J. Phys. Ther. Sci.
26: 111–115, 2014

Exercise Training Improves Cardiac Autonomic Nervous System Activity in Type 1 Diabetic Children

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Abstract. [Purpose] We investigated the effect exercise training has on cardiac autonomic nervous system (ANS) and cardiovascular risk profiles in children with type 1 diabetes mellitus (DM). [Subjects] Fifteen type 1 DM children (all boys; 13.0±1.0 years of age) were enrolled in the study. [Methods] The subjects received exercise training three times a week in a 12-week program. Each child was asked to walk on a treadmill to achieve an exercise intensity of VO_2max 60%. ANS activity was measured by power spectral analysis of the electrocardiogram (ECG). Blood samples were obtained for serum lipid profiles. To evaluate Doppler-shifted Fourier pulsatility index (PI) analysis, a 5-MHz continuous wave Doppler (VASCULAB D10) set was used to measure forward blood flow velocity (FLOW) in the radial artery. [Results] Total and low-frequency (LF) power of heart rate variability increased significantly after exercise intervention. Total cholesterol (TC) levels were significant lower after exercise intervention. Total and high-frequency (HF) power were significantly correlated with higher TC levels, but diastolic blood pressure and HF was significantly correlated with lower TC levels. [Conclusion] Regular exercise intervention should be prescribed for children with type 1 DM.
Key words: Autonomic nervous system, Exercise, Diabetes mellitus

(This article was submitted May 28, 2013, and was accepted Aug. 17, 2013)

INTRODUCTION

Insulin-dependent diabetes mellitus (IDDM) is associated with autonomic neuropathy and/or cardiovascular dysregulation, which are major complications of diabetes mellitus (DM). Type 1 DM patients have a fourfold to eightfold risk of coronary heart diseases, compared with the general population[1]. In a recent study, 69% of children with type 1 DM were found to have one or more cardiovascular risk factors[2]. Abnormal cardiac autonomic nervous system (ANS) is recognized as one of the early symptoms of cardiac autonomic neuropathy[3] and has been demonstrated in type 1 diabetic children[4–7]. Low ANS activity may also be associated with symptoms of coronary heart disease and related-risk factors in type 1 DM[8]. In our previous study[9], ANS activity levels were significantly decreased in type 1 diabetic children in comparison with children without diabetes.

Regular physical activity and/or exercise training play a critical role in treatment and management of type 1 DM. Regular physical activity reduces the blood glucose level and blood pressure, helps control weight, improves lipoprotein profile and insulin sensitivity, and decreases the risk of DM complications[10–13]. These benefits of physical activity remain controversial in type 1 DM patients. To the best of our knowledge, there has not been a study investigating whether 12 weeks of exercise training can modify ANS activities and cardiovascular risk profiles of type 1 DM children. Thus, this present study focuses on alterations in cardiac ANS activities and cardiovascular risk profiles following regular exercise training in children with type 1 DM.

SUBJECTS AND METHODS

The study was approved by the Medical Center Institutional Review Board of Dong-A University for use of human subjects. Fifteen type 1 DM children (all boys;

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13.0±1.0 years of age) volunteered for this study. All experimental procedures were explained in detail to all subjects and their parents, who then signed a statement of written informed consent. We considered children with type 1 DM and no predominant neuropathy, cardiovascular diseases, stroke, or retinopathy as potential subjects for the study. We also excluded subjects having kidney dysfunctions (creatinine > 2.0 mg/dl, glycohemoglobin > 10%, and fasting blood sugar > 200 mg/dl), hypoglycemia symptoms with consciousness disorder over at least 3 months, hypertension, or ketonemia. Body composition of the subjects was measured by means of bioelectrical impedance (Venus 5.5, Jawon Medical Co., Ltd., Kyungsan, Korea). The research reported in this paper was undertaken in compliance with the Medical Center Institutional Review Board of Dong-A University approval of the experiment for use of human subjects.

In order to determine cardiorespiratory capacity and exercise intensity of each subject for exercise training, a progressive exercise test was performed on a treadmill using the modified Balke protocol. This test was also used to measure aerobic capacity after exercise training. Maximal oxygen consumption (VO_2max) of each subject was measured using a metabolic gas analyzer (Quark b2, Cosmed, Rome, Italy) by the breath-by-breath method. Following warm-up exercise at 4.0 speed for 3 min, the exercise load at a walking speed of 4.8 kph was increased by increasing the grade by 2% every 2 min. Maximal heart rate (HRmax) was automatically recorded when the VO_2max value of each subject was measured. Children with type 1 DM took part in the walking exercise program 3 times per week for a total of 12 consecutive weeks. Exercise intensity of each subject was determined by VO_2max 60%. We also determined the exercise duration required for each individual to expend 250 kcal per exercise session by calculating VO_2 per min and calorie expenditure per min[14].

Our power spectral analysis procedures have been completely described elsewhere[15–17]. In brief, the analog value of the electrocardiogram (ECG) monitor (Life Scope, Nihon Kohden) was digitized through a 13-bit analog-to-digital converter (TransEra HTB 420) at a sampling rate of 1,024 Hz. The digitized ECG signal was differentiated, and the resultant QRS spikes and R-R intervals of the ECG were stored continuously in our computer. ECG measurements were conducted before the exercise training started, and after the 12 weeks of exercise training. The stored R-R interval data were shown and aligned sequentially with a sampling frequency of 2 Hz and displayed on a computer screen for examination, before power spectral analysis was conducted. Then, the DC component and trend were fully erased by digital filtering for the band between 0.007 and 0.5 Hz. Low filtering at 0.007 Hz was chosen to obtain the frequency components associated with thermogenic function. The root mean square value of the ECG R-R interval was calculated and represented the mean amplitude. After passing the data through the Hamming-type data window, ECG R-R interval analysis by means of fast Fourier transform was performed on consecutive 512-sec time series of R-R interval data obtained during the experiment[18]. To examine ANS activity, we analyzed very low-frequency (VLF) power (0.007–0.035 Hz), which expresses the thermogenic sympathetic activity; low-frequency (LF) power (0.035–0.15 Hz), which expresses the sympathovagal activity; the high vagal component (0.15–0.5 Hz, HF) associated with parasympathetic activity, and total power (0.007–0.5 Hz, total) which expresses all ANS activity. The average heart rate of each 512-sec period was also obtained with the standard error (SE).

Blood samples (10 mL) were collected from subjects via the antecubital vein for examination of serum samples after an 8-h overnight fast. Each blood sample was centrifuged for 10 min at 3,000 rpm at 4°C. The supernatant was decanted and stored in a −80°C freezer until analysis. Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) concentrations were assayed using an enzyme-linked immunosorbent assay (ELISA) kit. Serum glycosylated hemoglobin (HbAlc %) was measured by affinity chromatography.

Indexes of cardiovascular lipid profiles were used to calculate the TC/HDL-C (mg/dl) and TG/HDL-C (mg/dl) ratio.

This has completely been published in the previous study for the frequency power spectral analysis of ultrasound signal[19]. To evaluate the Doppler-shifted Fourier pulsatility index (PI) analysis, a 5 MHz continuous wave Doppler (VASCULAB D10) set was used to measure forward blood flow velocity (FLOW) in the radial artery. To present a single standardized numeric index expressing the degree of FLOW braking, a Fourier PI introduced in previous literature[20, 21] was used and was expressed as follows:

$$\mathrm{PI} = \sum_{n=1}^{\infty} \mathrm{An}^2 / \mathrm{Ao}^2 ,$$

where An means the amplitude of the Fourier harmonic and Ao expresses the mean value. For this experiment, the Doppler signal was band-pass filtered (100 to 10 kHz) and digitized at a sampling rate of 8,192 Hz. The digitized data were processed with the Hamming window function and 512-point FFT to obtain the frequency power spectra, the mean FLOW, and the Fourier PI.

All statistical analyses were performed using a commercial software package (SPSS version 11.5 for Windows, SPSS Inc., Chicago, IL, USA). Statistical differences for physical characteristics, cardiac autonomic nervous activities, and blood samples between the before and after exercise training were analyzed with the nonparametric Mann-Whitney U test. The relationships with cardiac autonomic activities and cardiovascular risk profile levels were examined with the Pearson correlation coefficients. A p value of < 0.05 was considered statistically significant. Data are expressed as means ± SE.

RESULTS

The physical characteristics of the subjects before and after exercise training are presented in Table 1. A significant difference was observed in height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) after exercise training.

Table 2 shows the alterations of cardiac autonomic nervous activities after exercise training in our subjects. Total power, representing overall ANS activity, was enhanced significantly after exercise training ($p<0.05$). LF power, which is associated with sympathetic and parasympathetic balance, and VLF power, which represents the thermogenic sympathetic activity, were also increased significantly after exercise compared with before exercise ($p<0.05$). However, the global sympathetic nervous activity index, sympathetic nervous system (SNS) index, and HF power, representing the parasympathetic nervous activity, were not significantly different between before and after exercise training.

Cardiovascular risk profiles of the subjects with exercise intervention are represented in Table 3. TC and HDL-C levels were significantly different in children with type 1 DM before and after exercise training. However, TG values were not significantly different after exercise training. In the anti-atherosclerosis profile indexes, the TC/HDL-C and TG/HDL-C ratios of the subjects were also not significantly different despite intervention in the form of exercise training. The HbA1c levels, which reflect glycemic control, were also not significantly different after the intervention of 12 weeks of exercise training. Fourier PI index and flow, predictors of arterial stiffness, were not also different after walking exercise training.

In the present study, we also examined the correlation with cardiac ANS activities and cardiovascular risk profiles after exercise training. The Pearson correlation coefficients for the cardiac ANS activities and cardiovascular risk profiles of the type 1 diabetic children are described in Table 4. The results showed that the total power of heart rate variability (HRV) was correlated with HbA1c levels, but the difference did not reach statistical significance ($p>0.066$). The VLF power also showed the correlation with TC levels, but there was no significant difference ($p>0.063$). However, total and HF power were significantly correlated with the DBP value ($p<0.01$, respectively).

DISCUSSION

This study evaluated the influence of a long-term walking exercise program on cardiac ANS activities and cardiovascular disease risk profiles including a metabolic control factor (HbA1c level). Cardiac autonomic neuropathy can be described as a result of dysfunction of sympathetic nervous system (SNS) activity, parasympathetic nervous system (PSNS) activity, or a combination of both[22] and is an important complication of type 1 DM since it is associated with increased risk to the cardiovascular system. Abnormal HRV in diabetes also shows an increased risk for ventricular arrhythmias and total cardiovascular morbidity and mortality[23]. Although HRV reduction is recognized as one of the early symptoms of cardiac autonomic neuropathy[6], little is known about the mechanism by which type 1 DM causes HRV reduction. Previous studies have suggested that HRV reduction and autonomic neuropathy are associated with impairment of PSNS activity[24], poor metabolic control[5, 24], age[25], and diabetes duration[5, 26]. Other studies have found no such associations[27, 28].

Table 1. Physical characteristics of the subjects between before and after exercise training

	Type 1 DM (n=15)	
Variables	Pre	Post
Age (yr)	13.0 ± 1.0	13.0 ± 1.0
Height (cm)	156.5 ± 7.1	157.7 ± 7.0**
Weight (kg)	49.3 ± 4.9	50.3 ± 5.1*
%Fat (%)	13.3 ± 2.6	13.7 ± 2.7
SBP (mm Hg)	111.4 ± 6.1	105.6 ± 4.1*
DBP (mm Hg)	66.4 ± 3.2	63.4 ± 2.1*
VO_2max (ml/kg/min)	41.4 ± 3.1	43.1 ± 3.0
DD (month)	36.7 ± 8.6	-

Values represent means ± SE. SBP, systolic blood pressure; DBP, diastolic blood pressure; DD, diabetic duration. * $p<0.05$; ** $p<0.01$

Table 2. The changes of cardiac ANS activities from HRV power spectral analysis in type 1 diabetic children

Variables	Pre	Post
Total (ms)	998.46±232.57	1587.47±449.25*
LF (ms)	541.26±187.59	942.44±397.84*
VLF (ms)	128.11±58.66	389.44±198.55*

Values represent means ± SE, *$p<0.05$
Total, total power; LF, low-frequency power; VLF, very low-frequency power

Table 3. The alterations of cardiovascular risk profiles of type 1 diabetic children

Variables	Pre	Post
TC (mg/dl)	179.9 ± 2.6	164.4 ± 11.4**
TG (mg/dl)	137.9 ± 38.8	124.2 ± 19.5
HDL-C (mg/dl)	64.7 ± 4.7	59.6 ± 4.5**
TC/HDL-C (mg/dl)	2.9 ± 0.3	2.8 ± 0.2
TG/HDL-C (mg/dl)	2.4 ± 1.0	2.1 ± 0.5
HbA1c (%)	8.2 ± 0.4	8.5 ± 0.5
Fourier PI	5.13 ± 0.3	5.11 ± 0.3
FLOW	34.09 ± 3.10	34.41 ± 2.35

Values represent means ± SE, ** $p < 0.01$

On the other hand, exercise plays a central role in the management of type 1 DM[29]. Regular physical activity can improve lipoprotein levels, blood pressure, insulin sensitivity, and blood glucose level in the general population. Additionally, regular exercise training has beneficial effects on cardiac ANS activity in healthy[30, 31] and obese children[32, 33]. However, its effects still remain controversial in type 1 DM. In this study, cardiac ANS activities improved significantly after exercise training. on the results for the HRV activities suggest that exercise intervention may play a primary role in management and treatment of autonomic neuropathy among type 1 DM children.

Since our most recent review of cardiovascular risk factors and physical activity in children with type 1 DM, two

Table 4. The correlation matrix of cardiac ANS activities and cardiovascular risk profiles measured after exercise intervention in type 1 diabetic children

	PI	SBP	DBP	TO-TAL	VLF	LF	HF	SNS index	TC	TG	HDL	TC/ HDL	TG/ HDL	HbA1c
PI	1	0.25	−0.01	0.06	0.10	0.14	−0.05	0.22	−0.20	−0.04	−0.28	0.10	0.02	−0.16
SBP		1	0.38	−0.36	−0.14	−0.20	−0.36	0.16	−0.12	0.39	−0.55*	0.52*	0.43	0.05
DBP			1	−0.69**	−0.02	−0.31	−0.77**	0.42	0.02	0.41	−0.31	0.42	0.29	−0.32
Total				1	0.62*	0.77**	0.79***	0.06	−0.12	−0.36	0.23	−0.39	−0.06	0.49
VLF					1	0.90***	0.08	0.43	−0.49	−0.39	−0.08	−0.42	−0.03	0.27
LF						1	0.22	0.33	−0.36	−0.41	0.05	−0.43	−0.01	0.42
HF							1	−0.40	0.16	−0.15	0.31	−0.19	−0.09	0.34
SNS index								1	−0.18	−0.01	−0.08	−0.12	0.30	0.14
TC									1	0.55*	0.59*	0.38	0.30	0.28
TG										1	−0.29	0.92***	0.89***	0.16
HDL											1	−0.52*	−0.40	0.37
TC/HDL												1	0.82***	−0.07
TG/HDL													1	0.40
HbA1c														1

Values represent means ± SE. * p<0.05; ** p < 0.01; *** p < 0.00

studies have been subsequently published in the English literature. These studies had also been performed by questionnaire surveys. The present study investigated the effects of exercise training on cardiovascular risk factors in pediatric patients with type 1 DM. A previous study[34] reported that increased physical activity in children with type 1 DM is associated with lower lipoprotein levels, a lower DBP, and better glycemic control. In the present study, we observed that TC levels and SBP and DBP values had significantly reduced after exercise training, which was consistent with findings from the previous study[34]. Other studies have also revealed contradictory results of exercise training with regard to the HbA1c value[35–38]. The differences in findings might be due to differences in study designs[35, 37] or because of differences in patient age. In these regards, the present study did not show any changes in HbA1c values after exercise training. Further studies are needed to evaluate whether exercise training reduces HbA1c levels in children with type 1 DM.

In adults with type 1 DM, atherosclerotic cardiovascular disease is the most common cause of mortality and morbidity[29]. One possible mechanisms for this may be vascular stiffness, which may be an independent risk factor for atherosclerosis[39, 40]. Arterial vascular alterations begin in childhood and adolescence[41]. In our previous study[19], Fourier PI measured by ultrasound technique was significantly associated with lipid profiles in healthy adults. It is suggested that a damping of the blood velocity waveform and increased arterial stiffness might accompany unfavorable distributions of lipids and lipoprotein. The present study investigated the relationship between two diagnosis indices of peripheral arterial disease and ANS activities. However, no correlation was found between the Fourier PI results and abnormal cardiac ANS activity in type 1 DM children.

These findings might have derived from the small number of subjects and the ages of the subjects. Although diabetes mellitus increases the progression of arterial diseases such as arterial stiffness and arteriosclerosis, arterial stiffness is a prominent marker of the aging process in humans[42] including cardiovascular disease mortality and morbidity. Nevertheless, there has been no study, to the best of our knowledge, that has investigated the correlation among long-term exercise training, cardiac autonomic dysfunction, and cardiovascular risk factors in children with type 1 DM. From this point of view, the present study may provide valuable information, although no significant correlation was found among them.

In conclusion, our results suggest that a regular walking exercise program may play an essential role in regulating diabetes complications such as subclinical autonomic neuropathy and cardiovascular disease risk in children with type 1 DM. Regular exercise intervention should be recommended in the management of children with type 1 DM.

ACKNOWLEDGEMENT

This study was supported by research funds from Dong-A University.

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