Research Article

Influence of high intensity interval training on adipose tissue PAI-2 and MMP-2 mRNAs expression in rat with high-fat diet-induced metabolic syndrome

Mojgan Banihashemi[1], Ensiyeh Yazdkhasti[1], Maryam Mahmoudi Haghshenas[2], Fatemeh Rostamkhani[3*]

Abstract

The aim of this study was to investigate the influence of high intensity interval training on adipose tissue PAI-2 and MMP-2 mRNAs expression in rat with high-fat diet-induced metabolic syndrome. In this experimental study, 32 male Wistar rats (120 to 130 g) were selected and after 12 weeks of high-fat diet and modeling of metabolic syndrome were randomly divided into 4 groups: control, metabolic syndrome (Mets), high intensity interval training (HIIT) and Mets + HIIT. The HIIT program included 5 to 10 intense running on the treadmill with an intensity of 80 to 95% of the maximum speed and in slow running with a speed of 55% of the maximum speed with a zero slope of the treadmill for 8 weeks. Data were analyzed using one-way analysis of variance (ANOVA). The results of one-way analysis of variance showed that there was a difference between the mean expression of MMP-2 and PAI-2 mRNA in adipose tissue of male rats with metabolic syndrome in different groups (P = 0.001). However, HIIT improve this gene after Mets in adipose tissue ($p<0.05$). It seems that HIIT program improve metabolic syndrome with controlling PAI-2 mRNA and have an anti-inflammatory effect in adipose tissue. However, it need to more studies especially on human sample.

Key Words: **High intensity interval training, Metabolic syndrome, MMP2, PAI-1**

Introduction

A glance at human societies shows that many people are overweight and this obesity is epidemic in developed societies (Gajda et al., 2007). Obesity is a long-term disease with various factors that depend on the complex interaction between genetic, environmental and epigenetic factors (Pereira-Lancha et al. 2012). Excessive accumulation of adipose tissue in the body, inactivity and excessive consumption of high-fat foods are the most important causes of obesity (Masoudi et al. 2015). The Metabolic syndrome includes a combination of risk factors such as central obesity, dyslipidemia, insulin resistance, and hypertension that occur at the same time and increase the risk of cardiovascular disease (almost twice as high as people without the syndrome) and eventually, it increases the mortality rate significantly (Juna et al. 2020). The underlying causes of metabolic syndrome are slightly unknown, but insulin resistance and visceral fat accumulation are known to be the precursors of metabolic syndrome (Hejazi et al. 2013). Many risk factors for metabolic syndrome are known, some of which are immutable such as genetics, age and sex, but some of which, such as high blood pressure, diabetes and overweight, can be modulated through lifestyle changes. Because a sedentary lifestyle prepares the ground for failure to regulate appetite (Saremi et al. 2014). Obesity is a chronic inflammatory disease in which adipocytes are affected by hypertrophy and hyperplasia due to excessive food consumption, this condition leads to cellular stress which causes oxidative stress and inflammatory response in adipose tissue. Which can lead to increased inflammatory status due to dysregulation of anti-inflammatory adipokines such as decreased adiponectin and increased proinflammatory factors including PAI-1 (Geagea et al. 2018).

Metabolic syndrome is characterized by increased plasma levels of coagulation factors as well as inhibition of the fibrinolytic pathway (increased PAI-1) (Skurk et al. 2004). Plasminogen is an active inhibitor of type 1 (PAI-1) adipokines that is used as an indicator of the interaction between the fibrinolytic system, inflammation, oxidative processes, adipose tissue, metabolic syndrome and atherosclerotic diseases. It al-

1. Student of Ph.D of Physical Education and Sport Sciences, Departement of Physical Education and Sport Sciences, Faculty of Education and Psychology, University of Mohagheghe Ardabili, Ardabil, Iran. 2. Department of Sport Physiology, Faculty of Physical Education, Islamic Azad University, Tehran, Iran. 3. Department of Biology, College of Basic Sciences, Yadegar-e-Imam Khomeini (RAH) Shahre Rey Branch, Islamic Azad University, Tehran, Iran.

*Author for correspondence: shirinrostamkhani@yahoo.com

M B: 0000-0001-5927-4661; E Y: 0000-0002-8298-2700; M M H: 0000-0002-6781-1145; F R: 0000-0001-9591-3870

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-so plays a significant role in tumor adhesion, cell migration and angiogenesis. Cell adhesion molecules are increased in patients with obesity, hypertension, type 2 diabetes and atherosclerosis (Pieters et al. 2017). It is well known that increased plasma PAI-1 levels are connected with body mass index, triglyceride and insulin levels and systolic blood pressure, and plasma PAI-1 levels are increased in obesity and insulin resistance (Garg et al. 2012).

PAI-1 is released by vascular endothelial cells, hepatocytes, adipocytes, cardiomyocytes, fibroblasts, and platelets. In pathological conditions, the production of PAI-1 can be regulated by inflammatory factors such as tumor necrosis factor alpha as well as insulin. Elevated plasma PAI-1 levels are associated with impaired fibrinolytic activity in stroke and coronary artery disease and increased cardiovascular events in diabetes, obesity, and insulin resistance (Jung et al. 2018). Thus, the association between PAI-1 and obesity as a result of increased production of PAI-1 in adipose tissue by different cell types such as prepadipocytes, adult adipocytes, macrophages, smooth muscle cells and Is considered endothelial (Somodi et al. 2018). Matrix metalloproteinases MMPS is a large group of protease enzymes that have been identified by 26 members of this family so far. These enzymes are produced by different types of cells such as adipocytes, smooth muscle, monocytes and endothelial cells, which are divided into 5 subgroups of collagenases, gelatinases, metalloproteinases and stromilysins based on structural similarity. The highest emissions and activity are related to 72 and 92 kDa collagen, which are related to MMP-2 and MMP-9, respectively (Opdenakker et al. 2001).

In pathological conditions such as obesity and various metabolic diseases and physical and mechanical stress, the expression and activity of these enzymes increase due to the secretion of proinflammatory cytokines, causing the breakdown of collagen and gelatinases and disrupting the microanatomical structure of body tissues and results in the intensification of inflammation and inflammation of various diseases such as heart lesions, destruction of the vascular wall, accelerating the spread of cancer cells, atherosclerosis, etc. over time (Furfaro et al. 2012). The two members of metalloproteinase, MMP2 and MMP9, are important factors in the invasion of cancer cells and their expression is probably associated with increased oxidative stress and inflammation caused by free radicals, thus inhibiting the process of oxidative stress and reducing Levels of antioxidants may possibly inhibit the progression of cancer cells by reducing the expression of these MMPs and improve it as a result (Gong et al. 2018). In HIIT the length and duration of each intense work or reconstruction time has an immense variety and considered to ra-

-nge from 6 seconds to 4 minutes (Tjonna et al. 2009). Intense intermittent HIIT training with minimal time is recommended to overcome the problem of opportunity to participate in training and thus increase physical activity and health of these people. This exercise is a powerful stimulant for cardiovascular and muscular adaptations and increases the maximum oxygen consumption (VO2max) metabolism, increases exercise performance, reduces carbohydrate and fat dependence, improves insulin function, lowers blood pressure and in heart patients and Hypertension improves cardiovascular fitness (Van 2008). There are many evidences that intense intermittent HIIT exercise can be a priority for weight loss and fat burning programs, both in terms of saving time and being more effective (Motta et al. 2016). Following HIIT, a decrease (Hemmati et al., 2013; Musafa and Abedi, 2018) and no significant change in PAI-1 have been reported (Santos et al .2016). Studies also show that exercise can help improve matrix metalloproteinase levels and their associated inflammatory factors. However, the results of studies in this field are inconsistent. Decreased expression and serum levels of MMP-2 have been reported in rats following voluntary exercise and intense intermittent exercise (Posa et al 2015).

It has been shown on the other hand that 12 weeks of resistance training increases MMP2 levels in rats (Leite et al .2013). Due to the importance of exercise in reducing obesity, the possible effects of intermittent exercise in reducing fat mass, the important role of MMP-2 and PAI-1 in modulating metabolic status and inflammation, as well as the lack of mechanisms of intense intermittent exercise in modulating these cytokines so the researcher investigate the effect of intense intermittent exercise on the expression of PAI-2 and MMP-2 genes in adipose tissue in rats with high-fat metabolic syndrome.

Materials and Methods

Animals

The present study was performed experimentally in a multi-group design with a control group and observing the Helsinki declaration on male Wistar rats. The statistical population of the study is 32 healthy male Wistar rats with a 4-week-old age and an average weight of 120 to 130 grams, which were purchased from the Animal Care Center of Baqiyatallah University of Medical Sciences. The statistical sample of this research was performed by purposive sampling method according to weight and age conditions. The rats were then kept under suitable conditions for one week (room temperature 22 ± 1.4 ° C with 50 to 55% humidity, 12-hour sleep-wake cycle, without food and water restrictions) to get used to the environmental conditions. After weighing, rats were randomly divided into two groups: standard diet and high fat diet (HFD). Rats eat a high-fat diet (30 to 40%

fat) for 12 weeks to induce model of metabolic syndrome. After 12 weeks, blood samples (fat profile, insulin resistance, fasting glucose) were taken consider model of disease and approve of model (Homayoun Far et al., 2013).

It is to be mentioned that the specific diet of each group continued in the same manner until the end of the protocol. After ensuring the development of the metabolic syndrome model in rats, the samples were divided into 4 groups based on the research design, including: control group (had a standard diet during the study and did not receive HIIT exercise); Metabolic syndrome group (they developed metabolic syndrome after receiving a high-fat diet); Metabolic syndrome group + HIIT (their metabolic syndrome is confirmed then they have received HIIT training); HIIT group (took a standard diet and practiced HIIT during the study).

High-intensity interval training (HIIT) protocol

Initially, the rates were put on a 3-to-5-sessions routine for a week to run on treadmill with the speed set to 7-10 m/h for 5-10 minutes per session in order to prepare them for the main training. Subsequently, the primary HIIT course began by putting the rats on the treadmill twice a week. The program description is as follows:

In the first week, the rats received 5 stages of high-intensity intervals with 80% of max running speed, and 5 stages of active resting intervals with 55% of the maximum running speed, During the second week, the program was followed by 6 stages of high-intensity intervals with 85% of max speed, and 6 stages of active resting intervals with 55% maximum running speed. In the third week, 7 stages of high-intensity intervals with 90% max running speed, and 7 stages of active resting intervals with 55% of the max speed were given to the rats. The fourth week continued by giving the rats 8 stages of high-intensity intervals with 90 percent of the max speed, and 8 stages of active resting intervals with 55 % speed. The rats' fifth week of training was followed by 9 stages of high-intensity intervals with 95% of the maximum speed, and 9 stages of active resting intervals with 55% speed. And finally, from the 6th week till the 8th week, 10 stages of high-intensity intervals of 95% running speed, with 10 stages of active resting intervals with 55% max run speed were given to the rats. The total training time with the warm-up & cool down times included was 20 minutes in the first week, and 30 minutes in the last week of training. The Maximal Exercise Running Test (MERT) was used for determining the maximum training capacity and the intensity of the training (Machado et al, 2017).

Sampling tissues and measuring lab variants

48 hours after the final training session (10-12 hours fasting), the subject rats from each test group were put to sleep by intra-protaneal injection of a mixture of Ketamine 10% (50mg/kg dosage) and Xylazine 2% (10mg/kg dosage). Thence, a sample was taken from the adipose tissue, and after rinsing using phsyiological serum, they were floated in RNAlaterTM1 at a 20% ratio in the 1.8 microtubes, and then were sent to the lab for genetic test. The gene expression of the desired factors was measured from visceral adipose tissue by real-time-PCR technique, and then the quantification of gene expression values was analyzed by the $2^{-\Delta\Delta ct}$ method. RNA was extracted from the sample tissue using Rneasy Protect Mini-Kit (QIAGEN) according to the company's given instructions. PCR reaction was performed using (Applied Biosystems) PCR master mix and SYBR Green in ABI Step one (Applied Bio systems, Sequence Detection Systems. Foster City, CA) according to the manufacturer's protocols.

In this study, the GAPDH gene was used as the internal control. The sequence of primers used in the present study is shown in Table 2.

Table 1. The HIIT program description.

High-Intensity Interval Training (HIIT)					
Week	Total Training Time (minutes)	Number of Training Stages	Training Intensity % (in relation to the max speed)	Number of Active Resting Stages	Active Resting Speed % (in relation to max speed)
1st	20	8	80	5	55
2nd	22	6	85	6	55
3rd	24	7	90	7	55
4th	26	8	90	8	55
5th	28	9	95	9	55
6th	30	10	95	10	55
7th	30	10	95	10	55
8th	30	10	95	10	55

Table 2. The sequence of primers

Gene	Primers	Sequence
PAI-2	Forward	TGAGAGAGGGCAAAGTGGTT
	Reverse	TGAGAGAGGGCAAAGTGGTT
MMP-2	Forward	GAACACCATCGAGACCATGC
	Reverse	GGTCCAGGTCAGGTGTGTAA
GAPDH	Forward	CAAGTTCAAGGGCACAGTCA
	Reverse	CCCCATTTGATGTTAGCGGG

Statistical analysis

The Komogrov-Smirnov test was used to ensure normal data distribution, and the Levin test was used to ensure homogeneity of variances. Descriptive statistics were used to describe the data and analysis of variance (ANOVA), and the Tukey post hoc test was used to compare the groups in the studied variables. The significant level was considered $P \geq 0.05$. All statistical analyzes were performed using SPSS / Win software version 20.

Results

The Average and standard deviation of the research's variables is being shown in different categories inside of Table 3. The results of the One-way ANOVA test, demonstrates that there is a difference between average MMP-2 gene expression of adipose tissue in male rats that are suffering from metabolic syndrome in various groups of this research (p = 0.001). The results of Tukey post hoc test showed that the difference between the gene expression of MMP-2 gene between HIIT group and metabolic syndrome + HIIT (2-58) was negative, which indicates a significant difference (p = 0.009).

Also, the results of one-way analysis of variance showed that there was a difference between the gene expression of PAI-1 gene in adipose tissue of male rats with metabolic syndrome in different groups (P = 0.000). The results of Tukey test show that the mean difference of PAI-1 gene expression between HIIT group and metabolic syndrome + HIIT (-1.67) and with the metabolic syndrome group (-5.49) is negative, which shows a significant difference ((p=0.000) & (p=0.035)).

Discussion

This study is meant to review the effects of high-intensity interval training on the PAI-2 and MMP-2 genes of the adipose tissue in rats that suffer from metabolic syndromes with high-fat food. The underlying metabolic mechanism of these relations tend to be intricate, and the fact that these factors are often interrelated makes the study of these effects and its determining factors of each of them arduous.

The results of the present study showed that metabolic syndrome decreased MMP-2mRNA and increased PAI-2. However, these changes were reversed with HIIT exercise, and also improved in the metabolic syndrome group that underwent HIIT. Consistent with these results, the evidence suggests that PAI-2 links three pathophysiological situations associated with metabolic syndrome obesity, cardiovascular events, and diabetes. Weight loss, dietary factors, and obesity surgery have been shown to have beneficial effects on fibrinolysis disorder and may therefore reduce cardiovascular risk in patients with obesity or metabolic syndrome. Due to the improved absorption of insulin-stimulated glucose and the increased differentiation induced by PAI-2 inhibition in cultured adipocytes in mice, PAI-2 deficiency can be expected to lead to greater accumulation of subcutaneous fat in the body under high-fat diets (Saremi et al. 2014). These findings suggest that the plasminogen activation system may be involved in controlling fat accumulation in a more systematic way than originally proposed. Several new features have been added to MetS over time because most of them are associated with metabolic syndrome. PAI-2, the main inhibitor of the fibrinolytic system, belongs to this cluster and can be considered a real component of MetS. The mechanisms that bind PAI-2 to MetS are complex and possibly related, and several inducers may co-synthesize at multiple sites. Thus PAI-2 may act as a feedback loop to limit adipose tissue proliferation. Further efforts with experimental and clinical studies are needed to better understand this complex interaction. In any case, these findings support the rationale for the development of PAI-2 inhibitors, as they may be useful in controlling atherothrombosis and insulin resistance. HIIT training can also be effective in metabolic degradation by negatively regulating PAI-2, which was also confirmed in the present study in the group with metabolic damage after HIIT training. The results of previous research show that performing HIIT reduces subcutaneous fat and total body mass and

Table 1. mRNA expression of MMP2 and PAI-1 in different groups (mean±SD)

	Control	Mets	HIIT	Mets+HIIT	P
MMP-2 mRNA	39.0±1.0	25.60±4.2	66.57±1.0	28.1±2.52	*0.001
PAI-2 mRNA	1.0±0.49	6.16±0.7	0.66±0.4	2.33±0.77	*0.001

-roves oxygen consumption and insulin sensitivity (Skurk et al. 2004). Also, some studies of metabolic adaptations are similar and more than traditional endurance training Also reported. In relation to HIIT, Buchan et al. Examined the effect of intensity and duration of exercise for seven weeks on PAI-1 values in adolescents. In this study, 47 boys and 15 girls were divided into two groups of moderate intensity training (MOD, and HIT). The results of this study showed that the values of 1-PAI decreased after training intervention in both MOD and HIT groups, but the decrease of PAI-1 only in the MOD group was significant. Whereas in the current study, PAI-2 was studied in rats (Jung et al. 2018). Nevertheless, it is advised to study both training types in the future researches.

The role of metalloproteinase matrices of skeletal muscles in the extracellular matrix proteins function is to assist them in dissolving, and rebuilding the matrices; while the release of metalloproteinase matrices into the bloodstream facilitates angiogenesis, it seems that the two types of metalloproteinase matrix (MMP2) are the most important metalloproteinase matrices that are related to skeletal muscle function or dysfunction. Therefore, increasing its secretion from adipose tissue and distribution in the bloodstream even affects skeletal muscle, which showed a significant increase in the amount of this factor in HIIT training. However, increasing this factor in adipose tissue itself can prevent metabolic damage.

Conclusion

Based on the results of the present study, it seems that HIIT exercise with negative regulation of PAI-2 and positive regulation of MMP-2 has a beneficial role on adipose tissue and minimizes the side effects of a metabolic disease.

What is already known on this subject?

Obesity can lead to increased inflammatory status due to dysregulation of anti-inflammatory adipokines such as decreased adiponectin and increased pro-inflammatory factors including PAI-1.

What this study adds?

HIIT exercise with negative regulation of PAI-2 and positive regulation of MMP-2 has a beneficial role on adipose tissue.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The NIH “Guide for the Care and Use of Laboratory Animals” (NIH publication No. 80-23, revised 1996) and the professional governmental guidelines, in compliance with the Institutional Animal Care and Use Committee (IACUC), had been observed in all experiments.

Informed consent Animal Study.

Author contributions

Conceptualization: M.B., E.Y.; Methodology: F.R., M.M.H.; Software: M.B., E.Y.; Validation: F.R., M.M.H.; Formal analysis: F.R.; Investigation: F.R., M.M.H.; Resources: M.B., E.Y.; Data curation: M.M.H.; Writing - original draft: M.B., E.Y.; Writing - review & editing: M.B.; Visualization: E.Y.; Supervision: F.R.; Project administration: M.M.H.; Funding acquisition: F.R.

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