Regulation of Metabolic Homeostasis by Reducing Selected Hepato-adipokines in Response to Three Types of Resistance Training in Men with Obesity

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Abstract

Introduction: Decreased physical activity is one of the main causes of the obesity epidemic. In the process of obesity, the secretion of some hepato-adipokines increases and causes metabolic disorders. Exercise plays an important role in improving the complications of obesity by regulating the levels of selected hepato-adipokine. The purpose of this study was to examine the effects of three types of resistance training methods on selected hepato-adipokine and lipid profiles in men with obesity.
Materials and Methods: The sample of the study included 44 sedentary men with obesity divided into 4 groups of traditional resistance training (TRT), circuit resistance training (CRT), and interval resistance training (IRT) as well as one control group. Fetuin-A, Fetuin-B, high-density lipoproteins (HDL), low-density lipoproteins (LDL), total cholesterol (TC), and triglyceride (TG) were measured using the ELISA method.
Results: The results of the mixed model ANOVA analysis showed a significant interaction between the type of training used and time at the levels of Fetuin-A ($F(1, 40) = 94273.16$, $P = 0.001$, ES = 1.00) and Fetuin-B ($F(1, 40) = 49697.67$, $P = 0.001$, ES = 0.99. In addition, within-group comparisons showed that lipid profile improved in TRT and CRT groups compared to the pretest ($P = 0.001$), while in the IRT group this improvement was not significant ($P > 0.05$).
Conclusion: The result of the present study shows that three models of resistance training reduced the select hepato-adipokines level in comparison to the control group. However, IRT and CRT had the greatest effect on reducing Fetuin-A and Fetuin-B, respectively.

Keywords: Exercise, Adipose tissue, Hepato-adipokines, Fetuin-A, Fetuin-B, Metabolic disorder, Homeostasis

Introduction

Obesity is a common and costly chronic disease diagnosed with a body mass index (BMI) above 30 kg / m^2 (1). The main cause of obesity is an imbalance between energy intake and energy consumption which occurs with excessive accumulation of subcutaneous and visceral adipose tissue (2). Obesity increases the risk for musculoskeletal disorders, diabetes, hypertension, dyslipidemia, cardiovascular failure, and a variety of cancers (3). According to the World Health Organization (WHO) in 2016, 1.9 billion adults over the age of 18 were overweight and 609 million adults were obese (4). It is predicted that by 2030, about 57.8% of the world's population will be overweight or obese (5).

Expansion and visceral accumulation of adipose tissue lead to changes in homeostasis and dysfunction of various organs of the human body, especially the

liver (6). It is known that the liver can act as an endocrine organ by producing "hepatokines" and plays a key role in regulating the body's metabolism (7). Fetuin-A (Alpha2_HS_glycoprotein) was the first and most important hepatokines proposed to regulate metabolic homeostasis in humans (8). This glycoprotein is also secreted from adipose tissue, especially visceral fat it is also called "hepato-adipokine" (9). Fetuin-A levels increase in obesity, type 2 diabetes, and fatty liver disease (10). Increasing Fetuin-A also suppresses adiponectin an anti-inflammatory adipokine as well as causes the secretion of proinflammatory cytokines from adipose tissue (11).

Fetuin-B is another hepato-adipokine, which is 22% similar to Fetuin-A and is encoded by the FETUB gene (12). Studies have shown that reducing the secretion of Fetuin-B lowers blood glucose levels and improves glucose tolerance in obese rats (13). Plasma Fetuin-B levels have been shown to increase in people with nonalcoholic fatty liver disease, obese rodents, obese adults with vitamin D deficiency (14).

Fetuins are associated with fat profiles. The lipid profile changes in obesity include decreased high-density lipoprotein (HDL), increased low-density lipoprotein (LDL), total cholesterol (TC), and triglyceride (TG) (15). The changes in the lipid profile are one of the major risk factors for coronary heart disease in obese people (16). Exercise and physical activity are effective ways to manage the effects of obesity by increasing energy consumption and decreasing the percentage of fat, especially visceral fat, and further regulating the metabolic pathways involved in the obesity process (17). Although in the past, only aerobic exercise (AE) was very popular in people with obesity, studies have shown that resistance training (RT) is an important part of the treatment plan for obesity (18). In this regard ,studies have shown that compared to AE with an intensity of 75 to 85% of maximum heart rate, 8 weeks of RT is more effective in reducing Fetuin-A and Fetuin-B in men with obesity and diabetes (19). It is also reported that 12 weeks of long-term combined training including AE and RT in sedentary men with obesity can increase insulin sensitivity by lowering Fetuin-A levels (20). On the other hand, the important and positive role of aerobic exercise in improving lipid profile by reducing harmful blood fats such as TC, TG, and LDL and increasing beneficial blood fats such as HDL has been proven. However, in the case of resistance training, some studies suggest that RT improves the lipid profile in people with obesity (21), while other studies have shown that RT does not affect (i.e., improve) the lipid profile (22).

In light of the prior information and considering that limited studies are comparing different types of RT, the purpose of this study was to examine the effects of three types of resistance training methods (traditional, circuit and interval) on selected hepato-adipokine (Fetuin-A and Fetuin B) and lipid profiles in men with obesity.

Materials and Methods

This was a quasi-experimental study with a pre-test vs. post-test design. The study population was non-athlete men with obesity among them, 44 individuals who met the inclusion criteria were recruited through a call in public and administrative centers. Participants were randomly divided into 4 groups of study, each consisted of 11 people including: traditional resistance training (TRT) (height 169.19 ± 2.76 cm, body mass 92.92 ± 2.85 kg), circuit resistance training (CRT) (height 167.28 ± 2.61 cm, body mass 92.41 ± 1.93 kg), interval resistance training (IRT) (height 168.22 ± 1.71 cm, body mass 33.14 ± 0.75 kg), and control group (height 168.99 ± 3.17, body mass32.90 ± 1.44 kg). Inclusion criteria were a) obese young men aged 18 to 32 years with a BMI of 30 to 40, b) no consumption of tobacco, drugs, and alcohol and not being afflicted with any

diseases. The ability to walk and engage in physical activity programs independently, confirmation by a physician of having no restriction on participation in sports activities, and not losing more than 5% of body weight in the two months before the study were other inclusion criteria.

The study protocol was approved by the ethics committee of the Faculty of Medicine, Tarbiat Modares University (Ethical code: IR.MODARES.REC.1399.174), and also was in accordance with the last update of the Helsinki Declaration.

First, the purpose and procedures of the research were fully explained to participants, and a written informed consent form was obtained. Individuals were then examined by a physician and asked to complete social and medical information questionnaires. One repetition maximum (1RM) was used to determine and control the intensity of exercises, which was calculated by the Brzycki equation (23). After taking 1RM from the participants, the intensity of training in the first 4 weeks was determined based on the principle of individual differences and at the end of each month, the intensity of the exercises changed accordingly with the new 1RM.

The height of the participants was measured using the SEKA wall height gauge (accuracy 0.1 cm) and their weight was measured by the standard SEKA scale (100% g). BMI was calculated using a person's height and weight (weight (kg) / height (m^2)). To measure the waist-hip ratio (WHR) (waist/hip (cm)) an anthropometric tape measure and Slim Guide caliper (± 1 mm) were used to determine the thickness of the skin fold by 3-point method (three arms, abdomen, and supra-iliac) on the right side of the body. Also, the percentage of body fat was calculated using Jackson and Pollack men's formula (24). Fasting blood samples were taken 48 hours before and 48 hours after the interventions from the right arm of the participants. Blood sampling was performed at 8 to 10 AM under standard conditions. After transferring the blood to special test tubes containing EDTA for plasma separation, the blood was centrifuged and centrifuged at 3000 rpm for 10 minutes. The isolated plasma was frozen and stored at -70 ° C. Fetuin-A and Fetuin-B were measured according to the manufacturer's protocol using ELISA commercial kits (Cat. No. RD 172037100, Cat. No. RD172172100 ELISA sandwich kit, Biovendor, Heidelberg, Germany). TC, TG, LDL, and HDL were assessed by calorimetric method via using quantitative detection kits of Pars Azmoun Company (Tehran, Iran).

All three RT groups participated in the exercises for 12 weeks and 3 sessions per week under the supervision of an instructor. They were asked not to do any other exercise or physical activity at this time. The control group did not engage in any physical activity outside of their routine during the study and no special training was provided for them. Details of training models are provided in Table 1.

Table 1. Comparison of three different types of resistance training protocols used in the present study.

Volume and Intensity	TRT	CRT	IRT
Session per week	3	3	3
Sets	3	3 circles	2
Repetitions	14	14	14
Rest time between exercises	30 seconds	> 15 seconds	Active rest with 25% of
Rest time between each set	90 seconds	180 seconds	1RM and 14 repetitions
Intensity	50% of 1RM	50% of 1RM	50% of 1RM

TRT: Traditional resistance training; CRT: Circuit resistance training; IRT: Interval resistance training; 1RM: 1- repetition maximum

RT protocols included three main phases: warm-up, the main exercises, and cooling-down periods. The main exercises included 10 movements: back squats, lat pull-down, leg press, chest press, leg extension, Lateral raise, leg curls, bicep's curl, standing calf

raise, triceps pushdown. It should be noted that to increase confidence in comparing the effect of three types of RT, all training protocols were controlled in terms of volume and intensity. The intensity of all movements in all 3 groups was 50% 1RM. The Baechle formula was used to determine the volume of exercise (25).

Statistical Analysis

The Shapiro-Wilk test was used to determine the normality of data distribution. Leven's test was used to examine the homogeneity of variance between groups. Differences between groups and within groups were examined by the mixed-model design ANOVA with repeated measure [groups (4) X time (2)] and if significant, Fisher LSD post hoc test was used to determine the differences between pairs of study groups. A significance level of less than 0.05 was considered. Data were analyzed using SPSS software, version 26.

Results

The normality test indicated that all variables were normally distributed. In addition, at the beginning of the study and before the interventions, all groups were homogeneous ($P > 0.05$) and no significant differences were observed in body mass, body fat, BMI, and WHR ($P > 0.05$).

The mixed model ANOVA test showed a significant interaction between the groups and time at the Fetuin-A levels ($F (1,40) = 94273.16$, $P = 0.001$, ES = 1.00) and Fetuin-B ($F (1,40) = 49697.67$, $P = 0.001$, ES = 0.99) (Figures 1 and 2). Within group comparisons also indicated a significant decrease in Fetuin-A ($F (1,40) = 1924.90$, $P = 0.001$, ES = 0.98) and Fetuin-B ($F (1,40) = 82.461$, $P = 0.001$, ES = 0.67) after 12 weeks of RT compared to pre-test.

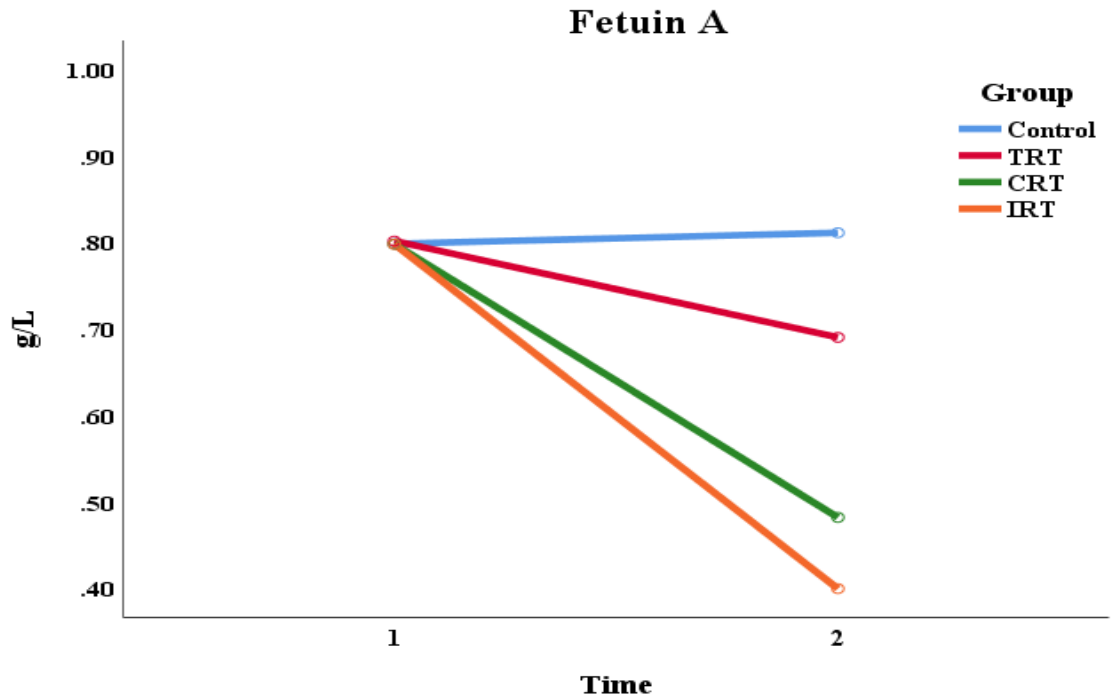

Figure 1. Plot of mean values comparing within-group differences in Fetuin-A level before exposure to the different types of resistance training intervention (1) and after that (2). **TRT**: Traditional Resistance Training; **CRT**: Circuit Resistance Training; **IRT**: Interval Resistance Training; **C**: Control

The results of post hoc testing indicated a significant difference in the levels of Fetuin-A in all paired groups comparisons; the IRT group showed a greater effect than the CRT and TRT groups (Table 2). Regarding Fetuin-B, a significant

difference between pairs of RT groups except for the IRT group with CRT as well as the IRT group with TRT was found. CRT group showed a greater effect than other groups (Table 2).

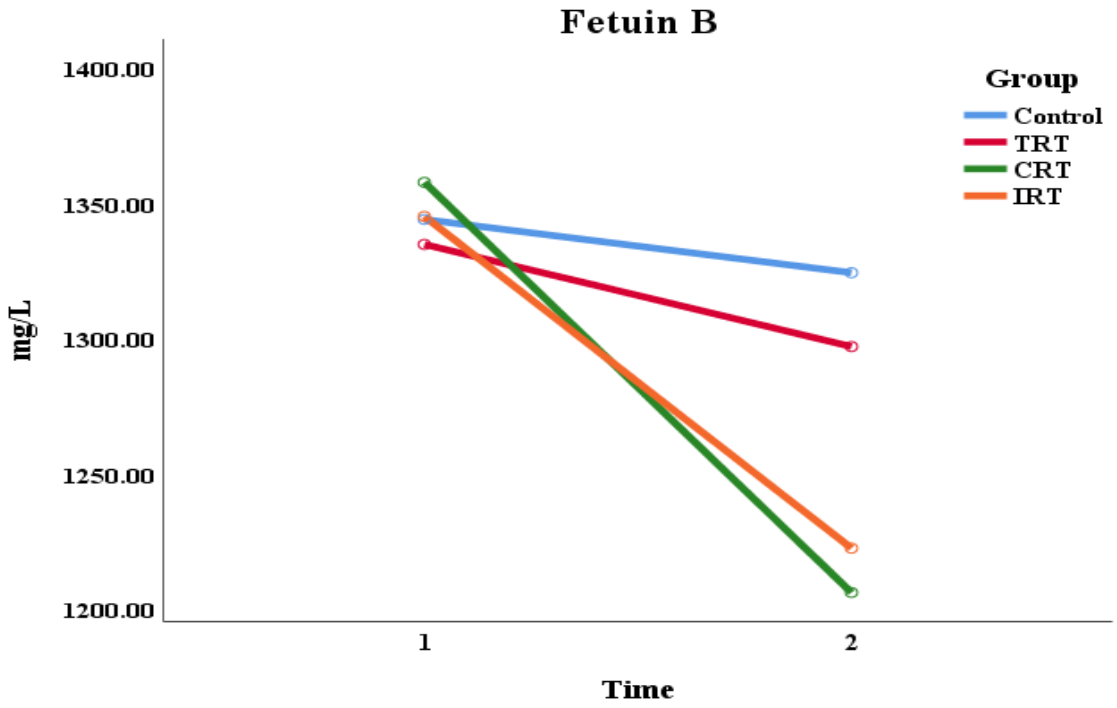

Figure 2. Plot of mean values comparing within-group differences in Fetuin-B level before exposure to the different types of resistance training intervention (1) and after that (2). TRT: Traditional Resistance Training; CRT: Circuit Resistance Training; IRT: Interval Resistance Training; C: Control.

Regarding lipid profile, within-group comparison showed that LDL, TG, and TC levels significantly decreased in TRT and CRT groups after 12 weeks of RT (P=0.001); however, in the IRT group, no significant decrease was observed compared to the pretest (P > 0.05) (Figure 3). In addition, in all training groups, except the IRT group (P = 0.57), HDL level significantly increased after RT (P = 0.001) (Figure 3D).

Considering the main effect of the group, there was a significant difference between TRT, CRT, and the control group at HDL, LDL, TC, and TG levels but this difference was not observed in the IRT group. As can be seen in Tables 3 and 4, the pairwise comparisons of the exercise groups also showed that there was a significant difference in HDL, LDL, TC, and TG levels between all resistance training groups except IRT and the control group. Significant differences were observed in the pair comparisons of training groups on all factors except TRT and CRT.

Discussion

The purpose of this study was to examine the effects of three types of resistance training methods (traditional, circuit and interval) on selected hepato-adipokine (Fetuin-A and Fetuin B) and lipid profiles in men with obesity. The results showed that all three models of resistance training reduced the levels of Fetuin-A. The largest decrease was observed in the IRT group and the lowest decrease was observed in the TRT group. Regarding Fetuin-B, the findings showed that IRT and CRT significantly reduced Fetuin-B levels, but in the TRT group, this decrease was not significant. The greatest impact was related to the CRT group. Regarding the lipid profile, a decrease in TG, TC, LDL, and an increase in HDL was observed in TRT and

CRT groups, but this improvement was not observed in the IRT group. TRT was more effective in improving the lipid profile compared to other groups.

Fetuin-A is a multifaceted protein and an important factor in the development and progression of obesity. In fatty liver, the amount of Fetuin-A and mRNA expression is increased (26). It has been made clear that Fatty acids (FA) increase the expression of Fetuin-A in human HEPG2 hepatocytes by binding to the capsular Nuclear Factor kappa B (NF-KB). All of these provide the basis for the onset and progression of obesity (27). Based on the results of the present study, it was found that all three resistance training models, reduced Fetuin A levels and the biggest impact was related to IRT. However, IRT and CRT had a greater effect on Fetuin-A than TRT. In this regard, it has been found that IRT compared to TRT increases energy consumption during and after exercise and helps to improve metabolism (28). Also, IRT and CRT with increased basal metabolism and maximal oxygen consumption as well as improving body composition have more benefits than TRT in reducing plasma Fetuin A levels and so the balance of homeostasis.

Table 2. Results of mean group comparisons between different types of resistance training and control group for Fetuin-A and Fetuin-B.

Variable	(I) Group	(J) Group	Mean Difference(I-J)	P value	95% Confidence Interval	
					Lower Bound	Upper Bound
Fetuin-A	C	TRT	0.05	0.005*	0.04	0.07
		CRT	0.16	0.005*	0.15	0.17
		IRT	0.20	0.005*	0.19	0.21
	TRT	C	-0.05	0.005*	-0.07	-0.04
		CRT	0.10	0.005*	0.09	0.11
		IRT	0.14	0.005*	0.13	0.16
	CRT	C	-0.16	0.005*	-0.17	-0.15
		TRT	-0.10	0.005*	-0.11	-0.09
		IRT	0.04	0.005*	0.02	0.05
	IRT	C	-0.20	0.005*	-0.21	-0.19
		TRT	-0.14	0.005*	-0.16	-0.13
		CRT	-0.04	0.005*	-0.05	-0.02
Fetuin B	C	TRT	18.24	0.277	-15.18	51.68
		CRT	52.20	0.003*	18.76	85.64
		IRT	50.30	0.004*	16.87	83.74
	TRT	C	-18.24	0.277	-51.68	15.18
		CRT	33.95	0.047*	0.51	67.39
		IRT	32.05	0.060	-1.37	65.49
	CRT	C	-52.20	0.003*	-85.64	-18.76
		TRT	-33.95	0.047*	-67.39	-0.51
		IRT	-1.89	0.909	-35.33	31.54
	IRT	C	-50.30	0.004*	-83.74	-16.87
		TRT	-32.05	0.060	-65.49	1.37
		CRT	1.89	0.909	-31.54	35.33

*Significant at level P < 0.05. TRT: Traditional Resistance Training; CRT: Circuit Resistance Training; IRT: Interval Resistance Training; C: Control.

Consistent with these results, another study showed that after 8 weeks of resistance training, Fetuin A levels in men with obesity and diabetes decreased (19). This

decrease was also observed after 12 weeks of combined training (20).

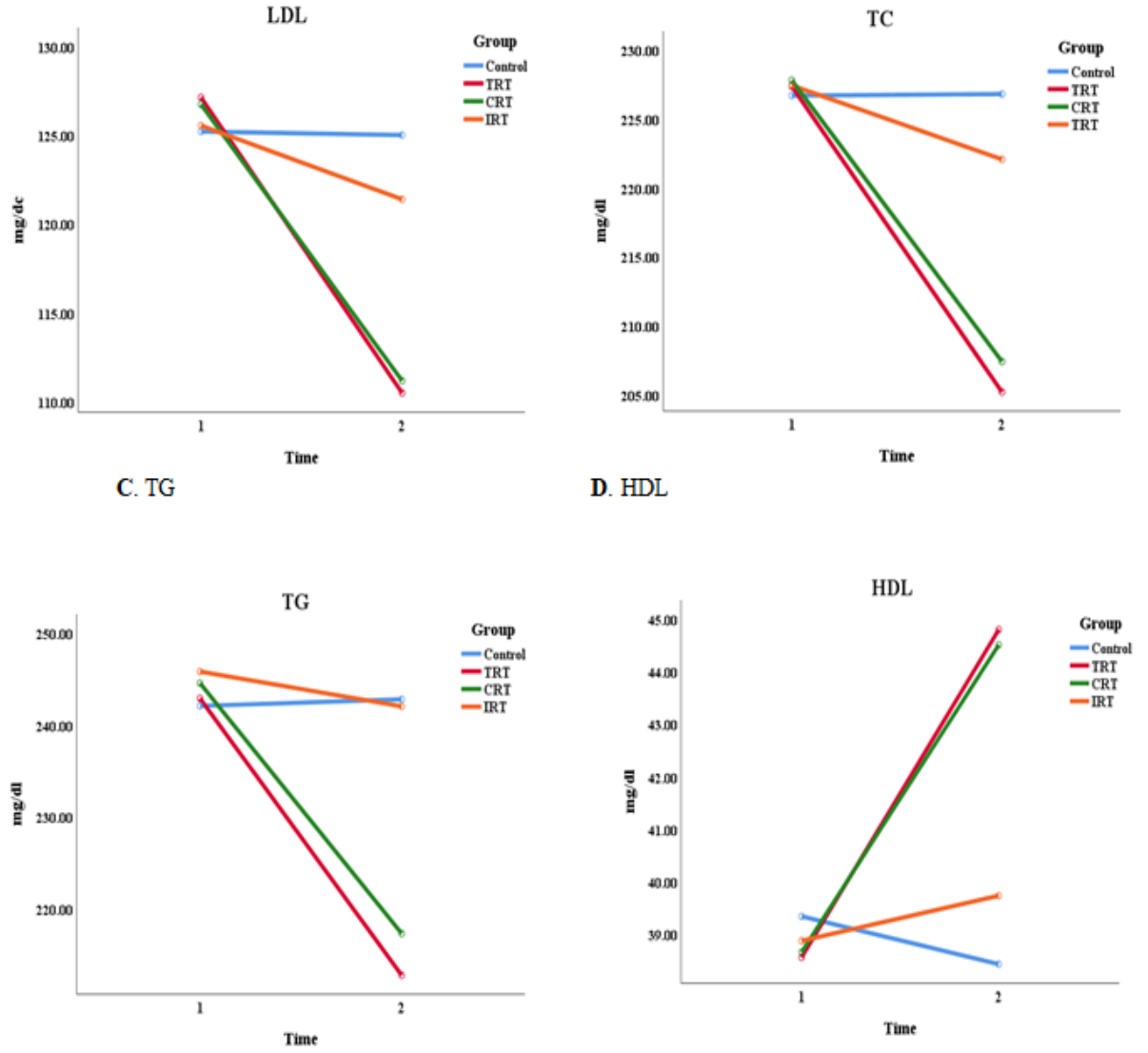

Figure 3. Plots of mean values comparing within-group differences in lipid profile before exposure to the different types of resistance training intervention (1) and after that (2). LDL: Low-Density Lipoprotein, TG: Triglyceride, TC: Total Cholesterol, HDL: High-Density Lipoprotein, TRT: Traditional Resistance Training; CRT: Circuit Resistance Training; IRT: Interval Resistance Training; C: Control

Reducing the fat content of the liver, reducing hepatic hyperglycemia by reducing pro-inflammatory mediators and modulating reactive oxygen species, as well as activating the AKT pathway are possible mechanisms for explaining the decrease in Fetuin-A after exercise (29). Contrary to our findings, there was no change in plasma Fetuin A levels after 12 weeks of combined exercise in women with obesity (30). Contradictory results can be attributed to the type of exercise in different studies, including aerobic or combination exercise, gender of participants, or time of Fetuin-A assessment.

Our results showed that CRT and IRT reduced Fetuin-B levels after 12 weeks, with the most significant decrease in the IRT group. Studies that have examined the effect of exercise on Fetuin-B levels are very limited in number and highly different populations. Consistent with our results, it has been found that 8 weeks of resistance training resulted in a greater reduction in

Fetuin-B than in aerobic exercise in men with obesity with type 2 diabetes (19). Also, 12 weeks of combined training significantly reduces Fetuin-B levels in people with diabetes (31). The effect of exercise on Fetuin-B can be related to the anti-inflammatory effects of exercise, as a link between levels of Fetuin-B and inflammation has been reported (32); however, more research is needed to confirm this theory.

In the present study, TRT and CRT decreased LDL, TC, and TG and increased HDL; the greatest impact was observed in the TRT group. IRT had no significant effect on improving the lipid profile. Exercise may also increase the ability of muscle fibers to oxidize lipids by increasing the activity of enzymes involved in lipid transport and metabolism (such as Lecithin-Cholesterol Acyltransferase (LCAT) and LPL) which improves the lipid profile (33). In confirmation of the results of the present study, it has been found that 8 weeks of RT reduced LDL, TC, TG levels, and increased HDL in elderly women with obesity (21). In another study examining the effect of 8 weeks of CRT in young men with obesity, the authors found that it improved lipid profile (34).

Tables 3. Results of mean group comparisons between different types of resistance training and control group for HDL and LDL.

Variable	(I)Group	(J)Group	Mean Difference(I-J)	P value	95% Confidence Interval	
					Lower Bound	Upper Bound
HDL	C	TRT	-2.79	0.001*	-4.29	-1.29
		CRT	-2.69	0.001*	-4.19	-1.19
		IRT	-0.41	0.575	-1.91	1.07
	TRT	C	2.79	0.001*	1.29	4.29
		CRT	0.09	0.897	-1.40	1.59
		IRT	2.37	0.003*	0.87	3.87
	CRT	C	2.69	0.001*	1.19	4.19
		TRT	-0.09	0.897	-1.59	1.40
		IRT	2.27	0.004*	0.77	3.77
	IRT	C	0.41	0.575	-1.07	1.91
		TRT	-2.37	0.003*	-3.87	-0.87
		CRT	-2.27	0.004*	-3.77	-0.77
LDL	C	TRT	6.30	0.001*	2.83	9.76
		CRT	6.15	0.001*	2.68	9.61
		IRT	1.63	0.345	-1.82	5.10
	TRT	C	-6.30	0.001*	-9.76	-2.83
		CRT	-0.15	0.931	-3.61	3.31
		IRT	-4.66	0.010*	-8.12	-1.19
	CRT	C	-6.15	0.001*	-9.61	-2.68
		TRT	0.15	0.931	-3.31	3.61
		IRT	-4.51	0.012*	-7.97	-1.04
	IRT	C	-1.63	0.345	-5.10	1.82
		TRT	4.66	0.010*	1.19	8.12
		CRT	4.51	0.012*	1.04	7.97

*Significant at level P < 0.05; TRT: Traditional Resistance Training; CRT: Circuit Resistance Training; IRT: Interval Resistance Training; C: Control; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein.

Tables 4. Results of mean group comparisons between different types of resistance training and control group for TG and TC.

Variable	(I)Group	(J)Group	Mean Difference(I-J)	P value	Confidence Interval	
					Lower Bound	Upper Bound
TG	C	TRT	14.56	0.001*	9.66	19.46
		CRT	1.47	0.001*	6.57	16.37
		IRT	-1.48	0.544	-6.38	3.41
	TRT	C	-14.56	0.001*	-19.46	-9.66
		CRT	-3.95	0.209	-7.99	1.80
		IRT	-16.05	0.005*	-20.95	-11.15
	CRT	C	-11.47	0.005*	-16.37	-6.57
		TRT	3.09	0.209	-1.80	7.99
		IRT	-12.95	0.005*	-17.85	-8.05
	IRT	C	1.48	0.544	-3.41	6.38
		TRT	16.05	0.005*	11.15	20.95
		CRT	12.95	0.005*	8.05	17.85
TC	C	TRT	10.45	0.005*	6.04	14.86
		CRT	9.13	0.005*	4.71	13.54
		IRT	1.99	0.366	-2.41	6.40
	TRT	C	-10.45	0.005*	-14.86	-6.04
		CRT	-1.32	0.548	-5.73	3.09
		IRT	-8.45	0.005*	-12.87	-4.04
	CRT	C	-9.13	0.005*	-13.54	-4.71
		TRT	1.32	0.548	-3.09	5.736
		IRT	-7.13	0.002*	-11.55	-2.72
	IRT	C	-1.99	0.366	-6.40	2.41
		TRT	8.45	0.005*	4.04	12.87
		CRT	7.13	0.002*	2.72	11.55

*Significant at level P < 0.05; TRT: Traditional Resistance Training; CRT: Circuit Resistance Training; IRT: Interval Resistance Training; C: Control; TG: Triglyceride; TC: Total Cholesterol

It has been stated that CRT improves lipid profile by increasing aerobic capacity and increasing lipid oxidation. In contrast, another study has shown that RT has no significant effect on lipid profile (22). The discrepancy in the results seems to be due to different training intensities in various studies.

RT plays an important role in improving the complications of obesity by reducing the levels of hepato-adipocytes and improving the lipid profile. As shown in this study, TRT has the least effect on Fetuin-A and Fetuin-B levels.

CRT and IRT appear to be more effective than TRT in regulating and modulating the hepato-adipokines and thus in regulating metabolic homeostasis, improving insulin resistance, reducing systemic inflammation, and inhibiting obesity. Therefore, it is suggested to the coaches in sports centers to use these two training methods for 12 weeks and with an intensity of 50% 1RM for controlling and reducing obesity.

Although more research is needed to make a definitive statement about the best method of RT in improving lipid profile, the results of the present study indicated that TRT is more effective in improving lipid profile compared to other types of RT. Therefore, it is recommended that along with other therapeutic methods, health care providers and coaches use TRT, to improve the possible complications of people with obesity. Homogeneity among research

groups at the beginning of the study and no drop off of participants from research and their attendance in all training sessions, and adjusting the intensity of exercises according to 1RM of each participant from the beginning to the end of the study were some of the strongest points of the present study. On the other hand, like any other study, the present study also suffers from several limitations. First, we were regrettably unable to control the participants' diet. Since the levels of Fetuins secreted by the liver and plasma lipids are affected by diet, it is suggested that this be considered and corrected in future studies. Second, the use of a small sample size and including only men in the present study may reduce its generalizability. It is suggested that future studies employee larger samples as well as include women to achieve more external validity. Lastly, future studies should also determine the effect of different exercise intensities of resistance training on the outcomes studied in the present study.

Conclusion

All three models of RT reduced the levels of Fetuin-A and Fetuin-B in comparison with the control group. IRT had the most effect and TRT had the least effect on Fetuin-A. Also, the highest decrease in Fetuin-B was observed in the CRT group and the lowest decrease was observed in the TRT group. Lipid profile also improved in the CRT and TRT group compared to the control group. The highest effect on lipid profile was observed in the TR group.

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Conflict of Interest

Authors declare that there are no financial or other relationships that might lead to a conflict of interest.

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