 ± 0.03 cm to 0.72 ± 0.04 cm; p < .01), PFV (from 67.26 ± 9.08 cm/sec to 77.32 ± 7.87 cm/sec; p < .05), EFV (from 22.04 ± 4.62 cm/sec to 28.08 ± 3.49 cm/sec; p < .05) were significantly increased respectively.

There were no significant differences in BMI (from 24.18 ± 1.48 kg/m² to 23.32 ± 1.87 kg/m²), WHR (from 0.94 ± 0.02 to 0.93 ± 0.03), 10 m of normal walking time (from 7.76 ± 0.78 sec to 6.95 ± 0.66 sec), TG (from 125.10 ± 17.85 mg/dl to 120.10 ± 20.48 mg/dl) and carotid artery IMT (from 0.77 ± 0.03 mm to 0.76 ± 0.03 mm) but it tended to decrease. On the other hand, there was no significant difference in HDL-C (from 53.60 ± 8.99 mg/dl to 57.96 ± 11.11 mg/dl) but it tended to increase.

In control group, there were no significant differences in body composition, body function, serum lipid, VEGF, and carotid artery LD, PFV, EFV after 12 weeks.

Regression analysis was conducted to clarify the connection between the change of VEGF and carotid artery function/structure by exercise. VEGF had the significant correlation with LD (r = .389, p < .01), PFV (r = .427, p < .01), EFV (r = .264, p < .05) but there was no significant correlation in IMT.

IV. DISCUSSION

Our study showed that the 12 weeks combined exercise program was effective to improve the carotid artery function and structure and augmented VEGF in obese older women.

And also, this program was effective in improving body composition, body function, and serum lipid in this population.

It has been reported that aerobic exercise for one year retards the increase in IMT of the carotid arteries\(^7\), and a regular exercise increases the number of small arterioles (<30—40 μm) and the diameter of large arterioles (<41—120 μm)\(^8\).

These changes of carotid artery structure are related to delaying the early progression of cardiovascular diseases\(^5\).

Sabatier et al. (2008)\(^9\) demonstrated that 14-week aerobic exercise for middle-aged obese women increased femoral artery LD. However, Olson et al. (2006)\(^9\) interestingly, reported that resistance exer-
Table 3. The change of body composition, physical function, serum lipids, VEGF, carotid artery structure and function at baseline and following 12 weeks of combined exercise training.

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Exercise group</th>
<th>F-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 weeks</td>
<td>Baseline</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.75±1.95</td>
<td>24.80±1.95</td>
<td>24.18±1.48</td>
</tr>
<tr>
<td>Percent body fat mass (%)</td>
<td>32.06±1.87</td>
<td>32.30±1.95</td>
<td>32.29±1.99</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.95±0.04</td>
<td>0.95±0.04</td>
<td>0.94±0.02</td>
</tr>
<tr>
<td><strong>Biological pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137.50±4.25</td>
<td>138.80±3.88</td>
<td>138.10±3.28</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82.00±3.16</td>
<td>83.90±3.11</td>
<td>83.00±3.59</td>
</tr>
<tr>
<td><strong>Physical function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sit-and-reach (cm)</td>
<td>13.10±2.57</td>
<td>12.41±2.64</td>
<td>12.88±1.53</td>
</tr>
<tr>
<td>10-m normal walk time (Sec)</td>
<td>7.59±1.15</td>
<td>7.84±1.07</td>
<td>7.76±0.78</td>
</tr>
<tr>
<td>10-m maximal walk time (Sec)</td>
<td>5.62±0.50</td>
<td>5.86±0.48</td>
<td>5.80±0.64</td>
</tr>
<tr>
<td>VO₂max/weight (ml/kg/min)</td>
<td>31.20±2.61</td>
<td>30.10±2.66</td>
<td>30.65±2.52</td>
</tr>
<tr>
<td><strong>Serum lipids and VEGF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>191.00±14.091</td>
<td>191.90±12.79</td>
<td>195.30±12.10</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>120.30±14.46</td>
<td>124.40±13.36</td>
<td>125.10±17.85</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (mg/dl)</td>
<td>109.42±18.23</td>
<td>110.53±12.91</td>
<td>113.98±15.69</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (mg/dl)</td>
<td>57.52±12.49</td>
<td>56.49±11.98</td>
<td>53.60±8.99</td>
</tr>
<tr>
<td><strong>Carotid artery structure and function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intima-media thickness (mm)</td>
<td>0.75±0.05</td>
<td>0.76±0.05</td>
<td>0.77±0.03</td>
</tr>
<tr>
<td>Luminal diameter (cm)</td>
<td>0.69±0.03</td>
<td>0.67±0.03</td>
<td>0.68±0.03</td>
</tr>
<tr>
<td>Peak-systolic flow velocity (cm/sec)</td>
<td>68.49±8.52</td>
<td>66.22±8.58</td>
<td>67.26±9.08</td>
</tr>
</tbody>
</table>

Values are means ±SD
* p<.05; ** p<.01; *** p<.001

Exercise during one year did not have any significant changes on carotid artery IMT and LD. Schjerve et al. (2006)[10] demonstrated that 12-week high and moderate intensity aerobic exercise and resistance exercise program did not affect brachial artery LD. To date, the improvement of arteriobvascular structure by exercise has not been disclosed clearly and there are no studies for the obese older women.

As the results of current study, carotid artery IMT in exercise group did not change significantly, but
the early induction of ischemic stroke\textsuperscript{6}, it was reported that PFVC and EFVE of carotid artery were higher for the participants doing regular exercises than sedentary people\textsuperscript{21}.

Anton et al.\textsuperscript{(2006)}\textsuperscript{8} demonstrated that 13-week resistance exercise for the average 52 year older people increased the blood velocity of femoral artery (3.7 cm/sec) significantly and Okamoto et al.\textsuperscript{(2007)}\textsuperscript{22} reported that 8-week combined exercise for the average 18 year males and females augmented the blood velocity of brachial artery significantly (p < .001).

However, to date there have been no studies on carotid artery PFV and EFV through exercise in the obese older women.

In this study, there were no changes in the carotid artery velocity of control group but PFV (10.06 cm/sec) and EFV (6.04 cm/sec) of exercise group were increased significantly (p < .05), which means that long-term exercise improves the carotid artery function.

Therefore, the 12-week combined exercise program is considered to improve the carotid artery function and structure related to the early development of cardiovascular and cerebrovascular diseases in the aged women of obesity.

VEGF is an important mediate factor in angiogenesis and arteriogenesis\textsuperscript{23}. Prior et al.\textsuperscript{(2003)}\textsuperscript{11} reported that VEGF was essential to keep the artery and the lack of VEGF resulted in defective arteries in the tissue. Bloor\textsuperscript{(2005)}\textsuperscript{23} demonstrated that the increase in VEGF through exercise had to do with the increases in internal diameter and the number of capillaries.

Gustafsson et al.\textsuperscript{(2002)}\textsuperscript{24} reported that 10-day knee extension exercise increased VEGF of skeletal muscle significantly. Seida et al.\textsuperscript{(2003)}\textsuperscript{25} demonstrated that 24-week aerobic exercise for men of overweight increased VEGF significantly (p < .05). Meanwhile, Wardyn et al.\textsuperscript{(2008)}\textsuperscript{25} reported that there was no changes in VEGF after 12-week aerobic exercise for males and females (19 to 35 years old). Brixius et al.\textsuperscript{(2008)}\textsuperscript{26} also demonstrated that 6-month aerobic exercise for men aged their 50 to 60 years did not have significant changes of VEGF. So far, the VEGF responses during exercise have shown different results among

Figure 1. After adjusted body fat percentage, blood pressure, maximal oxygen uptake, and serum lipid, correlation between the change of vascular endothelial growth factor and the carotid artery by exercise.

carotid artery LD was increased substantially from 0.68±0.03 cm to 0.72±0.04 cm after 12-weeks (p < .01) and so 12-week combined exercise is considered to improve carotid artery structure of the obese older women.
Exercise on atherosclerosis in obese women

researchers and the study on VEGF responses to exercise for the aged women is required because there are no studies for the aged women of obesity.

In the finding of current study, there was no change in VEGF of control group but VEGF of exercise group was increased from 10.78 pg/ml to 28.63 pg/ml (total 17.85 pg/ml) significantly and eventually VEGF in the aged women of obesity was increased effectively through the long-term combined exercise.

It has been reported that regular exercise in elderly was effective to improve body composition, body function, and serum lipid.

Kwon et al. (2008) reported that 24-week combined exercise in the aged women (MMSE ≥ 24) is effective to improve blood pressure, VO2max, and 10 m of maximal walk time. Park et al. (2008) reported that 48-week multicomponent exercise program was effective on mobility, such as 10 m walking speed and one-legged stand time, and bone metabolism. Vincent et al. (2006) showed that 24-week resistance exercise was effective to increase oxygen uptake and muscular strength but the body composition and serum lipid were no effective. In this study, body composition (body fat %, blood pressure), body function (sit-and-rich, 10 m of maximal walk time, VO2max ml/kg/min), and serum lipid (TC, LDL-C) were improved significantly respectively.

Our study showed that body composition, body function, and serum lipid were improved remarkably through the exercise program in the aged women.

VEGF can stimulate neovascularization in adults has come from the discovery of circulating endothelial progenitor cells (also called angioblasts) and the illumination of the role played by these cells in VEGF-driven postnatal vasculogenesis and angiogenesis.

Meanwhile, exercise imparts powerful stimulus for vascular remodeling evident by an increase in capillarity within the active muscle (angiogenesis) and an enlargement of conduit vessels (arteriogenesis) increasing flow capacity to muscle, especially when compromised by vascular obstruction. The vascular remodeling is intricate and involves a complex coordination among angiogenic growth factors (e.g., VEGF) receptors, and modulating influences including the angiopoietin and ephrins.

The exercise training is up-regulation controlled to the VEGF that by mechanical and haemodynamic stimuli such as increasing blood flow, shear stress, wall tension, stroke volume. Laufs et al. (2004) and Iemitsu et al. (2006) reported that the regular exercise augmented arterial diameter, the number and density of capillaries with the increase in VEGF through animal experiments.

In current study, carotid artery LD, PFV, and EFV were increased significantly with the rise of VEGF after long-term combined exercise in the obese older women.

We calculated the regression coefficients to investigate the relationship between carotid artery structure, function and the increase of VEGF throughout exercise. In our regression analysis, VEGF was associated closely with carotid artery LD (r = .389, p < .01) PFV (r = .427, p < .01) and EFV (r = .264, p < .05).

The result of this study may be that the increase of blood flow velocity contributes to make rise of VEGF, which means that carotid artery luminal diameter increased as the beginning of angiogenesis and arteriogenesis.

In conclusion, 12-week combined exercise program is effective to improve physical function, such as body composition and body function, and serum lipid, and also the exercise improves the VEGF, and carotid artery function and structure. Nevertheless, there are a few limitations to our study. First, we didn’t perform FBS (fasting blood sugar) and CRP (C-reactive protein) in the study. Therefore, the selection of the non-culprit and non-obstructive lesions include some bias. Second, further large number of prospective studies to investigate association between carotid artery structure/function and VEGF during exercise will be required.

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