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The Effect of a Conventional Resistance Training Course on Some of the Inflammatory Factors in Obese Men with Non-Alcoholic Fatty Liver

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Abstract

Background: Non-alcoholic fatty liver disease (NFALD) is a disease associated with metabolic syndrome. The purpose of the present study is to investigate the effect of a resistance training course on interleukin-17 (IL-17) levels, 70 kDa thermal shock protein (HSP70), insulin resistance, serum levels of alanine aminotransferase (ALT), and aspartate aminotransferase (AST) in obese men with NFALD.
Methods: In this semi-experimental study, 30 obese men with NFALD were selected through targeted sampling and they were randomly divided into one of two groups of intervention group (age = 41.28 $\pm$ 3.88 y, body mass index (BMI) = 33.92 $\pm$ 1.30 kg/m^2) and control group (age = 42.90 $\pm$ 4.20 y, BMI = 32.86 $\pm$ 1.07 kg/m^2). The training program included 12 weeks of resistive training and 3 training sessions per week. Before eating breakfast, blood samples were collected one day before the start of the training and 3 days after the last training session. The *t*-test was used for statistical analysis ($P \leq 0.05$).
Results: After the training course, a significant decrease was observed in body weight compared with the control group ($P = 0.016$), BMI ($P = 0.015$), body fat percentage ($P = 0.009$), insulin resistance ($P < 0.001$), HSP70 ($P = 0.001$), IL-17 ($P = 0.001$), and serum levels of ALT ($P = 0.004$) and AST ($P = 0.032$).
Conclusions: It seems that resistance training has an effective role in improving the liver function in patients with NFALD by reducing insulin resistance and the levels of inflammatory cytokines, this method of resistance training may be useful in the treatment of these patients.

Keywords: Obesity, Resistance Training, Interleukin-17, HSP70, Insulin Resistance

1. Background

The non-alcoholic fatty liver disease (NAFLD) is one of the diseases associated with metabolic syndrome, which one of its symptoms is the increased levels of fat in hepatocytes. The disease is one of the most common chronic liver disorders around the world (1). Non-alcohol fatty liver usually appears due to metabolic syndrome disorders such as obesity, insulin resistance, hypertension, dyslipidemia, and impaired fat metabolism and can increase the risk of death due to cardiovascular diseases (2). It affects 25% - 30% of the general population and the risk factors are almost identical to those of metabolic syndrome (1). The prevalence of NAFLD is as much as30% of the general population in the United States and other Western countries (3). Also, 12% - 24% of the general population in Asia is affected by the disease (4). There are no accurate statistics of patients with NAFLD in Iran but the probable outbreak is estimated to be between 3% and 24% (5). In the results of a study, Soodwandi's role in the population under study was reported to be 31.6% for NAFLD and 0.8% for cirrhosis (6). One study reported that the prevalence of NASH in Iranian males is twice than females (7), which indicates the importance of therapeutic and prophylactic strategies in these individuals. The pathogenesis of NAFLD is closely related to obesity and insulin resistance. Obesity and insulin resistance increase lipolysis in the adipose tissue and the free fatty acids leak into the liver and provide the basis for increased inflammation in the liver (8). Another part of the pathogenesis of this disease is the disruption of mitochondrial function, which leads to increased oxidative stress, increased levels of cytokines and pro-inflammatory agents that damage to the liver tissue (9). One of the most important risk factors for fatty liver is an inactive lifestyle, and longitudinal research suggests that fatty liver-susceptible individuals, especially obese or diabetic patients, will suffer from disruption of liver enzymes in case of decreased physical activity (10).

A growing number of macrophages in adipose tissue increases insulin resistance and metabolic abnormalities in obese people. One of these pro-inflammatory factors is interleukin-17 (IL-17), (11) which is expressed by leukocytes in adipose tissue (12). Insulin resistance in adipose tissue is due to the accumulation of dendritic cells and an increase in inflammatory factors. Dendritic cells are important regulators of inflammation in the adipose tissue, leading to cellular responses and increased TH17 cells. The TH17 cells are the source of IL-17 cytokine (13), which are involved in insulin resistance and inflammation (12), IL-17 plays an important role in inducing insulin resistance and fatty liver function; in a study, Tong et al. claimed that interleukin 17 increases hepatic steatosis and inflammation in patients with NAFLD. TH17 cells and IL-17 contributing to liver steatosis and anti-inflammatory responses in NAFLD facilitate the transfer of simple steatosis to static hepatitis (14).

Regarding the role of IL-17 as one of the relevant factors in Th17 cells, it can be used as a factor to evaluate the effectiveness of strategies designed to change the balance between Th17 cells and regulatory T cells and should be considered a means to prevent and control variable for therapeutic interventions of advanced liver disease in patients with NAFLD (14). However, there is limited research on the effect of training on IL-17.

Thermal shock protein 70 (HSP70) group proteins are expressed and synthesized in cellular stress responses that are associated with changes in IL-17 (15). HSP70 is a chaperone that is increased in response to oxidative stress, including metabolic diseases and hyperinsulinemia (16). There is an association between the circulating levels of HSP70 and inflammatory cytokines. On the other hand, HSP70 has a dual role in inflammation (dual activity in the production of anti-inflammatory and pro-inflammatory mediators). The anti-inflammatory activity of HSP70 results from inhibiting the production of pro-inflammatory cytokines by inhibition of the NF-κB pathway at the intracellular level (16, 17). The transcription factor NF-κB remains inactive in the cytoplasm when binds to its inhibitor, known as IκB, until the proper signal for activation is received (18). Besides, the pro-inflammatory cytokine activity is modulated through its release at the extracellular level and stimulation of the immune/inflammatory cells and the activation of the other immunologic factors associated with the production of pro-inflammatory cytokines (17). According to the danger signal theory (19), the pro-inflammatory activity of HSP70 is due to the fact that this thermal shock protein activates the cytokine cascade by releasing in the outside of the cell and entering the systemic circulation, and by binding to immune cell receptors. HSP70 activates the pathway of NF-κB on monocytes and secretes pro-inflammatory and inflammatory cytokines via TLR-2 and TLR-4 receptors (16).

The increase in HSP70 is due to the duration of diabetes and insulin resistance. Research has shown that pro-inflammatory cytokines increase HSP70 release (20). Therefore, the level of HSP70 is elevated in inflammatory diseases such as the liver disease associated with insulin resistance, and possibly the reduction of inflammation decreases the pro-inflammatory cytokines and increases the insulin sensitivity (21). Previous studies have shown that exercise improves body composition, controls blood glucose, increases insulin sensitivity, and improves the immune system (22, 23). Resistance training requires less cardiovascular power but it can have similar metabolic benefits to aerobic training (24). Resistance training is defined as an exercise in which the resistance generates force against a muscle that is progressively increased over time. Resistance exercise may be less demanding in terms of cardiorespiratory fitness and is associated with better compliance (25). Though the results of some studies established the role of resistance training on improving fatty liver and significant reduction of the hepatic enzymes of ALT and AST (26, 27); however, the results of some studies are different and the effect of exercise training on the improvement of fatty liver complications has not been confirmed (28, 29). According to the various results, more research is needed to elucidate the effect of the exercises on NAFLD disease by examining the variables associated with liver function, especially cytokines and liver enzymes.

Of the most important factors affecting NAFLD are obesity and cytokine-related obesity. Obesity triggers the activation of the IL-17 axis, which contributes to the development and progress of NAFLD to steatohepatitis. Considering the importance of IL-17 as a new therapeutic target (30) and the role of inflammation with insulin resistance and liver complications (31) in addition to the role of IL-17 (14, 30) in NAFLD pathogenesis and liver enzymes changes,

2. Objectives

The purpose of this study is to investigate the effect of 12 week resistance training on liver enzymes, insulin resistance, IL 17, and HSP70 in males with NAFLD.

3. Methods

In the present semi-experimental study, 30 males with NAFLD were selected through targeted sampling and then randomly divided into two groups of 15 subjects, intervention and control groups.

3.1. Inclusion and Exclusion Criteria

Inclusion criteria included NAFLD with a fatty liver level of 1 - 2, certified by a specialist physician, age range 35 - 50, body mass index (BMI) = 30 - 35 kg/m^2, inactive lifestyle (lack of regular exercise history during the last 6 months). Exclusion criteria included other inflammatory diseases, including rheumatoid arthritis, multiple sclerosis, discontinuation of training, sequential absence more than 2 training sessions, and regular attendance at training sessions other than training sessions of this study.

The initial information for admission into the plan was developed using a researcher-designed questionnaire containing information about name, age, sex, marital status, exercise history, and questions about the physical condition such as the history of pulmonary disease, history of cardiovascular disease, history of surgery and so on. The questionnaire was given to the subjects after a brief explanation and collected after being completed and signed by the patients. Also, after explaining how the research project was executed, written informed consent was signed by the subjects and they entered the research plan. The ethics of the research has been studied by the Ethics Committee of Islamic Azad University, Tide (20421423961001).

3.2. Measurements

To measure height, subjects were asked to stand without shoes at the side of the wall and at the time of measurement the back of legs, hips, head touched the wall and the soles of the feet (pairs) touched the ground with the body perfectly flat and forward. The height was measured using the SECA stadiometer. In order to measure weight, subjects were asked to be barefooted with the least amount of clothing, and with a body perfectly flat and forward. Using the SECA digital scale, the individual's weight was measured in kilogram scale. To calculate the BMI (kg/m^2), weight in kilogram was divided by height squared and the obtained number was considered BMI.

To calculate the maximum power, a maximum frequency was used (32). To measure the maximum power, the first period of the movement session was taught to the patients and they learned the correct performance of the movement. Then, each movement was performed using the weight that the patient was able to move with it and the amount of selected weight and the number of the repetitions performed for each person were recorded in the table, afterward, a maximum repeat for each movement was calculated using the Brzycki formula (32).

In the present study, 24 hours before the intervention and 72 hours after the intervention (in order to prevent the acute effect of exercise on the research variables), as well as after 8 - 10 hours of fasting at night, 5 cc blood sample of right radial vein was drawn using syringe from the subjects at 8 - 9 and placed in the clot tube and blood serum was used to assess the levels of glucose (Parsazmun, Tehran, Iran, sensitivity: 1 mg/dL), insulin (Monobind, CA, USA, sensitivity: 0.75 μIU/mL), HSP70 (ZellBio GmbH, sensitively: 0.15 ng/dL), IL-17 (Diaclone, Besancon, France, sensitivity: 2.3 pg/mL), ALT, and AST (Parsazmun, Tehran, Iran, sensitivity: 1 U/L).

Insulin resistance was calculated by the computational method, the homeostasis (HOMA) model and Matthias relation. In the HOMA hemostatic model, fasting blood glucose and fasting insulin are used to evaluate insulin resistance (16).

3.3. Protocol Training

In the present study, the resistance training group performed its training for 12 weeks, three non-sequential sessions per week and each session of training was done 45 - 60 minutes according to the designed program. The intensity and volume planning of resistance training was based on the previous studies (32).

3.4. Statistical Analyses

In this research, descriptive statistics, including mean and standard deviation were used. Shapiro-Wilk test was used to check the normal distribution of the data, Levene's test was used to examine the homogeneity of variances and Paired sample and Independent *t*-test were used for statistical analysis and a level of ($P < 0.05$) was considered significant using SPSS version 22.

4. Results

The demographic characteristics of the subjects are shown in Table 2.

Table 3 Summarizes the results of dependent *t*-test and independent *t*-test to consider in-group and inter-group changes, statistical results indicated the effect of the training intervention on the significant reduction of studied variables compared with the control group.

5. Discussion

5.1. Liver Function

In the present study, after 12 weeks of resistance training, there was a significant improvement in serum ALT and AST levels as indicators of liver function. Nabizadeh Haghighi and Shabani showed a significant decrease in ALT, AST enzymes, and BMI after a training course, which was consistent with the results of the present study (33). In

Table 1. Twelve-Week-Resistance Training

Week	No. of Weekly Meetings	Set	Repeat	Intensity (1RM)	Rest		Rest Type	
					Between Movements (s)	Between Sets (minutes)	Between Movements	Between Sets
1 - 2	3	2	15 - 20	40 - 50	40 - 60	3 - 5	Inactive, (Walking and light activities)	Inactive, (Walking and light activities)
3 - 4	3	2	15 - 20	50 - 60	40 - 60	3 - 5		
5 - 6	3	3	12 - 15	60 - 70	40 - 60	3 - 5		
7 - 8	3	3	12 - 15	60 - 70	40 - 60	3 - 5		
9 - 10	3	3	10 - 12	70 - 80	40 - 60	3 - 5		
11 - 12	3	3	10 - 12	70 - 80	40 - 60	3 - 5		

Table 2. Demographic Characteristics of the Subjects in the Research Groups

Variables	Intervention	Control	T	P
Age, y	41.28 ± 3.88	42.90 ± 4.20	-0.940	0.360
Weight, kg	89.16 ± 753	84.86 ± 5.28	1.479	0.156
Body mass index, kg/m^2	33.92 ± 1.30	32.86 ± 1.07	1.988	0.062
Body fat, %	30.96 ± 1.48	30.15 ± 1.17	1.359	0.191

consistent with the results of this study, Ismail et al. (34) also reported a significant decrease in the body weight, BMI, waist circumference, AST, and ALT after the intervention of aerobic training and caloric restriction. in the present study, although the only intervention in training was resistance training, there was a considerable improvement in the body composition that illustrated the role of this training style on weight control in obese individuals without any special dietary intervention.

5.2. Body Composition

Body composition and obesity are risk factors associated with NFALD (35). Previous research has also shown that NFALD as the effect of metabolic syndrome on the liver is lower in active individuals than inactive ones (23); former studies have represented that training and physical activity can be used to control weight and improve body composition (23, 36), in addition, as a non-pharmacological therapeutic strategy for NFALD treatment. In the present study, after the intervention of resistance training, there was a significant improvement in body weight, BMI and body fat percentage, indicating the role of resistance training on improving body composition.

5.3. Insulin Resistance

Insulin resistance is another complication of obesity that can affect the development of NFALD and in association with obesity constitute two important risk factors in the prevalence of NFALD (2, 37). In this study, the level of insulin resistance measured by insulin resistance homeostasis index (HOMA) indicated the insulin resistance in the studied subjects. Schwimmer et al. introduced insulin resistance as one of the most effective mechanisms for the development of fatty liver in obese individuals (38), which was in consistent with the results of the present study. The liver accumulated lipids in NFALD have a strong association with insulin resistance, with up to 69% of the patients with type 2 diabetes suffer from fatty liver. Studies have also shown that insulin resistance correlated with the progression rate of steatosis to NASH and fibrosis (39).

Hyperinsulinemia is a compensatory response to insulin resistance, which in part increases adipogenesis and lipogenesis by activating lipogenic genes in the liver (26). In the present study, there was a significant decrease in insulin resistance after intervention training, which was associated with a significant decrease in fasting blood glucose and fasting insulin levels. Kaki and Galedari (26) showed a significant reduction in insulin resistance and liver function in the patients with NFALD after training course, which was in agreement with the results of this study. Concerning the mechanism of training effects on insulin resistance and hepatic function improvement, Rabol et al. (40) found that training with increased muscle contraction improves insulin sensitivity and increases glycogen synthesis. It can reduce liver lipogenesis and ultimately improves liver steatosis by increasing the energy supply.

Table 3. Results of *t*-Test to Examine the Effect of Training on Research Variables

Variables	Pre-Test	Post-Test	t	P Value	Change	P Value
Weight, kg						0.016
Intervention	89.28 ± 7.53	87.92 ± 7.15	2.098	0.065	-1.36 ± 2.05	
Control	84.86 ± 5.28	87.97 ± 7.15	2.055	0.070	0.96 ± 1.83	
Body mass index, kg/m^2						0.015
Intervention	33.97 ± 1.41	33.46 ± 1.18	2.062	0.069	-0.52 ± 0.80	
Control	32.86 ± 1.07	33.24 ± 1.38	-1.716	0.120	0.38 ± 0.71	
Body fat, %						0.009
Intervention	30.96 ± 1.49	30.17 ± 0.73	2.301	0.042	-0.80 ± 1.09	
Control	30.15 ± 1.17	30.59 ± 1.19	-1.185	0.105	0.44 ± 0.76	
Fasting blood glucose, mg/dL						0.001
Intervention	6.37 ± 0.60	5.76 ± 0.40	3.764	0.004	-0.61 ± 0.51	
Control	6.30 ± 0.55	6.47 ± 0.50	-1.724	0.119	0.17 ± 032	
Insulin, μIU/mL						< 0.001
Intervention	11.17 ± 1.66	9.04 ± 1.75	6.206	< 0.001	2.13 ± 1.09-	
Control	10.94 ± 1.31	11.44 ± 1.71	-1.449	0.181	0.50 ± 1.09	
Insulin resistance, HOMA						< 0.001
Intervention	3.17 ± 0.61	2.29 ± 0.34	6.009	> 0.001	-0.87 ± 0.46	
Control	3.05 ± 0.34	3.28 ± 0.47	-2.60	0.050	0.23 ± 0.32	
Interleukin-17						0.001
Intervention	6.10 ± 1.46	4.54 ± 0.83	4.688	0.001	-1.56 ± 1.05	
Control	6.34 ± 1.40	6.43 ± 0.99	0.323	0.754	0.09 ± 0.87	
Heat shock protein 70 kDa						0.001
Intervention	7.02 ± 1.25	6.13 ± 0.99	3.77	0.014	-0.89 ± 0.92	
Control	6.62 ± 1.26	7.16 ± 1.27	-2.377	0.041	0.54 ± 3.74	
Alanine aminotransferase						0.004
Intervention	34.70 ± 7.50	31.10 ± 6.1	4.129	0.003	-3.60 ± 2.76	
Control	37.30 ± 5.33	38.60 ± 5.48	-1.057	0.318	1.30 ± 3.89	
Aspartate aminotransferase intervention						0.032
Intervention	32.30 ± 6.22	29.50 ± 7.17	2.941	0.016	-2.80 ± 3.01	
Control	34.60 ± 5.46	35.20 ± 6.03	-0.542	0.601	0.60 ± 3.50	

[a] The mean difference is significant at 0.05 level.

5.4. Inflammatory Markers

Cytokines are secreted materials from cells that play important roles in cellular function at physiological and pathological levels. One of the major factors affecting the levels of intracellular and extracellular cytokines is the thermal shock proteins and, especially the HSP70 group (16). The cellular stress response induces a rapid transcription of the thermal shock proteins, which is a mechanism for protecting the cell against pathogens. In other words, the HSP70 proteins are expressed and synthesized for cellular stress responses (41). HSP70 elevation is associated with the duration of diabetes and insulin resistance. Studies have shown that increased pro-inflammatory cytokines raise HSP70 (20). Therefore, in inflammatory diseases such as obesity, diabetes, and liver diseases associated with insulin resistance, the level of HSP70 is elevated and decreases in inflammation may lessen pro-inflammatory cytokines and increase insulin sensitivity (21). In the present study, after the training course, there was a considerable decrease in HSP70 levels, which may be due to improved

insulin resistance. In Tashakori-Zade and Mogharnasi (21) research, there was a significant decrease in the level of HSP70 and insulin resistance after the resistance training course, which was in consistent with the results of the present study. Sharifi et al. (16) also attributed a prominent decrease in HSP70 to reduced insulin resistance after the training course, which is consistent with the results of the present study. Ogawa et al. (42) conducted a low-intensity resistance training at least once a week after twelve weeks. The results showed that low-intensity resistance training leads to a significant decrease in HSP70 and fasting insulin but no effect was observed in fasting glucose and insulin resistance, which was somewhat in consistent with the results of the present study. In this research, the effects of training were observed as follow: significant reduction of fasting glucose, fasting insulin, and insulin resistance, which was higher than Ogawa's study. The possible reasons for this effect in the present study may be due to a higher frequency of resistance training per week or it may be as a result of differences in subjects' characteristics in two studies.

Another inflammatory factor that has recently been introduced as a therapeutic target in fatty liver disease is Interleukin 17 (43). IL-17 is a cytokine associated with adipose tissue, which has recently been shown to play a role in the pathogenesis of NAFLD and insulin resistance (12, 30). In the present study, there was a significant decrease in IL-17 level after the resistance training course. So far, no study has been conducted to evaluate the effects of exercise on this cytokine in patients with NAFLD. The present study showed that resistance training can play a beneficial role in the liver function of the patients because IL-17 may be considered an inflammatory marker secreted from adipocytes. Laboratory researches have shown that the neutralization of IL-17 in obese mice reduces liver damage caused by lipopolysaccharide, leading to lower levels of serum ALT and decreases in inflammatory cells in the liver (43). In the present study, the reduction of IL-17 was associated with a decrease in serum levels of ALT and AST enzymes, indicating the useful role of training in reducing inflammation and improving liver function in the NAFLD. The reduction of IL-17 in this research can be attributed to the reduction of insulin resistance (39) and improvement of the body composition (25), which is the beneficial effect of training on patient's health.

5.5. Conclusions

In total, the findings of this study showed that 12-week-resistance training improved liver function in obese individuals with the non-alcoholic fatty liver disease. The probable mechanism of amelioration in liver function can be explained in such a way that training may enhance liver function by improving body composition and reducing body fat percentage, as well as reducing insulin resistance on inflammatory pathways (decreasing levels of HSP70 and IL-17), which was evident as a decrease in serum levels of ALT and AST. Hence, resistance training can be useful for patients with obesity and NAFLD.

5.6. Limitations

One of the study limitations is individuals' lifestyle information, including the level of daily physical activity, the amount of nutrition and its type, and the level of rest within a day, which was not possible for the researchers.

Footnotes

Conflict of Interests: The authors declared no conflict of interests.

Ethical Considerations: After explaining how the research project was performed, written informed consent was signed by the subjects and entered the research plan. The ethics of the research was approved by the Ethics Committee of Islamic Azad University, Tide (20421423961001).

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