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Investigating the Levels of Liver Lipogenic and Lipolytic Enzymes in Rat with High-Fat Diet and Sucrose Solution Underwent Progressive Resistance Training

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Abstract

Objective: Consuming too much fat or carbohydrates stimulates lipogenesis and excess fat is stored in non-fat tissues, including the liver, and manifests as obesity and fatty liver disease. This study aimed to investigate the effect of eight weeks of progressive resistance training (PRT) on the liver levels of some enzymes affecting lipid metabolism in rats fed a high-fat diet and sucrose solution.

Materials and Methods: Twenty-four male wistar rats with 5 weeks of age were randomly divided into two groups: standard diet (SD) (n=8) and high-fat diet and sucrose solution (HFDS) (n=16). Twelve weeks later, HFDS group was divided into two groups: sedentary (HS) and PRT (HPRT). The PRT program was implemented 3 days a week for 8 weeks. Gene expression of AMPKα 1, SCD-1, ATGL and FASN enzymes affecting lipid metabolism in liver tissue and its fat content were investigated.

Results: HFDS significantly increased the body weight (*P*: 0.001) and significantly decreased the liver expression of ATGL and FASN (*P*: 0.001, *P*: 0.011). Eight weeks of PRT did not show a significant difference in the expression of AMPKα 1, SCD-1, ATGL and FASN genes. Rats fed HFDS had considerably higher levels of triglyceride (TG) and total cholesterol (TC) in their liver tissue (*P*: 0.004, *P*: 0.001) and PRT did not affect them (*P*: 0.959, *P*: 0.809 respectively).

Conclusion: It seems that eight weeks of PRT will not change liver lipid metabolism enzymes. Therefore, modifying the diet and changing it, will probably show different results after PRT.

Keywords: Liver, Enzymes, Exercise, Diet

QR Code:

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Introduction

The liver plays a crucial role in lipid metabolism where fatty acid is synthesized. Lipid metabolism involves multiple pathways that are at least partially inter-dependent and "cross-regulated" (1). Fatty liver disease is one of the main liver complications related to obesity. Current management of this disease largely focuses on lifestyle interventions through diet and exercise to reduce weight and improve metabolic and cardiovascular risk factors (2). Excessive consumption of carbohydrates and fats and decreasing physical activity have led to a significant increase in the prevalence of overweight and obesity around the world (3). Obesity is caused by an excessive intake of high fat diets and sugar-sweetened beverages, according to evidence from studies on humans and animals (4). Adipose tissue with obesity-induced peripheral insulin resistance (IR), experiences increased lipolysis and release of free fatty acids (FFAs), which are taken up by the liver and, in muscle tissue, IR leads an increase in the transfer of glucose to the liver (5). It is well known that IR greatly increases the influx of fatty acids in the liver in favor of lipogenesis and preventing lipolysis of fats. This action, in turn, leads to increased oxidative stress and mitochondrial functional disorders (6).

Stearoyl-CoA Desaturase 1 (SCD-1) is a microsomal enzyme that controls the metabolism of fatty acids and is highly expressed in liver cells. Studies support the hypothesis that SCD1 activity may be protective against oxidative stress caused by saturated fatty acid (SFA) accumulation and liver inflammation (7). Overall, these studies demonstrate that SCD1 is extremely involved in regulation of body weight and this feature is further underlined by the fact that SCD1-deficient animals exhibit resistance to diet-induced obesity, hepatic steatosis, and triacylglycerol accumulation (8). Therefore, it can be said that SCD1 is a double-edged sword, and its unqualified inhibition, whether systemic or restricted to a specific organ, may not be desirable. Deletion of SCD-1 induces fatty acid oxidation and thermogenesis genes, which are mediated by induction of AMP-activated protein kinase (AMPK). AMPK stimulation suppresses several lipogenic pathways and inactivates sterol regulatory element-binding protein 1 (SREBP-1), which is a main transcription factor for expression of acetyl coenzyme A carboxylase (ACC), fatty acid synthase (FAS), elongase and SCD1 enzymes (5). Also, the stimulation of AMPK leads to the activation of fatty acid oxidation and improves sensitivity to insulin and metabolic health (9).

Adipose triglyceride lipase (ATGL) is another enzyme involved in liver lipid metabolism, which plays a main role in initiating the lipolysis of triglyceride (TG) into FFAs and glycerol (10). Studies show that overexpression and improved hepatic ATGL activity are along with an increase in TG breakdown and FFA oxidation, whereas ATGL liver deficiency is along with steatosis, which indicates an excessive accumulation of triacylglycerols and is strongly associated with IR (11). Also, the specific inhibition of hepatic ATGL causes a decrease in autophagy/ lipophagy downstream of this enzyme and subsequently hepatic lipid droplets (LD) catabolism and oxidation of hydrolyzed FAs (12) and increases body weight and subsequently fat mass (13). The role of ATGL-mediated lipolysis in hepatocytes is less obvious than it is in white adipocytes and β -cells, and the information that is currently available on glucose homeostasis reveals conflicting findings (14). Researchers have acknowledged that liver ATGL overproduction in obesity conditions reduces hepatic steatosis and partially increases the sensitivity of the liver to insulin. They believe that the abundance of ATGL is decreased in the liver of insulin-resistant, NAFLD patients

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and that genetic changes in the ATGL gene are associated with type 2 diabetes and plasma TAG. These sentence also declare that ATGL-mediated enhancement of lipolysis in the liver is probably a novel therapy for NAFLD and liver IR (15).

FAS is the critical enzyme responsible for the conversion of glucose into fatty acids and *de novo* fatty acid synthesis. Specifically, FASN catalyzes the reaction leading to the generation of palmitate and 16-carbon long fatty acid from acetyl-CoA and malonyl-CoA (16). The regulation of FAS by hormones and the nutritional state has been described in the liver and adipocytes and is also largely determined by the intracellular fatty acid concentration, an increase of which lowers FAS activity (1). Recently, it has been shown that overexpression of hepatic FAS in chow-fed mice impairs fatty acid oxidation and mitochondrial respiration and increases hepatic lipid accumulation and IR (17).

Physical activity has a beneficial effect on fatty liver disease. Various aerobic and resistance training has been shown to reduce the hepatic fat content by improving IR, liver fatty acid metabolism, liver mitochondrial function, and activation of inflammatory cascades (5). Researchers have found that hepatic AMPK activity levels increase 10-100 minutes after acute treadmill running (18). Also, resistance training due to the activation of the AMPK pathway stimulates the oxidation of lipids in the liver and causes the down-regulation of lipogenic enzymes such as SREPB-1c, ACC, SCD-1, and fatty acid synthase (19). Evidence shows that exercise training increases lipid droplets dynamic markers such as triglyceride lipases, ATGL, as well as mitochondrial efficiency, potentially reducing the accumulation of lipotoxic mediators (20). It has been stated that the maximum running speed and endurance capacity in ATGL$^{-/-}$ rats are reduced by 42% and 46%, respectively, and these results show the essential role of ATGL in providing a sufficient amount of FFA to maintain the substrate metabolism at rest and during exercise (21). Among exercise trainings, although resistance training has little effect on weight loss (22), the lack of interest in continuous training and the increasing interest in weight training and resistance training have made people more inclined to these exercises. However, it seems that these exercises, which affect peripheral IR, especially in muscle tissue, cause a decrease in glucose delivery to the liver and have a positive effect in regulating the expression of lipogenic enzymes and subsequently the signaling pathway of lipolytic enzymes, along with high-fat and high-carbohydrate diets, which are exogenous stimulators of lipogenesis, and another source of fatty acid synthesis, provide variable results. Because the best exercise program is not adequately specified and because the processes by which exercise affects the liver are still, at least in part, unclear; this study was designed to investigate the effect of progressive resistance training on the enzymes affecting the lipid content of the liver, which is one of the most essential clinical requirements for managing of fatty liver disease.

Materials and Methods

Animal care

Twenty-four male Wistar rats with an average weight of 183.9±2.94 and 5 weeks of age bought from the Pasteur Institute in Tehran, Iran. Four rats were housed in each cage, and the animals were kept in regulated light/dark (12/12 h) and temperature (22 ± 2^{oC}) environments. After one week's adaptation by laboratory environment, the animals were randomly separated into two groups: standard diet (SD) (n=8) and high-fat diet and sucrose solution (HFDS) (n=16).

Obesity induction method

The SD group followed a standard diet and water in 500 cc bottles for laboratory mice, and the HFDS group consumed a high-fat diet for 12 weeks, which included a conventional food with the addition of 12% liquid cooking oil (4) and a 30% sucrose solution in water provided in a second bottle, to induce IR (23).

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The dietary intervention group was split into two groups 12 weeks later: sedentary (HS) and PRT (HPRT).

Progressive resistance training program

The PRT lasted for 8 weeks (3 days/week). To perform this training, a 1-meter ladder was used at an angle of 80° to the wall, and the training load was applied by adding weights to the rats' tails. The PRT program in the first session included eight ladder climbs with a load equal to 50% of the rats' body weight (2 min of rest between the repetitions). In the second session, the first climb was performed with this weight, and in subsequent tests, 10% of body weight was added to the previous weight to reach 100% of the body weight and continued with the same weight until the eighth repetition. The third session also started with 50% of body weight and the amount of weights in the next repetitions reached 75%, 90%, and 100% of the rats' body weight, and in the next climbs, 10% was added to the amount of weights for each repetition. The highest load was considered as the maximum carrying capacity (MCC) of the rat. In the next training sessions, animals carried 50, 75, 90, and 100% of their previous MCC, respectively, during the first four climbs of the ladder until the end of the period. Subsequent ladder climbs were performed by adding 10% of body weight to the previous day's MCC. Therefore, the daily workload of the rats progressed by 10% compared to the previous day.

Tissue's samples collection

In order to remove the acute effect of training, sampling was performed 72 hours after the final training session and after the anesthesia of rats with intraperitoneal injection of ketamine (50 mg/kg) and xylazine (3-5 mg/kg) in the fasting state (8 hours). Tissue samples were driven from the liver tissue and were separated. Finally, part of the separated tissues was frozen in liquid nitrogen and used for mRNA and lipid analyses.

Determination of lipid contents in liver tissue

To measure the lipid profile of liver tissue, 1 g of homogenized liver samples was dissolved in 10 ml PBS buffer. The solution was then shaken in a shaker at room temperature for 15-20 minutes. The homogenized sample was centrifuged (12000 rpm for 10 min, at 4 °C) to obtain a lipid phase for measurement. Contents of TG and total cholesterol (TC) in the homogenized liver were assessed using GPO-POD and enzymatic-colorimetric CHOD-POD methods, respectively with a sensitivity of 1 mg/dl. The kits were purchased from Bionik Co., Iran.

Isolation of RNA and quantitative real-time PCR

To measure liver gene expression of AMPKα 1, SCD-1, ATGL, and FASN, total RNA was first extracted from frozen liver tissue using RNA extraction kit and according to the manufacturer's instructions, and cDNA synthesis was performed. Finally, the gene expression levels were measured by using Cyber-green Real-time PCR method. In this study, specific primers were designed to amplify AMPKα 1, ATGL, SCD1, FASN and HPRT1 reference genes using by Primer Premier 5 software, and then the primers sequence was synthesized with Bioneer (South Korea). The reciprocating primers sequence for the above genes is presented in Table 1. The expression of the desired genes was calculated by Livak ($2^{-\Delta\Delta CT}$) method.

Statistical methods

All statistical analyses were performed using the SPSS statistical software (version 16) was used at a significant level of $P< 0.05$. The Shapiro-Wilk's test was used for evaluating the normality of distribution. A one-way analysis of variance (ANOVA) test was used to compare the mean of liver enzymes and lipid profiles between groups. LSD's post hoc test was used if significant differences were found. All of data were presented as means (± standard error of the mean) (S.E.M).

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Ethical considerations

All steps of the study were carried out in accordance with "Guiding Principles for the Care and Use of Research Animals" approved by the Ethical Committee of the University of Mazandaran (IR.UMZ.REC.1401.045).

Results

There was no significant difference between the study groups in the initial body weight, before starting the training program and the final body weight (*P*> 0.05) (Table 2). The final body weights were affected by the diet and increased (*P*: 0.001), but the weight gain (final body weight – initial body weight) of the intervention groups was not significantly different from the SS group, and PRT did not make a significant difference (*P*> 0.05). The expression of genes related to liver lipid metabolism was measured. The results showed that there was no significant difference between the investigated groups in the expression of AMPKα 1 (*P*> 0.05) and applying an HFDS did not affect this variable (Figure 1-A). It was also shown that HFDS did not cause a significant difference in the expression of SCD1 compared to the SS group, and PRT did not show a significant difference with other groups (*P*> 0.05) (Figure 1-B). Our investigations showed that HFDS significantly decreased the liver expression of ATGL and FASN enzymes compared with the SS group (*P*: 0.001, *P*: 0.011) (*P*: 0.003, *P*: 0.004 respectively, Figure 1- C & D). The findings indicated that tissue TG and TC levels increased significantly after consuming HFDS compared to the SS group (*P*: 0.004, *P*: 0.001 respectively) and PRT did not decrease their values (*P*> 0.05) (Table 3).

Table 1. Primers used in the Real Time PCR process

Gene	Sequence	Access number	Product length (open pair)
AMPKa1	F-5'-ATTATTTGCGTGTGCGAAGGA-3' R-5'-GAGTAGCAGTCCCTGATTTGGC-3'	NM_019142.3	150
ATGL	F-5'-CAGACAACTTGCCACTTTATGAG-3' R-'5-CTTCGAGAGGCGGTAGAGATT-3'	NM_001108509.2	164
SCD1	F-5'-ACGACCACCACTACCATCACAG-3' R-5'-CATTTCAGGACGGATGTCTTCT-3'	NM_139192.2	108
FASN	F-5´-TGATGAAGAGGGACCATAAAGATAA-3´ R-5´-GTGGGAACAAGGCATTAGGG-3´	NM_017332.2	102
HPRT1	F-5´-TTCTTTGCTGACCTGCTGGAT-3´ R-5´-TATGTCCCCCGTTGACTGGT-3´	NM_012583.2	123

AMPKα1 5'-AMP-activated protein kinase catalytic subunit alpha-1, *ATGL* adipose triglyceride lipase, *SCD1* stearoyl-coenzyme A desaturase 1, *FASN* fatty acid synthase, *HPRT1* Hypoxanthine phosphoribosyl transferase 1

Table 2. Body weight in experimental groups

Groups	Initial weight (g)	Weight before training program (g)	Final weight (g)	Weight gain (g)
SS	192.1 (±4.74)	368 (±15.14)	427.7 (±19.25)	235.6 (±16.32)
HS	179.7 (±4.94)	355.7 (±12.52)	440.4 (±21.49)	262.9 (±23.39)
HPRT	179.7 (±4.88)	369.5 (±11.72)	443.9 (±16.4)	264.1 (±13.44)
P	0.140	0.738	0.815	0.443

Body weights of rats in three stages included; initial weight, weight before training program, and final weights. The values are expressed as mean ± SEM (n=8). The experimental groups were: SS, standard diet and sedentary; HS, high-fat diet and sedentary; HPRT, high-fat diet, and progressive resistance training. Weight gain = Final body weight - Initial body weight.

Table 3. Statistical indices related to the lipid profile of liver tissue

Groups	SS	HS	HPRT
TG (mg/g)	156.25 (±8.26)	180.5 (±1.92)*	180.17 (±4.54)*
TC (mg/g)	137 (±6.37)	161 (±1.57)*	162 (±1.65)*

Abbreviations: SS, standard diet and sedentary; HS, high-fat diet and sedentary; HPRT, high-fat diet and progressive resistance training; TG, triglycerides; TC, total cholesterol. The values are expressed as mean ± SEM (n=8). * vs. SS, (*P*<0.05).

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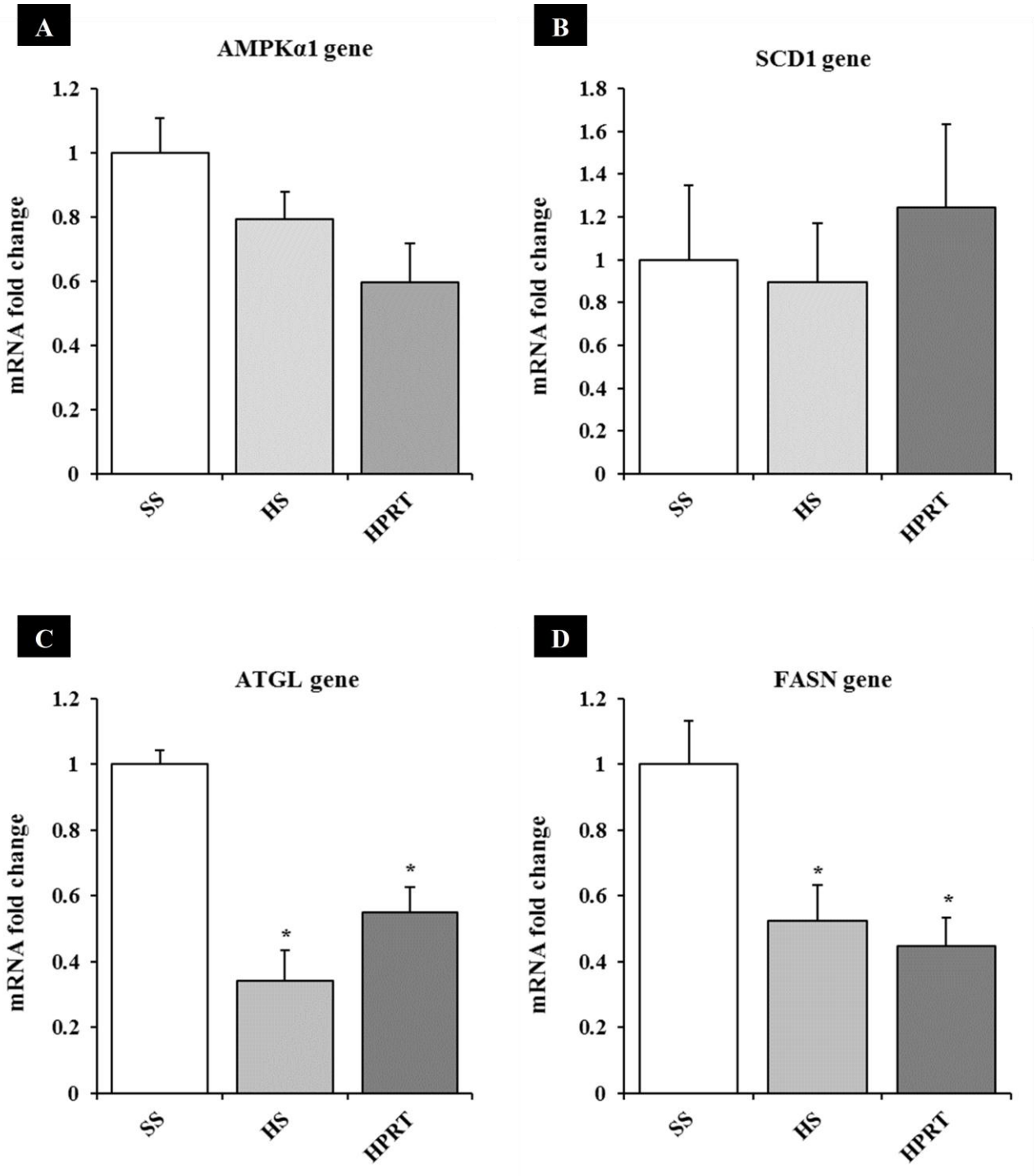

Figure 1. AMPKα 1, SCD1, ATGL and FASN gene expression levels in liver tissue of experimental groups. The values are expressed as mean ± SEM. SS, standard diet and sedentary; HS, high-fat diet and sedentary; HPRT, high-fat diet and progressive resistance training. * Significant difference compared to the SS group ($P< 0.05$).

Discussion

To comprehension the pathways of molecular involved in the effect of physical activity on fatty liver disease, it is important to pay attention to other outcomes than liver fat content. For example, IR appears to be a driving factor in NASH and its associated metabolic syndrome (5). In the present study, consumption of a high-fat diet and 30% sucrose solution, to induce IR (23), caused an

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increase in weight and levels of this metabolic disorder in rats. In line with our result, in another study, a mixture of 30% sucrose solution and 7.5% sunflower oil in diet increased blood glucose and liver steatosis in rats (24).

Despite the association between IR and SCD1 and AMPKα 1 enzymes in recent studies (25-27), the changes in the levels of these enzymes were not significant in our study. Van der Windt et al., (2018) in their review study to investigate the effects of various physical exercises on fatty liver disease, found that in addition to aerobic exercises, resistance exercises also reduce hepatic lipid content and improve steatosis, liver inflammation, and IR, and as a result of this decrease in exercise-mediated IR subsequently causes a decrease in the expression of lipogenic enzymes such as ACC, FAS, SCD1 and a decrease in the synthesis of fatty acids, as well as an increase in the expression of AMPK in the liver (5). Also, Domingos et al., (2012) reported activation of the AMPK pathway and stimulation of lipid oxidation in the liver following resistance training, which decreased lipogenic enzymes such as SREPB-1c, ACC, SCD-1, and fatty acid synthase (19). Resistance training improves IR in rats fed a high-fat diet (28). It appears that in our study, adding sucrose solution along with a high-fat diet had a significant effect on IR, and PRT could not have a significant effect on IR and consequently the expression of these enzymes. Because the effect of a high-fat diet alone on IR and its consequences was not investigated. Whereas Nikroo et al., (2020) in investigating the effect of resistance training on IR in high-fat diet-induced NAFLD male rats observed a significant reduction in IR in the HFD+RT group (29).This hypothesis is also supported in another study. Safarzade and Safarpour, (2021) who used a high-fat diet and sucrose solution in their study, found that progressive resistance training in the same period as the present study did not have a significant effect on glucose, insulin, and IR in the standard diet and HFDS groups (4). Therefore, it may be possible to partly explain the slight decrease and increase in AMPKα 1 and SCD1 following exercise, respectively. However, FASN values decreased slightly as a result of progressive resistance training, which was not statistically significant. Researchers state that FASN is significantly inactivated in conditions of IR (30). This evidence can be a reason for the reduction of this gene after the development of IR caused by HFDS.

On the other hand, the significant increase in body weight of the subjects at the end of the study, knowing that there is a relationship between SCD1, AMPKα 1 and ATGL enzymes, and body weight in previous studies (8,13,27), can probably be the reason for the observed changes in the main research variables. Hallsworth et al, (2011) also showed that resistance exercise had little effect on weight loss and specifically reduces NAFLD independent of any changes in body weight. After eight weeks of progressive resistance training, they elicited a 13% relative reduction in liver lipid and lipid oxidation, glucose control, and IR were all improved (22).

Our other finding was a significant decrease in ATGL following consumption of HFDS, in which progressive resistance training only slightly increased and did not reach the values of the SS group. Turpin et al., (2011) acknowledge that the abundance of ATGL is decreased in the liver of insulin-resistant, NAFLD patients and that genetic changes in the ATGL gene are associated with type 2 diabetes and plasma TAG (15), which is consistent with our finding that ATGL decreased following IR induced by dietary intervention. Based on the search conducted by the authors of the present study, it seems that there has been no research on the effect of resistance training on the expression of hepatic ATGL. However, overexpression and improved hepatic ATGL activity are along with an increase in TG turnover and FFA oxidation, whereas ATGL liver deficiency is along with steatosis (11). Therefore, the induction of IR in the present study can be a

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reason for the decreasing changes of this gene, which subsequently resulted in a significant increase in TG and TC in the liver tissue of rats, and PRT was not effective on the lipid profile of the liver tissue. On the other hand, the absence of a significant effect of PRT on ATGL and SCD1 values, due to the existence of a relationship between these enzymes and TG (10), can reflect the lack of change in TG values.

Conclusions

The outcomes of this study showed that the expression of liver lipogenic and lipolytic enzymes are partially affected by HFDS-induced IR, and progressive resistance training during this time, cannot have a significant effect on them. As a result, although different exercise regimens have been displayed to affect fat content in the liver, one exercise regimen cannot be definitively preferred over another. Therefore, it is suggested to investigate the expression of these enzymes following a high-fat diet alone, along with the dietary intervention applied in this research, so that the effects of fat consumption alone can be separated from the effects of high fat-high sucrose diet on liver lipid metabolism, and observed different possible results following progressive resistance training over a similar period of time.

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Conflict of Interest

The authors report no conflicts of interest.

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