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Original Article

Effect of the low- versus high-intensity exercise training on endoplasmic reticulum stress and GLP-1 in adolescents with type 2 diabetes mellitus

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Abstract. [Purpose] The primary objective of this study was to investigate the effect of low-intensity exercise training compare with high-intensity exercise training on endoplasmic reticulum stress and glucagon-like peptide-1 in adolescents with type 2 diabetes mellitus. [Subjects and Methods] The low-intensity exercise training group performed aerobic exercise training at an intensity of ≤ 45% of the heart rate reserve. The high-intensity interval exercise training group performed interval exercise training at an intensity of ≥ 80% of the heart rate reserve. The exercise-related energy consumption was determined for both groups on a per-week basis (1,200 kcal/week). [Results] Both groups showed improvement in the glucose-regulated protein 78 and dipeptidyl peptidase-4, but the size of the between-group effect was not statistically significant. The high-intensity interval exercise training group showed a significant reduction in percentage body fat. The C-peptide level increased after the 12-weeks programs and was significantly different, between the groups. Fasting glucose, insulin resistance in the fasting state according to homeostasis model assessment, and leptin decreased after the 12-weeks exercise program and were significantly different between the groups, and glucagon-like peptide-1 increased after the 12-week exercise programs and was significantly different between the groups. [Conclusion] In conclusion high-intensity interval exercise training, as defined in this study, may lead to improvements in body composition, glycemic control, endoplasmic reticulum stress, and the glucagon-like peptide-1 in adolescents with type 2 diabetes mellitus.
Key words: ER stress, GLP-1, Type 2 diabetes mellitus

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by hyperglycemia and, resulting from insulin resistance and impaired insulin secretion. Clinical management of T2DM consists of nutrition therapy, pharmacological therapy, and exercise[1)]. The American College of Sports Medicine (ACSM) and American Diabetes Association (ADA) have published positional statements recommending the use of exercise as an intervention for T2DM[2, 3)]. Regular exercise and physical activity are well known as an effective strategy for the prevention and treatment of T2DM. Most studies testing the therapeutic effects of exercise on T2DM involve continuous low- to moderate-intensity exercise, such as walking, jogging, or cycling, for ≥ 30 minutes per session[2)]. However, the variables inherent in these exercise training programs, such as type of exercise and intensity, have varied. Two separate meta-analyses, meanwhile, have concluded that high-intensity exercise may be more effective for improving glycemic control in T2DM[4, 5)]. Clinical tests comparing the effects of different exercise intensities on T2DM should be completed to better identify the precise intensity of exercise needed to achieve an optimal outcome[6)]. High-intensity interval exercise training (HIE), which involves repeated bursts of vigorous exercise interspersed with periods of recovery, may be an attractive option in implementing a high-intensity exercise training program in T2DM[7)]. The efficacy of HIE for improving disease outcomes has been demonstrated in patients with heart failure, chronic obstructive pulmonary disease, and metabolic syndrome (MS)[8)]. In low-intensity exercise training (LIE), energy consumption is increased, but fatigue and monotonous and generally dreary feelings make this option difficult to maintain.

However, the potential benefits of HIE on the disease parameters within T2DM have yet to be fully established. Recently, HIE protocols have been evaluated in participants with MS and T2DM[7, 9)]. These studies have demonstrated drastic improvement in body composition, glycemic control, and physical fitness factors, and although the high intensity training used may limit the feasibility of living freely under unsupervised conditions, it also highlights the potential of

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interval training modalities in T2DM patients[10, 11]. Recent studies have shown that HIE offers either similar or superior benefits in terms of glycemic control, insulin, and β-cell function outcomes compared with traditional continuous exercise[11–13].

Most of the previous studies have been centered around comparison between HIE and moderate-intensity exercise (MIE), and research data comparing HIE and LIE, under the assumption that LIE and T2DM patients perform different amounts of exercise. This study looks at the progress related to diabetes management in relation to the function of the endoplasmic reticulum[14–16]. The function of the endoplasmic reticulum and the onset of metabolic diseases are closely related. Also, in the pathogenesis of genetic and metabolic disorders, such as obesity, hyperlipidemia, and diabetes, it has been reported that there is a correlation between the function of the endoplasmic reticulum[15, 16]. Among the endoplasmic reticulum stress responses is a phenomenon that occurs in the regulation of synthesis and the transport of proteins that occurs through the endoplasmic reticula of eukaryotic organisms; not only does it have a close relationship with the differentiation of cells, survival rate, immunity and physiological changes, but it also has both direct and indirect relationships with various immunology and pathology related diseases[17]. Unfortunately, however, research on ER stress and glucagon-like peptide-1 (GLP-1), in relation to diabetes has been very scarce.

Therefore, the aim of this study was to test the feasibility of low-intensity exercise training compared with high-intensity exercise training in adolescents with T2DM. Furthermore, we compared the efficacy of HIE with energy expenditure-matched LIE with regard to changes in the endoplasmic reticulum (ER) stress level, GLP-1, and glycemic control. We hypothesized that exercise training could be successfully performed and that HIE would be superior to LIE with regard to improvements in ER stress and GLP-1, despite expected equal improvements in body composition.

SUBJECTS AND METHODS

Adolescents with T2DM were recruited by newspaper advertisements and by contacting local diabetes patient organizations. Initially, subjects were included in the study and randomized into two groups: the HIE group (n=10) and LIE group (n=10). Their mean age was 15.3 ± 2.2 years, mean height was 162.8 ± 11.5 cm, mean body mass index (BMI) was 24.0 ± 3.8 $kg \cdot m^{-2}$, and mean duration of diagnosis was 4.0 ± 2.2 years. All volunteers were selected from D university Hospital outpatients with result of a 2-hour glucose tolerance test of 140 mg/dL ≤ blood sugar ≥ 200 mg/dL and no other complicating diseases.

All volunteers underwent medical screening, including a health status interview, physical exam, and blood analysis. Written informed consent was obtained from all subjects. Also, no subjects received insulin therapy, and no medications were altered during the exercise treatments. The study was approved by the D University Hospital Institutional Review Board (IRB), and the subjects were included after medical examination and diagnosis by medical specialists. Before beginning the exercise program, all subjects underwent anthropometric measurements (body weight, body mass index, percentage of fat). Body composition was measured by the bioelectrical impedance method (Venus 5.5, Jawon Medical, Seoul, Republic of Korea). All subjects performed maximal exercise as determined by the modified Bruce protocol. Participants underwent a treadmill (S25T, Taeha Mechatronics Co., LTD., Gyeonggi-do, Republic of Korea) exercise test and maximum oxygen uptake (VO2max; ml·kg-1·min-1) was determined using a Quark b2 analyzer (Cosmed, Rome, Italy) after a 3-minute rest. Rating of perceived exertion (RPE) was rated every minute using the Borg scale. Attainment of VO2max was determined by the suspension of movement criteria of the ACSM in consideration of subject safety[18].

Based on each subject's VO2max and maximum heart rate (HRmax) in a maximal graded exercise test, it was possible to calculate treadmill speeds and heart rates for superordinate and subordinate goals using the metabolic equation for running of the ACSM[18]. In order to achieve the target heart rate (THR), workload was gradually increased during trials depending on the participant's heart rate which was monitored with a Polar Heart Rate Monitor (Polar Electro, Kempele, Finland), and RPE. The LIE performed supervised exercise on a treadmill six times weekly for 12 weeks at ≤ 40% heart rate reserve (HRR) (6 days/week, LIE). LIE subjects completed supervised exercise continuously during each session, which burned 200 kcal. The HIE group performed supervised walking and running on treadmill three times weekly for 12 weeks at ≥ 80% HRR (3 days/week, HIE). HIE Subjects completed supervised high-intensity interval exercise (30 s sprint, 30 s recovery) continuously throughout session, which burned 400 kcal.

Blood samples were drawn from the antecubital vein after an 8 h overnight fast. Blood samples were centrifuged for 15 minutes (3,000 rpm, 4 °C), stored at −80 °C, and directly analyzed. Biochemical analyses of serum glucose-regulated protein 78 (GRP78), glucagon-like peptide-1 (GLP-1), dipeptidyl peptidase-4 (DPP-4), and leptin were performed using enzyme-linked immunosorbent assays for quantitative detection of human Bip/GRP78, GLP-1, human DPP-4 (Abnova Corporation, Walnut, CA, USA) and leptin (R&D Systems, Minneapolis, MN, USA). All factors were quantified using polyclonal antibodies that recognized native human GRP78, GLP-1, DPP-4, and leptin a series of plates containing wells coated with predetermined amounts of recombinant human GRP78, GLP-1, DPP-4, and leptin. Serum glycosylated hemoglobin (HbAlc %) was measured by affinity chromatography. HbA1c levels were determined by high performance liquid chromatography using commercially available kit reagents (Bio-Rad, Hercules, CA, USA). Insulin resistance in the fasting state was determined by homeostasis model assessment (HOMA-IR) using the following formula: [fasting plasma glucose ($mg \cdot dl^{-1}$) × fasting plasma insulin ($\mu U \cdot dl^{-1}$)] ÷ 405.

Data analysis was performed IBM SPSS Statistics for Windows Version 19.0 (IBM Corp., Armonk, NY, USA). All data were expressed as the mean and standard deviation. Two-way ANOVA was used to control for differences between groups, test periods, body composition, and blood component changes caused by exercise type, and the paired and independent t-test method was used for the post hot test. A level of statistical significance of $p < 0.05$ was adopted for this study.

RESULTS

The characteristics of the HIE and LIE groups at the beginning of the study are shown in Table 1. There were significant difference in body weight and percentage body fat between the LIE and HIE groups ($p < 0.05$, respectively). Also, HIE resulted in a greater reduction in percentage body fat than the LIE ($p < 0.05$).

Table 2 shows the changes in glycemic control after the 12-week exercise training programs in the C-peptide level increased after the 12-week programs and was significantly different between groups ($p < 0.05$). The insulin level was significantly decreased after the 12-week exercise training program in the HIE group. Fasting glucose, HOMA-IR, and leptin decreased after the 12-week exercise programs and were significantly different between groups ($p < 0.05$, $p < 0.05$, $p < 0.05$, respectively). However, HbA1c showed no significant difference after the 12-week exercise training programs.

Table 3 shows the changes in ER stress factors after the 12-week exercise training programs. GLP-1 increased after the 12-week exercise programs and was significantly different between groups ($p < 0.05$). GRP78 and DPP-4 showed no significant difference after the 12-week exercise training programs.

DISCUSSION

The main findings of this study are that HIE can be implemented as an exercise treatment method in T2DM patients and that it is superior to energy expenditure-matched LIE with regard to improvements in body composition, glycemic control, and GLP-1 under the conditions used in this study. Our research design included careful and successful matching of the exercise training energy expenditures and mean intensities of the training groups. This justifies the comparisons between HIE and LIE.

The results of this study indicate statistically significant improvements in all outcomes in both groups. However, the gains in body composition (BMI) and ER stress factors (GRP78, DPP-4) were not significantly different between the groups. Participants in the HIE group demonstrated significant and similar gains in glycemic control and GLP-1 during the 3-month trial.

The ACSM and ADA recommend moderate- and vigorous-intensity exercise for people with T2DM and provide evidence-based guidelines for prescribing exercise training, in terms of intensity, volume, frequency, duration, and rate of progression[1, 18]. In this study, the variable of intensity was different between the groups, whereas the variables of volume, duration, and rate of progression were identical. On the basis of the findings of this study, individuals who have type 2 diabetes and participate in exercise training at either a moderate- or high-intensity level, as defined by the ACSM and ADA, may experience similar gains in body composition and glycemic control.

Table 1. The changes in body composition after 12 weeks of exercise training

Variable	Group	Pre	Post	Δdiff (%)
Weight (kg)	HIE	62.2±13.3	60.0±14.4*	−2.2 (3.5)
	LIE	66.7±20.9	65.4±23.0	−1.3 (1.9)
BMI (kg/m^2)	HIE	25.2±3.3	24.4±4.0*	−0.8 (3.2)
	LIE	22.8±4.2	22.4±4.8	−0.4 (1.8)
Fat (%)	HIE	29.9±2.9	27.6±3.3*†	−2.3 (7.7)
	LIE	24.2±4.1	23.9±4.9*	−0.4 (1.6)
VO_2max ($ml·kg^{-1}·min^{-1}$)	HIE	2,223.5±384.7	2,496.2±577.8*†	273 (12.9)
	LIE	2,382.5±665.1	2,505.2±547.2*	123 (5.2)

Values are means±SD, HIE: high-intensity exercise; LIE: low-intensity exercise; BMI: body mass index. *Significant difference within group (p<0.05). †Significant difference compared with LIE (p<0.05)

Table 2. The changes in glycemic control after 12 weeks of exercise training

Variable	Group	Pre	Post	Δdiff (%)
C-peptide (ng/ml)	HIE	2.9±1.3	4.7±2.1†	1.8 (62.1)
	LIE	3.9±2.3	5.4±2.2	1.5 (38.5)
Insulin (μU/ml)	HIE	42.1±27.4	18.7±8.81*	−23.4 (55.6)
	LIE	58.3±38.8	46.5±41.4	−11.8 (20.2)
Glucose (mg/dl)	HIE	174.3±25.5	138.8±35.7†	−35.5 (20.1)
	LIE	175.3±18.5	131.8±26.4	−70.2 (36.6)
HOMA-IR	HIE	17.4±10.5	6.5±3.4†	−10.9 (62.6)
	LIE	24.9±16.7	13.5±11.4	−11.4 (45.8)
HbA1c (%)	HIE	8.8±3.3	6.6±1.0	−2.2 (25.0)
	LIE	7.4±1.2	6.4±0.4	−1.0 (13.5)
Leptin (ng/dl)	HIE	1,923±670	1,178±406†	−745 (38.7)
	LIE	1,423±683	979±618	−444 (31.2)

Values are means±SD, HIE: high-intensity exercise; LIE: low-intensity exercise. *Significant difference within group (p<0.05). †Significant difference compared with LIE (p<0.05)

Table 3. The changes in GLP-1, GRP78 and DPP-4 after 12 weeks of exercise training

Variable	Group	Pre	Post	Δdiff (%)
GLP-1 (ng/dl)	HIE	0.21±0.02	0.39±0.04*†	0.18 (85.7)
	LIE	0.21±0.02	0.36±0.02*	0.15 (71.4)
GRP78 (ng/dl)	HIE	3.88±4.01	6.33±6.65*	2.45 (63.1)
	LIE	2.54±1.45	3.17±1.98*	0.63 (24.8)
DPP-4 (ng/dl)	HIE	29.23±20.23	22.85±21.43*	−6.38 (21.8)
	LIE	34.16±23.98	29.20±24.00*	−4.96 (14.5)

Values are means±SD, HIE: high-intensity exercise; LIE: low-intensity exercise; GLP-1: glucagon-like peptide-1; GRP78: glucose-regulated protein 78; DPP-4: dipeptidyl peptidase-4. *Significant difference within group (p<0.05). †Significant difference compared with LIE (p<0.05)

Our finding indicate that the HIE program resulted in more positive changes in weight, BMI, body fat percentage, and glycemic control (C-peptide, fasting glucose, HOMA-IR) in T2DM patients than the typical LIE program that is usually recommended to existing diabetic patients. HIE also showed positive changes in GRP78, DPP-4, and GLP-1, which are major factors of ER stress, showing more effective improvement for T2DM patients.

As low- to moderate-intensity exercise, the ACSM exercise guidelines[18] for diabetes patients recommends an aerobic exercise program involving more than 150 minutes of exercise per week. However, the HIE program maintains homeostasis; increases energy consumption; prevents metabolic diseases, such as obesity, and diabetes; and is known to reduce stress[7, 19, 20]. Sedentary diabetic patients report many barriers to physical activity, but the most common reason given is a “lack of time” for exercise. However, there is a growing body of literature that compares the metabolic risk factor reduction effects of traditional endurance training programs with the reduction of risk resulting from novel exercise interventions that require minimal amounts of time for patients. For this reason, HIE was recognized as an effective compromise that improves on the tediousness of LIE[21, 22]. Moreover, it is effective in inducing insulin sensitivity and controlling weight for T2DM patients[23]. It has been shown that the changes in physiological function, performance, and health-related markers resulting from HIE are similar to those resulting from LIE and that HIE results in more positive change in the health of patients than LIE[9]. In this study, the HIE group showed a significant reduction in body fat percentage after the exercise compared with before the exercise. In terms of the amount of reduction in body fat percentage, the HIE group showed a higher reduction (−7.69%) than the LIE group. Both groups showed improvement in glycemic control, but the HIE group was more effective. Previous studies showed that exercise proved to be effective in regulating glycometabolism by bringing about changes in body weight and percentage body fat.

Glycemic control is medically important for T2DM patient treatment and is an independent risk factor that can predict the possibility of diabetes patients developing complications[24]. In particular, most studies demonstrated that glycemic control is improved through HIE (≥ 80% peak power output) after body weight loss[25, 26]. It has the effect of reducing insulin secretion, cholesterol, and triglycerides; it also improves blood sugar levels and suppresses the direct stimulation of glucose intake in the skeletal muscle[20]. The present study shows improvements in blood glucose levels according to the change in body weight, with the HIE group showing a greater reduction than the LIE group. It also shows that leptin was reduced in both groups, but HIE was particularly more effective.

T2DM is caused by interactions between genetic and acquired factors, such as overeating and insufficient exercise, and is characterized by hyperglycemia due to relative insulin insufficiency and insulin resistacne[27]. The potential for exercise to improve insulin sensitivity is well established. Regular exercise has positive effects on insulin resistance in children and adolescnets[28]. Exercise has been studied regarding its role in improving insulin resistance and it has been classified by type, intensity, and activity period[29]. Dube et al.[30] recently reported that a graded dose-response relationship exists between exercise intensity and improvements in insulin sensitivity. When matched for caloric expenditure, high-intensity exercise appears to be at least as effective as moderate-intensity exercise for improving insulin sensitivity[31]. Our findings indicated that the HIE group showed more positive changes in C-peptide level, fasting glucose, and HOMA-IR than the typical LIE group. The imbalance between the protein handling capability of the ER and its load is referred to as ER stress[32]. Ozcan et al.[32] confirmed that reduction of ER stress in the hypothalamus resulted in improvement of leptin resistance; in addition, it was confirmed that ER stress is a major cause of leptin resistance[32] and that it is also a major factor that induces leptin resistance. The present study showed that ER stress increased as a result of the increase in physical stress during exercise in participants in the HIE group but not in those in the LIE group, but the changes in weight, obesity, and insulin resistance (characterized by positive changes in body fat) demonstrated that exercise also had positive effects on leptin changes in adolescents with T2DM.

GRP78 plays a significant role in maintaining the viability of cells exposed to various stress environments and helps in the response to immune attacks as well as in resisting the effects of various drugs[33]. GRP78 is increased in patients with T2DM, and it has been reported that insulin resistance can be improved through an exercise-induced increase in GRP78[34]. In addition, it has been reported that exercise during hypoxia improves insulin sensitivity. Treatment with hypoxia has been reported to be an effective for prevention and treatment of diabetes[35]. According to previous studies, exercise increases the amount of GRP-78, which has a positive effect on improvement of insulin resistance[36]. The present study showed that both groups had increased levels of expression of GRP-78, but the HIE group showed a larger increase. The cause seems to be an oxygen deficiency occurring during HIE, the exhaustion of glucose in the blood, and more physical stress during the exercise. Recently, the role of GLP-1 in the treatment of obesity and T2DM has emerged. GLP-1, an incretin hormone that regulates blood glucose levels[37], improves insulin sensitivity by stimulating the pancreas to secrete insulin[3] and is reported to increase the hydrolysis of triglyceride in adipose tissue[38]. GLP-1 appears to be damaged in T2DM patients[39]. Also, previous exercise-related studies have shown that healthy people have increased levels of incretin hormones such as GLP-1[15]. People who are obese showed similar results to people with normal weight through weight loss resulting from exercise[40]. Since exercise is considered to be the first line of intervention for the prevention and management of T2DM, improving GLP-1 through exercise is of the utmost importance. GLP-1, secreted through food stimulation, is decomposed at a very high speed by the enzyme dipeptidyl peptidase-4 (DPP-4), and its involvement in the physiological regulation of eating causes weight loss[41]. In this study, both groups were found to have significantly increased levels of GLP-1, with the HIE group appearing to have a greater increase. DDP-4 also affects the amount of GLP-1, and is an important factor in predicting the onset of insulin resistance and MS; it also has a direct association with insulin resistance[42–44]. Higher levels of it were also found in people with obesity or MS[43], and it is suggested to have a close relationship with the levels of BMI in healthy young people[44]. The present study showed that DPP-4 decreased in both groups, but the HIE group showed an approximately 21% greater reduction. These results are believed to be due to the reduction of BMI and body fat percentage, which resulted in suppression of DPP-4 activity and in turn creation of incretin hormones that normally control glucose levels, and this is believed to have resulted in the reduction of insulin resistance that ultimately improved the function of glycemic control in T2DM[45].

Therefore, high-intensity interval exercise training, as defined in this study, may cause improvements in body composition, glycemic control, and GLP-1 in adolescents with T2DM.

In summary, we compared the efficacy of HIE with energy expenditure-matched LIE in regard to changes in body composition, glycemic control, ER stress level (GRP78, DPP-4), and GLP-1. We have showed that HIE can be implemented in individuals with T2DM. Furthermore, we showed that HIE counteracts deteriorations in glycemic control, and that it is superior to LIE with regards to improvements in body composition (body fat percentage), glycemic control, and GLP-1. HIE may therefore be a good option when considering which type of exercise training T2DM patients should be recommended in primary care.

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