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Effect of high-intensity interval training versus moderate-intensity continuous training on plasminogen activator inhibitor-1 in Type 2 diabetic women

Ahmad Mahdi Ahmad*[1,A-F], Faten Ali[2,D-F], Heba Mohammed Ali[3,D-F]

[1]Department of Physical Therapy for Cardiovascular and Respiratory Disorders, Faculty of Physical Therapy, Cairo University, Giza, Egypt
[2]Department of Physical Therapy for Internal Medicine and Geriatrics, Faculty of Physical Therapy, Delta University for Science and Technology, Dakahlia, Egypt
[3]Department of Physical Therapy for Cardiovascular/Respiratory Disorders and Geriatrics, Faculty of Physical Therapy, Beni-Suef University, Beni-Suef, Egypt

Correspondence: Ahmad Mahdi Ahmad, Department of Physical Therapy for Cardiovascular and Respiratory Disorders, Faculty of Physical Therapy, Cairo University, Giza, Egypt; email: Ahmed.mahdy@pt.cu.edu.eg

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Abstract

Introduction: Thrombotic events in Type-2 diabetes are influenced by elevated plasminogen activator inhibitor-1 (PAI-1). This study compares the effects of high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) on PAI-1 level in Type-2 diabetic women.

Material and methods: Twenty-six women with Type-2 diabetes were recruited and assigned to two groups; of these, 18 completed the study: a HIIT group (n = 8, 42.1 ± 6.8 years, 33.1 ± 4.95 kg/m^2) and a MICT group (n = 10, 41.1 ± 2.9 years, 35.2 ± 2.6 kg/m^2). Outcome measures were PAI-1, glycosylated hemoglobin (HbA1c), and body mass index (BMI). The HIIT group performed 4 × 4-min working phases at 85–90% of peak HR (heart rate), followed by 3-min active rest intervals. At 65–75% of peak HR, the MICT group exercised for 30 minutes. Both exercise interventions included a warm-up and a cool-down period and were performed on a treadmill for eight weeks.

Results: The HIIT group showed significant reductions in PAI-1 (29.09 ± 2.67 vs. 37.42 ± 3.52 ng/mL, $p < 0.001$) and HBA1c (6.45 ± 0.50 vs. 8.34 ± 0.44%, $p < 0.001$) compared to baseline. The MICT group showed significant reductions in PAI-1 (30.37 ± 2.92 vs. 38.49 ± 2.40 ng/mL, $p < 0.001$) and HbA1c (6.78 ± 0.36 vs. 8.15 ± 0.63%, $p < 0.001$) compared to baseline. The differences in these outcomes between groups were not significant. BMI was not significantly changed in either group.

Conclusions: MICT could be as effective as HIIT for reducing elevated PAI-1 and HbA1c levels in obese women with Type 2 diabetes, regardless of BMI changes. However, the less vigorous MICT may be preferable in this patient population to improve fibrinolysis and hyperglycemia.

Keywords: body mass, exercise, fibrinolysis, hyperglycemia index, type 2 diabetes

Introduction

It was estimated that 537 million adults had diabetes in 2021, and this total is predicted to rise to 643 million by 2030 and 783 million by 2045 [1]. In the Middle East and North Africa, one in six adults lives with diabetes (73 million) [1]. Among these, 90%–95% of cases are believed to be Type 2 [2]. Diabetes mellitus (DM) is associated with increased morbidity and decreased lifespan, mainly due to thrombotic complications; these primarily result from a hypofibrinolytic state, characterized by higher levels of plasminogen activator

inhibitor-1 (PAI-1), an enzyme that inhibits fibrinolysis by blocking the conversion of plasminogen into active plasmin [3]. This thrombotic environment increases the risk for coronary artery disease, cerebrovascular disease, and peripheral artery disease [3]. Women with Type 2 diabetes have a 25–50% greater risk of cardiovascular diseases (CVD) than diabetic men, as they could be subjected to excess body fat and elevated CVD risk for a longer duration than men before developing diabetes [4].

Given the associations between elevated plasma PAI-1 and the increased likelihood of thrombotic events in patients with Type-2 diabetes, particularly diabetic women, it is important to seek efficient interventions to reduce circulating PAI-1 levels in those patients. Current treatment strategies aimed at improving the vascular system in DM focus on the early introduction of antithrombotic drug therapy where possible [5]. However, another promising anti-thrombotic non-pharmacological therapy that may reduce PAI-1 is exercise. Previous data suggests that moderate-intensity continuous training (MICT) effectively reduces PAI-1 in healthy individuals [6], patients with metabolic syndrome [7,8], and patients with Type-2 diabetes [9]. However, the effect of high-intensity interval training (HIIT) on plasma PAI-1 in patients with Type 2 diabetes, has only been investigated in one study to date [10]. As a result, there is still no agreement on the exercise intensity that most efficiently reduces plasma PAI-1 and promotes fibrinolysis in DM.

Therefore, the aim of the present study was to compare HIIT with MICT in terms of their induced changes in plasma PAI-1 levels, as a primary outcome, and in glycosylated hemoglobin (HbA1c) and body mass index (BMI), as secondary outcomes, in female patients with Type 2 diabetes. As exercise intensity is one of the most important determinants of the clinical outcomes of exercise training [11], we hypothesize that HIIT and the MICT may have significantly different effects on circulating PAI-1 levels. The findings of this study could help in the development of effective exercise training programs to reduce the risk of thrombosis in women with Type 2 diabetes.

Material and Methods

Ethical considerations

This study received ethical approval from the Ethics Committee of Scientific Research of the main author's institution (P.T. REC/012/004012). The research was performed in accordance with the Helsinki Declaration. All patients gave their consent prior to participation in this research.

Participants

The patients were recruited by convenience sampling (n = 26 patients with Type 2 diabetes) and assigned to either a HIIT group or a MICT group. A thorough medical history was taken. The inclusion criteria comprised the following: female sex, Type 2 diabetes diagnosed with an HbA1c > 6.5%, aged 30 to 50 years, obesity (BMI > 30 kg/m^2), receiving oral hypoglycemic medication, and having PAI-1 levels above 20 ng/mL. The exclusion criteria included pregnancy, cardiovascular disease, chest disease, diabetic foot, contraindications to exercise testing, and neurological or musculoskeletal limitations to exercise training. The patients maintained their usual lifestyle throughout the study. Eighteen patients completed the study: HIIT group (n = 8) and MICT group (n = 10). The flow of participants for the study is given in Figure 1.

Procedures

At baseline, a maximal symptom-limited treadmill exercise test was performed according to the modified Bruce protocol described by Fletcher et al. [12]. Patients underwent the test successfully with no adverse effects and ended the test upon maximal exertion. The peak heart rate (HR_{peak}) was recorded immediately after the end of the test using pulse oximetry (Heal Force, Prince-100B3, made in China). The determination of HR_{peak} at baseline was needed to calculate the target heart rate.

Outcome measures

The primary outcome was PAI-1. Venous blood samples were taken from patients, and plasma PAI-1 levels were assessed at baseline and after eight weeks with ELISA kits (Trinity Biotech USA, St. Louis, MO) according to the manufacturer's instructions.

The secondary outcomes were HbA1c and BMI. The blood samples were also analyzed for HbA1c before and after the study. Body weight and height were measured at baseline. The BMI was calculated as body weight (kg)/height (in meters squared) [13], at baseline and after eight weeks.

Interventions

The two types of exercise training were prescribed following the FITT principle for exercise prescription, as stated by the American College of Sports Medicine [14]. The total duration of exercise interventions was eight weeks. All patients in the two groups received oral hypoglycemic medication throughout the study, and received instructions on a healthy diet with no caloric restrictions. The exercise interventions are presented in Table 1. Heart rate was monitored by a fingertip pulse oximeter (Heal Force, Prince-100B3, made in China).

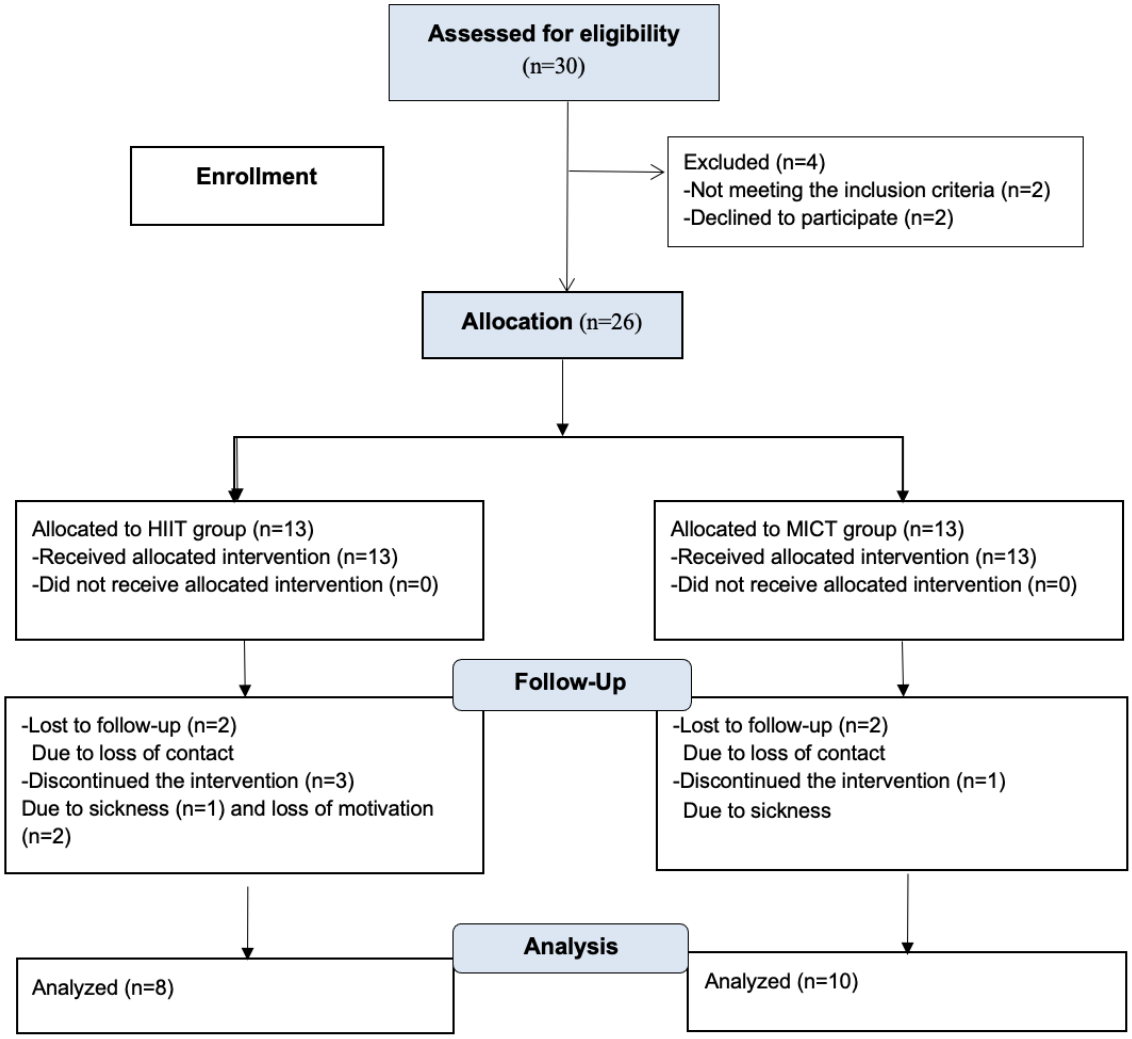

Fig 1. Flowchart of the study

Tab. 1. Description of the exercise interventions

	HIIT [15]	MICT
Frequency	Three days per week	Three days per week
Intensity	Low intensity for warming-up and cooling-down periods High intensity at THR of 85–90% of HR_{peak} for the high-intensity intervals Moderate intensity at a THR of 60–70% of HR_{peak} for active recovery	Low intensity for the warm-up and cool-down periods Moderate intensity at a THR of 65–75% of HR_{peak} during the working phase
Time or Duration	5 minutes warm-up Four 4 min high-intensity workouts with three-minute recovery intervals in between 3 minutes cool-down	The session lasted 45 minutes (5–10 minutes of warming up, 30 minutes of the working phase, and 3–5 minutes of cooling down)
Type/mode	Treadmill, interval walking exercise	Treadmill, continuous walking exercise

HIIT – high-intensity interval training, MICT-moderate-intensity continuous training, HR_{peak} peak heart rate, THR-target heart rate.

Statistical analysis

All variables were found to have a normal distribution (Kolmogorov-Smirnov test) and all independent samples demonstrated homogeneity of variance (Levene's test). The unpaired t-test was used to assess the differences in the means between the two groups at baseline and post-intervention, while the paired t-test was used to compare the mean changes within each group pre – and post-intervention. The values of $P < 0.05$ were considered statistically significant. Descriptive statistics were used and the data was presented as means ± standard deviations. Percent changes from baseline in the means of the outcome measures were computed. All statistical calculations were done using Social Science Statistics and GraphPad Prism software.

Results

No significant differences were found between the two groups with regard to age or baseline anthropometric characteristics (Tab. 2).

No significant differences in outcome measures were found between the two groups at baseline (Tab. 3). After eight weeks, the HIIT group showed significant reductions in PAI-1 (29.09 ± 2.67 vs. 37.42 ± 3.52 ng/mL, $p < 0.001$) and HbA1c (6.45 ± 0.50 vs. 8.34 ± 0.44%, $p < 0.001$) compared to baseline. The MICT group also showed significant reductions in PAI-1 (30.37 ± 2.92 vs. 38.49 ± 2.40 ng/mL, $p < 0.001$) and HbA1c (6.78 ± 0.36 vs. 8.15 ± 0.63%, $p < 0.001$) compared to baseline after eight weeks. After the interventions, non-significant differences in PAI-1 and HbA1c were found between the groups ($p > 0.05$). In addition, the two exercise groups showed non-significant changes in BMI compared to the baseline ($p > 0.05$).

The mean PAI-1 decreased by 22.26% and 21.09% in the HIIT and MICT groups, respectively (Fig. 2). The mean HbA_{1c} decreased by 22.66% and 16.8% in the HIIT and MICT groups, respectively (Fig. 2).

Tab. 2. Baseline age and anthropometric characteristics

Variable	HIIT group	MICT group	p-value
Age [years]	42.13 ± 6.81	41.10 ± 2.92	0.700
Height [cm]	157.25 ± 2.19	157.70 ± 2.06	0.659
Body weight [kg]	81.77 ± 12.10	87.58 ± 6.49	0.209
BMI [kg/m^2]	33.08 ± 4.95	35.22 ± 2.58	0.255

BMI – body mass index, HIIT – high-intensity interval training, MICT – moderate-intensity continuous training.

Tab. 3. Results of the two groups at baseline and post-intervention

Variables		HIIT group	MICT group	Levene's test	Unpaired t-test
				p-value	p-value
PAI-1 [ng/mL]	baseline	37.42 ± 3.52	38.49 ± 2.40	0.089	0.457
	post	29.09 ± 2.67	30.37 ± 2.92	0 .995	0.352
	p-value	< 0.001*	< 0.001*		
HbA_{1c} [%]	baseline	8.34 ± 0.44	8.15 ± 0.63	0 .297	0.482
	post	6.45 ± 0.50	6.78 ± 0.36	0 .377	0.127
	p-value	< 0.001*	< 0.001*		
BMI [kg/m^2]	baseline	33.08 ± 4.95	35.22 ± 2.58	0.079	0.255
	post	32.97 ± 4.29	34.76 ± 3.00	0.289	0.314
	p-value	0.783	0.239		

BMI – body mass index, HbA1c – glycosylated hemoglobin, HIIT – high-intensity interval training, MICT – moderate-intensity continuous training, PAI-1 – plasminogen activator inhibitor-1, * significant p-value based on the Paired t-test.

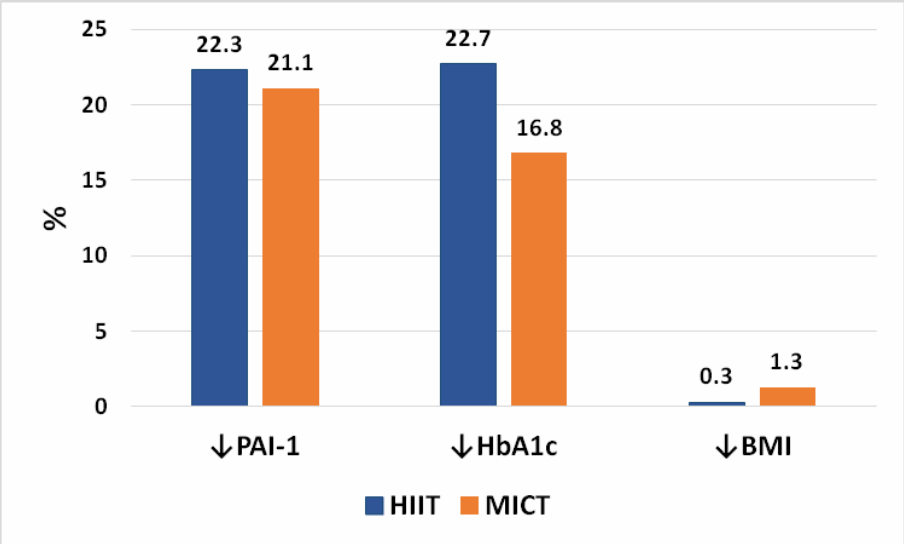

Fig. 2. Percent changes from baseline in the outcome measures in the two groups

Discussion

Recent guidelines from the American College of Sports Medicine (ACSM) address the therapeutic strength of exercise intervention for the management of Type 2 diabetes [16]. The purpose of this study was to compare HIIT and MICT with respect to exercise-induced changes in PAI-1 level, HbA1c, and BMI in Type 2 diabetic women.

Contrary to our hypothesis, no significant difference was found between HIIT and MICT regarding exercise-induced reductions in PAI-1 in the studied Type 2 diabetic women. Both HIIT and MICT were equally effective in reducing baseline PAI-1 levels in these patients. Likewise, HbA1c decreased significantly following HIIT and MICT, with no significant difference between them. All of the above-mentioned improvements occurred independently of BMI changes.

In line with our findings, Kalil et al. [9] showed that the combination of moderate-intensity aerobic exercises with a low-calorie diet reduced plasminogen activator inhibitor-1 levels to a greater extent than a low-calorie diet alone in patients with Type 2 diabetes. Also, moderate-intensity exercises effectively minimized PAI-1 concentrations in patients with metabolic syndrome [7,8]. In addition, Buchan et al. [6] showed that a seven-week moderate-intensity exercise program significantly improved plasminogen activator inhibitor-1 levels in healthy adolescents. Similarly, our present findings indicate significant reductions in PAI-1 levels in the MICT group compared to baseline.

Nonetheless, not only do moderate-intensity exercises reduce plasma PAI-1 in Type 2 diabetes, but HIIT also improved fibrinolysis and homeostasis in men with Type 2 diabetes by altering tissue plasminogen activator (t-PA) and the t-PA/PAI-1 complex [10]. Similarly, our present findings indicate that HIIT led to a significant reduction in plasma PAI-1 concentrations in women with Type 2 diabetes. It has also been found that highly-trained athletes show lower PAI-1 levels than sedentary subjects [17]. The mechanism underlying such favorable reductions in plasma PAI-1 could be attributed to exercise-induced adaptations within skeletal muscles involving a large series of gene expression and post-translational modifications [18]. Exercise training increases t-PA protein levels and reduces PAI-1 levels in the exercised muscles, thus enhancing the local fibrinolytic state and blood flow to the active muscles [18].

Interestingly, in both groups, although the patients remained obese, they showed a decrease in baseline PAI-1 levels. As such, it appears that other explanations for PAI-1 reductions than changes in BMI must be present. Since hyperglycemia increases PAI-1 expression by activating protein kinase C in endothelial cells [19], it is possible that exercise-induced reductions in hyperglycemia could have reduced PAI-1 expression, and hence its level, in our obese patients. This explanation could also be supported by Belalcazar et al. [20], who found that improved glucose control combined with lifestyle interventions contributed to lowering PAI-1 levels independent of marked adiposity changes. Therefore, our findings emphasize that exercise-induced reduction in plasma PAI-1 concentrations should be viewed as a benefit of exercise training itself, not merely as an avenue to weight loss.

Another finding in the present study was that both HIIT and MICT were equally effective at lowering HbA_{1c}. This finding is supported by a recent meta-analysis by de Mello et al. [21], which also suggests that both forms of training have similar effects on HbA_{1C} levels. Notably, the two exercise groups in the current study showed

significant reductions in HbA1c compared to the baseline without dietary restrictions. It has been shown that exercise programs without dietary regimens can improve glycemic control in patients with Type 2 diabetes [22]. The present study also demonstrated that, despite the absence of significant BMI reductions, reductions in HbA1c were observed in both groups. It has been reported that exercise programs lasting at least eight weeks can decrease HbA_{1c} in Type 2 diabetics, independently of significant BMI changes [23], suggesting that exercise can improve glycemic control even when no weight loss occurs.

The mechanisms responsible for exercise-stimulated glucose uptake by skeletal muscles involve improvement in insulin sensitivity and increase in the availability of glucose transporter 4 [24,25], enhancement of mitochondrial function [26], activation of AMP-activated protein kinase, ATP turnover and feedback signaling [27], increase in nitric oxide levels with resultant vasodilatation and greater glucose delivery to the muscles [28], and increase in muscle temperature [29].

Finally, the present study should be viewed in light of some limitations, such as a relatively small number of participants and the lack of controls and randomization. However, this study has several strengths. It is the first study to compare the effects of HIIT and MICT on PAI-1 in patients with Type 2 diabetes. Also, the exercise protocols in this study were designed according to the FITT principle for exercise prescription, as reported by the American College of Sports Medicine.

Conclusion

MICT could be equally effective as HIIT in reducing circulating PAI-1 and HbA1c in obese women with Type 2 diabetes, even if no changes in BMI occur. Our findings suggest that the less strenuous MICT may be preferable for inducing fibrinolytic and glycemic benefits, particularly in obese Type 2 diabetic women who may be physically unfit. Nevertheless, future research is warranted to confirm our findings.

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Conflicts of Interest
The authors have no conflict of interest to declare.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 10th ed n. Brussels,Belgium: 2021. Available from: https://www.diabetesatlas.org
2. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes 2021. Diabetes Care. 2021; 44(Suppl 1): S15-S33.
3. Cosentino F, Ceriello A, Baeres FMM, Fioretto P, Garber A, Stough WG, et al. Addressing cardiovascular risk in Type 2 diabetes mellitus: a report from the European Society of Cardiology Cardiovascular Roundtable. Eur Heart J. 2019; 40(34): 2907-19.
4. Huebschmann AG, Huxley RR, Kohrt WM, Zeitler P, Regensteiner JG, Reusch JEB. Sex differences in the burden of Type 2 diabetes and cardiovascular risk across the life course. Diabetologia. 2019; 62(10): 1761-72.
5. Ajjan RA, Kietsiriroje N, Badimon L,Vilahur G, Gorog DA, Angiolillo DJ. Antithrombotic therapy in diabetes: which, when, and for how long? Eur Heart J. 2021; 42(23): 2235-59.
6. Buchan DS, Ollis S, Young JD, Thomas NE, Cooper SM, Tong TK, et al .The effects of time and intensity of exercise on novel and established markers of CVD in adolescent youth. Am J Hum Biol. 2011; 23(4): 517-26.
7. Esmat S, Abd Al Salam RF, Rashed L. Effect of Exercise on Plasminogen acivator inhibitor-1 (PAI-1) level inpatients with metabolic syndrome. J Am Sci. 2010; 6(12): 1374-80.
8. Camarillo-Romero E, Dominguez-Garcia MV, Amaya-Chavez A, Camarillo-Romero Mdel S, Talavera-Pińa J, Huitron-Bravo G, et al. Effects of a Physical Activity Program on Markers of Endothelial Dysfunction, Oxidative Stress, and Metabolic Status in Adolescents with Metabolic Syndrome. ISRN Endocrinol. 2012; 2012: 970629.
9. Khalil OA, Sherif MM, Ghoniem ME, Fahmy D, Fawzy MS. Effect of aerobic exercises on blood coagulation and fibrinolytic system in Type 2 diabetic patients. IJAR. 2015; 3(5): 64-70.
10. Rezaeimanesh, D. The effects of high intensity interval training on fibrinolytic factors, D-dimer, and fibrinogen in men with Type 2 diabetes. Arch Pharma Pract. 2020; 11 suppl 1: S154-60.
11. Praet FE, van Loon JC. Optimizing the therapeutic benefits of exercise in Type 2 diabetes. J Appl Physiol. 2007; 103(4): 1113-20.
12. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention. Exercise Standards for Testing and Training. A Scientific Statement From the American Heart Association. Circulation. 2013; 128(8): 873-934.

13. Nuttall FQ. Body Mass Index: Obesity, BMI, and Health: A Critical Review. Nutr Today. 2015; 50(3): 117-28.
14. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2016.
15. Ahmad AM, Ali HM. Comparative effects of two exercise training programs on health-related quality of life in middle-aged women with non-alcoholic fatty liver disease. Adv rehab. 2020; 34(4): 1-10.
16. Kanaley JA, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, et al. Exercise/Physical Activity in Individuals with Type 2 Diabetes: A Consensus Statement from the American College of Sports Medicine. Med Sci Sports Exerc. 2022; 54 (2): 353-68.
17. Lira FS., Rosa JC, Lima-Silva AE, Souza HA et al. Sedentary subjects have higher PAI-1 and lipoproteins levels than highly trained athletes. Diabetol Metab Syndr. 2010; 2: 7.
18. Hittel DS, Kraus WE, Hoffman EP. Skeletal muscle dictates the fibrinolytic state after exercise training in overweight men with characteristics of metabolic Syndrome. J Physiol. 2003; 548(2): 401-10.
19. Rikitake Y, Liao JK. Rho-kinase mediates hyperglycemia-induced plasminogen activator inhibitor-1expression in vascular endothelial cells. Circulation. 2005; 111(24): 3261-8.
20. Belalcazar LM, Ballantyne CM, Lang W, Haffner SM, Rushing J, Schwenke DC, et al. Look action for health in diabetes research group. Metabolic factors, adipose tissue, and plasminogen activator inhibitor-1 levels in Type 2 diabetes: findings from the Look AHEAD study. Arterioscler Thromb VascBiol. 2011; 31(7): 1689-95.
21. de Mello MB, Righi NC, Schuch FB, Signori LU, da Silva AMV. Effect of high-intensity interval training protocols on VO2max and HbA1c level in people with Type 2 diabetes: A systematic review and meta-analysis. Ann Phys Rehabil Med. 2022; 65(5): 101586.
22. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care. 2016; 39(11): 2065-79.
23. American Diabetes Association. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes 2021. Diabetes Care. 2021; 44(Suppl 1): S53-S72.
24. Shambrook P, Kingsley M, Taylor N, Gordon B. Accumulated or continuous exercise for glycaemic regulation and control: a systematic review with meta-analysis. BMJ Open Sport Exerc Med. 2018; 4(1): e000470.
25. Stanford KI, Goodyear LJ. Exercise and Type 2 diabetes: molecular mechanisms regulating glucose uptake in skeletal muscle. Adv Physiol Educ. 2014; 38(4): 308-14.
26. Meex RC, Schrauwen-Hinderling VB, Moonen-Kornips E, Schaart G, Mensink M, Phielix E, et al. Restoration of muscle mitochondrial function and metabolic flexibility in Type 2 diabetes by exercise training is paralleled by increased myocellular fat storage and improved insulin sensitivity. Diabetes. 2010; 59(3): 572-9.
27. Jensen TE, Sylow L, Rose AJ, Madsen AB, Angin Y, Maarbjerg SJ, et al. Contraction-stimulated glucose transport in muscle is controlled by AMPK and mechanical stress but not sarcoplasmatic reticulum Ca2+ release. Mol Metab. 2014; 3(7): 742-53.
28. Hong YH, Betik AC, McConell GK. Role of nitric oxide in skeletal muscle glucose uptake during exercise. Exp Physiol. 2014; 99(12): 1569-73.
29. Koshinaka K, Kawamoto E, Abe N, Toshinai K, Nakazato M, Kawanaka K. Elevation of muscle temperature stimulates muscle glucose uptake in vivo and in vitro. J Physiol Sci. 2013; 63(6): 409-18.