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Research Article

Circulating concentrations of the BATokine 12,13-dihydroxy- 9Z-octadecenoic acid (12,13-diHOME) in different types of exercise training

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Abstract

Dear Editor-in-Chief

According to the investigation, Lipokines are a kind of bioactive compounds, derived from adipose tissue deposition, which manages multiple molecular signaling pathways. In recent years, 12,13-dihydroxy-9Z-octadecanoic acid (12,13-diHOME), an Oxylipin, has become increasingly important in the scientific literature. An increase of 12,13-diHOME in circulation was associated with an improvement in metabolic health, and the action of this molecule seems to be mediated by brown adipose tissue (BAT)(1). In fact, Oxylipins are oxidized metabolites of long-chain polyunsaturated fatty acids (PUFAs). PUFAs may be received immediately from the weight loss program or from the metabolism of linoleic acid and α-linolenic acid(2). Research indicates that Oxylipins are present in every tissue, urine and blood(3). Linoleic acid may be metabolized through cytochrome P450 (CYP) in order to produce 12,13-diHOME(4). Circulating concentrations of BATokine 12,13-dihydroxy-9Z-octadecenoic (12,13-diHOME) in rodents and humans have been shown to be elevated following exposure to cold and exercise. In other words, in mice, administration of 12,13-diHOME increased fatty acid absorption by brown/beige adipocytes and skeletal muscle after a session of moderate-intensity training, and in rodents using the same training protocol. Furthermore, investigation suggests that circulating 12,13-diHOME is associated with an increase in mitochondrial respiration capacity in the skeletal muscle. This information improves the opportunity that will increase in circulating 12,13-diHOME with exercising capabilities to assist expand the respiratory capacity of a training skeletal muscle and might increase exercise potential(5,6).Whereas the current examination has centered on the distinguishing proof of 12,13-diHOME as the primary BAT-derived molecule controlled by exercise, but be that as it may, the impact of 12,13-diHOME administration to human is as of now obscure.

All things considered, it seems in destiny research it'll be crucial to study the physiological results of the signaling lipids which are substantially reduced via types of exercise program and diet, as those elements might also additionally play important roles in regulating the metabolic results of the exercise.

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Research Article

Effect of resistance training and nanocurcumin supplementation on the expression of FNDC5 and PPARƔ genes in rat muscle tissue

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Abstract

Background: Irisin is released from the Fndc5 protein in muscle cell through physical activity and effects on metabolism through browning of white fat. The purpose of this study was to the effect of resistance training and supplementation of nanocurcumin on the expression of genes of FNDC5 and PPARɣ rat muscle tissue.
Materials and Methods: In this experimental study, 32 rats were randomly divided into four groups (Control, resistance training, nanocurcumin, resistance training + nanocurcumin). The training groups program included 4 weeks, 3 days a week from climbing on a stepladder. Nanocarcmine (80 mg / kg) was given gavage in complementary groups for four weeks daily. FNDC5 and PPARƔ gene expression were measured using the RT-PCR method. Data were analyzed using one-way ANOVA with a significant level of $P \leq 0.05$.
Results: The results showed that resistance training and supplementation of Nanocarcmine significantly increased the expression of the gene of FNDC5 and PPARɣ in muscle tissue of rat ($P < 0.05$).
Conclusion: It seems resistance training with nanocurcumin supplementation may stimulate secretion of FNDC5 & PPARƔ from muscle, that has a key role in the metabolism of adipose tissue and the conversion of white tissue to brown fat tissue.

Keywords:
Resistance training, Nanocurcumin, FNDC5, PPARƔ

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1. Introduction

Adipose tissue of the endocrine glands is a prominent link between obesity and metabolic diseases by producing some important factors called adipokines. (1). There are two types of adipose tissue, including white adipose tissue and brown adipose tissue in mammals. White adipose tissue is a source of energy storage and brown adipose tissue plays a role in increasing UCP-1 protein, heat production, energy consumption and weight regulation (2). Researchers have recently found that skeletal muscle plays an active role in regulating metabolic homeostasis through its ability to connect with adipose tissue and endocrine glands (3). Skeletal muscle is an active metabolic tissue whose contraction increases the release of several myokines, such as interleukins 6, 8, 10, and 15, leukemia inhibitory factor, fibroblast growth factor, brain-derived neurotrophic factor, and myokine called irisin, which are able to interact with adipose tissue. Irisin is a 112 amino acid protein that is secreted from skeletal muscle immediately after exercise (4). Exercise induces the expression of the PGC-1α gene in skeletal muscle, and PGC-1α stimulates the expression of the fibronectin type III gene containing the glycoprotein FNDC5 in muscle tissue (5). PGC-1α, on the other hand, is a coagulator for PPAR. PPAR is involved in energy metabolism, which in turn stimulates the expression of the FNDC5 gene (6). Hosseinzadeh et al. (2015) reported increased expression of FNDC5 twin muscle gene in male rats after eight weeks of endurance and resistance training (7). Han et al. (2017) investigated the effect of aerobic exercise on the expression of skeletal muscle FNDC5 gene due to high-fat diet. The results showed a positive effect of exercise with or without a high-fat diet on FNDC5 gene expression (8). However, Hashemi et al. (2015) stated that 4 weeks of HIIT training had no effect on the protein content of PPARɣ subcutaneous adipose tissue in obese diabetic rats (9). The possible effects of herbal medicines have been confirmed by several studies (10). Curcuminoids are one of the most important anti-inflammatory substances in nature (11). Curcumin has significant functional properties including anti-tumor and anti-cancer activities, lowering blood and liver cholesterol levels, enhancing immune function, inhibiting cardiovascular disease, anti-inflammatory, protection against Alzheimer's disease and antioxidant properties (12). Curcumin can increase UCP1 and other browning proteins such as PGC-1α, PRDM16 in white adipose tissue via the AMPK pathway and the norepinephrine-beta-adrenoceptor pathway (13). Modification of adipose tissue phenotype due to exercise and supplementation is a new theory that has recently been proposed and the identification of its molecular cellular mechanism is being investigated. A single study was not found that examined the simultaneous effect of resistance training and nanocurcumin supplementation on the expression of FNDC5 and PPARɣ genes in muscle tissue. Therefore, in the present study, the researcher intends to investigate the effect of resistance training and nanocurcumin supplementation on the expression of FNDC5 and PPARɣ genes in rat muscle tissue.

2. Materials and Methods

The present study is experimental. In this study, 32 2-month-old male Wistar rats with an average weight of 200 to 220 g were purchased from the Pasteur Research Institute. Rats after transfer to the laboratory environment and familiarity with the new environment, were randomly divided into 4 groups (8 heads) control, nanocurcumin supplementation, resistance training, resistance training + nanocurcumin. Rats were kept in standard conditions of laboratory animals (temperature 25-23 ° C, humidity 40-50% and light-dark cycle 12:12). All rats had free access to standard laboratory animal feed as well as water. Ethical principles of the study, in accordance with the principles of working with laboratory animals approved by the Islamic Azad University, East Tehran Branch and receiving the code of ethics IR.IAU.ET.REC.1400.032 were observed by researchers during the research.

Resistance training program was performed using a ladder for rat resistance training. The familiarity stage was performed for a week to climb the ladder to a height of 1 meter and a slope of 85 degrees by tying a weight to the mouse tail. The training program was performed for 4 weeks in 3 sessions per week in the form of 3 sets with 4 repetitions in each set. Rest intervals between sets were 3 minutes, rest intervals between repetitions in each set were 30 to 60 seconds. Applying resistance by tying weights to the tails of mice was equivalent to different percentages of body weight during the training period. The details of the exercise program are summarized in Table 1 (14).

Table 1: Resistance training protocol based on body weight percentage

Training time	**first week**	**second week**	**Third week**	**forth week**
Exercise resistance (body weight percentage)	30%	50%	80%	**100%**

80 mg of nano-curcumin (commercial nano-curcumin made by Exir Nano Sina Company (Tehran, Iran) per kg of body weight (mg / kg) in groups Supplements and exercises + supplements were given by gavage (15). Due to the half-life of gene expression 48 hours after the last training session, the animals were first sampled in a special area (sterile environment) with a combination of ketamine (30 to 50 mg per kg of body weight) and xylazine (3.5 mg / kg body weight were anesthetized. Blood samples were then taken from the left ventricle at a rate of 5 cc and immediately poured into test tubes containing EDTA anticoagulant and stored at -20 ° C. After blood sampling, soleus muscle tissue was separated through a slit on the lateral dorsal region of the lower limb and after weighing was placed in liquid nitrogen, then transferred to a freezer at -80 ° C. In order to extract mRNA, 50 mg of frozen tissue was used by homogenization method. For mRNA isolation, the German Qiagen kit was used according to the manufacturer's instructions.

The extracted RNA solution was cleaned of any DNA contamination and RNA-degrading enzymes using the German Qiagen kit. From the sample, two micrograms of mRNA was used to synthesize the first cDNA strand. CDNA synthesis was performed with the transcription first strand cDNA synthesis kit (Roche, Germany) and according to the kit instructions. Finally, Real time PCR was performed using a device (Rotrogene 6000, Corbet). Real time PCR program for genes based on cybergreen from Qiagen (Germany) and includes: initial washing at 95 ° C for 10 minutes and 45 cycles including: washing at 95 ° C for five seconds, binding of primers at appropriate temperature 57 ° C for 20 seconds, expansion at 72 ° C for 15 seconds, adjustment of melting temperature in the range of 55 to 99 ° C to form a melting curve diagram. Melting Curve was also plotted to ensure the specificity of the reaction product. Internal control for FNDC5 and PPARɣ genes was performed by GAPDH household gene (Pishgam, Iran). Finally, data quantification was performed using the formula 2 - ^ (ΔΔ).

Table 2: Primers used in Real-time PCR

	Gene	**sequence**
1	Rattus norvegicus fibronectin type III domain containing 5 (**FNDC5**)	Forward: AGGACCTCACTGTTCTGACG
		Reverse: AGGGGTTAGTTGGAGGCTTC
2	Rattus norvegicus peroxisome proliferator-activated receptor gamma (**PPARɣ**)	Forward: ATCCCGTTCACAAGAGCTGA
		Reverse: GCAGGCTCTACTTTGATCGC
3	**GAPDH**	Forward: CAAGTTCAAGGGCACAGTCA
		Reverse: CCCCATTTGATGTTAGCGGG

Kolmogorov-Smirnov test was used for normal distribution of data and Levene test was used to check the homogeneity of variances. To compare the differences between the groups, one-way analysis of variance was used and then Bonferroni test was used. Statistically significant difference was determined at the level (P≥0.05). SPSS software version 25 was also used for data analysis.

3. Results

Data analysis showed that there was a significant difference in the rate of changes in FNDC5 gene expression in muscle tissue between different groups (P <001) (Table 3). The results of Bonferroni post hoc test showed that there was a significant difference between the control groups and the resistance training group, nanocurcumin and nanocurcumin + resistance training (P <001). (Figure 1). Other results of the present study, there is a significant difference in the amount of changes in the expression of PPARɣ gene in muscle tissue between different groups (P <001) (Table 3). The results of Bonferroni post hoc test showed that there was a significant difference between the control groups and the resistance training group, nanocurcumin and nanocurcumin + resistance training (P <001). (Figure 2).

Table 3: Results of one-way analysis of variance FNDC5 and PPARɣ in four research groups

Variable		**Sum of squares**	**df**	**F**	**Sig**
FNDC5	Between groups	2. 485	3	67.77	0.000
	Within the group	0. 342	28		
PPARɣ	Between groups	397.197	3	24. 09	0.000
	Within the group	477.76	28		

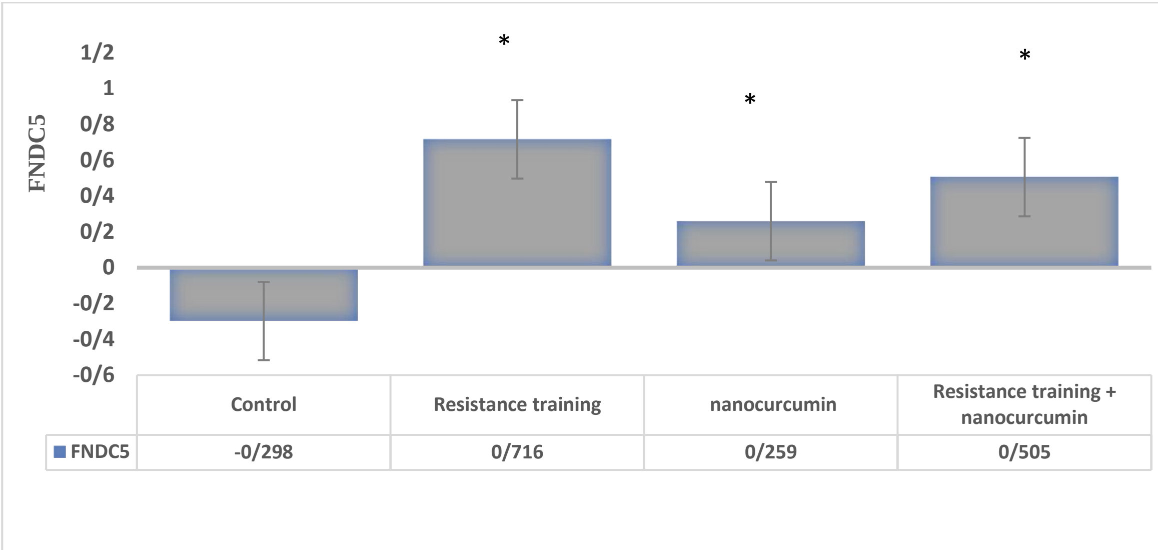

Figure 1: Comparison of mean FNDC5 gene expression in four groups: control, supplement, exercise, exercise + supplement.

*** Significant level P<0.05**

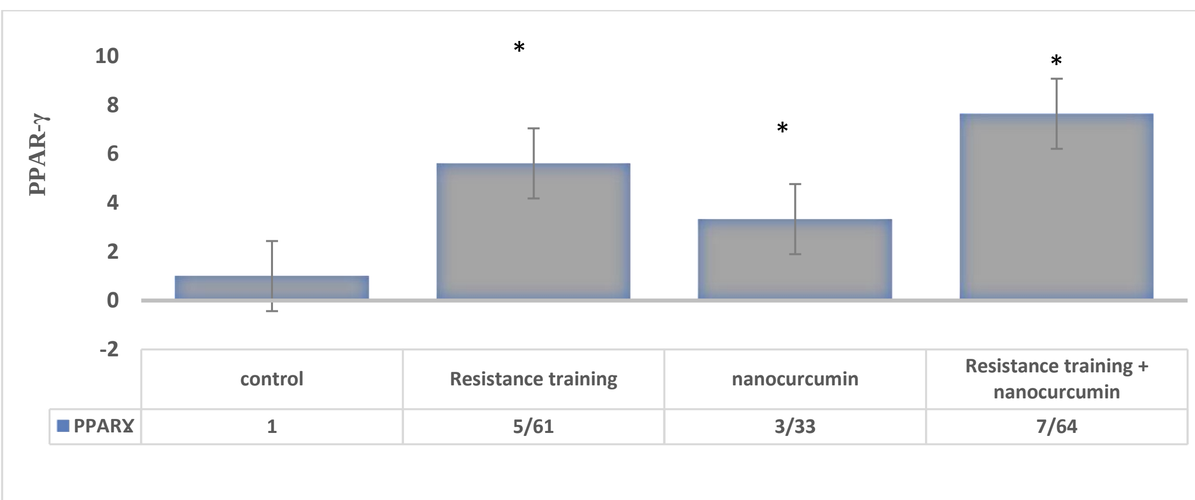

Figure 2: Comparison of mean PPARɣ gene expression in four groups: control, supplement, exercise, exercise + supplement.

*** Significant level P<0.05**

4. Discussion

In the present study, it was shown that resistance training and nanocurcumin consumption significantly increased FNDC5 gene in muscle tissue. PGC-1α is secreted into skeletal muscle following exercise, which completes the FNDC5 gene expression process. FNDC5 is then subdivided into a new form of irisin (9). During the 24-hour recovery phase, FNDC5 mRNA expression of protein and muscle tissue is maintained at a high level. The results show the coordinated expression of FNDC5 and PGC-1α in the increase of serum irisin levels after exercise (16). (16). Research has shown that irisin browns subcutaneous adipose tissue and increases energy costs and fat oxidation. Therefore, irisin is known as a new agent for the prevention and treatment of obesity (17). (17). The signaling pathway of PGC-1α expression and conversion of FNDC5 to irisin is activated through exercise (16). Khalfi et al. (2015) showed that high-intensity intermittent training significantly increased FNDC5 gene expression in diabetic male rats (18). (18). Ghaderi et al. (2017) stated that 14 weeks of endurance training with two different intensities significantly increased the expression of skeletal muscle FNDC5 gene in obese mice (19). However, Pang et al. (2018) reported that running on a rodent treadmill had no significant effect on serum levels of irisin, PGC-1α and FNDC5 in rats (17). These results are inconsistent with the results of the present study. Non-heterogeneity can be referred to the type of tissue evaluated, the species under study, the characteristics of the exercise practiced, the characteristics of the subjects under study and the measurement methods. Studies have shown that resistance training with a high number of repetitions in the muscle group can lead to increased muscle endurance and muscle group.

The metabolic effects (muscle growth) of resistance training appear to be associated with increased FNDC5 expression. Previous studies have shown increased muscle strength, mTOR signaling, and hypertrophy in response to resistance training (20). As a result of these exercises, different signals activate PGC-1α in skeletal muscle, which can subsequently stimulate the expression of FNDC5 and act on white adipose tissue in the long run by secreting irisin-induced FNDC5 into the bloodstream. Increases UCP1, which indicates an increase in calorific value and energy cost through its conversion into heat (21). Curcumin can also increase UCP1 and other browning proteins such as PGC-1α, PRDM16 in white adipose tissue via the AMPK pathway and the norepinephrine-beta-3-adrenoceptor pathway (22). A recent study reported that combination therapy with endurance training and curcumin increased AMPK phosphorylation, NAD / NADH ratio, PGC-1α distillation, CAMP levels, and PKA downstream targets. The combination of curcumin and exercise accelerates mitochondrial biogenesis by increasing CAMP levels in skeletal muscle (23). Zou et al. (2021) stated in a study that the improvement in basal metabolic rate by curcumin may be partially regulated by the FNDC5 / p38 mitogen-activated protein kinase (p38 MAPK) / extracellular signal-related kinase (ERK) pathway 1/2 (24). Another result showed that resistance training and nanocurcumin supplementation significantly increased PPARɣ gene expression in muscle tissue of healthy male rats. Shabani and Darianush (2018) reported that eight weeks of LICT training, repeated 4 days a week, increases the protein content of PPARɣ in the adipose tissue of overweight diabetic mice and is one of the mechanisms for converting white fat to brown through protein mediation. Because the protein has a positive regulatory region of 16

Turgut et al. (2018) reported a significant increase in PPARƔ gene expression in rat liver and muscle after running on a treadmill for 6 weeks / 5 days a week (26). Various PPAR isoforms, such as PPARβ, PPARƔ, PPAR-α, mediate the beneficial effects of exercise. Gene expression and protein levels of these factors increase as a result of exercise, and the greater the intensity and duration of exercise, the greater the response or adaptation.

There are various mechanisms for increasing gene expression of these factors after exercise. Natural PPARs ligands include unsaturated fatty acids, 15-deoxy-D12, 14-prostaglandin G2 (15d-PGJ2), and 9-and-13-hydroxy-octacadionic acid (Hode-9, 13) (possibly increasing this). Factors after exercise can also increase PPARƔ gene expression. Fatty acids and eicosanoids can also increase the activity and expression of the PPARƔ gene. Gene expression, activity and interaction of PPARs with other transcription factors are among the determinants of PPARs signaling effects and one of the most important factors affecting these cases is the oxidative stress state of the cell (28). Increased exercise-induced mitochondrial activity to produce energy leads to increased production of reactive oxygen species (ROS), or oxidative stress. Oxidative stress activates regulatory kinases with extracellular ERK signal, platelet-derived growth factor (PDGF), and signaling inositol 3-kinase / protein kinase B (PI3K / AKT), which stimulates the expression of PPARs, as a They are considered defense mechanisms. Increased lipid oxidation due to exercise not only increases oxidative stress, but also stimulates gene expression and PPARs activity (27). Curcumin also appears to activate the FNDC5 / irisin pathway in healthy male rats by increasing PGC-1α and UCP-1. The findings of the present study are consistent with the findings that show that curcumin is able to increase the expression of PGC-1α (29). Curcumin is also able to enhance several metabolic exothermic genes, including UCP-1, BMP8b, SIRT1, PGC-1α, and PRDM-16 (29). However, Hashemi Takmili et al. (2015) in a study examined the effect of 4 weeks of HIIT (4 days per week) on PPARƔ protein content in subcutaneous adipose tissue of obese diabetic male rats and did not observe a significant change (9).). Hemmati Farsani et al. (2019) mentioned PPARƔ as an adipogenic agent in bone marrow mesenchymal stem cells and stated that 8 weeks of resistance training (5 days per week) did not affect the expression of this substance in the tibia marrow. Slow (30). Important factors of this contradiction with the findings of the present study can be the type of exercise, intensity and duration and type of supplement under study and measurement methods.

5. Conclusion

Due to the increase in muscle content of FNDC5 and PPARɣ following resistance training combined with the use of nanocurcumin in this study and the important roles of these two variables in adipose tissue metabolism. It seems that doing resistance training with nanocurcumin can be an important mechanism to reduce white adipose tissue and turn it into brown adipose tissue.

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Compliance with ethical standards

Conflict of interest The authors of the article state that there is no conflict of interest in the present study.

Ethical approval the research was conducted with regard to the ethical principles.

Informed consent Informed consent was obtained from all participants.

Author contributions

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

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Research Article

Moderate aerobic exercise and probiotic intake on FOXA1 gene expression in non-alcoholic fatty liver animal model: An Experimental Study

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Abstract

Background: Fatty liver disease is also known as fatty liver syndrome and is also called hepatic steatosis the aim of this study was to evaluate the effect of eight weeks of aerobic exercise and probiotic intake on FOXA1 gene expression in rats with fatty liver.
Materials and Methods: This study is an experimental laboratory study. Thirty-two male wistar rats were divided into 4 groups of 8 in the healthy, steatosis, steatosis + probiotic, steatosis + probiotic +aerobic exercise groups and tested for 8 weeks. The exercise protocol was as follows: in the first week from 10 minutes of running at a speed of 18 meters per minute to the eighth week with 60 minutes of running at a speed of 28 meters per minute. Consumption of probiotics; Relevant groups received 109 CFU / ml of Lactobacillus rhamnosus GG by gavage daily for 5 weeks and 5 days a week. RT-pcr method was used to evaluate the expression of FOXA1gene. ANOVA were used for data analysis using SPSS 23 software at a significant level ($p < 0.05$).

Results: The results showed that eight weeks of aerobic exercise with probiotic intake had a significant decrease on the expression of FOXA1 gene and LDL in rats with fatty liver ($P < 0.05$).
Conclusion: According to the results of the study, It seems that aerobic exercise with probiotics intake can improve the liver function of non-alcoholic fatty liver patients.

Keywords:
Aerobic exercise, FOXA1, non-alcoholic fatty liver, probiotics

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1. Introduction

Fatty liver occurs when hepatocytes begin to accumulate fat droplets (mainly triglycerides) which, in turn, lead to the storage of fat in the hepatocytes, leading to nonalcoholic fatty liver disease (1). Fatty liver disease is divided into non-alcoholic fatty liver and alcoholic fatty liver based on its causes. Fatty liver disease is also known as fatty liver syndrome and is also called hepatic steatosis. Non-alcoholic fatty liver disease is the most common chronic liver condition that is emerging in current societies (2). Characteristics of fatty liver include damage to liver cells (enlargement, apoptosis, necrosis or unplanned cell death, and mitochondrial enlargement), inflammation, and turquoise of liver cells. Non-alcoholic fatty liver disease pathogenesis is often based on a two-step process consisting of triglyceride accumulation followed by the development of oxidative stress and cytokines mediated by inflammation and fibrosis of the liver (3).

Foxa1 is one of three members of the FoxA family, a subset of the forkhead family of transcription factors which play vital roles in development (4). Initially Foxa1 was discovered for its role in liver development (5) but has also been implicated in the development of a number of other organs. human and rat livers were analyzed to determine Foxa1 regulation in NAFL. Results demonstrate that Foxa1 is a potent inhibitor of hepatic triglyceride synthesis, accumulation and secretion by repressing the expression of multiple target genes of these pathways (e.g., GPAM, DGAT2, MTP, APOB) (6).

Foxa1 is an antisteatotic factor that coordinately tunes several lipid metabolic pathways to block triglyceride accumulation in hepatocytes (6). However, Foxa1 is down-regulated in human and rat NAFL and, therefore, increasing Foxa1 levels could protect from steatosis. Also, FOXA1 has also been shown to modulate the growth of human lung cancer, brain cancer, and endometrial cancer cells. Genomic distribution analysis showed that FOXA factors and ERα or AR frequently bound to adjacent *cis*-regulatory elements in the genome and the recruitment of ERα or AR to their binding sites was dependent on FOXA factors in breast and prostate cancer cells (7,8)

Probiotics are defined as a live microbial dietary supplement and, if consumed in humans or animals, have beneficial effects on the health of the host by affecting the intestinal microbial fluoride balance (9). Probiotics are mainly located in the end of the small intestine and clone after entering the gastrointestinal tract. These bacteria have a direct impact on the function and life of other microorganisms in the intestine and mainly strengthen the beneficial bacteria in the intestine (10). According to previous research, which has studied the effect of aerobic and resistance training on fatty liver, and the role of FOXA1 in non-alcoholic fatty liver, which increases to prevent the accumulation of triglycerides, and the importance of exercise in this study, effect of moderate aerobic exercise training and probiotic use on FOXA1 gene expression in an animal model of fatty liver was investigated.

2. Materials and Methods

This experimental study is of laboratory type and has been done with ethics code IR.IAU.SRB.REC.1399.019. The present study was experimental. After transferring the animals to the laboratory in polycarbonate cages, for one week in an environment with a temperature of 22 ± 2 ° C, humidity of 55 % and light cycle to darkness 12:12 with proper ventilation. This study consisted of 32 male Wistar rats in 2 models, healthy and with fatty liver. Rats weighing 200-250 which were randomly divided into the following 4 groups: healthy group (N = 8), modeled group. (Steatosis) (N = 8), steatosis + probiotic group (N = 8), steatosis + probiotic + exercise group (N = 8). To create a model of fatty liver (steatosis), tetracycline at a dose of 100 mg / kg at a volume of 1.5 cc per mouse was gavage daily for two weeks. The weight of mice was 300 gr on average, 100 mg per kg was used for 3 mice, 100 mg was dissolved in 4.5 cc and 1.5 cc was gavage to each mouse.

cultivation of Lactobacillus ramensus GG bacteria

Lactobacillus ramensus GG (PTCC1637) is purchased as lyophilized in standard vials from the Scientific and Industrial Research Organization of Iran (Tehran, Iran). Bacteria are cultured in MRS medium (Biogeya, Tehran, Iran) enriched with L-cysteine HCL and incubated for 24 hours in an incubator at 37 ° C. To evaluate the effect of probiotics; The respective groups received 109 CFU / ml of Lactobacillus ramensus GG by gavage daily for 5 weeks and 5 days a week (11).

Exercise protocol

The aerobic exercise protocol was moderate intensity for 8 weeks and 5 sessions per week. The duration of the training ranged from 10 minutes of running in the first week to 60 minutes of running in the eighth week. The speed of running on a treadmill started from 18 meters per minute and in the eighth week it reached 28 meters per minute. The slope of the treadmill was also considered to be zero degrees (12).

After the last exercise session and consumption of probiotic and after 12 hours of overnight fasting, the studied rats in each group by intraperitoneal injection of a mixture of 10% ketamine at a dose of 50 mg / kg and xylazine 2% and with Doses of 10 mg / kg were anesthetized. By cutting the abdomen and chest, about 10 ml of blood was taken directly from the hearts of the mice by syringe. Blood samples were centrifuged at 1000 g g for 20 minutes to separate serum and stored at -80 ° C to measure serum LDL. Tissue samples were isolated under sterile conditions and stored at -80 ° C for FOXOA1 gene expression. To measure the FOXOA1 gene in adipose tissue, RT-PCR was performed using the protocol of the manufacturer (Qiagen, Germany). Table 1 shows the pattern of primers.

Table 1: Primers used

Gene	Primer Sequence (5′-3′)	Product Size (bp)	Accession Number
FOXA1	F: GACGTTCAAGCGCAGTTACC	187	NM_012742.1
	R: CAGLDLAGLDLGCGAALDLGAGT		
GAPDH	F: CAAGTTCAAGGGCACAGTCA	102	NM_017008.4
	R: CCCCATTLDLALDLTTAGCGGG		

Kolmogorov-Smirnov test was used to ensure normal distribution of data and Levin test was used to ensure homogeneity of variances. The relative expression of the Delta City gene was measured. Descriptive statistics were used to describe the data and draw graphs, and analysis of variance (ANOVA) was used to compare the groups in the studied variables. Significant level was considered P≤0.05. All statistical analysis was performed using 23 SPSS software.

3. Results

According to Table 2, The results of one-way analysis of variance test with a significance level of less than 0.05 showed that there was a significant difference between the FOXA1 gene variable in the four groups ($p < 0.05$). As a result, eight weeks of aerobic exercise with probiotic consumption has a significant increase effect on the expression of FOXA1 gene and significant decrease LDL in rats with fatty liver and reduces its ($p < 0.05$).

Table 2: Changes in FOXA1, LDL levels between different experimental groups

Variables	steatosis + probiotic + Aerobic exercise	steatosis + probiotic group	modeled (Steatosis)	Healthy control	Sig
FOXA1 (ng / L)	2.81±1.23	0.43±0.22	0.52±0.35	1.05±0.32	0.000
LDL (mg/dL)	36.5±4.52	42.01±2.66	70.45±5.20	32.83±3.14	0.000

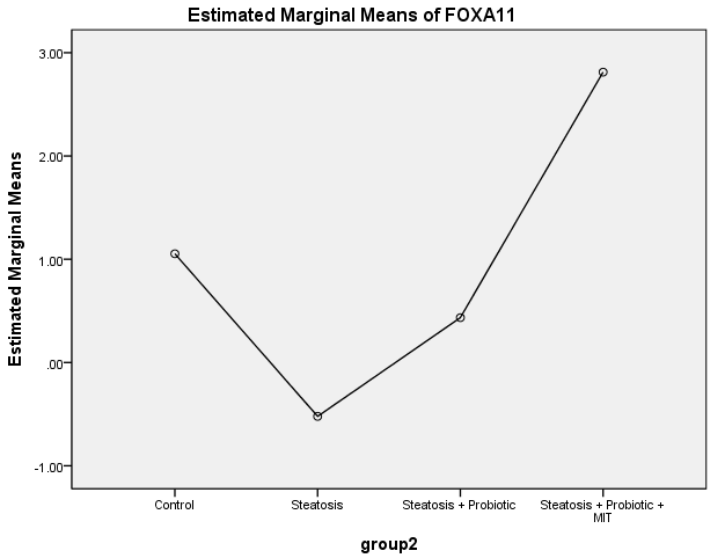

Figure 1: Comparison of FOXA1 expression in four groups of control (healthy), steatosis (patient), patient + probiotic, patient + probiotic + exercise

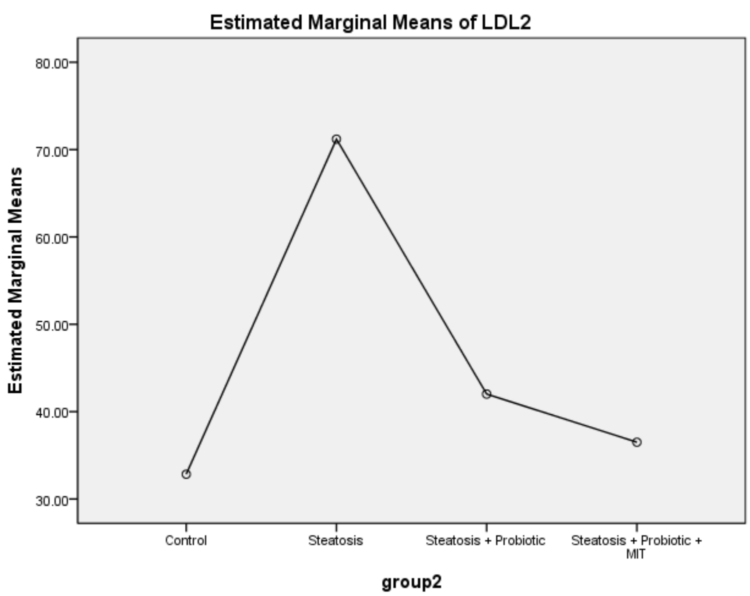

Figure 2: Comparison of LDL in four groups of control (healthy), steatosis (patient), patient + probiotic, patient + probiotic + exercise

4. Discussion

In the present study, the moderate aerobic exercise and probiotic intake on FOXA1 gene expression and LDL in non-alcoholic fatty liver animal model was investigated. The results of this study showed that FOXA1gene expression was significantly increased in the probiotic and aerobic exercise group compared to other groups. This study was consistent with research of the Sturgeon and colleagues, showed that aerobic exercise can improve fatty liver disease (13). Sturgeon and colleagues in their research with Physical activity induced protection against breast cancer risk associated with delayed parity title. data demonstrate patterns of delayed parity induced changes to the breast tissue which are both dependent and independent of exercise training completed between menarche and first pregnancy. While exercise training was beneficial for tumor latency and size, it did not mitigate enhanced collagen levels found in mammary tissue of delayed parity animals. Similarly, exercise training did not mitigate enhanced expression levels of several genes associated with breast cancer. However, there were exercise-dependent changes in the mammary gland. Exercise training prevented the development of inflammation and ductal hyperplasia. Exercise training also led to improved directional regulation of gene expression levels for Cdkn1c and Plau (13). Although this study was on breast cancer, however, some studies have shown that the foxa1 gene reduces triglyceride production in liver patients with a signaling pathway (6,14). In our study, the gene was severely reduced in mice with fatty liver. This is probably due to the increase in fat and improper regulation of this gene. However, with the use of probiotics and aerobic exercise along with probiotics, an increase in foxa1 gene was observed, which could be the effect of reducing the inflammatory pathway and the effect on foxa1 gene to prevent the formation of more fat in liver tissue.

The results also showed that the probiotic intake and aerobic exercise is able to significantly reduce the LDL in rats with fatty liver. It was reported Aerobic exercise, on average, HDL cholesterol increased by 4.6 % while triglyceride levels fell by 3.7 % and LDL cholesterol fell by 5 %. Total cholesterol remained unchanged, although the HDL: LDL cholesterol ratio improved considerably, suggesting that the increased intensity and structure normally associated with aerobic exercise has a more consistent impact upon triglycerides and LDL cholesterol than moderate levels of physical activity (15). Our study showed that the probiotic intake and aerobic exercise is able to significantly reduce the LDL in rats with fatty liver. The results of this study are not consistent with Shirpoor et al (16). They examined effect of moderate exercises and curcumin on hepatic transcriptional factors associated with lipid metabolism and steatosis in elderly male rat and concluded that a significant increase in FAT/CD36, PTP1B, significantly decreased HNF4α genes expression, increase in LDL and cholesterol in the aged group compared to the young control. Compared to those in the young control group, no significant changes in HDL and TG amounts in the aged control were observed. Moreover, compared to the young control, the aged group showed liver histological changes such as fibrosis and mild or grade 1 steatohepatitis. Moderate aerobic exercise and curcumin alone or in combination completely masked this effect (16). One of the reasons for the contradiction with the present study could be the use of the young group versus the old group in the study of Shirpoor et al Considering that only the old group is considered, LDL has decreased compared to it, or possibly using curcumin instead of probiotic.

This study was consistent with research of the Kazeminasab and colleagues, showed that There was a significant decrease in the concentrations of LDL-C after 4-week aerobic exercise (17). They consider Effects of A 4-Week Aerobic Exercise on Lipid Profile and Expression of LXRα in Rat Liver. Their experimental intervention study included twelve adult Wistar male rats (12-14 weeks old, 200-220 g) which were divided into the control (n=6) and training (n=6) groups. The training group received exercise on a motor-driven treadmill at 28 meters/minute (0% grade) for 60 minutes a day, 5 days a week for 4 weeks. Rats were sacrificed 24 hours after the last session of exercise. A portion of the liver was excised, immediately washed in ice-cold saline and frozen in liquid nitrogen for extraction of total RNA. Plasma was collected for high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and triglycerides (TG) measurements. That result showed A significant increase in LXRα transcript level was observed in trained rats. Plasma HDL-C concentration was also significantly higher in trained rats. There was a significant decrease in the concentrations of LDL-C and TC, and the ratios of TC/HDL-C and LDL/HDL-C in trained rats. However, the TG concentration was unchanged. Which had the same result as this study (17).

Consistent with our research there is ample evidence in animal models and human studies that probiotics improve fatty liver. Patients with nonalcoholic fatty liver disease have been reported to improve liver enzymes after three months of treatment with Lactobacillus, Bulgaricus and Streptococcus thermophilus (18). In this regard, a study by Duseja et al. (2019) on the effect of High potency multistrain probiotic improves liver histology in non-alcoholic fatty liver disease (NAFLD): a randomised, double-blind, proof of concept study showed that lifestyle modifications combined with probiotic preparations significantly damaged liver tissue. Improves in patients with non-alcoholic fatty liver (19). In their study, patients in the probiotic group showed a improve in hepatic.

5. Conclusion

In the present study, it was found that the moderate aerobic exercise and probiotic intake on FOXA1 gene expression significantly increased and LDL significantly decreased in non-alcoholic fatty liver animal model. Therefore, according to the results of the study, It seems that aerobic exercise with probiotics intake can improve the liver function of non-alcoholic fatty liver patients.

Compliance with ethical standards

Conflict of interest None declared.

Ethical approval the research was conducted with regard to the ethical principles (IR.IAU.SRB.REC.1399.019).

Informed consent Informed consent was obtained from all participants.

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Author contributions

Conceptualization: SH.R.M., H.M., S.A., O.S.GH.; Methodology: SH.R.M., H.M., M.T.; Software: SH.R.M., H.M., S.A.; Validation: M.T., S.A., O.S.GH.; Formal analysis: SH.R.M., S.A., O.S.GH.; Investigation: S.A., H.M., M.T., O.S.GH.; Resources: SH.R.M., H.M., S.A.; Data curation: SH.R.M., H.M., M.T.; Writing - original draft: SH.R.M., H.M., S.A., O.S.GH.; Writing - review & editing: M.T., S.A., O.S.GH.; Visualization: H.M., M.T., O.S.GH.; Supervision: M.T., S.A., O.S.GH.; Project administration: H.M., O.S.GH., M.T., S.A.; Funding acquisition: SH.R.M., M.T., H.M.;

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Research Article

The effects of detraining following a regular exercise program on plasma resistin concentrations in asthmatic patients

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Resistin, regular exercise, asthmatics, detraining

Abstract

Background: The purpose of this study was to investigate the effects of regular exercise and the following detraining on plasma resistin concentration in patients with asthma. Climate change and reduced rainfall have caused allergies and respiratory diseases to develop in different people, resulting in 8.9% of adults suffering from asthma by 2025, and 400 million by 2050. Asthma prevalence or symptoms increase as a result of the secretion of some adipokines, such as the hormone resistin. Detraining results when there is insufficient training stimulus, causing the loss of training-induced adaptations. Training cessation or insufficient training can alter the detraining characteristics.
Materials and Methods: In the present study, 30 available asthmatics were randomly divided into control and exercise groups. For three months, the exercise group followed a regular training regimen that included three 90-minute sessions each week. Each training session included 60 to 85% of the patients' maximum heart rate on the treadmill or pedaling on an ergometer. The control group did not do any physical exercise in addition to their normal routines throughout the same time period. Blood samples were drawn before the first session, 2 days, and 1 month after the last sessions.
Results: Serum resistin levels were not affected by the three-month regular training program or one-month detraining period. They did not differ significantly in the control group either (P >0.05).
Conclusion: Despite the benefits of regular exercise being beneficial for all individuals, asthma symptoms in asthmatics were relatively reduced, although these changes were not significant.

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1. Introduction

Globally, the World Health Organization (WHO) declares air pollution to be on par with smoking and unhealthy eating habits in regards to the potential threat to human health, and estimates that there are 7 million deaths annually caused by air pollution (1). One of the causes of cardiorespiratory problems is air pollution, and it increases the risk of asthma. The disease of asthma is characterized by chronic inflammation of the airways in the respiratory tract that is the result of genetics and environmental factors (2). The disease includes shortness of breath, wheezing, and coughing, also known as asthma triplets (3).

According to the WHO, approximately 339 million people are suffering from asthma in the world, and by 2025, the number will reach 400 million. In Iran, approximately 10.9% of children and adolescents and 8.9% of adults have asthma, while the world population has reached 339 million, and this figure is expected to reach 400 million by 2025 (4, 5). There are 13.8 million disability-adjusted life years lost annually because of asthma, equal to 18% of the total global disease burden (6). According to the global initiative for asthma (GINA) report in 2017, 1–16% of the population in 112 countries is affected by asthma symptoms. Based on this report, it is estimated that 300 million people worldwide suffer from asthma, which leads to 346,000 deaths every year (7). Tehran was the most polluted city in the world on April 10th, 2022, and pollution levels have increased in Iran's major cities (8).

Clinical research has been undertaken in recent years, resulting in the identification of numerous chemicals and molecules, such as mediators and inflammatory factors, that cause chronic conditions (9, 10). Cytokines are a type of hormone that consists of a collection of water-soluble protein molecules that transmit messages between cells. Adipocyte cells in the human body create adipocytokines, also known as adipokines, which are cytokines that are transported across the body via the bloodstream (9, 11, 12). The prevalence or rise in clinical symptoms of asthma is linked to the release of specific adipokines, such as the hormone resistin (13-15). Certain adipokines involved in appetite suppression, energy balance, insulin sensitivity, energy metabolism, and homeostasis are secreted by adipose tissue, and these adipokines are involved in the development of obesity and related diseases such as diabetes, hypertension, inflammatory diseases, and asthma (16, 17). Asthma is the most prevalent respiratory disease, and the number of asthmatics admitted to hospitals has soared in recent years (3, 18).

Chazenk et al. (2019) conducted a meta-analysis and reported that physical activity is beneficial to mental and physical wellbeing (19). Other studies have shown the advantages of exercise and physical training for asthmatics (18, 20-22).

However, exercise is among the most common triggers of asthma, known as bronchoconstriction due to exercise, despite obesity as one of the causes of the condition. According to Odege and Isa (2020), resistin may reduce the risk of developing asthma, but its impacts on the airways may trigger or aggravate asthma (21). A study in 2007 found that 8 weeks of aerobic exercise did not affect resistin concentrations (23). Furthermore, Jamurtas et al. (2006) found that a sub-maximal training session had no effect on resistance levels for up to 48 hours after ceasing physical exercise (24). Evidence has shown that resistin has a role in the prevalence of asthma, and its levels in asthmatics are substantially greater than in healthy people (13, 25). Additionally, some research has suggested that higher resistin concentrations are linked to higher levels of asthma severity (13, 26, 27). Some studies have also reported the same equal concentrations of resistin in healthy people and people with asthma. Following 8 weeks of physical exercise, resistin concentrations significantly decreased both during exercise (28) and with a proper diet (29). Dehghani et al. (2016) found that after 10 weeks of exercise, resistin concentrations decreased significantly (30), while increasing resistin concentrations after exercise (31), or no change in resistin concentrations (32), was also reported.

There is a discrepancy between the results of previous studies when comparing these factors between asthmatics and healthy individuals. Asthmatics are less likely to exercise than healthy people, and few studies have examined the effects of exercise and physical activity on blood resistin concentrations in asthmatics. Hence, since physical activity plays a significant role in preventing and reducing diseases, this study will examine how 12 weeks of regular exercise impacts the resistin concentrations in people with asthma after exercise and following detraining.

2. Materials and Methods

Subjects

In this study, 30 male adult asthmatics (age = 39±5 years, BMI = 29.06±3 $Kg.m^{-2}$) participated by accessible sampling and were randomly separated into exercise and control groups. Inclusion criteria for the study group were having a history of asthma for at least 2 years. None of the participants reported engaging in any type of exercise (more than once per week) before engaging in the study. The exclusion criteria included medication that alters carbohydrate metabolism, diabetes, a lack of exercise ability, and a history of hypertension or heart disease. A written and verbal explanation of the study's benefits was provided to all asthmatics before they signed a consent form.

Research Design

This study aimed to investigate the effects of regular exercise and the following detraining on plasma resistin concentration in patients with asthma. The research design of this study (Figure: 1) was carried out in three stages. According to the proposal submission of the Parand Branch/Islamic Azad University, this study was approved by the Ethics Committees at the Central Department of Islamic Azad University (No. 73/178599).

Protocol of the Study

The first stage was participant recruitment, where the spirometry test was performed (Minispire, Italy) to evaluate lung function and asthma severity. During a spirometry test, the respiratory system is evaluated by taking a medical history, conducting physical examinations, and testing pulmonary function. Before participating in the spirometry test, all participants were asked to refrain from consuming tea, coffee, and other airways dilator foods. The first blood sampling was after the spirometry test, and then for the second stage, they were divided into two groups of the study. In addition, they were asked to avoid any physical activity 48 hours before each blood sampling. The exercise group participated in regular exercise for 3 days during 12 weeks. The participants completed a 10-minute warm-up and exercised at a relative maximum heart rate of 60 to 80% controlled by a heart rate monitor (Polar, Finland). The exercise each day involved walking, running, or cycling on an ergometer for 25 to 40 minutes. Following each exercise, they cooled down for 10 minutes. At the end of the second stage was the second blood sampling at 48 hours after the last exercise session. In the third stage, there was a month of detraining for the exercise group, and then, after that, a final blood sample was drawn. All asthmatics in the control group were barred from contributing to any type of exercise participation during the study.

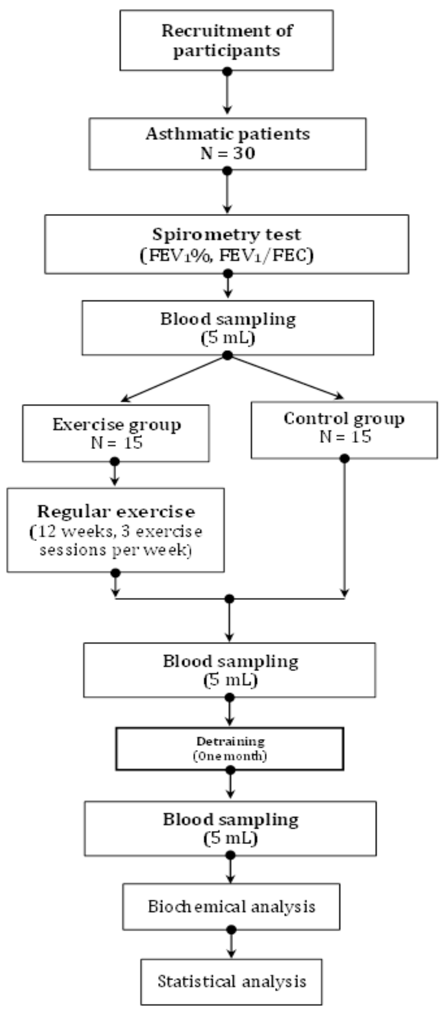

Figure 1: Research design

Laboratory Assessments

To assess the serum concentration of the resistin, blood samples (5 mL) were taken between 8:00 am to 9:00 am after 10 to 12 hours overnight fast from the brachial vein in a sitting position. Following centrifugation and serum separation, blood samples were stored at -80 ° C to measure serum resistin concentrations. The serum concentrations of resistin were measured by sandwich enzyme-linked immunosorbent assay (Mediagnost, E-50 ELISA kit, Germany) with a sensitivity of 0.012 ng/dL and coefficients of change for endometrial and exogenous changes of 6.8% and 5%, respectively.

Statistic calculations were performed using the IBM SPSS Software version 26 at a significance level of 0.05. Standard deviations (SD) and means were used to represent the distribution of the values of all variables. The Shapiro-Wilk test was used to test the hypothesis that the variables analyzed were normally distributed. An independent sample t-test was used to detect group mean difference at baseline. Pre- to post-training changes were determined by two-tailed t-tests.

3. Results

The serum resistin concentration of the participants during the study is shown in Figure: 2. At baseline, no significant differences were found between the exercise and control groups. After 12 weeks of regular exercise, the resistin serum concentrations in the exercise group decreased 48 hours after the last exercise session when compared with the baseline.

Resistin (ng/dL)	Exercise group			Control group		
	Baseline	After 12-week exercise	After 1 month of detraining	Baseline	After 12-week exercise	After 1 month of detraining
	5.71±1.1	4.33±1.2	5.03±1.3	5.41±0.8	5.23±0.15	5.01±1.3

Figure 1: The changes of the serum concentrations of resistin after 12 weeks regular exercise and the following detraining (N=30).

However, these changes were not significant. The concentrations of serum resistin did not decrease significantly over the 48 hours following the 12-week regular exercise or the baseline levels after a one-month detraining period.

4. Discussion

The current study was designed to determine the effects of regular exercise and the following detraining on serum resistin concentrations in asthmatic patients. Increased mucus production and reconfiguration of the lung epithelium, airway blockage, and airway overreaction are all linked to the development of asthma and its prevalence related to airway inflammation. Inflammation's role in the pathogenesis of asthma has attracted much interest in recent years. Asthma, according to the WHO is a chronic inflammatory illness of the respiratory tract in which certain cells play a key role in its prevalence. Although knowledge of the major mechanisms underlying the prevalence of asthma and inflammatory responses is still lacking, the issue has always been whether asthmatic inflammation is restricted to airway inflammation. As a result, a few studies have indicated a relationship between inflammatory cytokines in the blood and the severity of asthma or the patients' respiratory capacity once they participated in an exercise program regularly (33). A comparison of serum cytokine concentrations in active asthma patients in exercise programs versus inactive patients revealed that sedentary patients have higher serum concentrations of resistin than active patients (34).

Many chemicals in the body, including cytokines, are produced and secreted as a result of exercise. The results of the current study have shown that the serum resistin concentrations after 12-week regular exercise in asthmatics were reduced, which is consistent with the findings of earlier reports (30, 32, 35). Kadoglou et al. (2007) studied the effect of regular exercise on cytokine levels in overweight subjects with diabetes, which showed a significant reduction in resistin concentrations (36). Nakhaei et al. (2016) have also reported a reduction of serum resistin concentrations after exercise (37). Numerous studies have been published regarding physical training and exercise and their effects on the degree of resistance levels, including the type, duration, and intensity of exercise, as well as the effect on the participants' health situation. Obesity, overweight, and other illnesses related to metabolic syndrome raise resistin concentrations (32). Therefore, increasing resistin synthesis and secretion decreases or eliminates metabolic diseases, whereas some results have shown that reducing resistin lowers fasting insulin and glucose concentrations. It can be identified that serum concentrations of resistin in asthmatics are lower in active patients than in sedentary ones. Although the findings were not significant, however, these results support the idea that systemic inflammation has a role in the prevalence or incidence of asthma.

Detraining is identified as the lack of physiological and behavioral exercise-induced adaptation, and it has a wide range of consequences that are dependent on the type of previous exercise performed, such as resistance, aerobic, or mixed exercises. The serum concentrations of resistin in active asthmatics of this study had a non-significant change after one month of detraining. In accordance with the present results, previous studies have shown that resistin concentrations reductions after exercise.

Lin et al. (2008) reported that the serum resistin levels were significantly decreased with detraining (38). Abbasi et al. (2012) have also shown that the resistin serum concentrations were not changed significantly during the detraining period (17). But, Nakhaei et al. (2016) have indicated that serum resistin concentrations increased after the detraining phase (37). Increased adipose tissue around the lungs has a dramatic influence on the mechanical characteristics of the lung, resulting in significantly lower tidal breathing volumes.

Although spirometry is unchanged, a decrease in tidal functional residual capacity causes an increase in airway resistance during tidal breathing, increasing the risk of expiratory flow restriction, particularly during bronchoconstriction or supine position. As a result, the interaction between obesity's mechanical consequences and illness is likely to have substantial therapeutic implications, such as increased respiratory clinical signs in asthmatic patients that are unlikely to be improved by traditional medication.

Meanwhile both asthma and obesity are considered by inflammation, a common inflammatory pathway has been proposed as a plausible explanation for the frequent association of the two diseases (39, 40). In reality, obese people have higher levels of inflammatory indicators such cytokines. In obesity situation, the prevalence of systemic inflammation has been related to an increased risk of cardiovascular disease and type 2 diabetes. Adipocytes and macrophages are among the many cell types found in white adipose tissue. Adipocytes release a number of proteins known as adipokines, such as resistin. Thus, adipose tissue has been considered an active secretory organ that sends out and responses to signals that control hunger, energy expenditure, insulin sensitivity, the endocrine and reproductive systems, bone metabolism, inflammation, and immunity.

5. Conclusion

It is concluded that 12 weeks of regular exercise may affect inflammation in asthma patients. However, the reductions in serum concentrations of resistin were not significant after the 12-week regular exercise and as well as after one month of detraining. The results of the other studies have confirmed the inflammation effectiveness in asthmatics. As a result, no clear explanation for how regular exercise affects resistin concentrations can be proposed, although exercise specificity and target populations appear to be amongst the most important considerations in producing inconsistent results.

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Compliance with ethical standards

Conflict of interest the authors declare that there is no conflict of interest.

Ethical approval the research was conducted with regard to the ethical principles.

Informed consent Informed consent was obtained from all participants.

Author contributions

Conceptualization: D.T.; Methodology: D.T.; Software: D.T.; Validation: D.T.; Formal analysis: D.T.; Investigation: D.T.; Resources: D.T.; Data curation D.T.; Writing - original draft D.T.; Writing - review & editing: D.T.; Visualization: D.T.; Supervision: D.T.; Project administration: D.T.; Funding acquisition: D.T.;

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Research Article

Comparison of the effect of selected Pilates exercises, Traband training and weight training on strength and flexibility in elderly women

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Pilates, Traband, Weight, Flexibility, Lower limb strength, Elderly women

Abstract

Background: Changes in the human body due to the aging process, especially the loss of strength and flexibility of the lower limbs can increase the risk of falls. The aim of this study is to compare the effect of selected Pilates, Pilates with Traband and Pilates exercises with both factors such as strength and flexibility of the lower extremities of non-athlete 50-60 years old.
Materials and Methods: Thirty participants in this study have been randomly divided into three groups: quasi-experimental, Pilates (10), Pilates Traband (10) and Pilates (10). Before the beginning of the exercises, the strength of the lower limbs and static acceptance and the range of motion of extension and flexion of the thigh have been measured using the test of 30 sitting on a chair, static acceptance and goniometer, respectively. Moreover, all three groups as participated in a course of exercise. These exercises have performed for 8 weeks, 3 sessions per week for 1 hour and have performed after the participants. Data have been analyzed using paired t-test and ANOVA.
Results: As result, all three groups show the significant progress due to exercise but there is not any significant variance between the groups, as none of the methods is not better than other training methods.
Conclusion: performing Pilates exercises, Weight and Traband based on the availability of training equipment and facilities, is beneficial for the elderly, and this exercise may reduce the negative physical consequences and consequent treatment costs, and helps to slow down the aging process and is effective in improving the daily activities of the elderly.

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1. Introduction

The decline in functional capacity is associated with decreases in the level of flexibility, muscle strength, and lower limb strength. Simple functions (walking speed, sitting-up, and coping time) and muscle strength have been used to predict the onset of disability in older populations. (Hardy R 2003). With age, the function of most organs of the body and their physiological function gradually decreases, and the transformation and dysfunction of the organs of the body, including motor function, increase (1). However, in old age, due to the old age and reduced activity and physical activity, this decline will be greater. (2) With age, due to the inactivity and aging of muscle volume may lead to the muscle shortening due to a decrease in protein and muscle fibers, which can be directly affected by muscle strength, and on the other hand, poor performance in daily activities, Increases with decreasing muscle strength in the elderly (2, 3)

Because of ligaments, tendons, and cartilage harden with age, and this phenomenon usually results in changes in connective tissue and reduced elasticity, and overall reduced elasticity, as well as changes in connective tissue, a decrease in metabolism. It is associated with obstruction of blood vessels and wrinkles of the skin and restriction of joint movements (4, 5) Vojket et al. (2009). In the elderly, the main cause of decreased muscle strength is the result of aging, inactivity and both. A decrease in muscle volume can be due to a decrease in the total number of muscle fibers or an increase in type 1 slow-twitch fibers and a decrease in type II fast-twitch fibers (6). Falquito et al. (2007) stated that strength training is usually performed in three groups of static and dynamic contraction and introverted and extroverted, including the factors that neutralize age-related disorders (7).

Muscle strength also plays a very important role in maintaining independence and daily activities, especially in the elderly. Flexibility is defined as the ability to stretch motion in order to determine the appropriate amplitude for the associated joints. In old age, following a decrease in mobility, physiological changes occur in the structures which control the body's reception (8), including: wear and tear of tendons and ligaments, reduced adhesion of fluid inside the body, weak. Cartilage and their rupture indicated that this change would reduce the results (9, 10). It should be noted that physical flexibility as one of the fitness and physical capabilities related to health so particular importance to the middle-aged and elderly. Weakness in the muscles of the lower torso and reduced joint flexibility are among the causes of falls and reduced daily activities of the elderly. Regular and coordinated exercise is one of the ways to prevent daily inactivity and fractures caused by falling (11). Bagheri et al. (2010) by examining the effect of progressive resistance training on increasing lower limb strength and its impact on daily life activities of elderly women, concluded that resistance training increases strength in the lower limb and improves the ability of the elderly (12). Based on results of Mayer et al. (2011), the development of muscle volume is a suitable solution to reduce the processing of muscle breakdown and maintain strength capacity in the elderly. (13)

One of the exercises that have had many effects on the physical and mental performance of people, especially the elderly, in recent years, is the continuous and coordinated Pilates exercises in three positions: sitting, standing, lying down, and performing on the mat (14). Pilates largely avoids high impact, high power output, and heavy muscular and skeletal loading. Pilates largely avoids high impact, high power output, and heavy muscular and skeletal loading (14- 15). Pilates largely avoids high impact, high power output, and heavy muscular and skeletal loading. Pilates largely avoids high impact, high power output, and heavy muscular and skeletal loading. . There are six basic principles associated with the use of the body strength center that in Pilates exercise include control, concentration, accuracy, smooth execution of movement and breathing (14, 16) Perform movement with control with the help of centrality along with focus and accuracy of correct breathing Psychological performance of movements from one exercise to another, these six principles at the heart of every Pilates movement, must be performed in harmony with each other, the center of body strength in Pilates includes the abdominal muscles, pelvis, lower extremities, lower limbs (14 , 16) It is important to notice that the Pilates was more effective to improve abdominal muscle strength, and the most important issue in Pilates is understanding the concept and knowing the center of power of the body. (14, 16, 17).

Pilates largely avoids high impact, high power output, and heavy muscular and skeletal loading. Pilates largely avoids high impact, high power output, and heavy muscular and skeletal loading. Strengthens the body's power center connection with other organs, especially the lower limbs (16, 18).

There is evidence that mat Pilates improves dynamic balance, lower limb strength, hip and lower back flexibility, and cardiovascular endurance in elderly individuals. Furthermore, high-quality studies are necessary to clarify the effects of mat Pilates on other physical functional measurements among older adults (19).

Although many researchers have studied the effect of Pilates exercises on the elderly, but researchers have not been able to find the effects of different forms of Pilates in the elderly. Therefore, this study tries to compare the effect of selected Pilates exercises, Pilates with Traband and Pilates with weights on strength and flexibility of the lower limbs, which are the main factors in reducing muscle weakness, shortness and balance, and play a key role in maintaining stability and balance in the elderly.

2. Materials and Methods

The present study is an experimental (interventional) research with pre-test and post-test design. The subjects are 30 elderly women in the age range of 60-50 years who were randomly selected from among those who referred to a sports complex in Punak neighborhood, District 5 and were randomly divided into three groups of Pilates exercises (10 people), Pilates exercises. Traband (n = 10) and weight training Pilates (n = 10) were included

Inclusion criteria included no history of heart disease, no use of assistive devices such as canes and walkers, elderly health in terms of cognitive vision and hearing, avoidance of exercise or strenuous activity, and no diabetes and limb fractures. All subjects are fully justified before the conducted research on test materials and how to perform the exercises, as well as the hours of the exercises. Participated in sports exercises. These exercises have performed for 8 weeks, 3 sessions per week for 1 hour and then the participants have been tested.

In this study, 30 second sit to stand test is used to measure the muscle strength of the lower limbs (20). This test is considered a valid and reliable tool for measuring the strength of the lower limbs of the elderly in society. To perform this test, the subject sits on a chair with his back flat and his legs are shoulder-width apart and his hands are in front of his chest. They are looped with the face sign and the person starts to get up completely and returns to a sitting position. The subject is encouraged to do the maximum number of sit-ups in 30 seconds. The test score is the total number of correct stands in 30 seconds.

Sit and Reach Test were used to measure pelvic flexibility. To perform this test, the subject sits on the floor and attaches the soles of their paired feet to the flexibility box of the bench to the box on the floor. The other person prevents the subject's knees from bending. The subject bends forward to the palms of his outstretched hands, places his hands on the box, and pushes forward. The hands should be on top of each other or along each other, and the middle finger is the criterion. The distance between the edge of the box and the tip of the middle fingers in centimeters is a person's record (21). The standard box has also designed to perform this test has dimensions according to the figure. The box can flexibly measure those who are not even able to reach the fingertips. Test error: 1) The knees should not be bent during the performance. 2) The body and upper torso should not be bent during the performance as recorded. Stretching exercises should be performed before performing the test (22).

Static Flexibility is measured a goniometer. This device has a degree that calculates the angles of range of motion on the lower limb by placing the center of the goniometer on the joint.

To measure the range of motion of the hip flexion, the subject is asked to lie on his back on the table. The non-test thigh and knee are tested in the extension position as able to actively flex the thigh. The Volgen trunk was constant during the measurement. The center of the goniometer on the large trochanter of the thigh was at the fixed arm parallel to the axillary line of sedition and the movable arm parallel to the longitudinal axis of the thigh toward the external epicondyle (23).

To measure the range of motion of the thigh extension, the subject is asked to lie on his stomach with the thighs and knees of both legs in a neutral position and to perform active thigh extensions. The pelvic measurements have fixed with a strip band. The center of the goniometer is located on the large trochanter of the thigh with a fixed arm parallel to the axillary line of the trunk and a movable arm parallel to the longitudinal axis of the thigh toward the external epicondyle of the thigh (23).

3. Results

Table 1 shows the demographic characteristics of the participants. As result, the groups did not differ significantly in these variables.

Table 1: Demographic characteristics of the subjects in the research groups

Variable	group	N	Pre-test	Post-test
Age (Year)	Pilates	10	52.2±2.84	52.2±2.84
	Pilates Traband	10	54.1±3.46	54.1±3.46
	Pilates Weight	10	54.2±3.37	54.2±3.37
Standing height(Cm)	Pilates	10	152.4±4.08	152.70±4.08
	Pilates Traband	10	157.3±4.37	157.3±4.37
	Pilates Weight	10	156.4±5.35	156.4±5.35
Body mass(Kg)	Pilates	10	69.8 ±93.98	68.3±10.23
	Pilates Traband	10	74.9±5.12	73.8±5.06
	Pilates Weight	10	79.5±4.59	78.6±4.61
BMI (kg.m2)	Pilates	10	29.89±4.15	29.17±4.31
	Pilates Traband	10	30.34±2.85	29.78±2.81
	Pilates Weight	10	32.50±2.74	31.81±2.78

Due to the fact based on Kolmogorov-Smirnov test, the explanation of variables in the groups is normal, paired data have been used to examine the mean difference within the group and ANOVA test also used to examine the difference between the groups.

Table 2 describes the variables as studied in the research groups.

Table 2: Descriptive findings of research dependent variables with the results of paired t-test and ANOVA

Variable	group	N	Pre-test	Post-test	T	P	F	P	η2
Sit and stand (repeat)	Pilates	10	20.6±6.70	22.1±6.88	321.2	045.0*	2.108	0.141	0.135
	Pilates Traband	10	21.8±4.96	27.6±6.73	955.3	002.0 **			
	Pilates Weight	10	20.0±4.00	24.2±4.10	853.3	007.0 **			
Thigh flexion (degree)	Pilates	10	13.1±3.78	16.30±3.91	234.2	045.0*	0.821	0.451	0.057
	Pilates Traband	10	14.1±3.57	21.3±3.09	453.2	036.0*			
	Pilates Weight	10	13.4±3.94	22.6±4.19	571.2	017.0*			
Thigh extensions (degree)	Pilates	10	20.1±4.67	26.5±4.89	895.2	027.0*	2.333	0.116	0.147
	Pilates Traband	10	21.2±4.77	25.3±4.59	765.2	047.0*			
	Pilates Weight	10	18.6±4.29	24.2±3.62	993.2	035.0*			
Trunk flexibility (cm)	Pilates	10	11.9±7.93	17.3±8.28	11.9±7.93	008.0 **	0.207	0.815	0.015
	Pilates Traband	10	10.8±5.34	13.8±6.03	10.8±5.34	033.0*			
	Pilates Weight	10	10.40±5.21	12.45±5.27	10.40±5.21	040.0			

The findings of Table 2 shows that all three groups have made significant progress as a result of the exercises but there is no significant difference between the groups also none of the methods is better than the other training methods.

4. Discussion

Part of the results of the present study indicated that 8 weeks of Pilates, Pilates with weight and Pilates with Traband exercises have a positive effect on lower limb strength. Also, the effect of the group is not significant. In other words, there was no significant difference between the effect of the three selected Pilates exercises on sitting and standing tests. In fact, all three exercise programs have the same effect on the strength of the lower limbs of older women. To justify this finding, it can be said that various Pilates exercises include strength and stretching exercises that increase strength in the muscles and establish a direct connection between the mind and the body (24). According to the results of some studies, Pilates, when added to dance training, can improve postural alignment, flexibility, and abdominal strength in dancers. Additionally, it is well tolerated by dancers, making it a potentially valuable cross-training tool (25). Based on study of Aibar-Almazán et al (2020), a 12-week Pilates exercise intervention on community dwelling women over 60 years old shows beneficial effects on muscle strength, physical performance, and BMI, but failed to induce any changes on body composition (26). Arti (2015) stated that performing 12 weeks of strength training using Traband in women over 50 years of age significantly improves muscle function and increases the strength and endurance of the subjects (27). Secandis (2007) in a study entitled The effects of Pilates exercise on torso strength, and flexibility in sedentary elderly women, concluded that the positive effect of Pilates exercises on muscle strength and endurance, abdominal and lower back and lower extremity muscles and flexibility Posterior trunk flexibility was undeniable, but body weight and fat percentage did not differ significantly from Pilates exercises (28). Pilates and Theraband trainings lead to the increase of the dynamic balance and strength of lower limb in elderly women, but, Pilates training was more effective on strength of lower limb and Theraband training was more effective on dynamic balance (29). Pilates exercises can improve balance and reduce the percentage of body fat in older women, and it is a suitable and inexpensive alternative or complementary treatment to improve balance and reduce falls (30).

The Pilates training program was more effective for improving isometric hip and trunk extension strength, while the Muscular training program generated greater benefits on trunk and hip isokinetic strength. Moreover, both training programs showed moderate effects for the timed up and go (31).

In this research, the scores of flexibility factors (hip flexion, thigh extension and torso flexibility) improved from pre-test to post-test in all three groups, but in the post-test of the research groups, three selected exercise groups were Pilates, Pilates Traband and Pilates weight. No significance is observed. These results show the positive and identical effects of three training programs on flexibility factors, all three of which are able to increase flexibility factors over time (training duration) and therefore the interaction between group and time is very important factor. The present results are consistent with the results of other researchers regarding the positive effects of various Pilates exercises on flexibility and range of motion in the elderly (31).

The maximum range of motion of the hip and plantar flexion of the ankle while walking is lower in the elderly (whether or not they have a history of falls) than in the young. Because the range of motion of the thigh is affected by the stiffness of the antagonist muscles. Therefore, stretching exercises for hip flexors may improve performance in daily activities such as walking in the elderly. The results of Aires et al.'s research, 2011 disclosed that 12 weeks of Pilates training can be effective in preventing falls, increasing daily activities and increasing flexibility in some factors and reducing depression, as well as improving the quality of life of older women aged 50 to 60 years as consistent with the results of the present study (32). Neil et al. (2008) in a study entitled the effect of Pilates exercises on flexibility and body composition concluded that Pilates has a significant effect on flexibility. One of the advantages of trunk flexibility assessment is its simplicity and ease of assessment and its limitations are low accuracy and inability to measure the flexibility of each joint in particular. In this study, only the hamstring muscles (lower limbs) have been examined (33). Babigitt et al. (2010) revealed that Pilates largely avoids high impact, high power output, and heavy muscular and skeletal loading (34). Apple et al. (2012) in a study entitled the effect of 8 weeks of Pilates training on the physical characteristics of adults, concluded that in the flexibility test, they had improved 7.5 cm and flexibility after 8 weeks of training Pilates largely avoids high impact, high power output, and heavy muscular and skeletal loading (35).

Pilates largely avoids high impact, high power output, and heavy muscular and skeletal loading. In Pilates, a person achieves a kind of natural coordination through the complete repetition of movements in a gradual but progressive manner. This sport is known by doctors as a combination of strengthening, stretching and breathing muscles used to develop trunk muscles and restore muscle balance. Unlike traditional resistance exercises where the muscles are trained separately, Pilates largely avoids high impact, high power output, and heavy muscular and skeletal loading. Considering the Pilates exercises, it seems that flexibility is one of the most important components of Pilates exercises. Therefore, the increased flexibility is common factor in all studies, which is thought to be one of the reasons for increasing flexibility, frequent active and passive muscle stretching exercises, as well as focusing on the central muscles of the trunk and legs. In general, Pilates largely avoids high impact, high power output, and heavy muscular and skeletal loading. Pilates largely avoids high impact, high power output, and heavy muscular and skeletal loading.

5. Conclusion

According to the results of the present study, performing Pilates exercises, Weight and Traband based on the availability of training equipment and facilities, is beneficial for the elderly, and this exercise may reduce the negative physical consequences and consequent treatment costs, and can help to slow down the age processing. Finally, it is an effective way to improve the daily activities of the elderly.

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Compliance with ethical standards

Conflict of interest The authors of the article state that there is no conflict of interest in the present study.

Ethical approval the research was conducted with regard to the ethical principles.

Informed consent Informed consent was obtained from all participants.

Author contributions

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

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Research Article

The effect of 12 weeks aerobic training on TNF-α levels in the hippocampus and prefrontal cortex, and depression in rats with Alzheimer's disease

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Abstract

Background: Exercise training plays an important role in combating Alzheimer's disease. Present study aimed to investigate the effect of 12 weeks aerobic training on the levels of tumor necrosis factor alpha (TNF-α) in the hippocampus and prefrontal cortex, and also depression in rats with Alzheimer's disease.

Materials and Methods: The 40 Wistar rats were divided into four equal groups including saline (S), saline +training (ST), training +STZ (AT) and STZ (A). Alzheimer's was induced by injection of 3 mg/kg streptozotocin (STZ) into the ventricles of brain. The aerobic training program (each session lasted 30 minutes with 10-12 meters per minute speed) performed for 12 weeks and five sessions per week on a treadmill. The 48 hours after last training session, brain tissue (hippocampal and prefrontal cortex areas) was removed and TNF-α levels were measured by ELISA method. Data were evaluated using the statistical method of analysis of variance at a significant level ($P < 0.05$).

Results: TNF-α levels in the hippocampus were significantly higher in group A compared to S ($p = 0.010$), ST ($p = 0.014$) and AT ($p = 0.041$) groups. Moreover, no significant change was observed for TNF-α levels in prefrontal cortex in different groups ($p = 0.276$). In addition, a significant increase in inactivity duration (FST) was observed in group A compared to other groups ($p < 0.05$) and also a significant decrease in sucrose preference (SPT) was observed in group A compared to other groups. ($p < 0.05$).

Conclusion: The present study findings indicated that, the positive effects of aerobic training in rats with Alzheimer's disease are exerted partly by modulating the levels of inflammatory factors such as TNF-α in the brain especially the hippocampus.

Keywords:
Alzheimer's, Exercise Training, Inflammation, Tumor Necrosis Factor Alpha

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1. Introduction

Dementia is a very common syndrome in people over 65 years of age, characterized by a gradual decrease in memory and other mental abilities, and Alzheimer's is the most common type of dementia, which affects 62% of patients with dementia (1) . It was reported that 46.8 million people worldwide had dementia in 2015, which is estimated to reach 131.5 million by 2050 (2). Alzheimer's is a progressive neurodegenerative disease characterized by the accumulation of extra-neuronal stores of beta-amyloid (Aβ) fibrils and the intra-neuronal accumulation of hyperphosphorylated tau protein. It leads to the activation of glial cells and then a neuroinflammatory response involving oxygen reactive mediators and inflammatory cytokines such as IL-6, IL-1β, and tumor necrosis factor (TNF-α) (3). In addition, Aβ has been reported to stimulate inflammation (4). In fact, among the effective factors in the development of Alzheimer's disease are systemic inflammation and increased levels of inflammatory mediators such as levels of cytokines IL-6 and tumor necrosis factor alpha (TNF-α) centrally and peripherally. (5). Cytokines are small peptides, hormone-like, and messengers produced by cells activated by inflammatory elements (6). Based on in vivo activity, cytokines are divided into proinflammatory, anti-inflammatory, mitogenic (regulating cell growth and proliferation), hematopoietic, and chemotactic (chemokines) (7). It should be noted that some studies have generally divided cytokines into two categories, proinflammatory and anti-inflammatory. Inflammation is thought of as a tissue response to injury, pathogen attack, or irritants that is characterized by increased blood flow, redness, swelling, and pain. Inflammation is divided into two types: acute and chronic inflammation.

Short-term or acute inflammation is a protective attempt by the organism to eliminate the stimuli of injury or to initiate the healing process. Nevertheless, long-term or chronic inflammation leads to several inflammatory disorders and chronic diseases. The process of inflammation is very complex and is usually precisely regulated: in such a way that one mediator initiates and maintains the inflammation, and another mediator eliminates the inflammation. In the case of chronic inflammation, an imbalance between the two regulators occurs, which leads to cell damage and leads to different types of chronic diseases (8). Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine that can have direct effects on vascular endothelial cells to stimulate chemotactic agents, other cytokines, cell adhesion molecules, and facilitate leukocyte infiltration. These can play a role in the inflammatory process (9). TNF-α is produced by a variety of immune and non-immune cells, including lymphocytes, mast cells, endothelial cells, fibroblasts, and adipocytes, and is involved in regulating various physiological processes such as cell proliferation. Differentiation and apoptosis are involved in various inflammatory processes as well as in a variety of pathological conditions such as chronic inflammation and the onset of acute phase reactions by increasing inflammatory signaling and stimulating cell death, especially necrosis and apoptosis of tumor cells. Disruption of TNF-α production and secretion leads to the spread of diabetes, tumorigenesis, cardiovascular disease, rheumatoid arthritis, and inflammatory bowel disease (10).

In addition to the above, TNF-α has been reported to be involved in the pathogenesis of Alzheimer's disease, and increased levels have been observed in the brain tissue of elderly people with Alzheimer's disease (11). In contrast, the results of studies have shown that reducing the expression of inflammatory cytokines including IL-6, IL-1β and TNF-α in the brain tissue of Alzheimer's rats is associated with improved learning and memory. Shows the placement of inflammatory pathways in the recovery of Alzheimer's samples (12). In human samples, inhibition of the TNF-α signaling pathway also reduces the risk of Alzheimer's disease in the elderly (13). Exercise is one of the strategies that has been shown to reduce inflammation and modulate levels of inflammatory mediators such as IL-6 and TNF-α, and therefore, exercise is considered as an anti-inflammatory agent. (14). In addition to the anti-inflammatory effects of exercise, its role in the prevention and improvement of Alzheimer's risk factors has been reported, and exercise can delay the onset of Alzheimer's symptoms (15). Despite the positive effects of exercise, including its anti-inflammatory effects, changes in levels of inflammatory factors such as TNF-α in response to exercise in Alzheimer's samples have not been studied. Depressive behavior and cytokine measurement of tumor necrosis factor alpha (TNF-α) in the hippocampus and peripheral cortex of Alzheimer's patients.

2. Materials and Methods

The present study was experimental and basic and the statistical population of the present study consisted of Wistar rats in the age range of 90-80 days, of which 40 Wistar rats were purchased as a statistical sample from the Pasteur Institute and sent to the storage room. The animals were moved. Rats were randomly divided into 10 female mice in saline (S), saline + training (ST), training + STZ (AT) and STZ (A): Group 1 (S): Animals Do not exercise and receive saline, Group II (ST): Animals exercise and receive saline, Group 3 (AT): Animals exercise and receive STZ, and Group 4 Animals do not exercise and receive STZ. After the rats were transferred to the laboratory environment, they adapted to the new laboratory environment for one week. For this purpose, mice in groups of four in an environment with a temperature of 22 ± 1.4 ° C, humidity of 55% and a light cycle of darkness of 12:12 hours in special cages made of polycarbonate with dimensions of 47 × 27 × 20 cm were kept. Mice in different groups had free access to standard mouse food during the study, which was placed every two days in the cage net that was available to the mice. Water was also available to mice indefinitely in 500 ml bottles for rodents. The contents of the water bottles were changed daily and made available to the mice again. In addition, the rat lice were replaced every other day. In all stages of the research, the ethical and professional principles of working with animals were observed and the mice were moved and trained by only two people. Items such as painless killing, as well as prevention of surgical pain and sampling of animals were observed.

Exercise protocol

Aerobic exercise in the present study included 12 weeks of treadmill running, which began after one week of getting acquainted with the treadmill. In each session, first warm up for 5 minutes (with an intensity of 5 meters per minute), then the main part of the training program and finally 5 minutes of cooling (with an intensity of 5 meters per minute). The duration of the exercise program from the first week to 12 was the same and 30 minutes per session. The intensity of aerobic exercise in the first 6 weeks was equal to 10 meters per minute and in the last 6 weeks was 12 meters per minute. complete aerobic exercise program is shown in Table 1.

Table 1: 12-week aerobic exercise program

Exercise Training (week)	Warmup (meters per minute)	Main Exercise	Cooldown (meters per minute)	Time (minutes)
0-2	5	10	5	30
3-4	5	10	5	30
5-6	5	10	5	30
7-8	5	12	5	30
9-10	5	12	5	30
11-12	5	12	5	30

Alzheimer's induction

By the end of week 8, the rats will develop Alzheimer's by the Institute for Cognitive and Behavioral Disorders. This model is induced as follows: First, the animals were anesthetized with a combination of ketamine and xylazine (60 and 8 mg / kg, respectively). They are then placed inside a stereotaxic device for brain surgery. Then 3 mg / kg streptozotocin (STZ) was injected in 5 µl of sterile distilled water in the ventricular region of the brain: (anteroposterior: −1mm, mediolateral: ± 1.4mm and dorsoventral: -3.4).

Sucrose preference test (SPT)

On the fifth day after Alzheimer's induction, the test was performed for 48 hours. Two bottles, one with 2% sucrose solution and the other with plain water, were tested in the group cage. The amount of water consumed in the bottles was calculated immediately after the test. Dissatisfaction with sucrose bottles was considered as a depressive behavior in the studied rats and the Sucrose preference test score was calculated based on it.

Isolation of brain tissue (FST)

After completing the behavioral tests, the rats were given deep anesthesia with ketamine (50 mg / kg) and xylazine (5 mg / kg), and then perfusion was performed to remove blood from the brain, after which the animal underwent Dies. In the next step, the brain was extracted and the hippocampal and prefrontal areas were isolated.

Isolated brain samples were stored at -80 ° C until laboratory measurements. All steps of TNF-α cytokine assay were performed based on the working method in the company kit (R&D Co) using ELISA technique.

Statistical methods of data analysis

All data obtained from the present study were analyzed using SPSS software version 24. Shapiro–Wilk test was used to ensure the normal distribution of research data and one-way ANOVA test and Tukey post hoc test were used to compare differences between groups. Also, alpha was considered at the level of 0.05.

3. Results

The results of FST test as well as SPT test results are reported as mean and standard deviation in Table 2 for different groups. One-way analysis of variance test showed a significant difference between groups for FST test (p = 0.009). The results of Tukey post hoc test showed that the duration of physical inactivity in STZ group compared to STZ + training group (p = 0.022), saline (p = 0.028) and saline + training (p = 0.023) It has been significantly more. In addition, significant differences were observed between groups for SPT test (p <0.001) and Tukey post hoc test showed that FST test results in STZ group compared to STZ + training group (p = 0.021), saline (P = 0.001 and saline + exercise (p = 0.000) were significantly lower.

Table 2: FST and SPT test results

Variable	Group	Mean ± SD	P value
FST result	**saline (S)**	109.6± 18.73	0.011*
	saline +training (ST)	108.6± 25.92	
	STZ	143.1± 28.02	
	training +STZ (AT)	108.4± 28.23	
SPT result	**saline (S)**	64.1± 10.9	0.007*
	saline +training (ST)	66.2± 9.52	
	STZ	40.3± 15.57	
	training +STZ (AT)	57.2± 12.75	

Analysis of one-way analysis of variance showed that the difference between groups of TNF-α levels in the hippocampus was statistically significant ($p = 0.005$). The results of Tukey post hoc test to determine the location of differences between groups showed that TNF-α levels in the hippocampus in the STZ group compared with the STZ + group ($p = 0.041$), saline ($p = 0.010$) and saline + Exercise ($p = 0.014$) is significantly more (Chart 1). However, no significant intergroup differences were observed for TNF-α levels in the prefrontal cortex ($p = 0.276$) (Chart 2).

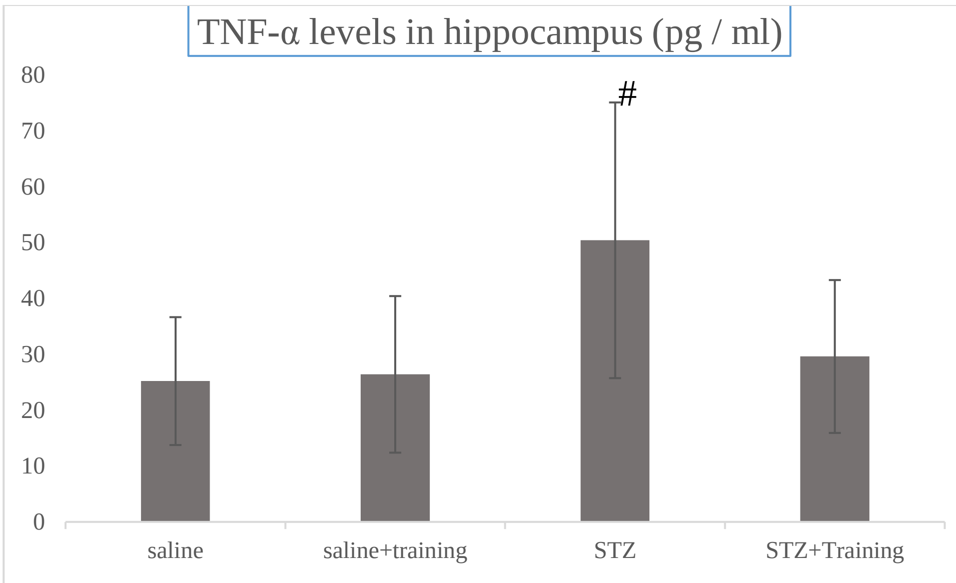

Chart 1: Changes in TNF-α levels in the hippocampus. # Signs of significant difference with groups

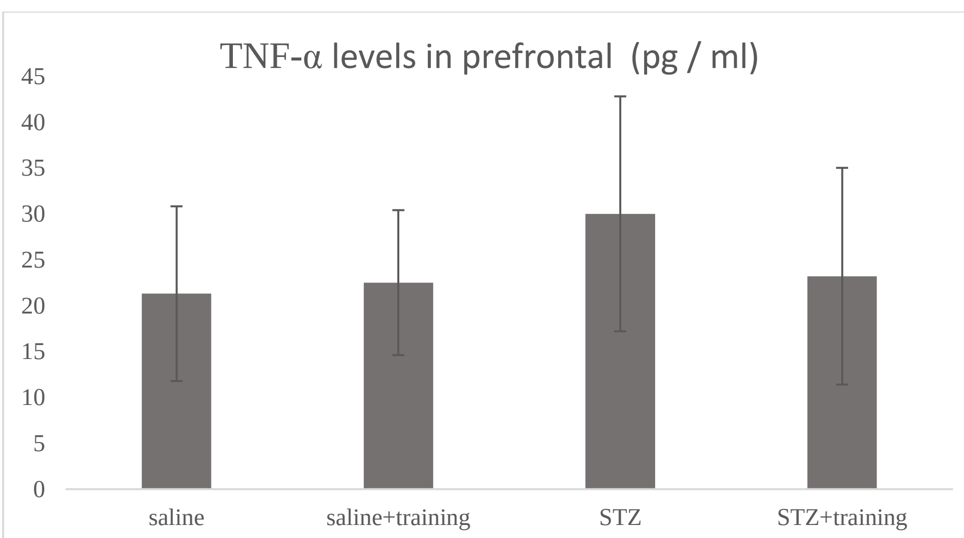

Chart 2: Changes in TNF-α levels in the prefrontal cortex

4. Discussion

The present study was performed to evaluate the effect of 12 weeks of aerobic exercise on TNF-α levels in the hippocampus and peripheral cortex and depression in rats with Alzheimer's disease. The main finding of the present study was that 12 weeks of exercise in Alzheimer's rats significantly reduced TNF-α levels in the hippocampus and TNF-α levels in the hippocampus of Alzheimer's rats compared to healthy rats. The face was more significant. In addition, the present results showed that although TNF-α levels in the prefrontal cortex were higher in rats with Alzheimer's disease than in the other groups, the differences between the groups were not significant and exercise and Alzheimer's disease had a significant effect on TNF-α levels were absent in the prefrontal cortex. These changes were associated with improved rat performance in the Depressive Behavioral Test (reduced immobility) as well as decreased sucrose preference. Studies have shown that changes in inflammatory cytokine levels can be at least partially effective in the disorders observed in the elderly, which in turn increases inflammatory cytokine levels, including TNF-α and IL1-β. Decreases in anti-inflammatory cytokines, including IL-4, have been observed in the elderly. Due to old age (16). Inflammatory mediators such as inflammatory cytokines are pronounced prominently in the vicinity of beta-amyloid stores and neurofibrillary tangles, and various types of inflammatory markers have been observed in Alzheimer's patients (17). Inflammatory cytokines such as IL-6, TNF-α and IL-1β, when produced and secreted chronically, are clearly involved in inflammatory processes near amyloid plaques, including cytotoxic effects. These cytokines can stimulate the production of beta-amyloid peptides (18). However, different types of pharmacological and non-pharmacological methods are used to reduce inflammation. Among the non-pharmacological strategies effective in reducing inflammation, exercise due to the lack of side effects has attracted a lot of attention and Is considered a strong anti-inflammatory agent (19).

In confirmation of the present findings, previous studies have also shown the neuroprotective effects of exercise in animal specimens with Alzheimer's disease. In confirmation of the present findings, Souza et al. (2013) reported that eight weeks of exercise in Swiss Alzheimer's mice injected with beta-amyloid injection resulted in decreased regulation of TNF-α levels in the hippocampus and prefrontal cortex. Decreased TNF-α levels were associated with decreased levels of other inflammatory cytokines such as IL-1β and at the same time increased levels of anti-inflammatory cytokines such as IL-10 as well as improved antioxidant capacity, which improved cytokine profile levels. Cognitive function resulted in the trained group (20). In addition, the findings of the above study in line with the present study showed that the induction of Alzheimer's disease in comparison with the healthy group leads to stimulation of inflammatory pathways (such as increased levels of TNF-α and IL-1β), which confirms Slow inflammatory pathways play a major role in the pathogenesis of Alzheimer's disease, and therefore researchers have identified exercise as an effective non-pharmacological solution to reduce the symptoms associated with Alzheimer's disease (20).

Findings similar to the present study were while the type and duration of exercise in the study of Nicole et al. (2008) was less than the present study and especially less duration of exercise compared to the present study on the positive effect of exercise even in short Duration emphasizes Alzheimer's samples (21).

Ding et al. (2006) in a study that examined the effect of 3 consecutive weeks of exercise (3 minutes daily) on Sprague Dawley rats after stroke / re-oxygenation increased TNF-α expression and its receptor (TNF-RI) Showed in the group in which the stroke was induced. Nevertheless, exercise was associated with decreased TNF-α and TNF-RI expression in both the stroke group, but no significant change was observed for them in the healthy group (22). Because TNF-α binds to TNFR1 and TNFR2 receptors and exerts its inflammatory effects by binding to its receptors (23), a decrease in TNF-α receptor levels plays a significant role in modulating activity. Inflammation has unfortunately not been studied in TNFRs in the present study. In another study on the positive effects of exercise training on brain tissue, Lane et al. (2020) reported that 12 weeks of swimming training in elderly rats stimulated the IGF1, PI3K, AKT, and AMPK pathways. SIRT1 and PGC1α suppress apoptosis and inflammation (including decreased TNF-α levels) in the hippocampus, thereby improving survival in elderly rats (24). In the present study, decreased TNF-α levels were associated with improved cognitive function and reduced depression, which is consistent with previous findings. In this regard, Sun et al. (2018) observed that tapeworm exercise in Alzheimer's rats could attenuate the destructive effects of beta-amyloid on brain tissue and improve cognitive function, which the researchers noted as positive adaptations.

In the trained group, MAPK was applied through the messenger pathway, which was also associated with decreased levels of inflammatory cytokines (TNF-α) in brain tissue (25). All of these findings underscore the fact that exercise can reduce and delay cognitive impairment as well as structural changes in brain tissue with Alzheimer's due to its anti-inflammatory effects.

Studies have shown that the reported anti-inflammatory effects of exercise are exerted through a variety of mechanisms, including the reduction of visceral fat mass, the secretion of various types of anti-inflammatory cytokines from contractile muscle (myokines). And reduced expression of Tol-like receptors (TLRs) is applied to monocytes and macrophages (with subsequent inhibition in downstream pathways such as the production of proinflammatory cytokines and the expression of MHC and co-stimulatory molecules). . In addition, based on studies in animal specimens, the anti-inflammatory effects of exercise can be attributed to other mechanisms such as inhibiting the penetration of monocytes and macrophages into adipose tissue and changing the phenotype of macrophages within adipose tissue. (14). Despite the presented findings, it seems that the effect of exercise training on changes in TNF-α levels can vary depending on the condition of the samples. In confirmation of this claim, Afzalpour et al. (2015) compared the effect of 12 weeks of moderate intensity training (with an intensity of 27 m / min) and intense intermittent training (HIIT) (2-6 3-minute intervals with a speed of 40 m). Per minute) in healthy rats showed that both types of exercise were associated with a significant increase in TNF-α and BDNF in brain tissue, which was significantly higher in the HIIT group compared to the continuous group (26) .

In confirmation of these findings, it has been reported that although chronic increases in TNF-α levels are involved in the pathogenesis of Alzheimer's disease (11), elevations in TNF-α levels in acute pathological conditions result in regular exercise in brain tissue. It can have neuroprotective effects and an increase in TNF-α in such a situation is associated with an increase in brain resistance to ischemia in the brain tissue of healthy rats (27). Therefore, the effect of exercise on TNF-α levels, including in brain tissue, can vary depending on the condition of the subjects. However, due to the few findings on the pathways of exercise in the brain tissue of Alzheimer's specimens and the lack of similar studies on the effect of exercise on different types of inflammatory and anti-inflammatory cytokines, the exact mechanism of effect of exercise on Brain tissue in Alzheimer's needs further investigation and will need to be addressed in future studies to identify unknown aspects of this area.

5. Conclusion

The present results showed that the positive effects of aerobic exercise in Alzheimer's rats are exerted by modulating the levels of inflammatory factors such as TNF-α in the brain (especially the hippocampus) and weakening the inflammatory pathways in Alzheimer's samples in addition to the role that ¬ Able to fight Alzheimer's and delay it, can reduce depression in Alzheimer's rats. These findings indicate the importance of exercise as an effective non-pharmacological intervention for the management and control of Alzheimer's disease, and the identification of precise mechanisms of this effect needs further investigation.

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Compliance with ethical standards

Conflict of interest None declared.

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Informed consent Informed consent was obtained from all participants.

Author contributions

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

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