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Original Article

Effects of 12 weeks combined aerobic and resistance exercise on heart rate variability in type 2 diabetes mellitus patients

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Abstract. [Purpose] This study evaluated the effects of 12 weeks combined aerobic and resistance exercise on heart rate variability in patients with Type 2 diabetes mellitus. [Subjects and Methods] The subjects were 16 female patients with Type 2 diabetes mellitus selected among the participants of a chronic disease management exercise class at C Region Public Health Center in South Korea. Subjects were randomly assigned to the exercise group (n=8; age, 55.97 ± 7.37) or the control group (n=8; age, 57.53 ± 4.63) The exercise group performed aerobic and resistance exercises for 60 minutes per day, 3 times per week for 12 weeks. Anthropometric measurements, biochemical markers, physical fitness, and heart rate variability were examined. [Results] After 12 weeks of exercise, weight, body fat percentage, waist circumference, blood glucose, insulin resistance, glycated hemoglobin level, systolic blood pressure, and diastolic blood pressure significantly decreased and cardiorespiratory fitness and muscular strength significantly increased in the exercise group. Although heart rate variability measures showed favorable changes with the exercise program, none were significant. [Conclusion] Although the exercise program did not show notable changes in heart rate variability in patients with Type 2 diabetes within the timeframe of the study, exercise may contribute to the prevention and control of cardiovascular autonomic neuropathy.

Key words: Exercise, Type 2 diabetes mellitus, Heart rate variability

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INTRODUCTION

Type 2 diabetes mellitus is a metabolic disease resulting from defects in the β-cell function of the pancreas and insulin resistance, which causes a variety of vascular complications[1]. Insulin resistance plays a key role in the development of Type 2 diabetes and may cause dyslipidemia and hypertension, thus increasing the risk of cardiovascular disease[2]. Furthermore, the resulting damage of autonomic nerves distributed in the heart and blood vessels in patients with Type 2 diabetes may cause cardiovascular autonomic neuropathy (CAN), increasing the risk of death[3]. Therefore, the prevention of CAN is considered important for patients with Type 2 diabetes. CAN caused by long-term hyperglycemia requires an early diagnosis, which involves an invasive heart rate variability test, and may be prevented by improved blood glucose control[4].

Heart rate variability refers to the periodic changes in heart rate and, as an index of the activity level of the autonomic nervous system, is associated with the risk of cardiovascular disease[5]. Heart rate variability can be calculated using a time domain analysis or a frequency domain analysis. The frequency domain analysis, in particular, is useful in evaluating the activity of the sympathetic and parasympathetic nervous systems. In the frequency domain analysis, low frequency (LF) reflects mainly the activity of the sympathetic nervous system, while high frequency (HF) involves parasympathetic stimula-

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tion[6, 7]. Diabetes is caused by problem in the autonomic nerve system balance. As s result, patients with Type 2 diabetes showed the findings of reduced heart rate variability index compared to normal people, which is related to the progression of CAN[8]. In a study by Liao et al.[9], a low heart rate variability in patients with Type 2 diabetes was reported to be related to the development of cardiovascular disease and metabolic dysfunction. Therefore, the prevention of CAN is considered important for patients with Type 2 diabetes.

Exercise is recommended for the prevention of and in the therapeutic intervention strategies of Type 2 diabetes[10]. Exercise promotes cardiopulmonary function by inhibiting the activity of the sympathetic nervous system while activating the parasympathetic nervous system[11]. In particular, enhanced function of the autonomic nervous system has been found to be effective in improving insulin resistance and reducing heart rate varaibility[12–14]. However, studies investigating the effects of exercise on heart rate variability in patients with Type 2 diabetes are scarce. Therefore, an examination of the change in heart rate variability attributable to an exercise program which serves to enhance the function of autonomic nervous system in patients with Type 2 diabetes was considered necessary. This study aimed to examine the effects of 12 weeks combined aerobic and resistance exercise on heart rate variability in patients with Type 2 diabetes, and to provide basic data on the preventative and therapeutic effects of exercise on CAN.

SUBJECTS AND METHODS

The subjects were 16 female patients with type 2 diabetes mellitus who were selected among the participants of a chronic disease management exercise class at C Region Public Health Center in South Korea. Subjects were randomly assigned to the exercise group (n=8) or the control group (n=8). This study was conducted in compliance with the ethical principles of the Declaration of Helsinki, and we obtained consent from the subjects after explaining in detail the objectives, methods, and expected effects of the exercise program. The physical characteristics of the subjects are shown in Table 1.

Height and weight were measured using an automatic anthropometer (Jenix, Korea). Body Mass Index (BMI) was calculated by dividing the weight (kg) by the square of the height (m^2). Waist circumference was measured at the midpoint between the bottom of ribs and the upper part of the bilateral crista iliac in an upright posture to an accuracy of 0.1 cm. Body fat % was measured using a body composition analyzer (Jawon Medical, Korea). Resting heart rate and blood pressure were measured after resting for 10 minutes. Resting heart rate was measured using a wireless heart rate meter (Polar Electro OY, Finland). Systolic blood pressure and diastolic blood pressure were measured using an automatic blood pressure monitor (Jawon Medical, Korea).

A blood test was performed using blood collected from the forearm arteries after confirming a fasting state for 10 hours. Fasting blood glucose, insulin, c-peptide, glycated hemoglobin (HbA1c), total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, and C-reactive protein levels were determined using a chemistry analyzer (Hitachi 7020, Japan). Insulin resistance was calculated using the homeostatic model assessment of insulin resistance (HOMA-IR) method[15]. The related formula is: HOMA-IR=[fasting plasma insulin (μU/ml)×fasting plasma glucose (mg/dl)]/405.

Heart rate variability was measured using a heart rate variability analyzer (LAXTHA, Korea) for 5 minutes after a 20-minute rest at 10 am. Heart rate variability analyses were conducted using a time domain analysis and a frequency domain analysis. With regard to the time domain analysis, the standard deviation of all normal R-R intervals (SDNN) and the root mean square successive differences (rMSSD) were calculated. SDNN and rMSSD represent the overall variability and parasympathetic nerve activity, respectively. For the frequency domain analysis, low frequency (LF), high frequency (HF), and the LF/HF ratio were calculated. LF indicates sympathetic activity and, to some extent, parasympathetic activity, while HF indicates parasympathetic activity and the LF/HF ratio reflects the balance of sympathetic /parasympathetic activity.

In a cardiorespiratory test, the maximal oxygen uptake (VO_2max) was calculated by a submaximal exercise test using a cycle ergometer (Helmas III, Korea). VO_2max was calculated by calculation corresponded to the maximum heart rate 75% in progressive exercise load. Muscular strength was measured by adjusting the width of the 2nd joint of the 2nd finger to an almost right angle while holding a dynamometer (TKK-5101, Japan). Leg muscular strength was measured as the force produced when pushing the right and left feet as much as possible while the upper body and thighs are fixed in a sitting position using a leg muscular strength measuring instrument (Helmas III, Korea). Muscular endurance was measured as the number of sit-ups performed after an individual has performed sit-up movements (draw up one's knees, hold hands behind one's neck, and raise and bend the upper body forward) for 30 seconds on a sit-up measurement board.

The exercise program consisted of aerobic and resistance exercises based on by the exercise recommendations of the

Table 1. Physical characteristics of the subjects

Group	Age (yrs)	Height (cm)	Weight (kg)	BMI (kg/m^2)	% Fat
Exercise (n=8)	56.0 ± 7.4	157.0 ± 6.5	58.9 ± 7.0	23.9 ± 2.9	31.7 ± 3.8
Control (n=8)	57.5 ± 4.6	156.9 ± 4.6	62.8 ± 8.2	25.5 ± 3.1	34.1 ± 3.0

Values are mean ± SD.
BMI: body mass index

American College of Sports Medicine and the American Diabetes Association[10] and was performed 3 times per week for 12 weeks. Aerobic exercise intensity was calculated using the formula by Karvonen[16] [target heart beat=exercise intensity×(maximum heart rate−resting heart rate)+resting heart rate]. Resistance exercise intensity was calculated and set using Fleck and Kramer's[17] 1-RM indirect measurement method [1-RM=Wo+$W_{1,}$ where Wo=a weight allowing 7–8 times repeated contractions and W_1=Wo×0.025×R (number of repetitions)]. Stretching as a warm-up and cool-down was performed for 10 minutes before and after the aerobic and resistance exercises, respectively. The aerobic exercise consisted of treadmill walking performed at an exercise intensity of 60% of the heart rate reserve (HRR) for 30 minutes. Exercise intensity was maintained by wearing a Polar Heart Rate Analyzer (Polar Electro OY, Finland) in order to accurately determine whether the aerobic exercise was performed within the target heart rate range. The resistance exercise followed the aerobic exercise and consisted of 2 sets of 9 exercise items using weight machines (chest press, lateral pull down, shoulder press, arm curl, leg press, leg extension, leg curl, calf raise, and curl-up) with 8–12 repetitions for 30 minutes at an I-RM of 60–80%. The data were analyzed using SAS (Statistical Analysis System, Version, 9.1). A two-way ANOVA with repeated measures was performed to test interaction effects on the measured variables between groups and measurement time. The statistical significance (α) was set at 0.05.

RESULTS

Regarding body composition, weight ($p<0.001$), body fat % ($p<0.001$), and waist circumference ($p<0.001$) in the exercise group were significantly decreased, compared to before exercise. In addition, blood glucose ($p<0.001$), insulin ($p<0.05$), insulin resistance index ($p<0.01$), HbA1c ($p<0.001$), systolic blood pressure ($p<0.001$), and diastolic blood pressure ($p<0.01$) in the exercise group were significantly decreased after the exercise program compared to before exercise. However, there was no significant change in C-peptide, total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, or C-reactive protein in the exercise group after the exercise period. The control group showed no significant difference in any variable of anthropometric measurements or biochemical indices between the pre and post periods (Table 2).

Regarding physical fitness, VO_2max ($p<0.05$), grip strength ($p<0.05$), left leg strength ($p<0.01$), right leg strength ($p<0.01$), and muscular endurance ($p<0.01$) in the exercise group were significantly increased after the exercise program compared to before exercise. The control group showed no significant difference in any variable of physical fitness between the pre and post periods (Table 3).

Regarding heart rate variability, there was no significant difference in SDNN, rMSSD, LF, HF, or LF/HF between the pre and post periods in either group (Table 4).

DISCUSSION

In patients with Type 2 diabetes, heart rate variability may appear low due to abnormalities in the autonomic nervous system if blood glucose levels are not properly controlled[3]. Exercise is known to be useful in treating Type 2 diabetes and improving heart rate variability[18, 19]. Thus, this study aimed to examine the effects of 12 weeks exercise program consisting of aerobic and resistance exercises on biochemical indices, physical fitness, and heart rate variability. The results showed that the exercise program was effective in decreasing obesity index, improving insulin resistance, decreasing HbA1c, reducing blood pressure (a risk factor for cardiovascular disease), and promoting physical fitness. However, there was no significant improvement in heart rate variability, which is an autonomic nerve activity and balance indicator.

Insulin resistance caused by obesity is central to the pathophysiological mechanism of Type 2 diabetes. In terms of treatment for Type 2 diabetes, it is considered critical to improve insulin resistance and maintain the target level of blood glucose control in addition to weight loss[20]. In the current study, the exercise program was found to significantly decrease the obesity index, fasting glucose, insulin resistance index, and HbA1c. In addition, C-peptide increased without statistical significance. These findings are consistent with those of the previous studies revealing that exercise in patients with Type 2 diabetes was effective in improving blood glucose control and insulin resistance by promoting the intake and use of blood glucose in the skeletal muscle[21–23]. Therefore, aerobic and resistance exercises are effective in improving insulin resistance and reducing HbA1c in patients with Type 2 diabetes.

Since patients with Type 2 diabetes have a high risk of atherosclerotic cardiovascular disease, it is important to prevent cardiovascular complications through the management of hypertension, dyslipidemia, and C-reactive proteins (an inflammatory marker)[24]. Exercise has been known to be effective in reducing the risk factors for cardiovascular disease in patients with Type 2 diabetes[25]. In the current study, the exercise program was found to be effective in reducing blood pressure in patients with Type 2 diabetes; however, there was no significant difference in the lipid profile or C-reactive protein levels. The reduction effect of blood pressure found in this study appears to be due to the improved obesity index and insulin resistance. Unlike the present study, previous studies have shown that exercise reduces lipid, lipoprotein levels, and inflammatory markers[26, 27]. Improvements in the lipid profile and C-reactive protein by exercise is known to be remarkably reduced when the baseline values are high. The baseline values in the present study were in the normal range and thus, may be the reason no significant differences were obtained. In addition, the results of this study revealed that an exercise program was effective in enhancing cardiorespiratory fitness and muscular strength in patients with Type 2 diabetes. These results are consistent with

Table 2. Changes in body composition and biochemical index variables

Variables	Group	Pre	Post
Weight (kg)	Exercise	58.9 ± 7.0	57.5 ± 6.7***
	Control	62.8 ± 8.2	62.6 ± 8.6
% Fat	Exercise	31.7 ± 3.8	30.6 ± 3.7***
	Control	34.1 ± 3.0	34.0 ± 3.1
Waist circumference (cm)	Exercise	83.6 ± 2.1	82.2 ± 2.4***
	Control	84.4 ± 2.2	84.2 ± 2.2
Blood glucose (mg/dl)	Exercise	139.5 ± 12.3	132.9 ± 11.6***
	Control	140.8 ± 7.2	140.1 ± 5.6
Insulin (μU/ml)	Exercise	6.9 ± 2.8	5.3 ± 1.9*
	Control	6.9 ± 3.4	7.5 ± 2.9
HOMA-IR	Exercise	2.4 ± 1.0	1.7 ± 0.6**
	Control	2.4 ± 1.2	2.6 ± 1.0
C-peptide (ng/ml)	Exercise	1.4 ± 0.4	1.6 ± 0.3
	Control	1.7 ± 0.6	1.7 ± 0.5
HbA1C (%)	Exercise	6.4 ± 0.6	5.9 ± 0.5*
	Control	6.4 ± 0.5	6.4 ± 0.6
Total cholesterol (mg/dl)	Exercise	187.5 ± 30.1	181.6 ± 31.3
	Control	180.3 ± 52.2	185.5 ± 56.0
Triglyceride (mg/dl)	Exercise	105.5 ± 55.6	86.1 ± 33.5
	Control	109.4 ± 29.1	108.3 ± 31.3
LDL-cholesterol (mg/dl)	Exercise	128.1 ± 28.5	121.6 ± 27.8
	Control	127.6 ± 40.3	116.5 ± 47.8
HDL-cholesterol (mg/dl)	Exercise	54.5 ± 10.7	55.9 ± 9.7
	Control	49.4 ± 6.8	49.9 ± 8.0
Systolic blood pressure (mmHg)	Exercise	132.3 ± 9.4	128.8 ± 7.6***
	Control	133.3 ± 6.3	131.4 ± 6.4
Diastolic blood pressure (mmHg)	Exercise	79.4 ± 6.1	77.8 ± 5.7**
	Control	80.1 ± 4.9	79.5 ± 4.6
C-reactive protein (mg/l)	Exercise	0.2 ± 0.1	0.2 ± 0.1
	Control	0.1 ± 0.1	0.1 ± 0.1

Values are mean ± SD, **p<0.01, ***p<0.001

Table 3. Changes in physical fitness variables

Variables	Group	Pre	Post
VO_2max (ml/kg/min)	Exercise	27.2 ± 2.4	28.5 ± 3.0*
	Control	26.4 ± 3.3	25.7 ± 2.4
Grip strength (kg)	Exercise	24.7 ± 2.1	25.7 ± 1.9*
	Control	23.9 ± 3.3	23.7 ± 2.9
Right leg strength (kg)	Exercise	26.2 ± 4.2	27.4 ± 4.4**
	Control	25.9 ± 2.2	25.7 ± 2.3
Left leg strength (kg)	Exercise	20.5 ± 4.3	22.1 ± 4.4**
	Control	20.5 ± 2.0	20.7 ± 2.0
Sit-ups (count/30s)	Exercise	5.1 ± 2.1	6.1 ± 2.0**
	Control	4.4 ± 1.7	4.5 ± 1.1

Values are mean ± SD, *p<0.05, **p<0.01

previous studies[28]. According to the results of a recent retrospective study, low physical fitness may be a powerful predictor of cardiovascular disease, and patients with Type 2 diabetes have been reported to have low cardiorespiratory fitness and muscular strength[29, 30]. Enhanced physical fitness by exercise serves to increase the ability to control blood glucose, and thus

Table 4. Changes in heart rate variability

Variables	Group	Pre	Post
SDNN (ms)	Exercise	25.5 ± 7.8	29.5 ± 6.4
	Control	23.4 ± 7.2	25.0 ± 5.7
rMSSD (ms)	Exercise	17.9 ± 5.4	19.9 ± 6.8
	Control	16.4 ± 5.9	16.5 ± 5.1
Low frequency (nu)	Exercise	51.6 ± 8.1	52.1 ± 7.2
	Control	49.9 ± 10.0	50.0 ± 10.3
High frequency (nu)	Exercise	47.3 ± 7.6	48.7 ± 7.1
	Control	44.0 ± 7.5	44.9 ± 6.5
LF/HF	Exercise	1.12 ± 0.3	1.1 ± 0.2
	Control	1.14 ± 0.2	1.1 ± 0.2

Values are mean ± SD.
SDNN: standard deviation of normal to normal intervals, rMSSD: root mean square successive differences

is important for the treatment of Type 2 diabetes.

Patients with Type 2 diabetes are also vulnerable to autonomic nervous system damage caused by the incongruity of sympathetic nerves and parasympathetic nerves distributed in heart and blood vessels. As a result, patients with Type 2 diabetes are prone to CAN, which is related to mortality rate[31], and have reductions in SDNN (overall autonomic nervous system activity) and rMSSD (parasympathetic nerve activity) compared to healthy individuals[32]. Exercise has been reported to be effective in improving heart rate variability as exercise serves to reduce the activity of sympathetic nervous system while increasing the activity of the parasympathetic nervous system[33, 34]. In other words, exercise is considered to positively affect the function of cardiovascular autonomic nervous system in patients with Type 2 diabetes. In the current study, the exercise program was found to increase SDNN, rMSSD, LF, and HF and reduce LF/HF in patients with Type 2 diabetes, but the differences were not significant. A study by Figueroa et al.[35], found that heat rate variability in patients with Type 2 was not improved after 16 weeks of aerobic exercise, consistent with our findings. However, in a study reported by Pagkalos et al.[36], a 6 month-aerobic exercise program at 70–85% HRR in Type 2 diabetes patients with autonomic neuropathy was found to improve heart rate variability. Thus, improvement of heart rate variability may be affected by the length of the exercise period. Therefore, as it is judged that long-term exercise intervention is expected to improve heart rate variability in patients with Type 2 diabetes, further long-term studies are considered necessary in the future.

In conclusion, a 12weeks combined aerobic and resistance exercise was found to be effective in enhancing blood glucose control, improving insulin resistance, and promoting physical fitness. These findings support the importance of exercise in the treatment of Type 2 diabetes. Although the exercise program did not markedly improve heart rate variability, SDNN, rMSSD, LF, and HF were increased and LF/HF was reduced. Thus, exercise may contribute to the prevention and management of CAN in patients with Type 2 diabetes.

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