High-intensity interval training ameliorates high-fat diet-induced elevation of aminotransferases in male Wistar rats

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Abstract
Background and aims: A high-fat diet increases triglyceride (TG) accumulations in hepatocytes and results in non-alcoholic fatty liver diseases (NAFLDs). In this regard, this study investigated the effect of high-intensity interval training (HIIT), along with a high-fat diet on the serum levels of aminotransferases in male Wistar rats.

Methods: Forty male Wistar rats were randomly assigned to the standard diet, high-fat diet, exercise + standard diet, and exercise + high-fat diet groups (each containing 10 animals). HIIT program consisted of 6-12 repetitions of 2-minute high-intensity exercise (85-90% of the maximum speed) interspersed with 1-minute low-intensity exercise (45-50% peak speed) with the frequency of 5 sessions a week over 12 weeks. High-fat diet groups received a diet regimen including 58% fat, 25% protein, and 17% carbohydrate, ad libitum. The blood samples were taken from the left ventricle 48 hours following the last intervention to assess TG, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) concentrations. Data were analyzed using one-way ANOVA and Tukey’s post-hoc tests.

Results: The findings showed the mean of ALT, AST, and TG in the high-fat diet group was significantly greater compared to the standard diet group ($P=0.001$). Furthermore, the mean of ALT, AST, and TG in the exercise + high-fat diet group was significantly lower in comparison with the high-fat diet group ($P=0.01$, $P=0.017$, and $P=0.012$, respectively).

Conclusion: Although HIIT ameliorated high-fat diet-induced elevations in the serum levels of TG, ALT, and AST, they did not reach the baseline levels. Thus, it may indicate that a diet as the underlying cause of NAFLDs is more important than any other interventions such as exercise.

Keywords: High-intensity interval training, Aspartate aminotransferase, Alanine aminotransferase, High-fat diet

Introduction
Recent lifestyle habits such as increased consumption of high-fat diets and limited physical activity are associated with obesity, hyperlipidemia, insulin resistance, and non-alcoholic fatty liver diseases (NAFLDs) (1,2). NAFLD is a metabolic condition which includes a wide range of diseases from steatosis to non-alcoholic steatohepatitis (3). Studies have shown that a high-fat diet increases triglyceride (TG) accumulations in hepatocytes (4, 5). Carmiel-Haggai et al suggested that a high-fat diet results in the progression of NAFLD and induces oxidative stress which aggravates the disease (6). NAFLD is characterized by the accumulation of TG in hepatocytes, which is formed by the esterification of free fatty acids and glycerol (7). Liver damage due to nonalcoholic fatty liver disease is defined as a condition in which the fat content of the liver determined is greater than 5% (8). Liver diseases can also be diagnosed by the circulatory levels of aminotransferase enzymes. The serum levels of these aminotransferases indicate the condition of hepatocytes, the increase of which is associated with liver disorders and diseases. Hou et al indicated an association between a higher alanine-aminotransferase level and elevated TG concentrations in NAFLD (9). Similarly, Suzuki et al found a relationship between elevated alanine aminotransferase (ALT) levels and the risk of NAFLD (10). Lifestyle modifications such as a healthy diet and increased physical activity have been recommended to prevent liver disorders.

Aerobic exercise training is the most common exercise modality that is generally suggested to improve health status (11). Exercise recommendations to experience health effects include 150 m exercise with moderate intensity during a week (11). Exercise training reduces visceral fat levels while improving lipid profile and insulin resistance and has the potential to improve hepatic function (11). Slentz et al reported that aerobic and resistance training decreased liver and visceral fat accumulations and ALT levels in overweight subjects (12). High-intensity interval training (HIIT) has recently received attention because it is time-efficient and increases energy expenditure to higher levels. Falcone et al reported that HIIT requires more calories compared to steady-state exercise (13). Likewise, Yoshioka et al showed that HIIT leads to lesser body fat which may be associated...
with elevated post-exercise energy metabolism (14). Six weeks of HIIT protocol has been reported to improve lipid profile, body fat percentage, and fitness levels in overweight and obese males (15). Regarding the effects of HIIT on fatty liver diseases, Hallsworth et al indicated that the modified HIIT program reduces liver fat and alanine transaminase (ALT) and aspartate aminotransferase (AST) levels (16). It has been suggested that HIIT is superior to traditional exercise modalities with regard to improving body fat levels in obese participants (17). In contrast, Weege et al concluded that HIIT and moderate-intensity exercise exhibit similar effectiveness on the measures of body composition (18). More recently, Kalaki-Jouybari et al suggested that HIIT is an effective intervention for improving NAFLD in diabetic rats and seems to have a greater impact in comparison to continuous exercise training (19). Although the physiological and health effects of HIIT have received attention in recent decades, research in this area is not as extensive as other exercise modalities. Thus, the present study aimed to determine whether elevations in TG and aminotransferases induced by a high-fat diet can return to baseline levels by the HIIT program. HIIT is known to elicit high energy expenditure during exercise that can remain elevated for hours post-exercise. Therefore, this study focused on identifying whether incorporating exercise training with high energy expenditure has the potential to compensate for impaired liver function as a result of high-fat diet ingestion. More precisely, the study sought to investigate the effect of 12-week HIIT on TG and aminotransferases levels during high-fat diet ingestion in male Wistar rats.

### Materials and Methods

#### Animals and exercise

Forty male Wistar rats (age: 10-12 weeks) were housed in a quiet and controlled condition (temperature: 20±2°C, humidity: 50±10%) under a 12-hour light/dark cycle. Animals were familiarized with exercise protocols over a familiarization week (treadmill exercise with incline: 0%, speed: 10-15 m/min, duration: 5-10 min/d). Then, the maximal speed was assessed by an incremental exhaustive exercise test on a motorized treadmill. The initial speed was 10 m/min with a graded increase of 3 m/min every 2 minutes until exhaustion. The animals were defined to be exhausted if they could not perform running in spite of electric shocks. After the incremental exercise test, the animals were matched based on the weights and were randomly divided into four groups (each consisting of 10 cases) including a standard diet, high-fat diet, exercise+standard diet, and exercise + high-fat diet. HIIT program consisted of 6-12 repetitions of 2-minute high-intensity exercise (85%-90% of the maximum speed) interspersed with 1-minute low-intensity exercise (45%-50% peak speed). The exercise protocol was applied 5 sessions a week over 12 weeks. The running speed increased to the average of 5% every week and repetitions increased fortnightly throughout the experimental period.

#### Diet

Groups of the standard diet were fed ad libitum with the standard rat chow and water (4% fat, 21% protein, 52% carbohydrate, and 13% fiber). The high-fat diet included 58% fat, 25% protein, and 17% carbohydrate ad libitum (20). The water intake and feed of the animals were measured during the experimental period.

#### Measurements

Animals were anesthetized by ketamine and xylazine (90 mg/kg and 10 mg/kg, respectively). Blood samples were collected from the left ventricle 48 hours after the last session. Then, blood samples were centrifuged at 3000 rpm to separate serum samples to assess AST, ALT, and TG levels. ALT and AST levels were evaluated by commercial kits (Pars Azmoon, Iran) by the photometric method, and the TG level was assessed by commercial kits (Pars Azmoon) using an enzymatic colorimetric assay.

#### Statistics

Statistical analysis was performed by SPSS software, version 25. The normal distribution of the data was determined by the Shapiro-Wilk test. Thus, a one-way ANOVA statistical test was used to determine the difference between the groups and Tukey’s post-hoc test, and P<0.05 was considered statistically significant.

### Results

Based on the results (Table 1) the mean values for all variables (ALT, AST, and TG) significantly differed between the groups (P<0.001). Tukey’s post hoc analysis indicated that there was a significant increase in the mean ALT, AST, and TG in the high-fat diet group (106%, 79%, and 150%, respectively) compared to the standard diet group (P=0.001). Moreover, the mean of ALT, AST, and TG in the exercise + high-fat diet group was significantly lower compared to the high-fat diet group (P=0.01, P=0.017, and P=0.012, respectively, Figures 1-3). In

### Table 1. Mean ± SD of variables between groups

|                     | Standard Diet | High-fat Diet | Exercise + Standard Diet | Exercise + High-fat Diet | P value |
|---------------------|---------------|---------------|--------------------------|--------------------------|---------|
| TG (mg/dL)          | 79.1±11.4     | 198.3±20.5    | 74.9±10.3                | 177.5±21.7               | <0.001  |
| ALT (U/L)           | 47.4±6.2      | 97.8±10.9     | 44.1±6.5                 | 74.2±8.4                 | <0.001  |
| AST (U/L)           | 76.5±8.7      | 137.3±10.1    | 65.8±6.7                 | 118.5±11.3               | <0.001  |
| Weight (g)          | 194.0±15.6    | 208.4±11.7    | 192.6±14.6               | 195.2±10.0               | <0.05   |

Note: TG, triglyceride; SD, Standard deviation; ALT, Alanine amino-transferase; AST, Aspartate amino-transferase.
addition, there was a significant difference between the standard diet and exercise + high-fat diet groups, indicating that the serum levels of variables did not return to baseline values by HIIT.

Discussion

According to the main findings of the present study, a high-fat diet elevated the serum levels of TG which was accompanied by the elevation of aminotransferases. HIIT program significantly ameliorated the elevation of TG, ALT, and AST induced by a high-fat diet. However, it could not return the elevated variables to baseline levels.

As regards the effect of a high-fat diet on TG levels, our results are in line with those of Srinivasan et al, indicating that a high-fat diet significantly elevated plasma TG levels by 2-fold in Male Sprague-Dawley rats. Elevated TG concentrations due to fat intake increase its accumulation in hepatocytes. Duarte et al reported that a high-fat diet elevated hepatic TG contents in mice, and this is due to the reestrlification of the existing or ingested lipids (21). Likewise, Delgado et al indicated that hepatic TG concentrations increased about 3-fold within the first week when rats were fed with a high-fat diet, revealing the high sensitivity of hepatic TG contents to diet modifications. The components of hepatic TG may be derived from fat intake or may be synthesized within the liver by de novo lipogenesis. Similarly, Delgado et al suggested that the elevated hepatic TG concentration during a high-fat diet is almost entirely caused by dietary uptake and plasma fatty acid esterification. This shows that the contribution of de novo lipogenesis during a high-fat diet in hepatic TG is extremely little. The accumulation of TG in hepatocytes eventually leads to NAFLD (22). Dhibi et al also reported that a high-fat diet, especially the intake of trans-fatty acids, results in NAFLD (5). They further reported a significant elevation in the plasma levels of the indicators of hepatic injury, including ALT, AST, and ALP following a high-fat diet. Our results are also in conformity with the findings of Guo et al, demonstrating that a high-fat diet elevated the levels of ALT, serum cholesterol, and hepatic TG confirming that a high-fat diet induces hepatic steatosis (23). In another study, Khan et al also found that a high-fat diet led to a remarkable increase in ALT and AST in animal models (24). According to Dhibi et al, a high-fat diet causes a remarkable elevation in liver lipid peroxidation while a reduction in antioxidant defense, which can eventually, damage hepatocytes. The disrupted plasma membrane in damaged hepatocytes consequently results in the leakage of enzymes and the elevation of serum concentrations. This is manifested by a considerable increase in the circulatory levels of ALT and AST, which conforms to our results and those of the aforementioned studies.

In contrast, exercise training has been suggested to exert a protective effect on hepatocytes. It has been suggested that both continuous and accumulated exercises have the potential to reduce postprandial lipemia (25). Hao et al concluded that exercise training on the treadmill significantly reduced intra-abdominal lipemia and liver fat accumulations in ovariectomized rats (26). Regarding the effect of HIIT on the liver tissue, it has been indicated that HIIT improves insulin sensitivity while reducing fat accumulations and TG contents. Botezelli et al also reported that a fructose-rich diet decreased insulin sensitivity whereas increasing TG and AST levels in Wistar rats. They showed that exercise training successfully reduced the variables and prevented NAFLD (27). Currently, Kalaki-Jouybari et al demonstrated that HIIT effectively improves NAFLD in diabetic rats and is more potent than continuous...
exercise training (19). Our findings corroborate with the results of the aforementioned studies, implying that the HIIT program has the potential to reduce elevated levels of the indicators of NAFLD. Several mechanisms may explain this effect of the HIIT protocol. Some studies represented that the hepatic secretion of extremely low-density lipoprotein triacylglycerol and postprandial triacylglycerol concentrations reduces following HIIT (28,29). Furthermore, there is a link between dysglycemia and NAFLD, indicating that glucose control is of particular importance in preventing NAFLD progression. Although glucose levels were not assessed in the present study, it was found that HIIT potentially stabilizes glucose control which is practically of high importance to NAFLD (30). In addition, elevated calorie expenditure by HIIT may have a role as suggested by Smart et al representing that calorie burning elicits liver fat reductions and liver enzymes (31). HIIT has been shown to elicit more calorie burn compared to steady-state exercise during and following exercise training (13). Thus, it is assumed that the HIIT program can attenuate the progression of NAFLD by its potential effects on energy expenditure, glucose control, dyslipidemia, and accumulation of liver fat. This finding supports the results of Gao et al, suggesting that exercise training and dietary intervention can ameliorate fat accumulations in the liver tissue (32). Baek et al also concluded that moderate-intensity aerobic exercise training reduced fat accumulations in the liver tissue (33). It is thought that incorporating HIIT would return the elevated levels of TG and aminotransferases during continuing the high-fat diet. Although HIIT significantly ameliorated the serum levels of TG, ALT, and AST caused by the high-fat diet, they did not revert to baseline levels by exercise training. One might have speculated that a dietary intervention plays a critical role in metabolic abnormalities such as NAFLD. As suggested by Delgado et al, hepatic TG concentrations can return to baseline values by rats fed with standard chow (20).

**Conclusion**

In general, a high-fat diet regimen over 12 weeks significantly elevated the serum levels of TG, ALT, and AST in male Wistar rats which is an indicator of NAFLD. HIIT program ameliorated the elevated levels of these variables, but it had no potential to return the variables to baseline levels. Although exercise training may attenuate the progression of NAFLD, it may not be as potent as a dietary regimen to prevent NAFLD.

**Conflict of Interests**

The authors declared that they have no conflict of interests.

**Ethical Approval**

The study procedures complied with the codes of Helsinki Declaration for animal research and were approved by the Ethics Committee of the Islamic Azad University of Tabriz (Approval No. IR.IAU.TABRIZ.REC.1399.018).

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