Research Article

Long-term adaptation in lipolysis due to aerobic interval training in rats with metabolic syndrome

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Abstract

Exercise training is known to enhance lipolysis in response to hormonal challenges, but the impact of different exercise modalities on fat metabolism remains unclear. This study aimed to investigate the effects of eight weeks of interval training on enzymes and hormones involved fat breakdown in rats with metabolic syndrome, focusing on the expression of hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), as well as plasma levels of glucagon and epinephrine. Thirty-five male rats were randomly divided into five groups (7 rats/group): Experimental Group1 (6 weeks of fructose solution), Experimental Group2 (6 weeks of fructose+8 weeks of interval training), Experimental Group3 (14 weeks of fructose), Control Group1 (6 weeks without intervention), and Control Group2 (14 weeks without intervention). Western blot analysis assessed HSL and ATGL expression, while ELISA measured plasma glucagon and epinephrine levels. Fructose consumption for 6 and 14 weeks induced metabolic syndrome in male rats, leading to a significant reduction in HSL and ATGL protein expression ($P = 0.024$ and $P = 0.034$, respectively). Interval training for 8 weeks significantly increased HSL and ATGL levels ($P = 0.011$ and $P = 0.025$, respectively), indicating enhanced fat tissue breakdown. Moreover, interval training significantly decreased glucagon levels ($P = 0.015$), though it did not affect epinephrine levels ($P = 0.159$). Interval training effectively reverses some metabolic syndrome-associated impairments in fat metabolism, specifically increasing key lipolytic enzymes and reducing glucagon levels. This suggests a potential therapeutic role for interval training in managing metabolic syndrome.

Key Words: **Lipolysis, ATGL, HSL, Epinephrine, Glucagon, Metabolic syndrome**

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Introduction

Studies have shown that fructose consumption contributes to insulin resistance, obesity, hypertension, and dyslipidemia, altering the characteristics of metabolic syndrome in both humans and research animals (Amaral et al., 2015) Managing and maintaining balanced body fat is crucial for the prevention and treatment of conditions such as weight gain, diabetes, metabolic syndrome, and fatty liver disease. Recent studies have demonstrated that impaired lipid metabolism in skeletal muscle is associated with an increase in lipid mediators and insulin resistance (Guadalupe-Grau et al., 2018; Trites, Clugston, & Disease, 2019). Although exercise typically raises blood pressure, it also plays a key role in lipolysis—the breakdown of stored fats in tissues. This process is regulated by the hormone activation of lipolytic pathways, which involve cyclic adenosine monophosphate (cAMP) and cAMP-dependent protein kinase (PKA), along with several enzymes and proteins such as adipose triglyceride lipase (ATGL), perilipin, and comparative gene identification-58 (CGI-58), as well as hormone-sensitive lipase (HSL) (Kato et al., 2020). The breakdown of stored triacylglycerols (lipolysis) is primarily mediated by ATGL, which catalyzes the first step of this process (Mengeste, Rustan, & Lund, 2021). In fact, the coordinated activation of ATGL, HSL, and monoglyceride lipase (MGL) enzymes is essential for the complete breakdown of triglycerides. When these enzymes are activated, fatty acids are sequentially cleaved from the glycerol backbone, producing three fatty acids and one glycerol molecule. ATGL releases the first fatty acid, followed by HSL, which removes the second, and finally MGL, which catalyzes the release of the third fatty acid (Mougios, 2019). HSL and ATGL work together in regulating overall lipolysis (Wen, Chen, & Konrad, 2022).

During exercise, the release of adrenaline increases, stimulating lipolysis in skeletal muscles and adipose tissue by breaking down triglycerides into fatty acids and glycerol. This rise in lipolysis, driven by epinephrine, occurs through the activation of the protein kinase A (PKA) pathway, which leads to the phosphorylation and activation hormone-sensitive lipase

(HSL). HSL subsequently hydrolyzes diglycerides (DAG), releasing fatty acids that are metabolized in other tissues (Koh et al., 2007). When catecholamines activate beta-adrenergic receptors, PKA phosphorylates HSL, prompting its translocation from the cytoplasm to lipid droplets. There, HSL interacts with perilipin A, a protein that coats lipid stores, facilitating the process of lipolysis (Liu et al., 2020). Moderate exercise training significantly reduces body fat and increases the levels of key proteins involved in lipolysis, such as adipose triglyceride lipase (ATGL), HSL, comparative gene identification-58 (CGI-58), and perilipin-5. Both CGI-58 and perilipin-5 are crucial for the activation of hormone-sensitive lipases, making them essential regulators of fat metabolism (Hashimoto, Sato, & Iemitsu, 2013).

One effective way to maintain a healthy weight is by stimulating fat catabolism through increased physical activity. Properly planned exercise can lead to the hydrolysis of triacylglycerols stored in adipose tissue, releasing free fatty acids into the bloodstream for oxidation in muscles and other tissues (Mika, Macaluso, Barone, Di Felice, & Sledzinski, 2019). Some studies suggest that low-intensity endurance training increases fat oxidation, though the available evidence remains inconclusive (Cao et al., 2019). The reduction of triacylglycerol in adipocytes following exercise is primarily due to increased lipolysis (Chen et al., 2015). However, conditions like metabolic syndrome and obesity can impair catecholamine-stimulated lipolysis (Laurens, De Glisezinski, Larrouy, Harant, & Moro, 2020). Obese individuals often exhibit lower levels of lipoproteins, as well as reduced ATGL (adipose triglyceride lipase) and HSL (hormone-sensitive lipase) compared to lean individuals. Although basal lipolysis is typically higher in obese individuals, stimulated lipolysis is significantly diminished in their adipocytes (Faridnia, Mohebbi, Khalafi, & Moghaddami, 2019). Additionally, obesity increases the risk of insulin resistance, type 2 diabetes, and heart disease—conditions that are key components of metabolic syndrome. Obesity results from an imbalance in lipolysis, where cells are unable to effectively use excess energy (Khodamoradi, Talebi Garakani, Mir Mohammad Rezaei, Fathi, & Exercise, 2017).

High-intensity interval training (HIIT) has recently gained popularity due to its short duration and low volume, offering numerous health benefits (Jo et al., 2020; Racil et al., 2013). One study found that 15 weeks of HIIT resulted in greater body fat reduction compared to continuous training (Abdelbasset, Tantawy, Kamel, Alqahtani, & Soliman, 2019). Researchers suggest that this more significant reduction in visceral and subcutaneous fat may be due to increased levels of lipolytic hormones in response to high-intensity sessions, though further investigation is needed to confirm this (Liu et al., 2020; Zhang et al., 2015). In a study on aged rats, both high-intensity interval training and moderate-intensity continuous training increased the expression of hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) compared to sedentary controls. Notably, HIIT also enhanced steroid hormone biosynthesis (Sun et al., 2020). Additionally, Kato et al. reported that 12 weeks of regular resistance training produced significant improvements in lipolysis, weight loss, and body fat reduction in postmenopausal women. This training regimen reduced triglyceride and monoacylglycerol lipase levels while increasing hormone-sensitive lipase activity (Kato et al., 2020).

In contrast to previous findings, several studies have reported that the expression levels of hormone-sensitive lipases are not significantly affected by high-intensity interval training (Maillard et al., 2019). Given these conflicting results, further research is needed to better understand the regulation of fat metabolism, particularly in response to different physical activities. Investigating the role of genes and metabolic pathways involved in fat metabolism is crucial for improving our knowledge in this area. Therefore, the aim of this study is to determine whether eight weeks of rest or training impacts the levels of proteins and hormones associated with tissue lipolysis in mice with metabolic syndrome.

Materials and Methods

Animals

The current research is experimental and classified as basic research in terms of its application of results. The study's statistical population consisted of male Wistar laboratory rats, with 35 rats aged 10 weeks and an initial weight of 220 ± 20 g. These Wistar rats were randomly divided into five groups (7 rats per group):

Experimental Group 1 (FG-6): This group received a fructose-containing solution starting at 11 weeks of age for a duration of 6 weeks.

Experimental Group 2 (FGT): This group received a fructose-containing solution for 6 weeks starting at 11 weeks of age, followed by intermittent treadmill exercise for 8 weeks.

Experimental Group 3 (FG-14): This group received a fructose-containing solution starting at 11 weeks of age for 14 weeks.

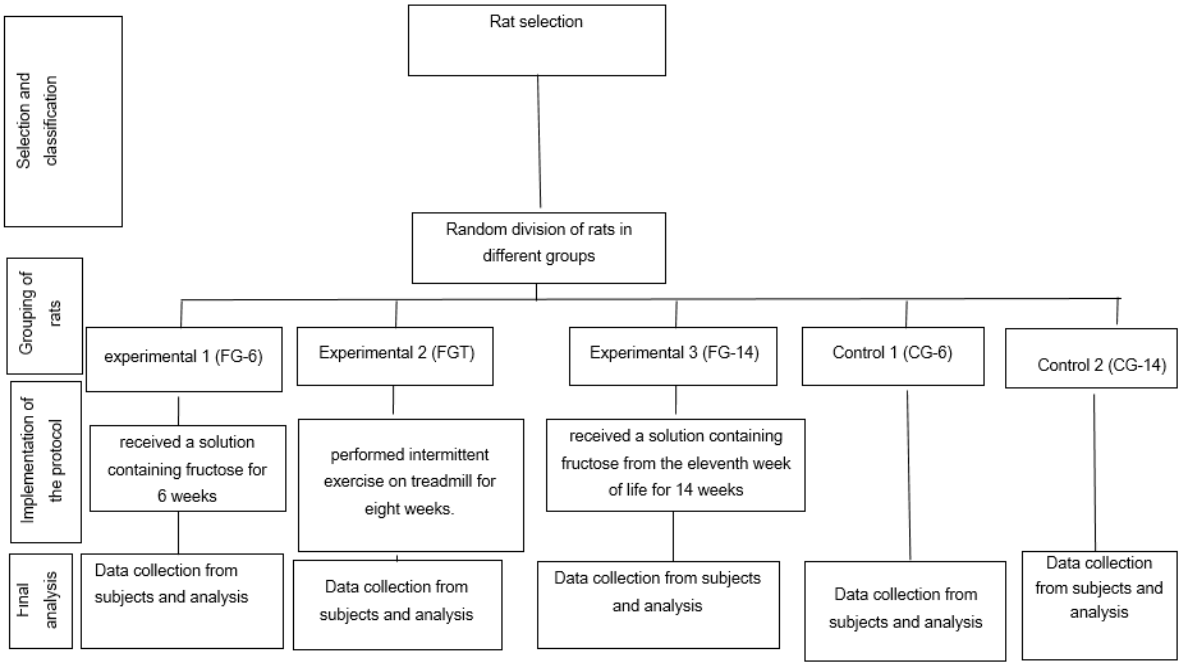
Control Group 1 (CG-6): This group received a normal diet starting at 11 weeks of age for 6 weeks as a control.

Control Group 2 (CG-14): This group received a normal diet starting at 11 weeks of age for 14 weeks as a control.

Experimental design

Fructose is a sugar with the molecular formula C6H12O6, commonly obtained from sources such as honey, fruits, added sugars, and food sweeteners. In the liver, fructose is metabolized into fructose 1-phosphate, which triggers the dissociation of gluc-

Table 1. Diagram of different stages of the research.



-okinase from its regulatory protein, causing it to exit the liver cell nucleus. High dietary fructose intake, along with high carbohydrate consumption, promotes fat synthesis in the liver. The conversion of fructose into fat leads to hyperlipidemia and elevated triglyceride levels (Axelsen et al., 2010). Excessive fructose consumption contributes to features of metabolic syndrome. In mice, some of these effects—such as the activation of the sympathetic nervous system and the renin-angiotensin system—have been replicated. The role of oxidative stress has also been demonstrated, as chronic fructose intake disrupts antioxidant mechanisms. In experiments conducted on fasted rats that received oral doses of fructose, decreases in systolic blood pressure, glucose, insulin, uric acid, glutathione (GSH), and the insulin sensitivity index were observed. The mechanisms involved were studied through short-term pretreatment with controlled doses of lipoic acid, methyldopa, losartan, and streptozotocin. Additionally, hyperglycemia and oxidative stress induced by a single dose of fructose in rat's mimic postprandial hyperglycemia and oxidative stress in humans. Most of these responses, which develop after chronic fructose consumption, are key components of metabolic syndrome (Moreno, Hong, & Diseases, 2013).

The experimental group received 100 grams of fructose per liter of water daily. The total caloric intake in the control group was 2.89 calories per kilogram of body weight, while in the experimental group, it was 4 calories per kilogram of body weight per day (Amaral et al., 2015). At the end of the sixteenth and fourteenth weeks, following ether anesthesia (used because it has minimal impact on metabolic indices), measurements were taken.

Laboratory measurement

Blood samples were collected from the right ventricle of the rats at 8:00 am, and the samples were coded to minimize the risk of bias during experimentation. The lipid profile was measured using Parse assay kits. Western blotting with specific antibodies was employed to assess the levels of hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) in the gastrocnemius muscle (Abdelbasset et al., 2019). In Western blotting, proteins are first separated using polyacrylamide gel electrophoresis (PAGE) and then transferred to a nitrocellulose membrane via an electric current. This membrane, resembling ordinary paper, has a well-defined pore size and a high protein-binding capacity. After the proteins are transferred to the nitrocellulose membrane, the remaining steps are similar to those in an ELISA, except that each sample is cut into strips and placed in separate containers with ribbon-shaped slits. All subsequent steps are performed within these containers. Glucose, epinephrine, and serum glucagon levels were measured using specific assay kits. Plasma levels of epinephrine and glucagon were determined with an ELISA kit from Hangzhou Steve Farm, China, featuring a sensitivity of 0.01. Additionally, radioimmunoassay (RIA) was employed for further measurements. Blood glucose was measured using a kit from Pars Azmoun, while plasma insulin levels were measured with a kit from the Italian company Diametra, also with a sensitivity of 0.01.

Exercise training

The FGT rats underwent treadmill training for 15 minutes, with the speed gradually increasing from 0 to 15 m/min before comm-

-encing a 1-week training program (5 days a week). Over the course of 8 weeks and 5 days, a predictive model was applied. During the final week of training, each exercise session lasted 30 seconds and began at a speed of 29 meters per minute. By the end of the first week, the treadmill speed had increased to 36 meters per minute. Rest periods between exercises were 1 minute. The number of treadmill repetitions started at 7 in the first week and increased to 14 by the final week. It is important to note that the model used for running does not include any degree adjustments for the treadmill. The intensity of the exercise is estimated to be 80-85% of maximal oxygen consumption (Egan & Sharples, 2023). During the 10 training sessions, the mice were gradually acclimated to an intensive interval training protocol. On the first day, the mice were gently and quietly placed on the treadmill, and the training session began at a slow, constant speed. In the following sessions, as the mice became comfortable and stable on the treadmill, they were introduced to interval training to adapt them to the intermittent low-speed protocol. Over the two-week training period, both the duration and intensity of the sessions increased, culminating in 18 minutes of training by the end of the two weeks. After this initial period, with the mice successfully adapting to the protocol, they began 10 weeks of intensive training. It is important to note that the treadmill incline was set to zero throughout all exercise phases, including for the non-exercise control groups. At the end of the two-week acclimation period, the maximal oxygen consumption of the mice was measured. Training then proceeded according to a protocol based on a percentage of maximal oxygen consumption (converted to meters per minute). Every two weeks, a maximal oxygen consumption test was conducted, and the training pace was adjusted accordingly for the following week (Pirani, Peeri, & Azarbayjani, 2018).

Statistical analysis

In this study, the Shapiro-Wilk test was employed to assess the normality of the data, and the Levene's test was used to evaluate the homogeneity of variances. The t-test was applied to determine the differences in means between research variables. Additionally, one-way analysis of variance (ANOVA) was conducted to compare the groups across the studied variables. When the one-way ANOVA indicated significant differences, Tukey's post hoc test was utilized for pairwise comparisons. All data analyses were performed with a significance level set at 0.05.

Results

Based on the data presented in Tables 2 and 3, there was a significant increase in triglycerides (TG) and low-density lipoprotein (LDL) levels, along with a decrease in high-density lipoprotein (HDL) levels, at the end of six weeks. Additionally, body weight, TG, and LDL levels increased. The decrease in HDL and the rise in fasting glucose at fourteen weeks suggest that the fructose diet had an impact on metabolic syndrome at both six and fourteen weeks.

According to the one-way ANOVA results (Table 4), there was a significant decrease in the protein levels of hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) in the fructose-fed groups at both the sixth and fourteenth weeks. Tukey's post hoc test revealed that eight weeks of short-term training significantly affected HSL tissue levels in male Wistar rats, resulting in an increase in this enzyme (P = 0.011 and P = 0.024). Similarly, eight weeks of intermittent exercise significantly influenced ATGL tissue levels in male Wistar rats, leading to an increase in this enzyme (P = 0.025 and P = 0.034).

Table 3. Percentage changes of variables at the end of the sixth and fourteenth week

group	variable	Mean ± standard *deviation*	Sig
FG-6	weight (gram)	235.12±13.80	0.068
	HDL (mmol/L)	39.63±3.40	0.041*
	LDL (mmol/L)	24.70±3.61	0.012*
	TG (mmol/L)	84.46±14.69	0.019*
	Fasting glucose(mg/dL)	121.52±4.19	0.105
FG-14	weight (gram)	269.18±16.09	0.015*
	HDL (mmol/L)	27.31±5.29	0.001*
	LDL (mmol/L)	56.30±4.33	0.001*
	TG (mmol/L)	49.11±17.54	0.001*
	Fasting glucose (mg/dL)	161.49±7.35	0.007*

*significant difference (p<0.05)

Table 2. Interval training protocol

eighth week	seventh week	sixth week	fifth week	forth week	third week	second week	first week	
420	390	360	330	300	270	240	210	**Training duration (seconds)**
36	35	34	33	32	31	20	29	**Treadmill speed (meters per minute)**
14	13	12	11	10	9	8	7	**Repetitions of training**

According to one-way ANOVA (Table 5), significant increases in epinephrine and glucagon levels were observed at both the sixth and fourteenth weeks in the fructose diet groups. Eight weeks of repeated training had no significant effect on adrenaline levels in male Wistar rats (P = 0.211 and P = 0.159), as indicated by Tukey's post hoc test. However, training did have a significant effect on epinephrine and glucagon levels, resulting in a significant decrease in these hormones (P = 0.038 and P = 0.015).]

Discussion

The results of this study demonstrated a significant decrease in body weight, fasting glucose, triglycerides (TG), and low-density lipoprotein (LDL) levels, along with a decrease in high-density lip-

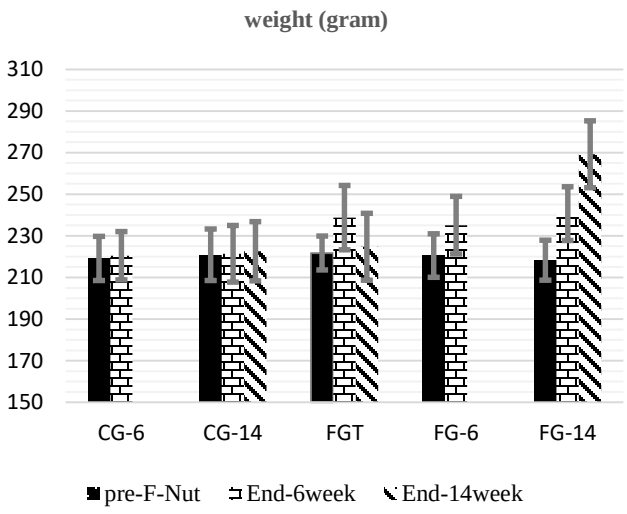


Figure 1. Weight changes of rats in the studied groups. Data are presented as mean ± standard deviation.

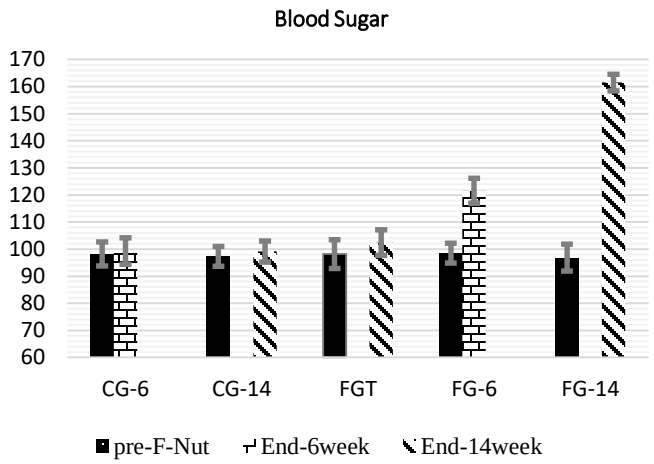


Figure 2. Changes in blood glucose levels in the studied groups. Data are presented as mean ± standard deviation.

-oprotein (HDL) levels, at the end of the sixth week of fructose diet consumption. These changes indicate the development of metabolic syndrome. Additionally, significant effects on the tissue levels of hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) enzymes were observed in eight-week-old male Wistar rats, with notable increases in these enzymes (P = 0.011 and P = 0.025). Epidemiological and biochemical evidence supports that high fructose consumption is a contributing factor to metabolic syndrome. Recent research on carbohydrates suggests that high intake of refined carbohydrates is linked to an increased risk of developing insulin resistance. Animal studies have shown that high-fructose diets lead to metabolic disturbances, resulting in weight gain, obesity, and hypertension (Lubawy, Formanowicz, & health, 2023). Consuming large amounts of fructose increases levels of uric acid and blood pressure. Elevated uric acid lead to inflammatory infiltrates in the

Table 4. Values of indicators related to the induction of metabolic syndrome in the groups at the end of the sixth week.

	LDL	HDL	TG	Glucose	Insulin	Insulin resistance
FG-6	24.70±3.61	39.63±3.40	84.46±14.69	98.52±4.09	6.31±1.74	27.62±1.86
CG-6	21.35±2.90	44.60±2.59	69.20±12.53	98.22±3.17	3.21±0.66	14.02±0.64

Table 5. The results obtained from the one-way ANOVA test to examine the changes of the studied variables in the groups.

		Average of squares	F	Sig
HSL	Intergroup	37.18	31.66	0.001*
	within a group	1.174		
	Total			
ATGL	Intergroup	58.98	24.17	0.001*
	within a group	2.44		
	Total			
Epinephrine	Intergroup	112.829	11.908	0.034*
	within a group	9.475		
	Total			
Glucagon	Intergroup	110.344	20.283	0.001*
	within a group	5.44		
	Total			

*significant difference (p<0.05)

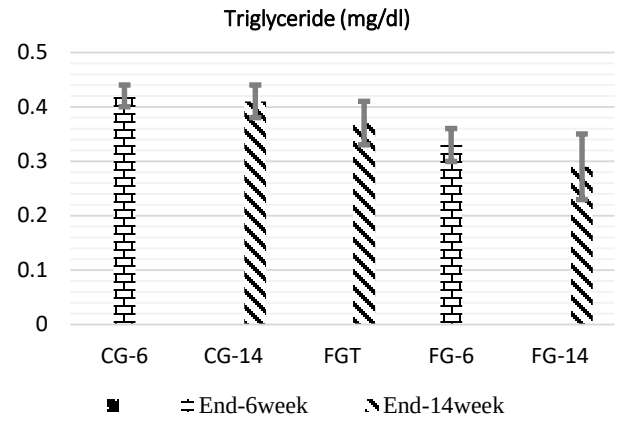


Figure 3. Changes in triglyceride in different research groups. Data are presented as mean ± standard deviation.

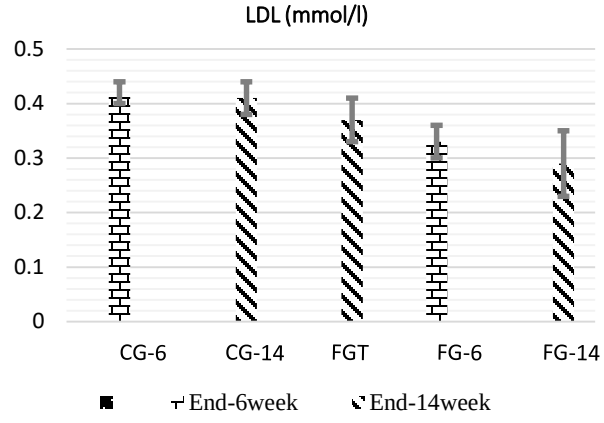


Figure 5. Changes in LDL values of the groups at the end of the 6th and 14th week. Data are presented as mean ± standard deviation.

macrophages, oxidative stress, and the differentiation of xanthine oxidase into foam cells, which contribute to atherosclerosis. Additionally, high uric acid levels enhance the production of inflammatory cytokines released by these foam cells or macrophages (Wang et al., 2023). Additionally, a small proportion of fructose metabolized by the liver is converted into glucose and released into the bloodstream. Fructose contributes to fat formation by inducing hyperlipidemia and increasing triglyceride levels following a meal (Stockert & Mild, 2022).

Metabolic syndrome and obesity impair the ability to break down fat, and catecholamine levels are reduced (A. Muscella, E. Stefàno, P. Lunetti, L. Capobianco, & S. J. B. Marsigliante, 2020b). Several studies have investigated this mechanism. Langen et al. (2005) found that β2-adrenergic receptor (β2-AR) activity in adipocytes is similar in obese and hypercholesterolemic subjects. However, obese individuals have lower levels of hormone-sensitive lipase (HSL), an enzyme crucial for fat breakdown (Langin et al., 2005). Perilipin, an impor-

-tant protein that regulates lipid droplet breakdown, is also involved in this process (Langin et al., 2005). The lipolytic defects observed in humans may result from the interaction of perilipin with other lipases. During exercise, HSL is responsible for nearly all lipase activity, highlighting its critical role in lipolysis (Muscella et al., 2020b) Increased muscle triglyceride levels after lipid adaptation suggest enhanced synthesis rather than degradation. Lipid adaptation may lead to positive autoregulation of active enzymes. A potential regulatory signal for these proteins is a chronic decrease in serum insulin concentrations, coupled with increased free fatty acid concentrations resulting from fat adaptation. This paradox arises because fat adaptation inhibits muscle glycogenolysis during exercise. Additionally, the accumulation of fatty Acyl-CoA during high-intensity training may also inhibit HSL activity. These opposing pathways suggest the existence of a mechanism that regulates HSL activity based on the intensity and duration of exercise (Fahed et al., 2022).

Skeletal muscle relies heavily on fat oxidation during rest and ex-

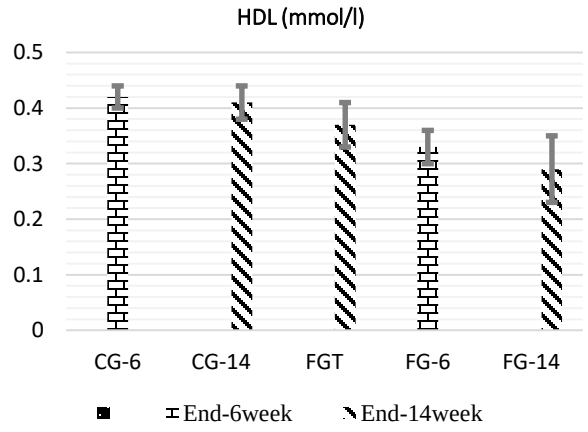


Figure 4. Changes in HDL values of the groups at the end of the 6th and 14th week. Data are presented as mean ± standard deviation.

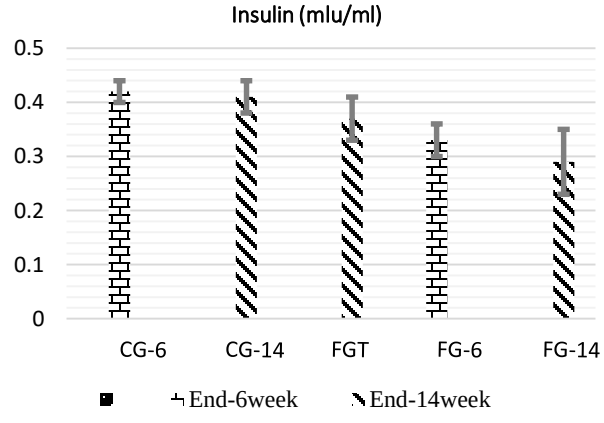


Figure 6. Changes in blood insulin values of the groups at the end of the 6th and 14th week. Data are presented as mean ± standard deviation.

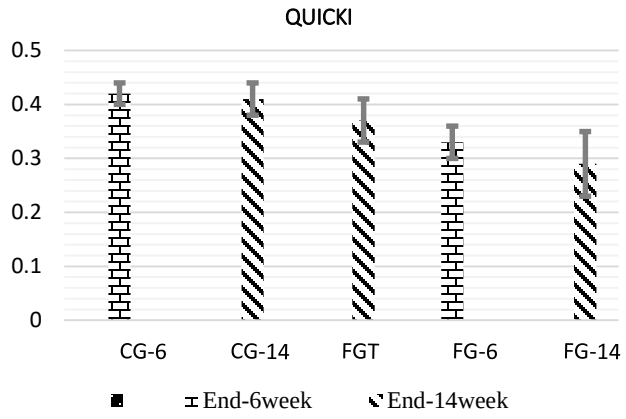


Figure 7. Changes in insulin sensitivity index values (Quickie) of the groups at the end of the 6th and 14th week. Data are presented as mean ± standard deviation.

-ercise (Holloway et al., 2006). However, at higher concentrations, although lipolysis in adipose tissue increases, plasma free fatty acid levels may not change significantly. In rats with metabolic syndrome, increased expression of adipose triglyceride lipase (ATGL) enhances lipolysis, leading to increased secretion of fatty acids and glucose, which provides energy to cells. Other factors, such as insulin deficiency and alpha-adrenergic pathways, have also been reported to enhance lipolysis in individuals with metabolic syndrome (Sztalryd et al., 2003). Lipid adaptation results in positive autoregulation of active enzymes. Indicators of this positive autoregulation include a chronic decrease in blood insulin concentrations and an increase in free fatty acid levels due to lipid adaptation (Hargreaves, Pharmacology, & Physiology, 2000).

The results of the current study indicate that eight weeks of interval training had no significant effect on epinephrine levels in male Wistar rats (P = 0.159). However, this training regimen resulted in a significant decrease in glucagon levels (P = 0.015). Epinephrine secretion is influenced by various factors, including exercise intensity. At intensities between 25-50% of VO2max, sympathetic tone increases, and epinephrine concentration approximately doubles. As intensity rises to 50-75% of VO2max, epinephrine concentration can increase up to fourfold. At intensities exceeding 75% VO2max, plasma epinephrine concentrations can be 17-20 times higher than at rest (A. Muscella, E. Stefàno, P. Lunetti, L. Capobianco, & S. Marsigliante, 2020a). The lack of significant changes in epinephrine concentrations after 8 weeks of interval training in this study may be attributed to the effects of metabolic syndrome on hormone secretion. Additionally, the observed decrease in glucagon levels could be related to metabolic syndrome and elevated blood glucose levels resulting from fatty acid consumption. It remains unclear whether glucose-mediated regulation of glucagon secretion requires changes in pancreatic alpha cells. The study results suggest that increased glucose levels negatively affect pancreatic alpha cells and reduce glucagon secretion. While the exact mechanisms are not fully understood, cyclic AMP (cAMP) might play a role. Increased glucose levels could lower cAMP concentrations in α cells, potentially inhibiting glucagon release (Dibe, Townsend, McKie, & Wright, 2020).

Conclusion

In general, intense interval training enhances tissue lipolysis. The weight loss associated with this type of exercise reduces markers of metabolic syndrome, including insulin resistance and triglyceride levels.

What is already known on this subject?

Interval training effectively reverses some metabolic syndrome-associated impairments in fat metabolism, specifically increasing key lipolytic enzymes and reducing glucagon levels. This suggests a potential therapeutic role for interval training in managing metabolic syndrome.

What this study adds?

It seems that high-intensity interval training can reduces markers of metabolic syndrome, including insulin resistance and triglyceride levels.

Organ Cross-Talk Tips:

- Cross-talk between muscle and fat tissue through intracellular signaling cause increase metabolism, which will ultimately increase lipolysis.
- Cross-talk between hormonal system and regulatory proteins according to the intensity of the exercises that cause changes in body fat mass.

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Compliance with ethical standards

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

Ethical approval This research was approved by the animal care and use committee at University of Medical Sciences of Ilam, Iran (Approval reference number: IR.MEDILAM.AEC.1401.00).

Informed consent Not applicable

Author contributions

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

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