Effect of Exercise Intervention on Changes in Free Fatty Acid Levels and Metabolic Risk Factors in Stroke Patients

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Abstract. [Purpose] The present study investigated the effects of regular exercise on the improvement of free fatty acid (FFA) levels and metabolic risk factors of stroke patients. [Methods] The subjects were 20 male patients aged 47−59 years who were diagnosed as having hemiplegia resulting from stroke. Exercise was conducted using a stationary bicycle, a rehabilitative exercise machine. The exercise program utilized the heart rate reserve (HRR) method to create an exercise intensity amounting to 50−70% of the target heart rate (THR). The program lasted for 30 minutes and was conducted 5 times per week for a total of 12 weeks. [Results] In stroke patients, 12 weeks of exercise training yielded a significant interaction effect with weight, body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR). There were also significant differences in triglycerides (TG) according to the time of measurement, and an interaction effect was observed for triglycerides (TC). High-density lipoprotein cholesterol (HDLC), an important marker of improvement in metabolic risk factors, showed a significant interaction effect with exercise training. In addition, free fatty acids (FFA) showed a significant difference based on the time of measurement and showed a significant negative correlation with HDLC (r = −0.77). [Conclusion] The results of the present study suggest that regular exercise by stroke patients reduces their risk of metabolic complications and stroke recurrence by reducing obesity indices, improving serum lipid and FFA levels, and increasing HDLC levels. Key words: Stroke patient, Metabolic risk factors, Free fatty acids (FFA)

INTRODUCTION

Stroke is one of the leading causes of death among middle-aged men, along with cancer and cardiovascular disease1). Stroke is categorized as either cerebral hemorrhage, which arises from the rupture of blood vessels in the brain, or cerebral infarction, which is caused by blocked or narrowed blood vessels2).

Limitations in activities of daily living (ADL) are found after the occurrence of stroke. An extended bedridden state can lead to sarcopenia and reduced muscle strength, muscle endurance, and cardiopulmonary function3, 4). Thus, under such circumstances metabolic risk factors rapidly increase5, 6). Motor disabilities due to stroke-induced hemiplegia and hemiparesis limit physical activity and motor function, and can lead to the accumulation of visceral fat, which is a metabolic risk factor7). The accumulation of visceral fat results in the excessive release of free fatty acids (FFA) and glycerol, which are degradation products of triglycerides (TG)7), when FFA and glycerol are excessively introduced into skeletal muscle cells, they interfere with insulin-dependent glucose absorption. This process leads to the development of hyperglycemia, hyperlipidemia, and insulin resistance.

In cases of abdominal obesity resulting from visceral fat accumulation, blood and tissue concentrations of FFA increase simultaneously. FFA reduces insulin sensitivity in the liver by suppressing insulin-dependent glucose uptake. This disorder reduces the amount of glucose that available for glycogen synthesis and increases TG build up. An increase in glucose and FFA levels increases insulin secretion from the pancreas, causing hyperinsulinemia. Hyperinsulinemia leads to increased sodium re-uptake, sympathetic nervous system (SNS) activation, hypertension development, and circulating FFA levels8). In addition, low concentrations of high-density lipoprotein cholesterol (HDLC) are more closely related to the risk of stroke than high TG9). Low HDLC increases the risk of all arteriosclerotic diseases such as myocardial infarction, stroke, and sudden death. Particularly in stroke patients, improvements in HDLC concentration are considered an important goal in the treatment and reduction of these multiple risks10).

Since metabolic risk factors have various components and interactions, multifaceted prevention and treatment methods are necessary. In particular, stroke patients have a
significantly higher chance of metabolic syndrome (MetS) than to individuals without a stroke history or other specific disease states. Studies have suggested that stroke and MetS require multifaceted care, rather than separate treatment of each condition\textsuperscript{10}. FFA serves as the link in a vicious cycle of metabolic risk factors; therefore, it cannot be ignored. It was recently reported that exercise is a non-pharmacologic treatment method that may be effective at preventing brain diseases, enhancing cerebral function, and improving diabetic neuropathy\textsuperscript{12-14}.

Recent cohort studies have highlighted the importance of metabolic risk factors, as the improvement of these risk factors in stroke patients reduced total stroke recurrence by 19–30%\textsuperscript{11}. However, in previous studies, the primary goal of exercise programs for stroke patients was the enhancement of functional capacity, as measured by markers such as walking ability, falls, ADL, and quality of life\textsuperscript{15}. In addition, there were very limited applications of exercises that addressed cardiovascular risk factors or metabolic factor modulations intended for the improvement of metabolic abnormalities. Therefore, the present study aimed to specifically investigate the effects of aerobic exercise as a means of reducing metabolic risk factors of stroke patients.

**SUBJECTS AND METHODS**

This study was conducted as a pretest-and-posttest and control group study. The subjects of the present study were chronic stroke patients diagnosed as having stroke-induced hemiplegia with onset at least 12 months previously. Twenty male patients aged 47–59 years without orthopedic conditions that would have affected the study were selected. Subjects were included in the study if they could walk 10 meters within 60 seconds without supplementary assistance\textsuperscript{16}, were able to understand and follow verbal commands, and agreed to participate in the exercise program. Those currently taking drugs were not excluded. Selected subjects were placed into either the exercise group (n = 10), which performed an aerobic exercise program in addition to receiving rehabilitative therapy, or the control group (n = 10), which received utilized only the rehabilitation. All subjects completed the pretest before starting the exercise program, as well as the posttest at the conclusion of the 12-week exercise program. All participants provided their written informed consent to participation in this study prior to their enrollment. Kyungwoon University approved this study, which complies with the ethical standards of the Declaration of Helsinki. The physical characteristics of the subjects in each group are shown in Table 1.

Body measurements were made as follows: height (cm) and weight (kg) were measured and then used to calculate the body mass index (BMI) with the equation BMI = weight (kg)/height squared (m\(^2\)); and waist and hip circumference were measured with a tape measure to calculate the waist-to-hip ratio (WHR). Blood pressure was measured after patient had rested in a sitting position for 5 minutes, using an automatic blood pressure monitor (FT-500R, Jawon Medical, Seoul, Korea) to obtain the systolic (SBP) and diastolic (DBP) blood pressure. Blood pressures measurements were obtained twice, and the average values were used in the data analysis; the time between measurements was 3 minutes. Mean arterial pressure (MAP) was calculated as MAP = DBP + (SBP – DBP)/3.

For the intervention, all subjects received physical therapy consisting of posture, gait and strength training for 30 minutes/day which was conducted by a physical therapist with more than 5 years of Bobath technique experience. The exercise group additionally performed aerobic exercise after finishing the rehabilitative therapy. The exercise was conducted using a stationary bicycle (Full Body Exercise Active, Super Dynamic 3, Seoul, Korea), a rehabilitative exercise machine designed to move the arms and legs together. The exercise program utilized the heart rate reserve (HRR) method to achieve an exercise intensity corresponding to 50–70% of the target heart rate (THR). The program lasted for 30 minutes and was conducted 5 times per week for a total of 12 weeks. The exercise intensity was initially set at THR 50%, and was increased in 5% increments at 3-week intervals to the maximum of THR 70%. During exercise, the heart rate was continuously observed using an automatic pulse monitor by the patient, a professional physical therapist, and an exercise specialist to determine when the THR was achieved. In prior studies, the “220-age” equation has been used to predict the maximum heart rate (HRmax). Although this equation is easy to use due to its simplicity, the rate of change is high. Therefore, HRmax is underestimated in men and women less than 40 years of age, whereas it is overestimated in men and women aged ≥40 years. The recent American College of Sports Medicine (ACSM) guidelines\textsuperscript{17} recommend the equation of Gellish et al.\textsuperscript{18} as the most accurate equation. The present study used this recommended equation to calculate the subjects’ THRs as follows: THR = (206.9 – [0.67 × age] − HRrest) × % intensity + HRrest.

Blood samples were drawn before and after completion of the 12-week exercise program, under identical conditions and at the same time of day. Serum was separated from the collected blood using a centrifuge. Then, the concentrations of TG (Vitros TRIG DTD, Johnson & Johnson, New Brunswick, NJ, USA), total cholesterol (TC; Vitros CHOL DTD, Johnson & Johnson), and glucose (Vitros GLU DTD, Johnson & Johnson) were analyzed with a Vitros Chemistry DT60 II (Johnson & Johnson) using slides. HDL-C was analyzed using magnesium chloride and dextran sulfate to precipitate apo B-containing cholesterol; HDL-C (Vitros HDLC DTD, Johnson & Johnson) slides were used for Vitros Chemistry DT60 II analysis (Johnson & Johnson). FFA (Nefa HR kit, Wako, Osaka, Japan) was analyzed using a Hitachi 7180 (Hitachi, Tokyo, Japan).

Two-way repeated measure analysis of variance (ANOVA) was conducted for all data variables in order to express the average and standard deviation values, and to test the group trends before and after the exercise program. Comparisons of changes in the average values of measurement variables before and after the 12-week exercise program were analyzed using the paired samples t-test. In addition, the variation (Δ) between baseline measurements and measurements after 12 weeks of exercise was calculated, and
that considered individual patients’ abilities. However, no
resulting appropriate amounts of exercise through a program
of obesity indices. This finding is likely a result of implementing
interaction effect with the measurement time and group,
ables of weight, BMI, WC, and WHR demonstrated an
The results of the present study show that the changes of vari-
accepted for values of \( p \leq 0.05 \).
RESULTS
Table 2 shows the comparative results of the changes in
in obesity indices and blood pressure of stroke patients af-
after the 12-week exercise program. The obesity markers of
weight (\( p < 0.01 \)), BMI (\( p < 0.01 \)), WC (\( p < 0.01 \)), and WHR
(\( p < 0.01 \)) showed a significant interaction effect. However,
no significant effect was observed for blood pressure.
Table 3 shows the results of the changes in blood lipids
and FFA in stroke patients after 12 weeks of exercise train-
ing. There was a significant difference in TG according to
measurement time (\( p = 0.04 \)), and an interaction effect was
observed with TC (\( p < 0.01 \)). HDLC, an important marker
of improvement in metabolic risk factors, showed a signifi-
cant interaction effect (\( p = 0.02 \)) with exercise training. Ad-
ditionally, there was a significant difference in FFA levels
according to the measurement time (\( p < 0.01 \)).
Table 4 shows the correlation between changes (\( \Delta \) score)
in the measurement variables of the 12-week exercise pro-
gram. FFA levels, a direct cause of metabolic risk factors,
showed significant positive correlations with weight (\( r = 0.66, p < 0.05 \)), BMI (\( r = 0.65, p < 0.05 \)), TG (\( r = 0.72, p < 0.05 \)), and TC (\( r = 0.66, p < 0.05 \)), and a significant negative correlation with HDLC (\( r = -0.77, p < 0.01 \)). Conversely, the
metabolic improvement factor HDLC showed significant
negative correlations with the obesity indices of weight (\( r = -0.76, p < 0.05 \)) and BMI (\( r = -0.76, p < 0.05 \)), as well as a
significant negative correlation with FFA (\( r = -0.77, p < 0.01 \)).

DISCUSSION
Weight, BMI, WC, and WHR are reported to be predic-
tive factors of stroke. Weight and stroke risk are positively
Pearson’s correlation coefficient was used to test for cor-
relations between the measurement variables (\( \Delta \) score =
change in score between pre-test and posttest). All statisti-
cal analyses were conducted with the Statistical Package for
the Social Sciences (SPSS)-PC (version 18.0; IBM Corpora-
tion, Endicott, NY, USA), and statistical significance was
accepted for values of \( p \leq 0.05 \).

| Variable                      | Exercise (N=10) | CON (N=10) |
|-------------------------------|-----------------|------------|
| Age (years)                  | 53.7±3.6        | 52.8±4.1   |
| Height (cm)                  | 167.8±5.8       | 166.4±5.0  |
| Weight (kg)                  | 86.2±5.2        | 82.3±6.2   |
| BMI (kg/m²)                  | 25.7±1.5        | 24.7±2.4   |
| Time since stroke (months)   | 47.1±6.6        | 44.8±7.3   |
| Stroke type                  | Hemiplegia      | 7 / 3      |
| Hemiplegia side              | Stroke (Rating) |            |
|                               | 3 / 7           | 2 / 8      |

Data are means ± SD.

The various types of metabolic factors examined in
the present study are intricately connected in a metabolic
cascade. Unlike specific pharmacologic agents, exercise is
thought to induce overall metabolic improvements without
incurring side effects. Individualizing the exercise intensity
to patient fitness and characteristics is the most important

Table 1. Physical characteristics of the participants of this experiment.
Table 2. Changes in obesity indices and blood pressure with 12-week exercise training

| Measured Variable | Group     | Pretest  | Posttest | ∆score  |
|-------------------|-----------|----------|----------|---------|
| Weight (kg)       | Exercise  | 86.2±5.2 | 83.3±3.0 | −2.9±3.2 |
|                   | CON       | 82.3±6.2 | 83.0±6.6 | 0.7±1.8  |
| BMI (kg/m²)       | Exercise  | 25.7±1.5 | 24.8±0.8 | −0.8±0.9 |
|                   | CON       | 24.7±1.4 | 24.9±1.4 | 0.2±0.5  |
| WC (cm)           | Exercise  | 94.0±7.6 | 88.5±8.1 | −5.4±2.8 |
|                   | CON       | 92.3±6.7 | 92.4±6.8 | 0.1±0.8  |
| WHR               | Exercise  | 0.9±0.03 | 0.89±0.04| −0.05±0.05 |
|                   | CON       | 0.96±0.04| 0.96±0.06| 0.01±0.03 |
| SBP (mmHg)        | Exercise  | 133.7±12.8| 127.9±5.4| −5.8±9.3 |
|                   | CON       | 131.3±15.6| 132.1±7.5| 0.8±7.2  |
| MAP (mmHg)        | Exercise  | 87.1±10.4| 82.4±4.5 | −4.6±8.8 |
|                   | CON       | 85.7±11.2| 86.1±11.8| 0.4±5.1  |
|                   | Exercise  | 102.6±10.6| 97.6±4.2 | −5.0±8.4 |
|                   | CON       | 100.9±12.4| 101.4±13.4| 0.5±5.3  |

Data are means±SD. ∆score = change in the score * p value of paired t-test (**: p<0.05, ***: p<0.01, ****: p<0.001), † p value of two-way ANOVA test (group×time, †: p<0.05, ††: p<0.01, †††: p<0.001), BMI: body mass index, WC: waist circumference, WHR: waist to hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure

Table 3. Changes in serum lipids and free fatty acid (FFA) levels elicited by exercise training

| Measured Variable | Group     | Pretest  | Posttest | ∆score  |
|-------------------|-----------|----------|----------|---------|
| TG (mg/dL)        | Exercise  | 172.6±66.8| 134.5±48.9| −38.1±53.7 |
|                   | CON       | 173.4±58.9| 161.5±51.5| −11.9±51.8 |
| TC (mg/dL)        | Exercise  | 208.2±55.7| 168.8±27.4| −39.4±46.2 |
|                   | CON       | 205.5±34.1| 207.6±36.9| 2.0±21.4  |
| HDLC (mg/dL)      | Exercise  | 41.0±11.2 | 53.0±8.2  | 12.0±10.3  |
|                   | CON       | 39.8±8.5  | 43.4±8.4  | 3.6±2.7   |
| Glucose (mg/dL)   | Exercise  | 101.7±13.8| 94.2±4.3  | −7.5±14.3 |
|                   | CON       | 102.5±13.4| 103.8±10.6| 1.3±9.8   |
| FFA (µEq/L)       | Exercise  | 431.4±139.2| 324.3±73.2| −107.1±146.4 |
|                   | CON       | 449.3±109.0| 411.1±80.4| −38.2±87.2 |

Data are means±SD. ∆score = change in the score * p value of paired t-test (**: p<0.05, ***: p<0.01, ****: p<0.001), † p value of two-way ANOVA test (group×time, †: p<0.05, ††: p<0.01, †††: p<0.001), TG: triglycerides, TC: total cholesterol, HDLC: high density lipoprotein cholesterol, FFA: free fatty acid.

Table 4. Correlation between the measured factors and the degree of changes elicited by 12-weeks of exercise training

| Measured Variable | Weight | BMI     | WC     | TG     | TC     | HDLC   | Glucose | FFA    |
|-------------------|--------|---------|--------|--------|--------|--------|---------|--------|
| Weight            | 1      | 0.999** | −0.282 | 0.505  | 0.447  | −0.762*| 0.297   | 0.667* |
| BMI               | 0.999**| 1       | −0.286 | 0.511  | 0.428  | −0.762*| 0.289   | 0.657* |
| WC                | −0.282 | −0.286  | 1      | 0.066  | −0.220 | 0.311  | 0.640*  | −0.064 |
| TG                | 0.505  | 0.511   | 0.066  | 1      | 0.501  | −0.457 | 0.601   | 0.726* |
| TC                | 0.447  | 0.428   | −0.220 | 0.501  | 1      | −0.575 | 0.274   | 0.669* |
| HDLC              | −0.762*| −0.762* | 0.311  | −0.457 | −0.575 | 1      | −0.194  | −0.776**|
| Glucose           | 0.297  | 0.289   | 0.640* | 0.601  | 0.274  | −0.194 | 1       | 0.550  |
| FFA               | 0.667* | 0.657*  | −0.064 | 0.726* | 0.669* | −0.776**| 0.550   | 1      |

* Correlation is significant at the 0.05 level (2-tailed), ** Correlation is significant at the 0.01 level (2-tailed)
factor in achieving this effect. Since stroke patients have concomitant limitations in physical activity and motor disabilities, and may also have several metabolic comorbidities such as hypertension, diabetes, cardiovascular disease, and obesity, the intensity of the prescribed aerobic exercise must be determined through accurate testing. Furthermore, detraining can occur because of personal disposition or various other factors, resulting in rapid changes in adapted physical responses. Therefore, further research is necessary to develop exercise programs that patients can enjoy over the long term.

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