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Synergistic Effect of High Intensity Interval Training and Atorvastatin in Treatment of NAFLD in Rats Fed High Fat/Fructose Diet

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) is a prevalent chronic liver disease that ranges from steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and liver carcinoma. With the increasing prevalence of NAFLD, there is a growing need for effective prevention and treatment strategies. Stable pharmaceutical compositions containing atorvastatin have been developed to treat hypercholesterolemia and related conditions. In addition, high-intensity interval training (HIIT) can have positive effects on NAFLD.

Methods: Twenty-one male Wistar rats were divided into 2 groups: 1) high fat-fructose diet (HFFD) + HIIT, 2) HFFD + HIIT + atorvastatin. The groups received HFFD for 15 weeks to induce NAFLD. Atorvastatin was administrated at the dose of 2 mg/kg/day. The interventions (atorvastatin and HIIT) were done for 8 weeks.

Results: Triglyceride (TG), Alanine transaminase (ALT), and aspartate transaminase (AST) were significantly reduced in the HFFD + HIIT + atorvastatin. The groups had no significant difference in weight, low-density lipoprotein (LDL), alkaline phosphatase (ALP), and HDL/LDL ratio.

Conclusion: Although atorvastatin along with HIIT reduced aminotransferase, HIIT has benefits in improving lipid profile. Combining atorvastatin and HIIT may offer synergistic benefits in managing NAFLD by targeting both liver enzymes and inflammation.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) arises as a consequence of an excessive buildup of fat in the hepatocytes, the main functional cells of the liver, resulting in impaired liver function and subsequent adverse health outcomes (1). The global prevalence of NAFLD has witnessed a steady rise owing to the prevalent lifestyle changes characterized by sedentary behavior, unhealthy dietary patterns, and the increasing burden of obesity, thereby necessitating urgent attention and the implementation of preventive measures to curtail its escalating prevalence (2). Furthermore, epidemiological investigations have revealed that the prevalence of NAFLD in Iran is estimated to be approximately 31.15% and 21.5%, highlighting the alarming magnitude of the disease burden in this specific geographical region (3) (4). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), and alkaline phosphatase (ALP) are of paramount importance in assessing the well-being of the liver. Patients with NAFLD often exhibit elevated levels of these liver enzymes, namely ALP, AST, GGT, and ALT, in their serum. Additionally, these enzymes experience an increment in situations such as diabetes and alcoholism (5).

In light of the intricate pathophysiological mechanisms underlying NAFLD, characterized by the upregulation of triglyceride (TG), total cholesterol (TC), and low-density lipoprotein (LDL) levels, it is crucial to devise effective strategies aimed at mitigating the aberrant lipid metabolism implicated in the pathogenesis of NAFLD (6). Consequently, the identification and deployment of therapeutic agents that possess

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potent antioxidant properties emerge as a promising avenue to combat the multifaceted challenges posed by obesity and its associated complications. Specifically, the administration of atorvastatin, a pharmacological agent renowned for its well-documented minimal side effects profile, holds tremendous potential in fortifying the body's antioxidant defenses, thereby exerting a pivotal role in the prevention and management of obesity-induced inflammation and its subsequent sequelae. By harnessing the inherent antioxidant capacity of atorvastatin, healthcare providers and researchers can potentially unlock novel therapeutic approaches to tackle the burgeoning epidemic of NAFLD with utmost efficacy and safety, ultimately striving towards the attainment of improved public health outcomes and a better quality of life for affected individuals (7, 8).

Physical activity plays a crucial role in managing inflammation-related diseases like NAFLD by reducing the mass of visceral fat, enhancing lipolysis, and subsequently decreasing the release of pro-inflammatory cytokines, thus establishing an anti-inflammatory environment (9). High-Intensity Interval Training (HIIT) has been shown to effectively reduce fat tissue and promote increased oxygen consumption post-exercise through enhanced oxidation. This highlights the significance of physical activity in mitigating the detrimental effects of inflammation and underscores the potential of HIIT as a therapeutic approach in combating NAFLD and other related conditions (10). HIIT has been shown to effectively reduce fat tissue (11) and promote increased oxygen consumption post-exercise through enhanced oxidation. This highlights the significance of physical activity in mitigating the detrimental effects of inflammation and underscores the potential of HIIT as a therapeutic approach in combating NAFLD and other related conditions (8). Atorvastatin is a key enzyme involved in cholesterol synthesis. By reducing cholesterol production, atorvastatin effectively lowers LDL levels and improves lipid profiles (12). Atorvastatin treatment also led to a decrease in intracellular ATP levels and an increase in cytotoxicity in HepG2 cells (13). This drug has been found to inhibit 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase, leading to up-regulation of LDL receptors and increased clearance of LDL-cholesterol from the plasma (14). Additionally, atorvastatin has been shown to modulate microRNA expression, with up-regulation of miR-124a and down-regulation of GAMT expression in hepatocytes (15). Repression of hsa-mir-20a-5p, a microRNA, has been associated with increased LDL receptor expression in HepG2 cells (16). High doses of statins, including atorvastatin, were found to induce key enzymes involved in VLDL production in rat liver, potentially through overexpression of SREBP-2 (17). However, it is important to note that higher doses of atorvastatin have been associated with hepatotoxicity, as evidenced by increased liver enzyme activity and degeneration of liver cells (18). Overall, the mechanism of action of atorvastatin on liver enzymes involves modulation of gene expression and potential disruption of VLDL production.

These findings suggest that atorvastatin can effectively improve lipid profiles, reduce fatty liver, and regulate liver enzymes in NAFLD. However, it is important to note that the effects on different lipid parameters may vary, and careful monitoring of liver enzymes is necessary during treatment. The potential synergistic effects of combining HIIT and atorvastatin in the treatment of NAFLD have also been explored. However, research in this area is limited, and further studies are needed to fully understand the benefits and mechanisms of combined therapy. It is possible that the combination of HIIT and atorvastatin may provide additive or synergistic effects in improving liver health and lipid metabolism in individuals with NAFLD. So, we aimed to assess the simultaneous effect of HIIT and improving NAFLD in rats fed HFFD.

Material and Methods

Animal and Design

Twenty-one male Wistar rats weighing between 180-200 grams were obtained from Shahid Mirghani Research Institute (Golestan, Iran). These rats were selected as the subjects for this experiment due to their suitability for research purposes. Throughout the duration of the experiment, the rats were provided with unlimited access to both feed and water, ensuring that their nutritional needs were met adequately. In order to maintain a consistent environment, the rats were housed in a controlled setting with a 12-hour dark/light cycle and a temperature ranging from 20 to 24 C.

To ensure accurate results, a period of one week was allotted for the rats to acclimate to their new surroundings and become familiar with their living conditions. Following this adaptation period, the rats were subjected to the induction of NAFLD in alignment with the protocol developed by Eslami et al. (19). Normal diet will contain 4.30 kcal per gram including 3.87% fat (soy oil), 17.46% casein protein, 68.7% carbohydrates, 8.97% minerals, and 1% vitamins (20). For inducing NAFLD, the rats consumed HFFD (45% fructose and 35% olive oil (gavage)) (18) for 15 weeks. In addition to consuming HFFD, the groups had free access to normal diet. At the end of the 15th week, a selection of blood samples and liver tissue were taken at random from 5 rats in order to assess the levels of serum ALT and observe any changes in the liver tissue. The biochemical and histopathological findings indicated that NAFLD had been induced in the rats. Following this, the animals were divided into two distinct groups; 1) HFFD + HIIT (n=8), HFFD + HIIT + atorvastatin (n=8). The interventions, consisting of administering atorvastatin at a dosage of 2 mg/kg (dissolved in 6% DMSO, gavage) (Raha Pharmaceutical co, Iran) (21) and implementing HIIT, were maintained for a duration of eight weeks.

Measurement of Biochemical Indices

The rats were rendered unconscious through the administration of ketamine (50 mg/kg) and xylazine (5 mg/kg, Merck, Germany) via intraperitoneal injection (22), thereby inducing anesthesia. In order to assess the presence and quantity of aminotransferases and ALP, standard enzymatic techniques were employed, while levels of TG, LDL, and HDL were measured using an auto-analyzer (BT-3500, Biotecnica Instruments, Italy).

Table 1. Protocol of HIIT

Week	1st	2nd	3rd	4th	5th	6th	7th	8th
Repetition	4	5	6	8	8	10	12	12
Min	2	2	2	2	2	2	2	2
%	90%	90%	90%	90%	90%	90%	90%	90%

HIIT Protocol

The protocol of HIIT is mentioned in Tables 1 (23).

Statistical Analysis

The distribution of the data was determined using the Shapiro-Wilk test, while the homogeneity of variances was assessed using Levene's test. Furthermore, ANOVA was employed to compare the means of the desired variables. The analysis was conducted using SPSS software version 16, with a significance level set at P≤0.05.

Ethical Statement

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). Diligent measures were taken to mitigate animal distress and minimize the quantity of animals employed.

Table 2. Mean and standard deviation of weight changes in groups during 8 weeks

Group	W1	W2	W3	W4	W5	W6	W7	W8
HFFD + HIIT	377.60 ± 28.90	375.35 ± 26.08	372.25 ± 31.42	378.81 ± 34.09	362.68 ± 27.54	352.79 ± 26.88	362.68 ± 29.61	368.49 ± 30.49
HFFD + HIIT + Atorvastatin	379.05 ± 30.88	373.18 ± 36.78	379.58 ± 40.82	381.48 ± 39.94	368.78 ± 36.33	363.87 ± 29.98	372.06 ± 28.81	378.70 ± 31.26
F	0.006	0.01	0.10	0.01	0.09	0.37	0.25	0.27
P	0.94	0.97	0.75	0.91	0.77	0.55	0.62	0.61

Table 3. Mean and standard deviation of biochemical parameters in groups during 8 weeks

Group	TG	LDL	HDL	LDL/HDL	ALT	AST	ALP
HFFD + HIIT	47.32 ± 4.49	1.10 ± 0.43	31.12 ± 4.53	0.03 ± 0.01	87.82 ± 11.12	146.12 ± 14.86	232.33 ± 43.60
HFFD + HIIT + Atorvastatin	57.00 ± 5.78	3.02 ± 2.25	36.60 ± 4.18	0.08 ± 0.07	54.24 ± 1.99	98.22 ± 2.58	299.60 ± 42.71
F	7.48	2.74	3.54	1.63	45.30	51.75	5.41
P	0.02*	0.14	0.10	0.24	0.00*	0.00*	0.05

* P<0.05

Results

The results of ANOVA and the average of weight and biochemical parameters are mentioned in Table 2 and 3, respectively. The findings of the analysis of the two groups reveal that the levels of TG (P= 0.029), ALT (P= 0.000), and AST (P= 0.000) in the HFFD + HIIT + Atorvastatin are notably diminished in comparison to the HFFD + HIIT. While there was no significant difference in LDL, HDL and ALP indices between the two groups. On the contrary, the evaluation of weight comparison over the course of eight successive weeks during the implementation of the intervention similarly indicated that there were no statistically significant disparities between the two groups. The results of the study showed significant improvements in the lipid profile and liver enzymes in the HFFD + HIIT + atorvastatin compared to the HFFD + HIIT. These findings suggest that HIIT along with atorvastatin may be a promising strategy for managing NAFLD.

Discussion

The aim of this investigation was to determine the effect of HIIT on NAFLD with the intention of ascertaining its efficacy. Furthermore, considering the HIIT + atorvastatin group, the objective was to determine whether there was a change in the effectiveness of the interventions on NAFLD with the simultaneous administration of atorvastatin and HIIT. By comprising two groups, we wanted to assessment these changes are due to the effect of HIIT alone or the HIIT + atorvastatin can cause an increasing effect on these changes.

HIIT has gained significant attention as an exercise intervention for various health conditions, including NAFLD. HIIT involves short bursts of intense exercise alternated with periods of rest or low-intensity exercise. This type of training has been shown to improve metabolic health, cardiovascular fitness, and body composition (24). Our results showed that HIIT for 8 weeks could improve TG, LDL, and LDL/HDL ratio which it considered as a potential approach for preventing fat accumulation in hepatocytes. This results along with the study by Mirghani et al (25). In addition, administration of atorvastatin along with HIIT, reduced aminotransferase. HIIT and Moderate Intensity Training (MIT) possess the capability to counteract the obesity epidemic. Nevertheless, investigations that compare the impacts of these training methods on obesity present contradictory discoveries pertaining to the reduction of body weight (26). HIIT has been found to exhibit superior efficacy compared to MIT in decreasing certain indicators of obesity in obese rats fed a high-fat diet (HFD). Nevertheless, this particular mode of exercise does not yield any notable influence on insulin resistance (27).

In a study by Kalaki-Jouybari et al., the researchers investigated that HIIT significantly decreased the expression of fatty acid synthase (FAS), Acetyl-CoA carboxylase (ACC), and sterol regulatory element-binding protein-1c (SREBP-1c) compared to the diabetic control group. Additionally, HIIT partially increased the expression of miR-122, suggesting its potential role in improving NAFLD. These findings indicate that HIIT can alleviate NAFLD features through the induction of miR-122 in the liver (24). Eslami et al., investigated that receiving atorvastatin 10 mg/kg for eight weeks, alongside the HFFD exhibited significant reductions in TG, cholesterol, aminotransferases, gamma-glutamyl transferase levels compared to HFFD control (22). In a separate investigation, it was demonstrated that the ingestion of atorvastatin 10 mg/kg/day in rats afflicted with NAFLD is correlated with a reduction in TG and cholesterol concentrations. Conversely, in healthy rats, the consumption of atorvastatin results in heightened cholesterol and HDL levels (5).

HIIT can increase fatty acid oxidation-related gene expression and decrease adipogenesis-related gene expression, leading to improved liver metabolism and lipid metabolism disorders (28). HIIT also increases liver mitochondrial biosynthesis-related gene expression and restores mitochondrial dynamics-related gene expression, which may contribute to the improvement of lipid metabolism (29). Additionally, it can reduce liver inflammation by decreasing the expression of inflammatory factors and macrophage markers associated with M1 macrophages, while increasing the expression of markers associated with M2 macrophages (30).

Motta et al. investigated the effect of HIIT on improving metabolism in obese rats with NAFLD. HIIT significantly reduced body mass, blood glucose, glucose tolerance and lipid profile,

improved insulin sensitivity, reduced visceral fat and hepatic steatosis (31). Another study found that four weeks of HIIT did not result in significant changes in liver enzymes in overweight women (30). Additionally, a study on men with metabolic syndrome (MetS) found that eight weeks of HIIT led to significant improvements in liver enzymes, with greater improvements observed when combined with sodium alginate supplementation (32). Endurance training and adenosine may serve as probable stimulants for the expression of the UCP-1 gene and exhibit efficacy as lipolytic agents in the context of obesity. By adhering to a nutritious diet and engaging in aerobic exercises, the MAPK p38 pathway can augment insulin-mediated glucose uptake and subsequently instigate oxidative phosphorylation in mitochondria (33, 34). In a study by Mirghani et al, indicated that Endurance training and the administration of vitamin D have the potential to yield substantial reductions in certain anthropometric indices (35).

Guiyuan Ji et al. showed that both dietary control and atorvastatin effectively improved serum and liver lipid metabolism and liver function compared to the HFD control. Interestingly, the combination of atorvastatin and dietary control led to further reductions in liver weight, hyperlipidemia, and liver steatosis compared to atorvastatin or dietary control alone. However, the combination therapy did not significantly improve TG and FFA metabolism compared to dietary control alone. These findings suggest that combining atorvastatin with dietary control may have synergistic effects in improving lipid profiles, liver function, and liver steatosis. However, the specific mechanisms underlying this synergy require further investigation (36).

Conclusion

The management of NAFLD requires a comprehensive approach that addresses abnormal lipid profiles, liver function, and associated health complications. Atorvastatin, a medication known for its cholesterol-lowering effects, has shown promise in improving lipid profiles and liver function in individuals with NAFLD. Additionally, the efficacy of atorvastatin therapy may vary depending on the dosing regimen. HIIT has also emerged as an effective exercise intervention in reducing visceral fat and promoting overall metabolic health. This suggests that HIIT could be a potential approach for preventing fat accumulation in hepatocytes. The combination of atorvastatin and HIIT may offer synergistic benefits in managing NAFLD by targeting both lipid metabolism and hepatic enzymes. By combining the antioxidant properties of atorvastatin with the anti-inflammatory effects of exercise, healthcare professionals can develop comprehensive treatment strategies to improve the lipid profiles, liver function, and overall health outcomes of individuals with NAFLD. Further research is needed to elucidate the optimal dosage, duration, and timing of combined training interventions. Additionally, long-term studies are required to assess the sustainability and long-term effects of this approach. Nevertheless, the integration of atorvastatin and HIIT in the management of NAFLD holds promise and warrants further investigation for its potential impact on public health and the prevention of NAFLD-related complications.

Declarations

Ethical considerations

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

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Author's contribution

Raouf Moradian and Amir Haji Ghasem conceived and planned the experiments, Raouf Moradian carried out the experiments, Saleh Rahmati and Lida Moradi contributed to the interpretation of the results. Raouf Moradian wrote the manuscript, Amir Haji Ghasem helped supervise the project.

Conflict of Interest

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

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