Short Communication

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Changes in Fetuin-B and RBP4 During A Course of High-Intensity Interval Training in Women with Nonalcoholic Fatty Liver

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ABSTRACT

BACKGROUND AND OBJECTIVE: Non-alcoholic fatty liver is one of the most common causes of chronic liver disease and is considered as one of the hepatic manifestations of metabolic syndrome, and since one of the effective treatments for this disease is exercise, the aim of this study was to evaluate the changes in Fetuin-B and retinol binding protein 4 (RBP4) during eight weeks of high-intensity interval training (HIIT) in women with fatty liver.

METHODS: This experimental study was performed on 25 women with fatty liver disease in the age range of 30-50 years in two groups of training (n=13) and control (n=12). The training group was included in the intermittent high-intensity exercise protocols (8 weeks and four sessions per week and each session for 48 to 60 minutes) and the control group participated in the study without any intervention. Fetuin-B and RBP4 were evaluated and compared by ELISA using a kit made by Elabscience Inc.

FINDINGS: The results of the present study showed that the levels of Fetuin-B in the training group (752.50±191.23) had a significant decrease compared to the control group (1141.90±227.23) (p=0.001). Moreover, RBP4 had a significant decrease in the training group (25.42±1.11) compared to the control group (30.33±3.09) (p=0.001).

CONCLUSION: The results of the study showed that a course of high-intensity interval training can be a suitable and preventive strategy to improve Fetuin-B and RBP4 levels in women with fatty liver.

KEY WORDS: *Non-Alcoholic Fatty Liver, Fetuin-B, Retinol Binding Protein 4, High-Intensity Interval Training.*

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Introduction

Normally, the metabolism of fats consumed in the food chain takes place in the liver, and fatty liver syndrome occurs when liver cells begin to accumulate fat droplets (mainly triglycerides), and this sequential storage of fat in liver cells leads to non-alcoholic fatty liver disease (1). Fatty liver disease, along with viral hepatitis, can lead to increased liver damage and accelerate the progression of the disease till fibrosis of liver tissue and its destruction (2, 3). Hyperlipidemia, obesity and diabetes, all of which are components of the metabolic syndrome, have been associated with fatty liver disease. For this reason, some researchers consider fatty liver disease to be a hepatic manifestation of insulin resistance or metabolic syndrome (4). On the other hand, in recent years, researchers have paid attention to the factors involved in metabolic diseases such as adipokines and hepatokines (5).

Known and studied adipokines such as adiponectin, leptin, resistin, retinol binding protein 4 (RBP4), visfatin, chemerin, omentin (adipose tissue) (6), and hepatokines, which are mainly produced by the liver, include the fetuin family, fibroblast growth factor-21, selenoprotein P, sex hormone-binding globulin, angiopoietin-related protein, and leukocyte cell-derived chemotaxin-2 (LECT2) (7). Recently, serum RBP4 levels have been shown to be positively correlated with body fat (8). Furthermore, RBP4 levels in people with type II diabetes are twice as high as in people without diabetes (2). Elevated levels of RBP4 are inversely related to GLUT4 levels, which mediate insulin-stimulated glucose uptake, which in turn leads to insulin resistance and appears to be partly due to decreased GLUT4 levels (3).

The main function of RBP4 in the liver is the expression and transport of retinol from the liver to the pancreatic tissues. Some studies have shown that elevated RBP4 is a risk factor for NAFLD, and that serum RBP4 levels are positively correlated with liver fat accumulation and the levels of liver enzymes, including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT) (2, 3). On the other hand, Fetuin – B is a member of the cystatin family and cysteine protease inhibitors, which contain 22% hemoglobin with Fetuin-A (9-11). Elevated Fetuin-A and Fetuin-B in the liver has been observed in patients with hepatic steatosis and metabolic syndrome, and Fetuin-A and Fetuin-B have been reported as prognostic factors in fatty liver (12, 13). Unlike Fetuin-A, Fetuin-B is secreted by hepatocytes in high-fat diets and is increased in hepatic steatosis, and induces insulin resistance (14). These findings suggest a possible role for Fetuin-B in metabolic regulation and clinical management of metabolic diseases, including fatty liver (15, 16).

Therapeutic measures such as control over nutritional behavior and exercise can be effective in reducing the prevalence of the disease as well as improving the metabolic functions of the liver (17). One of these exercises is high-intensity interval training (HIIT). HIIT includes high-intensity exercise activities and low-intensity active rest (18). High-intensity interval training can reduce body fat percentage as well as insulin resistance (19). On the other hand, high-intensity interval training, which includes high-intensity exercise with low-intensity active rest, has attracted the attention of researchers. This training method has been a very efficient method in terms of time, which stimulates various metabolic adaptations (20).

Aghaei et al. showed that high-intensity interval training decreased RBP4 expression in the training group and increased its expression in the diabetes group (21). The results of the study by Keihanian et al. showed that the levels of Fetuin-A and Fetuin-B decreased significantly after aerobics training and resistance training compared to the control group (22).

Considering the prevalence of non-alcoholic fatty liver disease caused by high body fat in obese people, the role of adipokines (RBP4) and heptokines (Fetuin-B) in metabolic diseases including non-alcoholic fatty liver and the positive effects of exercise in the prevention and treatment of fatty liver disease, as well as lack of adequate research on the effect of high-intensity interval training on Fetuin-B and RBP4 in fatty liver patients, this study was conducted to investigate changes in Fetuin-B and retinol binding protein 4 (RBP4) during a course of high-intensity interval training in women with non-alcoholic fatty liver.

Methods

After approval by the Research and Ethics Committee of Tabriz University of Medical Sciences

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with the code IR.TBZMED.REC.1399.472, this experimental study was conducted on 25 women with fatty liver disease (grades 1 or 2) in the age range of 30-50 years of who referred to medical centers and were willing to participate in the study voluntarily. Diagnosis of fatty liver was based on ultrasound by a physician (based on ultrasound and liver enzymes). All volunteers with grade 1 or 2 fatty liver were included in the study if they were not prohibited from participating in sports activities, and did not exercise regularly in the past year. In case of smoking, alcohol consumption, respiratory, inflammatory, cardiovascular, renal and other chronic diseases, as well as severe weight loss in the past month, they were excluded from the study. After fully explaining the subject, objectives, research methods, completing and obtaining the consent form and completing the health and sports history questionnaire and examination by a physician, the subjects were randomly divided into two groups of training (13 people) and control (12 people) after fulfilling the mentioned conditions.

It is also noteworthy that the number and volume of samples based on research backgrounds were used in interventions related to sports activities and the groups were homogenized based on physical condition, age, body fat percentage and BMI. The training group performed an eight-week training program that consisted of four sessions per week, with each session lasting at least 48 minutes in the first two weeks and a maximum of one hour in the last two weeks (Table 1). The control group followed their normal lifestyle during the study. After selecting the subjects, blood samples were collected from them to evaluate the plasma levels of Fetuin-B and RBP4. Subjects in the case group performed an exercise program for eight weeks (23) and at the end of the eighth week, blood samples were taken for the second time.

Blood sampling method: Blood samples (5 ml) were collected from the vein in the forearm and in a sitting position in two stages, one day before the first training session (pre-test) and 24 hours after the last training session in the eighth week and after 10-12 hours of fasting. After completion of blood sampling, the samples were poured into tubes containing anticoagulant (3 to 4 mg/ml ethylenediaminetetraacetic acid) and then plasma was separated by centrifugation and samples were kept at -70 °C for further analysis. Plasma values of Fetuin-B and RBP4 were measured by ELISA method using kits made by Elabscience (USA) (Fetuin-B kit with sensitivity and range of 56.25 pg/mL and 93.75-6000 pg/mL) and (RBP4 kit with sensitivity and range of 0.94 ng/mL and 1.56-100 ng/mL). Moreover, insulin was evaluated using ELISA method by kits made by Elabscience (USA) with sensitivity and range of 0.47 µIU/ml and 0.78-50 µIU/ml, and insulin resistance index was assessed by the relevant formula. For statistical analysis and comparison of groups, after confirming the normal distribution of data using Shapiro-Wilk test, paired and independent t-test were performed by SPSS software and $p<0.05$ was considered significant.

Table 1. High-intensity interval training

Warm up	Active rest		Training			Cool down	Week
	*Intensity	Duration	*Intensity	Duration	Frequency		
15 min	50-55 %	2 min	80%	1 min	6	15 min	First-second
	50-55 %	2 min	80%	1 min	6		Third-forth
	50-55 %	2 min	85%	1 min	8		Fifth-sixth
	50-55 %	2 min	85%	1 min	10		Seventh-eighth

*Intensity based on maximum heart rate

Results

The results of intragroup and intergroup evaluations showed that the indices of weight, body fat percentage, BMI, WHR and VO2max were significantly different in both cases ($p<0.05$). There was no significant difference in insulin and insulin resistance based on intragroup evaluations in the control and training groups ($p=0.051$ and $p=057$), but intergroup evaluations showed a significant difference in insulin and insulin resistance ($p=0.003$ and $p=019$). Evaluations showed significant differences in intragroup and intergroup ALT ($p=0.005$ and $p=0.020$) but there was no significant difference in

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intragroup and intergroup AST (p=0.740 and p=820) (Table 2). Fetuin-B showed a significant decrease in intragroup and intergroup evaluations (p=0.001 and p=0.006) (Figure 1) and RBP4 showed significant changes between group and intragroup evaluations (p=0.001) (Figure 2).

Table 2. Comparison of means of physical, physiological and biochemical variables of training and control groups in pre-test and post-test

Stage	Control (n=12)		Training (n=13)		p-value	p-value
Variable	Post-test	Pre-test	Post-test	Pre-test	(Intergroup)	(Intergroup)
Weight (kg)	73.91±5.18	72.26±5.35	69.66±4.26	74.50±4.69	0.001**	0.034*
Percentage of body fat	29.56±1.35	29.02±1.53	26.14±1.49	29.64±1.67	0.000**	0.001*
BMI (kg/m²)	28.07±1.69	27.45±1.52	26.03±1.51	27.85±1.83	0.000**	0.004*
WHR	0.83±0.03	0.81±0.03	0.77±0.02	0.82±0.03	0.001**	0.001*
VO_2max (ml/kg/min)	32.50±2.38	34.28±2.40	38.41±2.70	34.78±2.46	0.001**	0.001*
Insulin (international unit of micro per ml)	16.36±2.06	15.84±1.29	13.70±1.87	15.47±1.76	0.051	0.003*
Insulin resistance	4.64±1.31	4.49±0.97	3.36±1.20	4.54±1.29	0.057	0.019*
ALT (IU/L)	16.21±3.97	14.38±4.37	12.25±3.96	16.58±3.35	0.005**	0.020*
AST (IU/L)	36.17±6.32	35.21±5.03	33.72±8.62	34.76±4.60	0.740	0.820

*Significant changes in the training group compared to the control group in the post-test, **Significant changes in the training group compared to the control group in the pre-test

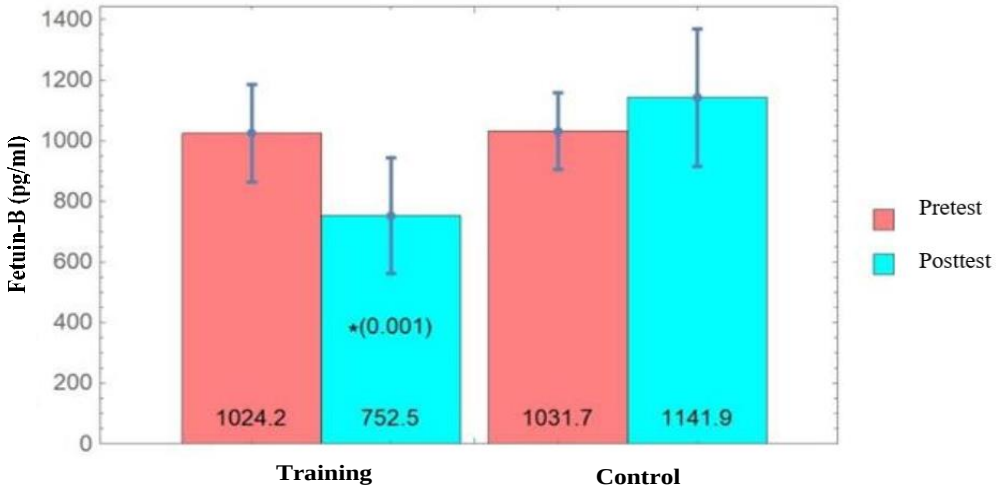

Figure 1. Changes in Fetuin-B after eight weeks of high-intensity interval training in both training and control groups

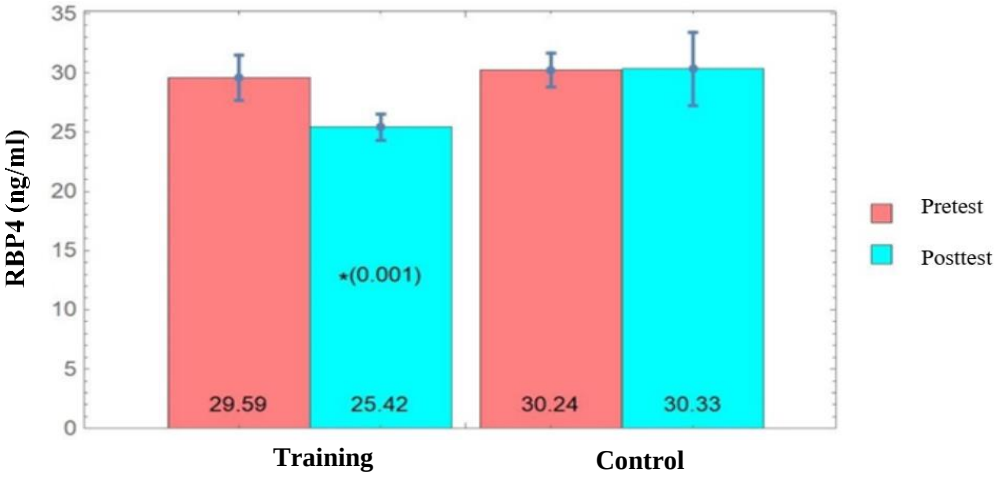

Figure 2. Changes in RBP4 after eight weeks of high-intensity interval training in both training and control groups

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Discussion

In this study, the level of RBP4 in the training group was significantly reduced. Studies in line with the present study include the studies of Choi et al., and Soori et al. (24, 25). Choi et al. examined the effect of combined exercise, including 45 minutes of aerobic exercise with an intensity of 60 to 75% of maximal oxygen consumption and 20 minutes of strength training among obese Korean women and reported a decrease in serum RBP4 levels. Soori et al. also examined the effect of exercise on RBP4 levels in human subjects with type 2 diabetes and stated that the level of RBP4 in strength training groups showed a significant decrease, which is due to an increase in muscle mass and has been reported to be effective in improving insulin resistance and affected RBP4.

Probably one of the reasons for the decrease in RBP4 in the mentioned studies and the present study was the weight loss of the participants in the exercise program (26). Another possible factor is the negative regulation of GLUT4 in obesity and overweight conditions, the expression of which varies in visceral and subcutaneous adipose tissues. Further research has shown that the expression of GLUT4 in visceral adipose tissue is inversely related to the expression of RBP4 (27). On the other hand, exercise has been shown to reduce the expression of RBP4 in subcutaneous and visceral fat (27). Probably the same mechanism occurred in the present study and caused a significant decrease in RBP4 in the training group. On the other hand, increased serum RBP4 is associated with obesity, insulin resistance and metabolic diseases including fatty liver and type 2 diabetes (14).

High-intensity interval training reduces systemic inflammation and increases insulin efficiency. It also reduces the insulin resistance index in overweight and obese subjects and decreases serum insulin levels due to increased tissue reactivity to insulin (28, 29). In the present study, insulin and insulin resistance were significantly reduced. Therefore, this finding regarding the decrease in RBP4 along with a decrease in insulin and insulin resistance in the training group confirms the positive effect of training in the present study. Another finding of the present study is a significant decrease in Fetuin – B in the training group. Studies on the effect of exercise on the Fetuin family, especially Fetuin-B, in patients with non-alcoholic fatty liver disease are very limited. Studies consistent with the present study include the study of Malin et al. and Zhang et al. (30, 31). Malin et al. examined the effect of short-term aerobic exercise with a treadmill on 13 obese adults with fatty liver, whose results showed a decrease in Fetuin-A (30). Zhang et al. examined the effect of 12 weeks of aerobic exercise on 32 men and women with type 2 diabetes, whose results showed that serum Fetuin-A levels were reduced (31).

Along with the decrease in Fetuin-B in the present study, insulin resistance also decreased. Researchers reported the reduction in hepatokines (Fetuin-A and B and fibroblast growth factor 21) and insulin resistance in metabolic diseases such as type 2 diabetes and fatty liver through exercise (32). Mechanisms involved in exercise may include normal regulation of inhibitors of insulin receptor tyrosine kinase in the liver, insulin sensitivity, GLUT4, glycogen synthesis and hexokinase activity, muscle glucose delivery and changes in muscle composition (33). Other positive mechanisms of exercise in fatty liver, which may have occurred in high-intensity interval training in the present study, can be the effect of exercise on the pathway of antioxidant enzymes (33).

Exercise reduces oxidative stress by increasing antioxidant enzymes, which in turn reduces inflammation (34). Reduced inflammation will prevent steatosis, insulin resistance, reduction in hepatic glycogen, and ultimately improve non-alcoholic fatty liver (35). On the other hand, by increasing mitochondrial function, exercise increases lipid oxidation, lipogenesis and VLDL and thus prevents liver steatosis and reduces insulin resistance and improves fatty liver disease (35). Finally, the present study showed a significant reduction in Fetuin-B, RBP4, insulin resistance, insulin, ALT and anthropometric indices. Therefore, this training method can be useful for patients with non-alcoholic fatty liver.

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