Effects of combined resistance and interval training in females with nonalcoholic fatty liver disease

Sima Esmaeili (sima.esmaeili93@gmail.com)
Azarbaijan Shahid Madani University https://orcid.org/0000-0002-4230-3830

Research Article

Keywords: Interval training, Fibroblast growth factor21, Fetuin-A, liver enzymes, Fatty liver, Insulin resistance

Posted Date: September 23rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2094137/v1

Abstract

Background

Nonalcoholic fatty liver disease (NAFLD) describes liver inflammation due to excessive fat accumulation and leading to conditions such as liver failure or cirrhosis. Exercise and physical activity can potentially reduce fat levels in the liver. Also, it is shown that combined resistance and interval training (CRIT) is a stronger stimulation for reducing inflammation, through decreasing body fat. Therefore, this study investigated the effect of CRIT on serum levels of fibroblast growth factor 21, fetuin-A, aspartate aminotransferase, alanine aminotransferase, insulin resistance, and lipid profile in females with nonalcoholic fatty liver disease.

Methods

Twenty-nine females (age range: 49.92 ± 7.16 years) with NAFLD participated in this study and were randomly divided into CRIT (n = 17) and control (n = 12) groups. The CRIT group did combined body weight resistance and interval exercises for eight weeks (three times a week and 40 minutes per session) with a constant increase in the workload, while the individuals in the control group followed their routine daily activities.

Results

Eight weeks of CRIT decreased fetuin-A, HOMA-IR, LDL and increased HDL and fibroblast growth factor 21. Levels of liver enzymes such as ALP, ALT and AST were also decreased by eight weeks of CRIT.

Conclusion

Eight weeks of CRIT improved liver enzymes, body composition, lipid profiles, and the serum levels of two hepatokines (fetuin-A and FGF-21) in inactive obese females with NAFLD. Our findings support the view that CRIT may be an effective non-medical therapeutic strategy to decrease NAFLD risk factors and obesity-induced disorders.

Introduction

Nonalcoholic fatty liver disease (NAFLD) has a prevalence of 25–30% and affects more than 90% of persons who are morbidly obese (BMI > 35) (1, 2). Levels of NAFLD in the US are anticipated to increase by 21% (to ~ 101 million) in the next decade (2). The accumulation of lipids and inflammatory mediators can exacerbate NAFLD (1). A lack of physical activity also increases the risk of NALFD, where the risk of NAFLD is estimated to increase by 4% for each hour of physical inactivity per day (3, 4). The incidence of NAFLD is associated with other metabolic abnormalities such as glucose intolerance, insulin resistance

(IR) and type 2 diabetes mellitus (T2DM) (3, 4). Large number of hepatokines— proteins that are secreted from hepatocytes which affect metabolic processes through autocrine, paracrine and endocrine signaling — are released by the liver (5). Some hepatokines include selenoprotein P13, sex hormone-binding globulin14, fetuin-A, and fibroblast growth factor 21 (FGF-21). FGF-21 causes fatty acid oxidation, ketogenesis and gluconeogenesis, while it also suppresses lipogenesis in the liver (6), suggesting that FGF-21 may be a therapeutic target in the management of obesity, T2DM and cardiovascular diseases (7) as concentrations of FGF-21 correlate with the grade of steatosis and with levels of triglycerides and IR (8). Fetuin-A contributes to IR by inhibiting auto phosphorylation of insulin receptors and It has been shown that fetuin-A induces inflammatory cytokines. In this way, fetuin-A may be involved in the development of metabolic syndrome (9).

NAFLD is characterized by increases in liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (10, 11). Although obesity, physical inactivity, and IR can lead to NAFLD, the pathogenesis of NAFLD is not fully understood; in particular, the role of these liver enzymes in managing NAFLD through exercise training is unclear (6). Physical activity decreases visceral fat, potential beneficial therapeutic effects on NAFLD (3, 12). There are only limited studies on the effects of physical activity on NAFLD, with no consensus on the most effective physical activity program for the treatment of NAFLD (3), in part due to methodological issues such as 1) heterogeneity of participants related to their health status and the duration of being diagnosed with NAFLD, 2) poor control of factors such as the nutritional intake that can affect the levels of systemic fetuin-A, FGF-21 and liver enzymes, and 3) lack of data on changes in Homeostatic Model Assessment of IR (HOMA-IR), lipid profiles (6).

A combined resistance and interval training (CRIT) involves larger groups of muscles, resulting in a greater expenditure of calories during and even after physical activity and it might be more beneficial in weight reduction and fat loss (13, 14). To our knowledge, the benefits of CRIT in individuals with obesity and NAFLD have not been investigated. We evaluated the potential benefits of a combined exercise training program in individuals with an abnormal BMI and NAFLD to examine the hypothesis that eight weeks of CRIT can improve fetuin-A, FGF21, lipid profiles, liver enzymes, and IR in individuals with NAFLD.

Methods

2.1. Participants

Twenty-nine females clinically diagnosed with NAFLD participated in this study and were recruited from the Imam Reza Hospital (Tabriz, Iran) using posters/flyers, email, and social media communications. A sports medicine physician and a gastroenterologist screened all individuals to ensure that they were eligible and able enough to participate in the study. Inclusion criteria were as follow: individuals diagnosed with NAFLD (stage I and II), the age range of 40–60 years, duration of NAFLD > 2 years and BMI range of 27–37 kg/m^2. Exclusion criteria were: evidence of viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis or other metabolic disorders, a history of T2DM, ischemic heart disease or other contraindications for exercise training, clinical hyperlipidemia (fasting plasma TG > 3.0 mmol/L or total

cholesterol levels > 7.0 mmol/L), were current smokers or if they had a history of excessive alcohol intake (weekly consumption of > 21 U). Written consent was obtained from all individuals before the study. All study procedures and protocols were approved by the local University Research and Ethics Committee (ethics code: IR.TBZMED.REC1399.641) and performed according to the latest revision of the Declaration of Helsinki (15).

2.2. Experimental Design

Participants were randomly assigned to either CRIT (n = 17) or control (n = 12) groups. Participant randomization was generated using a random number table, and an independent researcher assigned participants to either of these groups. All participants were instructed to continue their current medications and maintain their diets. Individuals in the CRIT group were asked to participate in a supervised, structured exercise program for eight weeks, while those in the control group participants were asked to continue their current lifestyles until the end of the study. All participants were asked to fast for 8–10 hours, avoid rigorous physical activity for 48 hours, and remain well hydrated prior to blood draws that were taken 48 hours before the start of the study and 48 hours after the eight-week study period. Levels of BMI were calculated by measuring height and body mass: BMI = weight (kg) divided by height^2 (meters^2). All participants were asked to complete the physical activity readiness (PARmed-X) and physical activity readiness questionnaires (PAR-Q) (16).

2.3. Peak oxygen uptake (VO_{2peak})

A motorized treadmill was used to obtain VO_{2peak}. Participants were encouraged to provide their maximal efforts. Measurements of VO_{2peak} started with a 4-minute warm-up period during which the velocity of the treadmill was continuously increased, after which a ramp protocol was initiated where the incline of the treadmill remained at a 0% grade. The speed increased every three minutes by 1–2 km/h until the individual reached volitional exhaustion. The HR (beats/minute) of individuals was continuously recorded throughout the test using an HR monitor (Polar, Finland) and blood pressures recorded using an automated blood pressure system (Omron M6 Comfort, Kyoto, Japan). Participants reported their rating of perceived exertion (RPE) using the Borg scale (6–20) during the last 15 seconds of each stage of the ramp test (17). The criteria used for achieving maximal effort were: 1) a plateau in VO_2 (or failure to increase VO_2 by 150 mL· min^2), 2) RER ≥ 1.10, 3) an RPE of 17, and 4) peak HR ≥ 95% of age-predicted maximal HR (208–0.7×age) (18). A maximal effort was considered attained if at least three out of these four criteria were met.

2.4. CRIT Program

The CRIT group performed exercises three times a week for eight weeks, each session lasting 40 min, beginning with a five-minute warm-up period, followed by 30 minutes of CRIT at 80–90% HRpeak, and 5-minute cool-down at the end of each session. The CRIT protocol consisted of four sessions, including bodyweight resistance exercises at 80% of HRpeak for 4 min (one minute for each exercise) interspersed with 45 seconds of active recovery (jogging) intervals at 60% of HRpeak. Also, the heart rate

(beats/minute) of participants was continuously recorded by using an HR monitor (Polar, Finland). In order to meet the overloading principle, the intensity of resistance exercises increased every two weeks and became more complex (Table 1).

Table 1
CRIT program for eight weeks

Body weight resistance	Duration	Intensity	Recovery intervals	Duration	Intensity	Bouts
1–2 weeks						
T-stand	1-min	80%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
Squats	1-min	80%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
Knee-touches	1-min	80%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
Lateral-lunges	1-min	80%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
3–4 weeks						
Plank	1-min	85%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
Crab-touch	1-min	85%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
Wall-sit	1-min	85%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
Jumping-jack	1-min	85%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
5–6 weeks						
Mountain-climbers	1-min	90%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
Jumping-squat	1-min	90%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
Skater	1-min	90%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
Crunches	1-min	90%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
7–8 weeks						
Jack-squat	1-min	90%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
Burpee	1-min	90%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
Cross-jack	1-min	90%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4
High-knee	1-min	90%HR_{peak}	Jogging	45-sec	60%HR_{peak}	4

2.5. Blood Analysis

Blood samples (10cc) were taken from the antecubital vein of seated participants. Samples were collected in tubes containing EDTA and then centrifuged at 3500 rpm for 15 minutes at 4° C. Plasma concentrations of insulin were determined using a commercially available radioimmunoassay kit (Diagnostic Systems Laboratories, Webster, Texas, USA), while fast blood glucose (FBG) concentrations were measured with a colorimetric-enzyme (glucose oxidase) method using glucose assay kits (Pars Tests Company Kit, Tehran, Iran) with a 1 mg/dl sensitivity. The HOMA-IR model was measured by using IR index = fasting plasma glucose (mmol/L)×fasting serum insulin (μU/mL)/22.5 (19). High-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC) levels were measured with a standard biochemical analyzer (DAX 96; Bayern Diagnostics, Milan, Italy). AST and ALT were assessed by the Japan Society of Clinical Chemistry transferable method. Serum levels of fetuin-A and FGF-21 serum concentrations were measured in duplicate using a commercially available enzyme immunoassay (EIA) or enzyme-linked immunosorbent assay (ELISA) kits (BioVendor Laboratorni Medicina a.s., Brno, Czech Republic).

2.6. Statistical analysis

Data are presented as the mean ± standard deviation (mean ± SD). Statistical analyses were completed using IBM SPSS statistical software (Version 24.0). A normal distribution of data was assessed using the Shapiro-Wilk test, and the Leven test measured homogeneity of variances ($p \geq 0.05$). Paired t-test was used to determine intragroup changes; the analysis of covariance (ANCOVA) test was applied to compare intergroup changes at the significant level of $p < 0.05$. The sample size was designed to detect a difference in study variables with a 95% confidence interval and ≥ 80% power value.

Results

a) FGF-21, fetuin-A and HOMA-IR levels

CRIT for eight weeks increased the levels of FGF-21 ($p = 0.04$), decreased the levels of fetuin-A (Fig. 1). Following the decrease in insulin ($p = 0.03$), we saw a decrease in HOMA-IR ($p = 0.03$) in CRIT group. In addition, no changes in these variables were observed in the control group after 8-weeks ($p \geq 0.05$) (Table 3).

b) Liver enzymes and lipid profile

There were decreases in liver enzymes, including ALT ($p = 0.003$), AST ($p = 0.034$), and ALP ($p = 0.010$) in the CRIT group. At the same time, there were no changes in the control group. LDL levels, decreased in the CRIT group compared to their baseline levels ($p = 0.001$) but There were no significant change in HDL and cholesterol in the CRIT and control groups ($p < 0.05$).

Table 2
Body composition variables of the study groups.

Variables	Groups	Mean ± standard deviation	
		Pre	**Post**
Age (years)	**CRIT**	50.73 ± 8.12	
	Control	46.72 ± 5.62	
Height (cm)	**CRIT**	156.77 ± 5.70	
	Control	159.36 ± 7.89	
BW (kg)	**CRIT**	80.63 ± 14.62	75.00 ± 6.48
	Control	81.54 ± 12.56	80.38 ± 10.06
Waist (cm)	**CRIT**	106.45 ± 8.62	102.45 ± 9.26
	Control	106.05 ± 9.66	105.50 ± 9.34*#
Hip (cm)	**CRIT**	114.27 ± 11.55	107.18 ± 13.65
	Control	115.00 ± 8.63	113.66 ± 8.28*#
WHR (cm)	**CRIT**	0.930 ± 0.047	0.823 ± 0.243
	Control	0.918 ± 0.060	0.916 ± 0.581*#
RHR (beats per min)	**CRIT**	77.83 ± 12.88	75.83 ± 12.43
	Control	82.09 ± 11.77	82.09 ± 11.77
VO2peak (mL/kg/min)	**CRIT**	33.42 ± 5.04#	36.81 ± 4.01
	Control	32.72 ± 4.78	32.63 ± 4.76

RHR: Resting heart rate, **WHR**: Waist-to-hip Ratio, **BMI**: Body mass index. *Significant differences compared to the control group ($p < 0.05$). # Significant difference from baseline ($p < 0.05$).

Table 3
The results of covariance test for Liver enzymes, glucose, lipid profile and insulin

Variables		Mean ± standard deviation		P value*
		CRIT	**Control**	
ALP (U/L)	Pre	215.80 ± 24.58	207.00 ± 24.58	0.03
	Post	194.12 ± 56.71#	214.70 ± 77.30	
ALT (U/L)	Pre	28.52 ± 14.53	30.60 ± 16.12	0.03
	Post	23.73 ± 13.31#	32.10 ± 13.33	
AST (U/L)	Pre	25.86 ± 10.29	27.16 ± 16.91	0.01
	Post	21.13 ± 7.21#	30.37 ± 21.56	
LDL (mmol/L)	Pre	108.06 ± 22.89	112.45 ± 26.23	0.00
	Post	95.13 ± 20.47#	112.66 ± 23.93	
HDL (mmol/L)	Pre	49.00 ± 12.42	50.83 ± 7.35	0.01
	Post	52.91 ± 9.41#	47.84 ± 5.96	
Cholesterol (mmol/L)	Pre	191.73 ± 39.85	208. 08 ± 38.35	0.19
	Post	187.80 ± 42.01	175.32 ± 62.22	
FBG (mmol/L)	Pre	114.22 ± 44.78	119.36 ± 41.53	0.61
	Post	112.64 ± 42.26	115.15 ± 14.60	
Insulin (μU/ml)	Pre	17.03 ± 12.18	19.61 ± 8.43	0.03
	Post	13.41 ± 5.30	18.41 ± 42.78	
HOMA-IR	Pre	5.32 ± 5.88	5.90 ± 4.39	0.03
	Post	3.86 ± 2.25#	4.67 ± 2.33	

ALP: Alkaline Phosphatase, **ALT**: Alanine amino transferase, **AST**: Aspartate amino transferase, **LDL**: Low-density lipoproteins, **HDL**: High-density lipoprotein, **FBG**: fast blood glucose, **HOMA-IR**: Homeostatic Model Assessment of IR. *Significant differences compared to the control group ($p < 0.05$). #Significant difference from baseline ($p < 0.05$).

Discussion

We measured changes in plasma levels of FGF-21, fetuin-A, HOMA-IR, insulin, LDL, HDL, and also liver enzymes such as ALT, ALP and AST after eight weeks of CRIT in NAFLD patients. There were decreases in fetuin-A levels after eight weeks of CRIT. Elevations in fetuin-A are associated with metabolic diseases (6), with fetuin-A suggested to have a central role in glucose tolerance, IR and liver fibrosis (20). Other reports support our findings that 16 weeks of swimming reduced serum fetuin-A levels and improved the

HOMA-IR rodent models of metabolic syndrome (21), or that seven days of endurance exercise training reduced fetuin-A levels and IR in obese NAFLD patients(22). It has been suggested that reduced plasma fetuin-A levels could be used to predict changes in the expression of genes related to inflammation, such as toll-like receptor (TLR) signaling in macrophages and adipose tissue (23). It is possible that exercise training-induced reductions in fetuin-A could downregulate TLR4 signaling and mediates the anti-inflammatory effects of exercise training in obese patients with NAFLD (4, 23, 24). Our results differ from those of Sargeant et al. (2019), who reported that aerobic exercises did not alter systemic levels of fetuin-A in healthy individuals with obesity (25). Reasons for this discrepancy could be differences in the participants studied and exercise modalities; our study used combined exercise training, which provide more benefits than aerobic exercise training in reducing fat mass, as shown by our findings that CRIT decreased lipid profile and WHR (Table 2) (13, 14).

Our study also indicates that CRIT increased FGF-21 levels. There are increases in plasma levels of this hepatokine in metabolic-related diseases associated with NAFLD (6), suggesting that FGF-21 could be a biomarker for diagnosing and treating NAFLD. Circulating FGF-21 modulates free fatty-acid levels during exercise training (26). The transcription levels of FGF-21 are upregulated by activating transcription factor 4 (ATF4)/peroxisome proliferator-activated receptor alpha (PPARα) in palmitic acid-treated FaO cells (a differentiated hepatoma cell line frequently used in studies of lipoprotein synthesis), suggesting a role for the ATF4/PPARα pathway in promoting hepatic FGF21 production during exercise-mediated lipid degradation (27, 28). We also report improvements in LDL and HDL after eight weeks of exercise in patients with NAFLD. Our study suggests that eight weeks of CRIT might regulate lipid metabolism to improve NAFLD through increasing FGF-21 levels (26). However, the exact underlying mechanisms are unclear, and more studies are needed to clarify the potential cellular effects of long-term physical activity on FGF-21 in improving the severity of NAFLD.

We report that CRIT reduces levels of liver enzymes in NAFLD patients. In addition, the reductions in liver enzymes were accompanied by improvements in HOMA-IR, LDL and HDL. NAFLD is associated with elevated ALT, AST ALP, and fat production by hepatocytes (29). Exercise training decreases systemic levels of ALT and AST in patients with NAFLD (29, 30). Exercise training also improves antioxidant defence mechanisms and reduces the release of pro-inflammatory factors by decreasing body fat and visceral fat, leading to reductions in AST and ALT levels (4, 12, 29–31).

Limitations

There are some limitations to our study, including 1) NAFLD was not diagnosed based on histology; 2) fat content in the liver was not measured by biopsy; 3) the HOMA-IR formula used to estimate insulin sensitivity has a lower accuracy than the euglycemic hyperinsulinemic clamp method; 4) we did not investigate the potential effects of gender on changes in liver enzymes and hepatokines and their responses to the exercise training.

Conclusions

Eight weeks of CRIT improved liver enzymes, body composition, lipid profiles, and serum levels of hepatokines (fetuin-A and FGF-21) in inactive obese females with NAFLD. Our findings support the view that CRIT may be an effective non-medical therapeutic strategy to decrease NAFLD risk factors and obesity-induced disorders. Further studies are needed to understand how hepatokines (particularly FGF-21) change in response to exercise training in different populations.

Declarations

Acknowledgements: The authors thank all participants for their time and effort in making this study possible

Conflict of interest: The authors declare that they have no competing interests.

References

1. Abd El-Kader SM, El-Den Ashmawy EMS. Non-alcoholic fatty liver disease: The diagnosis and management. World J Hepatol. 2015;7(6):846-58.

2. Sherif ZA, Saeed A, Ghavimi S, Nouraie S-M, Laiyemo AO, Brim H, et al. Global Epidemiology of Nonalcoholic Fatty Liver Disease and Perspectives on US Minority Populations. Dig Dis Sci. 2016;61(5):1214-25.

3. Qiu S, Cai X, Sun Z, Li L, Zügel M, Steinacker JM, et al. Association between physical activity and risk of nonalcoholic fatty liver disease: a meta-analysis. Therap Adv Gastroenterol. 2017;10(9):701-13.

4. van der Windt DJ, Sud V, Zhang H, Tsung A, Huang H. The Effects of Physical Exercise on Fatty Liver Disease. Gene Expr. 2018;18(2):89-101.

5. Carneros D, López-Lluch G, Bustos M. Physiopathology of Lifestyle Interventions in Non-Alcoholic Fatty Liver Disease (NAFLD). Nutrients. 2020;12(11):3472.

6. Martínez-Garza Ú, Torres-Oteros D, Yarritu-Gallego A, Marrero PF, Haro D, Relat J. Fibroblast Growth Factor 21 and the Adaptive Response to Nutritional Challenges. Int J Mol Sci. 2019;20(19):4692.

7. Flisiak-Jackiewicz M, Bobrus-Chociej A, Wasilewska N, Tarasow E, Wojtkowska M, Lebensztejn DM. Can hepatokines be regarded as novel non-invasive serum biomarkers of intrahepatic lipid content in obese children? Adv Med Sci. 2019;64(2):280-4.

8. Barb D, Bril F, Kalavalapalli S, Cusi K. Plasma Fibroblast Growth Factor 21 Is Associated With Severity of Nonalcoholic Steatohepatitis in Patients With Obesity and Type 2 Diabetes. J Clin Endocrinol Metab. 2019;104(8):3327-36.

9. Haukeland JW, Dahl TB, Yndestad A, Gladhaug IP, Løberg EM, Haaland T, et al. Fetuin A in nonalcoholic fatty liver disease: in vivo and in vitro studies. Eur J Endocrinol. 2012;166(3):503-10.

10. Sanyal D, Mukherjee P, Raychaudhuri M, Ghosh S, Mukherjee S, Chowdhury S. Profile of liver enzymes in non-alcoholic fatty liver disease in patients with impaired glucose tolerance and newly detected untreated type 2 diabetes. Indian J Endocrinol Metab. 2015;19(5):597-601.

11. Mandal A, Bhattarai B, Kafle P, Khalid M, Jonnadula SK, Lamicchane J, et al. Elevated Liver Enzymes in Patients with Type 2 Diabetes Mellitus and Non-alcoholic Fatty Liver Disease. Cureus. 2018;10(11):e3626.

12. Thoma C, Day CP, Trenell MI. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. J Hepatol. 2012;56(1):255-66.

13. Zouhal H, Zare-Kookandeh N, Haghighi MM, Daraei A, de Sousa M, Soltani M, et al. Physical activity and adipokine levels in individuals with type 2 diabetes: A literature review and practical applications. Rev Endocr Metab Disord. 2021.

14. Saeidi A, Haghighi MM, Kolahdouzi S, Daraei A, Abderrahmane AB, Essop MF, et al. The effects of physical activity on adipokines in individuals with overweight/obesity across the lifespan: A narrative review. Obes Rev. 2021;22(1):e13090.

15. Nathanson V. Revising the declaration of Helsinki. British Medical Journal Publishing Group; 2013.

16. Bredin SSD, Gledhill N, Jamnik VK, Warburton DER. PAR-Q+ and ePARmed-X+: new risk stratification and physical activity clearance strategy for physicians and patients alike. Can Fam Physician. 2013;59(3):273-7.

17. Borg G. Perceived exertion as an indicator of somatic stress. Scandinavian journal of rehabilitation medicine. 1970.

18. Pescatello LS, Riebe D, Thompson PD. ACSM's guidelines for exercise testing and prescription: Lippincott Williams & Wilkins; 2014.

19. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27(6):1487-95.

20. Dogru T, Kirik A, Gurel H, Rizvi AA, Rizzo M, Sonmez A. The Evolving Role of Fetuin-A in Nonalcoholic Fatty Liver Disease: An Overview from Liver to the Heart. Int J Mol Sci. 2021;22(12):6627.

21. Sakr HF, Al-Hashem FH, El-Naby WM, Alkhateeb MA, Zaki MS, Refaey HM, et al. Preventive roles of swimming exercise and pioglitazone treatment on hepatic dysfunction in a rat model of metabolic syndrome. Can J Physiol Pharmacol. 2014;92(2):162-70.

22. Malin SK, Mulya A, Fealy CE, Haus JM, Pagadala MR, Scelsi AR, et al. Fetuin-A is linked to improved glucose tolerance after short-term exercise training in nonalcoholic fatty liver disease. J Appl Physiol (1985). 2013;115(7):988-94.

23. Lee S, Norheim F, Gulseth HL, Langleite TM, Kolnes KJ, Tangen DS, et al. Interaction between plasma fetuin-A and free fatty acids predicts changes in insulin sensitivity in response to long-term exercise. Physiol Rep. 2017;5(5):e13183.

24. Glass OK, Radia A, Kraus WE, Abdelmalek MF. Exercise training as treatment of nonalcoholic fatty liver disease. Journal of Functional Morphology and Kinesiology. 2017;2(4):35.

25. Willis SA, Sargeant JA, Thackray AE, Yates T, Stensel DJ, Aithal GP, et al. Effect of exercise intensity on circulating hepatokine concentrations in healthy men. Applied Physiology, Nutrition, and Metabolism. 2019;44(10):1065-72.

26. Cuevas-Ramos D, Almeda-Valdés P, Meza-Arana CE, Brito-Córdova G, Gómez-Pérez FJ, Mehta R, et al. Exercise increases serum fibroblast growth factor 21 (FGF21) levels. PLoS One. 2012;7(5):e38022-e.

27. Kim KH, Jeong YT, Kim SH, Jung HS, Park KS, Lee HY, et al. Metformin-induced inhibition of the mitochondrial respiratory chain increases FGF21 expression via ATF4 activation. Biochem Biophys Res Commun. 2013;440(1):76-81.

28. Kim KH, Kim SH, Min Y-K, Yang H-M, Lee J-B, Lee M-S. Acute exercise induces FGF21 expression in mice and in healthy humans. PLoS One. 2013;8(5):e63517-e.

29. Smart NA, King N, McFarlane JR, Graham PL, Dieberg G. Effect of exercise training on liver function in adults who are overweight or exhibit fatty liver disease: a systematic review and meta-analysis. British Journal of Sports Medicine. 2018;52(13):834.

30. Shamsoddini A, Sobhani V, Ghamar Chehreh ME, Alavian SM, Zaree A. Effect of Aerobic and Resistance Exercise Training on Liver Enzymes and Hepatic Fat in Iranian Men With Nonalcoholic Fatty Liver Disease. Hepat Mon. 2015;15(10):e31434-e.

31. Sreenivasa Baba C, Alexander G, Kalyani B, Pandey R, Rastogi S, Pandey A, et al. Effect of exercise and dietary modification on serum aminotransferase levels in patients with nonalcoholic steatohepatitis. J Gastroenterol Hepatol. 2006;21(1 Pt 1):191-8.

Figures

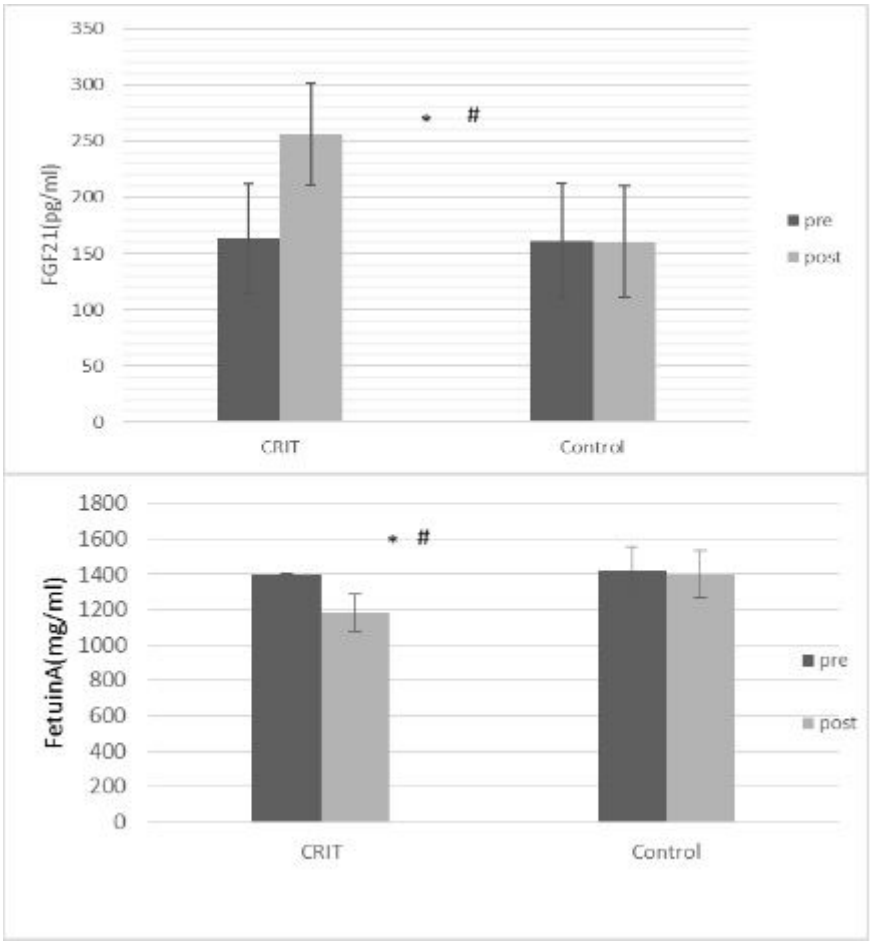

Figure 1

FGF-21 and Fetuin-A levels before and after eight weeks of CRIT and control groups. *significant differences compared to the control group ($p<0.05$). #significant difference from baseline ($p<0.05$).