Investigation of the simultaneous effect of resistance training and atorvastatin in improving nonalcoholic fatty liver disease in Rats fed high high-fat/fructose diet

Running title: Resistance training and atorvastatin in NAFLD

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD), a highly prevalent and chronic liver disease, is characterized by a diverse range of conditions that span across a broad spectrum. Engaging in consistent physical activity has proven to be a successful method in effectively managing NAFLD, as it has demonstrated the ability to enhance crucial elements implicated in the development of the condition

Methods: Twenty-one male Wistar rats were divided into three groups: 1) NAFLD, 2) NAFLD + resistance training (RT), 3) NAFLD + RT + atorvastatin (ATO). The groups received high fat/fructose diet (HFFD) to induce NAFLD and it was confirmed through evaluation of histopathological analysis (H&E staining) and measurement of aminotransferase enzymes. ATO was administrated at the dose of 2 mg/kg/day. The interventions were done for eight weeks.

Results: Triglyceride (TG), Alanine transaminase (ALT), and aspartate transaminase (AST) were significantly reduced in the NAFLD + RT + ATO. Also, low-density lipoprotein (LDL) had lower level in NAFLD + RT in compared to NAFLD + RT + ATO. Alkaline phosphatase (ALP) was reduced in both NAFLD + RT and NAFLD + RT + ATO groups compared to NAFLD. There was no significant difference in weight between the groups except first, second, and forth week.

Conclusion: RT in combination with the administration of ATO can be deemed as an efficacious and supplementary strategy for the purpose of effectively controlling and addressing NAFLD.

Keywords: NAFLD; Resistance training; Lipids; Liver enzymes; Atorvastatin

Introduction

NAFLD is a highly prevalent and persistent liver disease that encompasses an extensive range of conditions, commencing with the relatively benign accumulation of fat in the liver, known as simple steatosis, and potentially advancing to a more severe form called non-alcoholic steatohepatitis (NASH), which is characterized by inflammation and liver cell injury, and further progressing to fibrosis, a process whereby excessive connective tissue is deposited in the liver, culminating in the development of cirrhosis, a late-stage condition characterized by extensive scarring and impaired liver function, and ultimately presenting a heightened risk for the occurrence of liver carcinoma, a malignant tumor originating from liver cells (1). As the prevalence of NAFLD continues to rise, the prevention and treatment of this disease have become increasingly important.

One effective approach to managing NAFLD is through regular physical activity, which has been shown to improve key factors involved in the pathogenesis of the disease, such as hypertriglyceridemia, hyperglycemia, and obesity (2). Among the various types of physical activity, resistance training has gained attention for its potential benefits in reducing liver fat and improving liver function (3). Resistance training, also known as strength training or weightlifting, is a form of exercise that focuses on building and maintaining muscular strength, endurance, power, and mass. While traditionally viewed as a complement to aerobic exercise, resistance training has shown promise in improving liver health in NAFLD patients (4). In addition to reducing liver fat, RT had several positive effects on NAFLD. These effects are important for overall health and can contribute to improved metabolic function (5). Moreover, the RT had significant reductions in serum ferritin and total cholesterol levels. Lowering ferritin levels is particularly beneficial in NAFLD, as high ferritin levels have been linked to liver inflammation and fibrosis. By reducing ferritin and cholesterol levels, RT may help mitigate the progression of NAFLD (2, 6). There are multiple therapeutic interventions available to address this complication. One of the approaches encompasses the administration of ATO, a prescribed medication intended for the treatment of this particular ailment. ATO belongs to the category of statin drugs, which, when utilized over an extended period of time or in high doses, may potentially give rise to liver complications, mortality, and an increase in cell apoptosis. Furthermore, ATO effectively reduces levels of cholesterol (CHO), TG, LDL-C, while simultaneously elevating high-density Lipoprotein-C (HDL-C) concentrations within the bloodstream. In addition, ATO exhibits antioxidative, anti-apoptotic, and anti-inflammatory attributes (7). The mechanism of ATO involves protein prenylation inhibition, mitochondrial dysfunction, oxidative stress, and damage in various cell types. ATO also affects fatty acid metabolism, oxidative stress, and mitochondrial dysfunction in the kidneys, leading to nephrotoxicity (8). Recently, a multitude of investigations have unveiled that the administration of ATO exhibits efficacy and safety in the management of individuals afflicted with NAFLD or NASH accompanied by hyperlipidemia (9). ATO exhibits dual effects in patients, as it not only reduces liver transaminase levels but also effectively suppresses hepatic steatosis (10). The aim was to determine the simultaneous effect of RT and ATO in improving NAFLD in rats fed HFFD.

Methods

Twenty-one male Wistar rats (200-250 gr), were procured from Shahid Mirghani Research Institute (Golestan, Iran). The animals were provided unrestricted access to both feed and water throughout the entire experiment and were housed in a controlled facility with a 12-hour dark/light cycle and a temperature ranging from 20 to 24 C. A period of one week was allocated for the rats to adapt to their new surroundings and familiarize themselves with their living conditions. Subsequent to this acclimation period, the rats were exposed to the induction of NAFLD in accordance with the established protocol developed by Eslami et al (11). After a period of 15 weeks, NAFLD had been induced in the rats by assessment of biochemical and histopathological findings. Following this, the animals were divided into three groups; 1) NAFLD, NAFLD+ RT+ ATO, and NAFLD + RT. The interventions, consisting of administering ATO at a dosage of 2 mg/kg/day (12) and RT, were maintained for a duration of eight weeks.

The rats were rendered unconscious through the administration of ketamine (50 mg/kg) and xylazine (5 mg/kg, Merck, Germany) via intraperitoneal injection, thereby inducing anesthesia (13). Standard

enzymatic techniques were utilized for the evaluation of the aminotransferases and alkaline phosphatase (ALP), and an auto-analyzer (BT-3500, Biotecnica Instruments, Italy) was employed for the measurement of TG, LDL, and HDL levels (Pars Azmoon, Tehran, Iran).

At the conclusion of the 23rd week, the rats were euthanized. Following the acquisition of blood samples, the livers were promptly excised and rinsed with physiological saline. Subsequently, liver tissue samples were obtained through incisions and preserved in a 10% buffered formaldehyde solution. These samples were then embedded in paraffin for hematoxylin-eosin (H&E) staining and grading of NAFLD.

The period of adaptation involved engaging in climbing sessions on a wooden ladder that measured 110 cm in height and 18 cm in width, featuring an incline of 80 degrees. Positioned at the ladder's summit, there existed a designated rest area where the animals were stationed for a duration of two minutes before embarking on the subsequent repetition. Within this timeframe, the animals acquired the skill of ascending the ladder by means of stimuli being applied to their tails utilizing forceps. Upon the fulfillment of the adaptation phase, which entailed a maximum of six successive sessions spanning across a week, the training protocol no longer necessitated the presence of any stimuli. The training sessions consistently occurred in the afternoon, transpiring five times per week over an eight-week span, accumulating a total of 40 sessions. Each training session involved completing the task of climbing 15 times (14). The protocol of RT is mentioned in Tables 1.

The sample size was determined using G*Power software. We considered significance level (α) at 0.05 and power ($1 - \beta$) at % 80 to determine sample size. The determination of the data distribution was accomplished through the utilization of the Shapiro-Wilk test, while the evaluation of the equality of variances was performed by means of Levene's test. Moreover, for group comparisons, we used One-Way ANOVA and Tukey post hoc test. The execution of this analysis was carried out utilizing version 16 of the SPSS software, with the significance level established at $P \leq 0.05$.

The investigation was conducted in compliance with the guidelines outlined in the publication "Guide for the Care and Use of Laboratory Animals" issued by the National Institutes of Health (NIH publication No. 85–23, revised 1996). The research protocol was granted approval by the ethics committee of the local institution (IR.SSRC.REC.1402.121).

Results

To validate the induction of NAFLD, blood samples were randomly extracted from three rats for the purpose of evaluation hepatic enzymes. In addition, their liver tissue was excised to undergo pathological examination (Figure 1).

The weight of studied groups mentioned in Table 2.

The findings provide evidence suggesting that there were statistically significant variations in the average weight alterations during the 1st, 2nd, and 4th weeks among the groups, whereas no discernible dissimilarities were detected in the other weeks.

The comparison of serum levels of triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), AST, ALP and ALT in the study groups is shown in Table 3. Additionally, the results of Levine's test were shown in Table 4 and 5.

The results of the Tukey post hoc test indicate a notable dissimilarity in the TG levels among the various study groups (P=0.000). Similarly, the LDL (P=0.019) also exhibited statistically significant differences. The analysis of liver enzymes further substantiated these findings, highlighting a significant distinction in the levels of ALT (P=0.017), AST (P=0.000), and ALP (P=0.006) across the study groups (Table 4). The findings of the group comparison reveal that TG (P=0.000), LDL (P= 0.001), AST (P= 0.002), and ALP (P= 0.10) levels decreased in NAFLD + RT compared to NAFLD. The NAFLD + RT+ ATO group exhibited reduced levels of TG (P= 0.000), AST (P= 0.001), ALT (P=0.021), and ALP (P= 0.015) in comparison to the NAFLD control group, similarly to the aforementioned manner. Although the lipid indices and liver enzymes have decreased compared to the control group, the difference between the intervention groups was not significant. This suggests that RT not only reduces lipid profile but also contributes to improved liver enzymes in NAFLD.

Discussion

ATO administration alone can improve lipid profile in patients with dyslipidemia. Furthermore, combining ATO with other interventions can enhance its therapeutic efficacy in managing dyslipidemia. This combination can lead to improvements in insulin resistance, endothelial function, oxidative stress markers, lipid profile and metabolic control. RT has also shown promise in improving NAFLD. conducted a study using male rats with NAFLD and found that RT significantly improved liver fat content compared to other exercise modalities (15). The present study examined the simultaneous effect of RT and ATO in improving NAFLD in rats fed HFFD.

A randomized clinical trial conducted by Zelber-Sagi et al. investigated the effect of RT on NAFLD patients. The study enrolled patients without secondary liver diseases, such as viral hepatitis or excessive alcohol consumption, and randomly assigned them to either a RT group or a control group that performed home stretching exercises. The RT program consisted of exercises such as leg press, chest press, seated rowing, and latissimus pull down, with 8-12 repetitions and 3 sets for each exercise, performed three times a week for a total duration of 40 minutes (2). Oh et al. found that high-intensity aerobic exercise improves hepatic fat content in NAFLD patient (16). Exercise therapy, a widely recognized and well-established approach, has proven to be highly efficacious in addressing a multitude of metabolism-associated diseases. The incorporation of both resistance and aerobic exercises in a comprehensive treatment plan has been deemed more logical and fruitful in the realm of clinical practice. This combined exercise regimen has demonstrated remarkable success in yielding positive outcomes (17). S. Pekkala et al., demonstrated that both High Intensity Interval Training (HIIT) and Moderate Intensity Training (MIT) showed an equivalent level of efficacy in mitigating the weight gain caused by a HFD in rats (18). In a study conducted by Eslami et al., it was demonstrated that the implementation of aerobic exercise over a duration of 12 weeks resulted in a noticeable reduction in the expression of the mitogen-activated protein kinase (MAPK) P38 gene within the subcutaneous adipose tissue of rats that were fed a HFD. This finding is of great significance as it highlights the potential of aerobic exercise in modulating the genetic factors involved in adipose tissue metabolism, specifically targeting the MAPK P38 gene. The implications of this study extend beyond the realm of animal models, as it provides valuable insights into the potential therapeutic applications of exercise interventions in combating the detrimental effects of a HFD on adipose tissue function (19, 20). Also, it was demonstrated that endurance training exhibited a significantly reduction in anthropometric indices subsequent to a duration of 12 weeks in obese rats (21) that results along with Mirghani et al. study (22).

An exercise regimen that focuses on aerobic activities over a span of 24 weeks was implemented in a group of postmenopausal women diagnosed with NAFLD. The results of this program revealed significant enhancements in certain parameters, including reduction in waist circumference, increase in high-density lipoprotein cholesterol levels, and improvement in cardiopulmonary performance. These positive outcomes potentially contribute to the amelioration of cardiovascular risk factors within this specific demographic (23). Moderate-intensity aerobic training, which refers to physical activities that increase heart rate and breathing but can still be sustained for a prolonged period without exhaustion, along with resistance training, which involves repetitive exercises that use resistance or weights to build strength and endurance, when combined with dietary modification, which involves making changes to one's eating habits and food choices, have been found to have an equal level of effectiveness in the reduction of intrahepatic fat, which is the accumulation of fat within the liver, and improvement of the underlying insulin resistance, which is a condition where the body's cells do not respond properly to insulin, among patients who have NAFLD, a condition characterized by the buildup of fat in the liver that is not caused by excessive alcohol consumption (24). In addition, it has been deduced that the implementation of concurrent training has the ability to impede the reduction of serum HDL levels that may occur as a result of engaging in strength training among young males (25, 26).

Based on the findings of this study and previous research, RT can be considered an effective and complementary approach to managing NAFLD. The American Heart Association and the American College of Sports Medicine recommend incorporating RT at least twice a week in addition to aerobic

exercise for overall health benefits. For NAFLD patients, RT can serve as an alternative or complementary form of exercise, especially for those who may have physical limitations or low motivation to engage in aerobic activities. Before starting a RT program, NAFLD patients need to consult with their healthcare providers and undergo a thorough evaluation to ensure they can safely engage in this form of exercise. Working with a certified fitness professional or exercise physiologist can also help design an appropriate RT program tailored to individual needs and goals. Studies have also investigated the effects of ATO in the context of NAFLD. Studies conducted on a rat model of NAFLD found that ATO treatment improved lipid profiles and liver function. TG, cholesterol, and liver enzyme levels were significantly reduced in the group receiving ATO compared to the control group. ATO was found to effectively control liver enzymes and improve the lipid profile in rats with NAFLD (7, 13). Ji et al. investigated that ATO treatment was found to be highly effective in improving hyperlipidemia associated with NAFLD and also in inhibiting liver steatosis. These beneficial effects were observed in conjunction with the modulation of genes that are involved in the regulation of lipid metabolism. Furthermore, the addition of ATO to dietary control interventions was found to greatly enhance their efficacy in reducing the levels of serum total cholesterol and LDL-C, although it did not have a significant impact on TG levels, free fatty acid levels, or hepatic steatosis in rats with high-fat diet-induced fatty liver and hyperlipidemia (27).

RT and ATO have been studied individually for their effects on NAFLD, but there is limited research on their simultaneous effect. The current literature suggests that exercise, including RT, can improve liver enzymes, body composition, and lipid profiles in individuals with NAFLD. Additionally, aerobic exercise and RT have both been shown to reduce intrahepatic fat in patients with NAFLD (28). Furthermore, acceleration training (AT), a form of exercise that increases gravitational acceleration with vibration, has been found to be effective in reducing hepatic fat content and improving liver function in obese patients with NAFLD (29). However, there is a lack of research specifically investigating the simultaneous effect of RT and ATO in improving NAFLD. Conducting such research could provide valuable insights into the potential synergistic effects of these interventions on NAFLD management.

Conclusion

RT and ATO have been studied separately for their effects on NAFLD, but there is no specific information available on their simultaneous effect. Studies have shown that RT can improve liver enzymes, hepatic fat, and histologic markers in NAFLD. ATO, on the other hand, is a medication used to lower cholesterol levels and has been shown to improve liver function in NAFLD patients. However, there is no direct evidence on the simultaneous effect of RT and ATO in improving NAFLD. Further research is needed to determine the combined effect of these interventions on NAFLD.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Ethical statement

The research protocol was approved by the ethics committee of the local institution (IR.SSRC.REC.1402.121).

Author contributions

RM: Preparation of manuscript, analyzed and interpreted the data. AH: Conception and design, overall scientific management. SR and LM: Conception and design. All authors read and approved the final manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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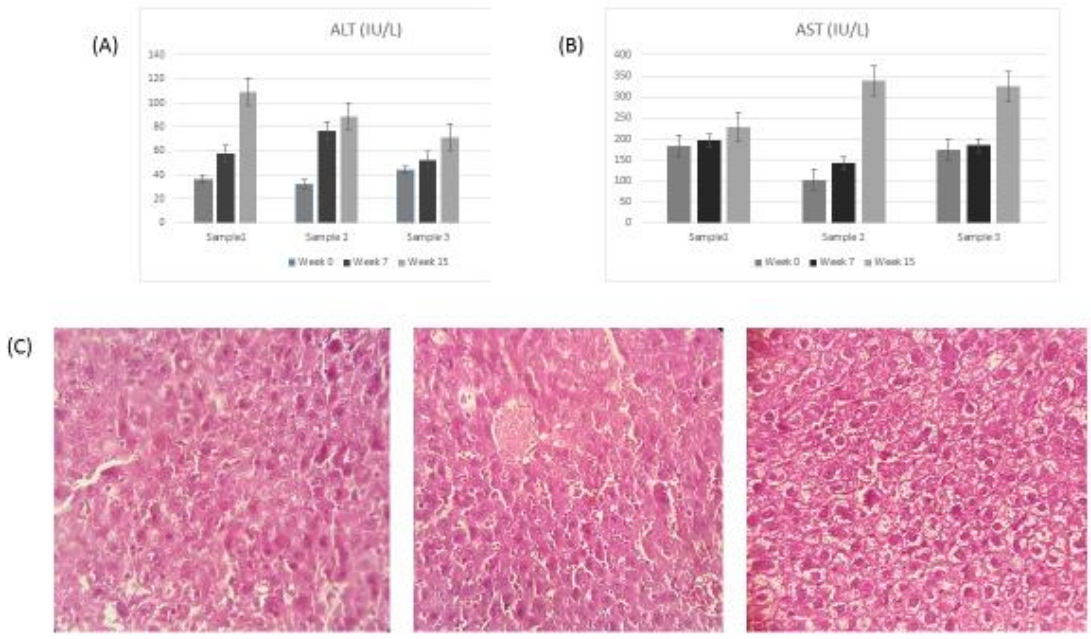

Figure 1. (A) Serum ALT levels, (B) Serum AST levels, (C) H and E staining of liver tissues in 3 sample

Table 1. The protocol of RT

	Session	1st	2nd	3rd	4th	5th	6th	7th	8th	9th
1st week	Repetition	2	3	2	2	2	2	2	-	-
	%	0%	20%	30%	40%	30%	20%	0%	-	-
2nd week	Repetition	1	1	4	3	4	1	1	-	-
	%	0%	20%	30%	40%	30%	20%	20%	-	-
3rd week	Repetition	1	2	2	1	2	2	1	2	-
	%	20%	30%	40%	50%	40%	30%	20%	0%	-
4th week	Repetition	1	1	1	2	2	2	2	1	1
	%	0%	20%	30%	40%	50%	40%	30%	20%	0
5th week	Repetition	1	1	2	2	3	2	2	1	1
	%	0%	20%	30%	40%	50%	40%	30%	20%	0%
6th week	Repetition	1	1	2	3	2	3	1	1	1
	%	0%	30%	40%	50%	60%	50%	40%	30%	0%
7th week	Repetition	2	2	3	3	3	1	1	-	-
	%	0%	40%	50%	60%	50%	40%	0%	-	-
8th week	Repetition	1	2	4	5	2	1	1	-	-
	%	0%	40%	50%	60%	50%	40%	0%	-	-

Table 2. Mean and standard deviation of weight (gr) in studied groups

Group	1st week	2nd week	3rd week	4th week	5th week	6th week	7th week	8th week
NAFLD	368.75 ± 50.07	347.62 ± 44.27	380.26 ± 45.54	406.61 ± 45.44	405.59 ± 47.34	409.26 ± 46.27	414.52 ± 49.25	423.73 ± 52.64
NAFLD + RT	361.15 ± 41.96	376.62 ± 49.21	373.90 ± 48.61	385.21 ± 46.12	393.14 ± 44.83	377.43 ± 47.51	384.40 ± 51.86	391.32 ± 48.28
NAFLD + RT + ATO	360.97 ± 53.12	384.02 ± 77.27	386.56 ± 72.50	379.30 ± 69.61	388.21 ± 68.30	384.14 ± 65.33	389.95 ± 67.42	389.81 ± 68.10
P	0.00*	0.01*	0.06	0.02*	0.23	0.16	0.29	0.30
Sig (Shapiro-Wilk Test)	0.49	0.45	0.38	0.55	0.13	0.01	0.06	0.02

*Significant: P≤0.05

NAFLD: Non- Alcoholic Fatty Liver Disease, RT: Resistance Training, ATO: Atorvastatin.

Table 3. Mean of biochemical indicators in the studied groups

Group	TG	LDL	HDL	ALT	AST	ALP
NAFLD	114.43± 11.8	2.45± 1.02	38.74±10.99	141.66±56.12	240.01±38.81	409.43±77.68
NAFLD + RT	49.65 ± 6.12	0.66 ± 0.20	37.35 ± 3.98	81.07 ± 16.79	148.85 ± 23.98	262.00 ± 58.38
NAFLD + RT + ATO	46.00 ± 3.74	6.80 ± 5.16	38.35 ± 8.99	61.32 ± 3.55	119.10 ± 35.85	277.50 ± 50.33
P	0.000*	0.019*	0.971	0.017*	0.000*	0.006*
Sig (Shapiro-Wilk Test)	0.34	0.46	0.73	0.20	0.32	0.08

*Significant: P≤0.05

NAFLD: Non- Alcoholic Fatty Liver Disease, RT: Resistance Training, ATO: Atorvastatin. TG: Triglycerides, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase.

Table 4. Levine's test to assess the homogeneity of weight variance in study groups

Group	1st week	2nd week	3rd week	4th week	5th week	6th week	7th week	8th week
F	5.16	2.92	2.18	2.64	1.41	1.62	1.26	1.25
Sig	0.00*	0.01*	0.06	0.02*	0.23	0.16	0.29	0.30

Table 5. Levine's test to assess the homogeneity of lipid and liver enzymes variance in study groups

Group	TG	LDL	HDL	ALT	AST
F	27.20	25.19	2.68	4.26	10.24
Sig	0.234	0.146	0.125	0.136	0.136