Comparison of the effects of 12 weeks of three types of resistance training (traditional, circular and interval) on the levels of neuregulin 4, adiponectin and leptin in non-athletic men with obesity

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Summary

Objectives: The purpose of this study was to compare three types of resistance training including traditional, circular and interval in non-athletic men with obesity in comparison to a control group for neuregulin 4, adiponectin and leptin responses.
Material and method: The sample of the study included 44 non-athletic men with obesity, who were randomly divided into the 4 equal groups (10 per each group): traditional, circular, and interval resistance training as well as a control group. Neuregulin 4 , leptin and adiponectin were analyzed using ELISA commercial kits.
Results: The results of mixed-design ANOVA with repeated measures showed that there was a significant interaction between the type of resistance training used and time on neuregulin 4 (F (3, 40) = 80.22, P= 0.005, ES = 0.85), leptin (F (3, 40) = 27.53, P= 0.005, ES = 0.67) and adiponectin (F (3, 40) = 12.44, P= 0.005, ES = 0.48). Considering the main effect of groups, results indicated that there was a significant difference between types of resistance training and control group in neuregulin 4 (F (1, 40) =41.31, P=0.005, ES = 0.75), adiponectin (F (1, 40) =15.08, P=0.005, ES = 0.53) and leptin (F (1, 40) =32.05, P = 0.005, ES = 0.70).
Conclusion: Findings suggest that resistance training, especially interval resistance training can lead to increase the plasma level of neuregulin 4 , adiponectin and decrease leptin in non-athletic men with obesity. Interval training showed superior effects on all study outcomes followed by circular and traditional training, respectively.

Key words:
Adiposity. Resistance training. Adipokines.

Comparación de los efectos de 12 semanas de tres tipos de entrenamiento de resistencia (tradicional, circular e intervalado) sobre los niveles de neuregulina 4, adiponectina y leptina en hombres no atléticos con obesidad

Resumen

Objetivo: El propósito de este estudio fue comparar tres tipos de entrenamiento de resistencia, incluido el tradicional, el circular y el intervalo en hombres no atléticos con obesidad, en comparación con un grupo de control para las respuestas de neuregulin 4 , adiponectin y leptin.
Material y método: La muestra del estudio incluyó a 44 hombres no deportistas con obesidad, que fueron divididos aleatoriamente en 4 grupos iguales (10 por cada grupo): entrenamiento de resistencia tradicional, circular e intervalado, así como un grupo de control. Se analizaron neuregulin 4 , leptin y adiponectin utilizando kits comerciales de ELISA.
Resultados: Los resultados del ANOVA de diseño mixto con medidas repetidas mostraron que hubo una interacción significativa entre el tipo de entrenamiento de resistencia utilizado y el tiempo con neuregulin 4 (F (3, 40) = 80,22, p = 0,005, ES = 0,85), leptin (F (3, 40) = 27,53, p = 0,005, ES = 0,67) y adiponectin (F (3, 40) = 12,44, p = 0,005, ES = 0,48). Considerando el efecto principal de los grupos, los resultados indicaron que hubo una diferencia significativa entre los tipos de entrenamiento de resistencia y el grupo de control en neuregulin 4 (F (1, 40) = 41,31, p = 0,005, ES = 0,75), adiponectin (F (1, 40) = 15,08, p = 0,005, ES = 0,53) y leptin (F (1, 40) = 32,05, p = 0,005, ES = 0,70).
Conclusión: Los resultados sugieren que el entrenamiento de resistencia, especialmente el entrenamiento de resistencia a intervalos, puede aumentar el nivel plasmático de neuregulin 4 , adiponectin y disminuir leptin en hombres obesos no atléticos. El entrenamiento por intervalos mostró efectos superiores en todos los resultados del estudio seguido del entrenamiento circular y tradicional, respectivamente.

Palabras clave:
Adiposidad. Entrenamiento de resistencia. Adipokines.

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Introduction

The World Health Organization (WHO) defines overweight and obesity as abnormal or excessive accumulation of fat that may impair health[1]. The prevalence of overweight and obesity is increasing worldwide[2]. Worldwide Obesity has almost tripled from 1975 to 2016, so that in 2016, of adults aged 18 years and over, 39% were overweight and 13% were obese[1]. It is predicted that by 2030, nearly 40% of the world's population will be overweight and one in five will be obese[3]. This high prevalence of obese people imposes heavy costs on society. It has been estimated that the cost of treating obesity-related diseases will increase by $ 66 billion a year by 2030[4]. Obesity is a major risk factor for cardiovascular disease, different types of cancers, and diabetes mellitus[5]. In addition, obesity increases the risk of diseases such as musculoskeletal disorders, hyperlipidemia and liver disease[5] and so decreased quality of life, reduced life expectancy and lower social performance such as the higher rate of unemployment[6].

Adipokines are biologically active compounds secreted by adipose tissue. They are involved in modulating metabolic homeostasis and act on various organs and tissues such as muscle, liver, and hypothalamus[7,8]. The profile of adipokines changes in response to the amount of adipose tissue. Accordingly, in obesity some adipokines, such as leptin are produced excessively, while plasma levels of adiponectin and neuregulin 4 (Nrg4) decrease[9,10].

Leptin and adiponectin are reliable markers of obesity, as hypo adiponectinemia and hyper leptinemia have also been reported in obese individuals[11]. The severity of obesity is directly proportional to the concentration of circulating leptin[12]. Although leptin mainly affects the hypothalamus, it also affects adipose tissue. The autocrine properties of leptin are produced by the conversion of fat cells in white adipose tissue to mitochondrial-rich fat cells, which in turn reduce appetite and increase energy expenditure[13]. Hyperphagia and increased fat mass in the presence of increased leptin may lead to endogenous leptin resistance[14].

Another adipokine, adiponectin, is released from white fat adipose tissue cells and plays an essential role in energy metabolism[15,16]. Adiponectin is inversely related to obesity compared to leptin and most adipokines[17] and its receptor expression is significantly reduced in obesity[18].

Neuregulin 4 (Nrg4), which has recently been identified, is another adipokine that decreases in obesity. Brown adipose tissue expresses the highest level of Nrg4[19] which is the ligand for Receptor tyrosine-protein kinase (ErbB4) which is gene polymorphisms associated with obesity[20]. Nrg4 is involved in modulating glucose and lipid metabolism and energy homeostasis[21]. New findings suggest that obesity may lead to a potential reduction in Nrg4 expression[10].

Studies show that lifestyle choices, such as being active and performing exercise, are acceptable options to prevent obesity as exercise can reduce leptin and increase adiponectin[22]. On the other hand, the role of exercise on Nrg4 has received less attention and is not entirely clear. However, it has been hypothesized that Nrg4 may be affected through exercise. Study on the effect of exercise on Nrg4 could provide a broad new approach to obesity prevention[23].

Resistance training is a highly popular type of training among people with obesity, mainly due to the fact that this type of training is better tolerated in most obese people with orthopedic and cardiopulmonary problems and are easily performed in sports centers[24,25]. As resistance training increases caloric expenditure, lean body mass and resting metabolic rate, it is an effective component of weight loss programs[26,27]. Resistance training improves physical fitness, performance, muscle size and strength as well as reduces body fat[28,29].

On the other hand, studies on the effect of resistance training on leptin and adiponectin in obesity have been limited and contradictory. For example, in a study on men with obesity, performing 12 weeks of resistance training for 3 days a week, reduced leptin levels, while no change in adiponectin was observed[25]. Also, in another study after 12 weeks of circular resistance training, no significant change in adiponectin was reported[30]. In the study of Praet *et al*., [31] after 10 weeks of interval resistance training for 2 days a week, there were no changes in leptin and adiponectin concentrations. In other studies circular resistance training was associated with an increase in adiponectin concentration[32,33].

Among the previous studies, the effect of different types of resistance training such as circular, traditional and interval on leptin and adiponectin levels has not been compared. In addition, there is no study to determine the effects of resistance training on the levels of Nrg4. Therefore, the purpose of this study was to compare 12 weeks of 3 types of resistance training including traditional, circular and interval on Nrg4, adiponectin and leptin in non-athletic men with obesity.

Material and method

Participants

Forty-four non athletic men with obesity, aged 18-34 years volunteered to participate in a 12-week study. Participants were randomly divided into equal number of 11 persons in 4 groups: 1) control, 2) circular resistance, 3) traditional resistance and 4) interval resistance training.

Inclusion criteria included men with obesity (body mass index above 30), aged from 18 to 34 years, with no experience of participating in regular exercise training. Exclusion criteria included any medical problems that affect the safety of the protocol prescribed to the participants, attendance in other training programs or physiotherapy courses at the same time with the study protocol that interfered with the effect of the study training program.

Procedure

After selecting 44 people with inclusion criteria as participants, they were examined by a physician to confirm that they had no serious health problem for attending the training sessions and then entered the study. Participants were then asked to complete a medical information questionnaire and signed a written consent form. They were then randomly divided into 4 groups. In the first session, complete explanations and procedures were given to the participants about the study and exercises and how to perform the exercises correctly. In the second session, the 1RM of each exercise was determined and was calculated using the Brzycki equation[34].

The intervention lasted 12 weeks. Data were collected before and after the intervention. Finally, statistical analysis was performed and the results were interpreted.

Anthropometric measurements

Body weight of participants was measured without shoes, and with the least clothing possible using an analytical scale (SECA, Germany, 707 1314004). Similarly height was measured with the barefoot participant stood completely flat with his heels, hips and head against the wall and his head parallel to the horizon using a wall mounded gauge. Body mass index was calculated as weight (kg) divided by height (meters) squared. Skinfold thickness was measured using a caliper, using a three-point method. Subcutaneous fat in the abdomen, chest and thighs was measured three times according to the instructions[35]. To determine body density, the mean measurements of skinfold thickness used in the Jackson and Pollock formulas[36]. Then the Siri formula was used to calculate the body fat percentage[37].

Exercise training programs

The training protocol consisted of 3 times of resistance training sessions per week, for 12 weeks. Resistance training in all groups consisted of 10 stations, which included 5 upper body and 5 lower body exercises which included squat, let pull down, leg press, bench presses, leg extension, shoulder press, leg curl, standing dumbbell curl, calf raise, and triceps extension. The resistance training programs were made by authors based on the several programs that were used in previous studies[38-40].

The first and last 10 minutes of each exercise session were dedicated to warming up and cooling down. Training intensity was 50 % of 1RM. It should be noted that at the end of every four weeks, 1RM was taken again and the intensity of the exercises was adjusted based on the new 1RM.

Traditional resistance training (TRT) consisted of 10 stations. In each station, the exercises were performed with 3 sets, 14 repetitions, 30 seconds rest between each set and with 50% 1RM.

Circular resistance training (CRT) consisted of 10 stations. In each station, exercises were performed with 3 sets, 14 repetitions, 5 minutes rest between each set, with 50% 1RM.

Interval resistance training (IRT) included 10 stations where the exercises were performed with 2 sets of 14 repetitions with 50% 1RM. Active rest time was 2 sets of 14 repetitions with 25% 1RM for each station. Exercise training protocols are listed in Table 1.

Table 1. Comparison of resistance training protocols.

Volume & Intensity	TRT	CRT	IRT
Session per week	3	3	3
Exercises	10	10	10
Sets	3	3	2
Repetitions	14	14	14
Intensity	50% of 1RM	50% of 1RM	50% of 1RM

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

Participants in control group did not perform any kind of specific exercise training during the time of intervention and they just had their regular life activity.

Blood sampling and analyses

Blood sampling was collected in two stages before and after 12 weeks of the resistance training intervention. The fasting blood sample was obtained 48 hours before and after the training period. Blood samples were taken from the right arm vein of the participants and then transferred to special test tubes for preparation of plasma (tubes containing EDTA) which were centrifuged for 10 minutes at 3000 rpm. The resulting plasma was stored at -70 ° C. It should be noted that all stages of the test were performed in the same and standard conditions from 8 to 10 a.m.

Biochemical analysis was performed to measure plasma level of Nrg4 using ELISA and commercial kits (ELISA kit, antibodies-online, Germany, Cat number: ABIN1571585). Plasma level of leptin was determined using ELISA and commercial kits (sandwich ELISA kit, BioVendor, Heidelberg, Germany, Cat. No. RD191001100). Plasma adiponectin was also analyzed using ELISA and commercial kits (ELISA kit, BioVendor, Czech Republic, Cat. No: RD195023100).

Statistical analysis

Descriptive statistics were used to describe the participants. The Shapiro -Wilk test was used to test normal distribution of data. Leven's test also was used to check the homogeneity of variance. The mixed-design ANOVA with repeated measure (groups [4] * time [2]) was used to examine intra-group and inter-group differences. Fisher's LSD post hoc test was used for pairwise comparison of groups. All analyzes were performed using statistical software SPSS version 25. The level of significant was considered equal or less than 0.05.

Results

Before testing the research hypotheses, the normality of the data distribution as well as the homogeneity of between groups variance were examined. The results showed that the distribution of data for all variables in the experimental and control groups was normal. Leven's test results also showed that the assumption of homogeneity of variance was assumed ($P>0.05$).

Changes in anthropometric variables

The demographic characteristics of the participants in the pretest and posttest evaluations are presented in table 2. Groups were homogeneous in terms of height, weight, fat percentage and Body mass index.

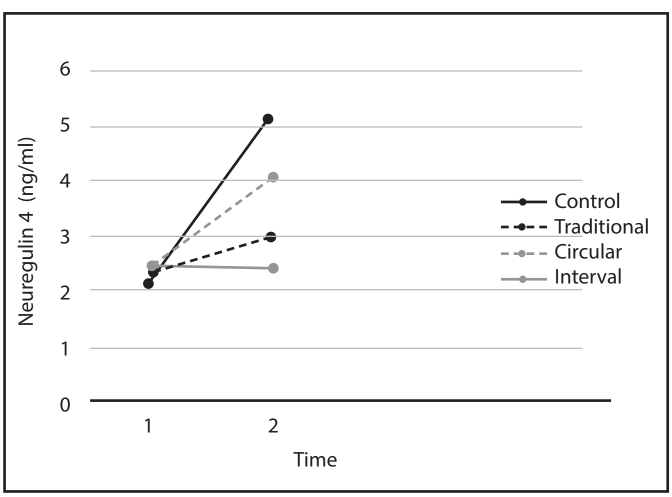
Plasma biochemistry

The results of mixed-design ANOVA showed that there was a significant interaction between the type of resistance training used and time on neuregulin 4 ($F (3, 40) = 80.22$, $P= 0.005$, $ES = 0.85$) (Figure1). Considering the main effect of time (pre vs. post), level of neuregulin

Table 2. Demographic characteristics of the participants in the pretest and posttest.

	Group	Pretest Mean	Pretest SD	Posttest Mean	Posttest SD	Sig
Age (year)	Traditional	25.8	2.6	-	0.94	
	Circular	26.3	4.1			
	Interval	26.5	2.7			
	Control	26.4	2.3			
Height (cm)	Traditional	169.1	2.7	-	0.32	
	Circular	167.2	2.6			
	Interval	168.2	1.7			
	Control	168.9	3.1			
Weight (kg)	Traditional	92.9	2.8	90.8	1.8	0.36
	Circular	92.4	1.9	88.8	1.6	
	Interval	93.7	1.9	87.0	2.1	
	Control	93.8	2.0	93.0	2.2	
Body mass index (kg/m^2)	Traditional	32.4	1.4	31.7	0.8	0.62
	Circular	33.0	1.2	31.7	1.2	
	Interval	33.1	0.7	30.7	0.9	
	Control	32.9	1.4	32.6	1.4	
Percentage of body fat (%)	Traditional	29.6	0.7	28.5	0.8	0.14
	Circular	29.9	1.1	27.2	0.8	
	Interval	30.4	1.0	26.8	1.0	
	Control	30.5	1.0	30.5	1.1	

Figure 1. Intragroup changes in nrg4 level in pretest and posttest.



4 (F (1, 40) = 315.80, P = 0.005, ES = 0.88) was significantly increased after the training. In addition, considering the main effect of groups, the findings showed that there was a significant difference between resistance training groups and control group in neuregulin 4 (F (1, 40) =41.31, P=0.005, ES = 0.75). Post hoc analysis further indicated that there was also a significant difference in neuregulin 4 in all 4 groups compared to each other (P<0.05). The increase in neuregulin 4 level was greater for the IRT group compared to the other groups (see Table 3).

Also, the results of mixed-design ANOVA on adiponectin showed that there was a significant interaction between the type of resistance training used and time (F (3, 40) = 12.44, P= 0.005, ES = 0.48) (Figure 2). Considering the main effect of time (pre vs. post), level of adiponectin (F (1, 40) = 70.95, P = 0.005, ES = 0.63) was significantly increased after the training. In addition, considering the main effect of groups, the findings showed that there was a significant difference between resistance training groups and control group in adiponectin (F (1, 40) =15.08, P=0.005, ES = 0.53). The results of post hoc test showed that there is no significant difference between the comparison pair of the CRT group with the TRT group (P=0.145) and the IRT group (P=0.252), but there is a significant difference in the comparison pair of other groups with respect to each other (P<0.05).The increase in adiponectin level was greater for the IRT group compared to the other groups (see Table 3).

Regarding the plasma level of leptin, the results of mixed-design ANOVA showed that there was a significant interaction between the

Figure 2. Intragroup changes in adiponectin level in pretest and posttest.

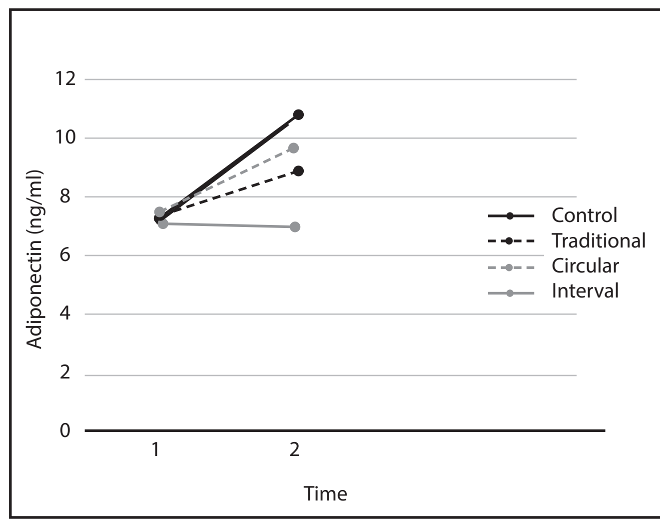


Figure 3. Intragroup changes in leptin level in pretest and posttest.

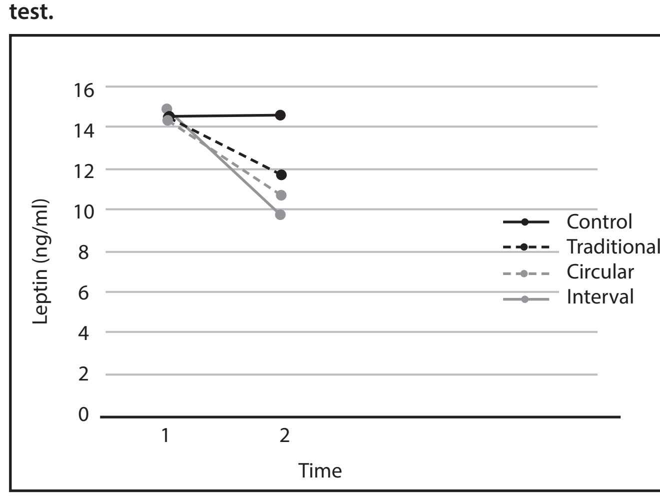


Table 3. Pairwise comparisons of outcomes among study groups using LSD test.

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Neuregulin 4	Control	Traditional	-.24	.052	-.48	.00
		Circular	-.79*	.000	-1.03	-.55
		Interval	-1.21*	.000	-1.45	-.96
	Traditional	Control	.24	.052	-.00	.48
		Circular	-.55*	.000	-.79	-.31
		Interval	-.97*	.000	-1.21	-.72
	Circular	Control	.79*	.000	.55	1.03
		Traditional	.55*	.000	.31	.79
		Interval	-.41*	.001	-.66	-.17
	Interval	Control	1.21*	.000	.96	1.45
		Traditional	.97*	.000	.72	1.21
		Circular	.41*	.001	.17	.66
Adiponectin	Control	Traditional	-1.11*	.001	-1.73	-.50
		Circular	-1.56*	.000	-2.18	-.95
		Interval	-1.92*	.000	-2.53	-1.30
	Traditional	Control	1.11*	.001	.50	1.73
		Circular	-.45	.145	-1.06	.16
		Interval	-.80*	.012	-1.42	-.19
	Circular	Control	1.56*	.000	.95	2.18
		Traditional	.45	.145	-.16	1.06
		Interval	-.35	.252	-.96	.26
	Interval	Control	1.92*	.000	1.30	2.53
		Traditional	.80*	.012	.19	1.42
		Circular	.35	.252	-.26	.96
Leptin	Control	Traditional	1.51*	.000	.99	2.03
		Circular	1.97*	.000	1.45	2.48
		Interval	2.32*	.000	1.81	2.84
	Traditional	Control	-1.51*	.000	-2.03	-.99
		Circular	.45	.083	-.06	.97
		Interval	.81*	.003	.29	1.33
	Circular	Control	-1.97*	.000	-2.48	-1.45
		Traditional	-.45	.083	-.97	.06
		Interval	.35	.169	-.15	.87
	Interval	Control	-2.32*	.000	-2.84	-1.81
		Traditional	-.81*	.003	-1.33	-.29
		Circular	-.35	.169	-.87	.15

*The mean difference is significant at the 0.05 level.

type of resistance training used and time ($F(3, 40) = 27.53$, $P = 0.005$, ES = 0.67) (Figure 3). Considering the main effect of time (pre VS. post), level of level of leptin ($F(1, 40) = 191.44$, $P = 0.005$, ES = 0.82) was significantly reduced after the training. In addition, considering the main effect of groups, the findings also showed that there was a significant difference between resistance training groups and control group in leptin ($F(1, 40) = 32.05$, $P = 0.005$, ES = 0.70). The results of post hoc test further showed that there is no significant difference between the comparison pair of the CRT group with the TRT group ($P = 0.083$) and the IRT group ($P = 0.169$), but there is a significant difference in the comparison pair of other groups with respect to each other ($P < 0.05$). The increase in leptin level was greater for the IRT group compared to the other groups (see Table 3).

Discussion

The purpose of this study was to compare three types of resistance training including traditional, circular and interval in non-athletic men with obesity in comparison to a control group for neuregulin 4 , adiponectin and leptin responses. The findings indicated that after all types of resistance training the plasma levels of neuregulin 4 and adiponectin increased and the plasma level of leptin was decreased. Interval training showed superior effects on all study outcomes followed by circular and traditional training, respectively.

New findings suggest that in obesity, Nrg4 expression is significantly down regulated[10]. More specifically, Nrg4 mRNA levels are inversely related to body fat percentage and liver fat content[41]. Consistent with the research of Wang *et al*.,[41] in the present study, a decrease in body fat percentage and body weight and an increase in plasma Nrg4 levels were significantly caused following resistance training. The results of the present study also confirmed the hypothesis that Nrg4 is improved through exercise training[23]. According to previous studies, circulating concentration of Nrg4 or Nrg4 mRNA levels are inversely related to body fat mass in obese people[42,43]. In the present study, a significant reduction in participants' body fat percentage could be a justification for the increase in Nrg4 after resistance training. Also, studies have shown that norepinephrine, which increases after resistance training, leads to Nrg4 overexpression[19].

The present findings also indicated that 12 weeks of three types of resistance training increased adiponectin level significantly. In agreement with us, other researchers have shown a significant increase in adiponectin levels after resistance training[32,33,44].

After 8 weeks of resistance training in overweight men adiponectin increased significantly[33]. There was also a significant increase in adiponectin after 10 weeks of circular resistance training in obese men, in which some features of the training protocol and the characteristics of the participants were similar to the present study[32]. On the other hand, the results of the present study are inconsistent with other studies in which no change in adiponectin levels was observed[25,30]. Possible reasons for inconsistency between studies include differences in participants' characteristics such as age, gender, health status, body weight and body composition as well as training protocol characteristics, such as duration and intensity of intervention.

The mechanism of the effect of training on adiponectin levels is not fully understood. In the present study, a significant decrease was observed in the mean body mass index and body fat percentage of the participants after resistance training. Resistance training increases protein synthesis in the muscles, which in turn increases resting energy expenditure and consequently reduces body fat percentage[45]. Since body fat percentage is inversely related to adiponectin levels[46], so this can be considered as a reason for increasing plasma adiponectin. Also, decrease in body mass index has been associated with adiponectin levels[47]. Catecholamines can also be involved in changes in adiponectin following exercise training. In this way exercise stimulates the sympathetic nervous system, which leads to the release of the hormones epinephrine and norepinephrine, which cause lipolysis[48,49]. In addition, exercise training may affect adiponectin mRNA expression by reducing interleukin-6 following adipose tissue reduction[50,51].

In addition the present findings suggest that 12 weeks of three types of resistance training decreased leptin level significantly. The findings of the present study are in line with some previous studies[25,52,53]. After 8 weeks of interval resistance training on men with overweight, leptin decreased significantly[52]. In this study, in line with the present study, body mass index, weight and body fat percentage of the participants were significantly reduced. Also leptin decreased after 6 months of resistance training in men with overweight in low, moderate and high intensity groups, which was associated with a decrease in body mass index[53]. It has also been reported that after 3 months of resistance training on men with obesity, plasma leptin levels decreased significantly by 21% after training[25].

Whereas, there are studies that their findings are inconsistent with the present study[54,55]. Ara *et al*.,[54] showed that after 6 weeks of resistance training, the serum leptin concentration did not change significantly in men, which can be attributed to the short duration of exercise training intervention. According to research, short-term training has no significant effect on leptin levels, while long-term training causes a significant decrease in leptin, which is probably due to the weight loss and adipose tissue reduction with long-term training[56].

The mechanism of the effect of training on leptin levels is not known exactly. Resistance training causes a significant increase in blood lactate, which can be due to increased glycogenolytic activity and a decrease in muscle glycogen stores, and may eventually reduce leptin secretion[57,58]. Also leptin levels may be related to body composition, weight loss, body mass index, and body fat distribution[49]. Resistance training impacting the secretion of leptin in obese people by reducing fat mass, increasing muscle mass and energy expenditure at rest[45,53]. Moreover, similar to adiponectin, catecholamines may also cause a decrease in leptin[49].

Based on our finding, research on the effect of resistance exercise on Nrg4 has received less attention, so investigating the effect of resistance exercise on Nrg4 in the present study can provide new information to researchers in this field. Also, based on the researcher's findings the effect of these three types of resistance training on Nrg4, leptin and adiponectin has not been studied in a joint study. Therefore, these points can be considered as strengths for this research.

A major limitation of the present study was that it was not possible to accurately control the participants' diets, which could affect changes in adipokines. In addition, it was not possible for researchers to research more samples as well as more frequent measurements due to financial constraints. There was also a limit to the research background on the effect of training on Nrg4, which made it difficult to compare and discuss.

Conclusion

In conclusion, the results of the present study showed that 12 weeks of traditional, circular and interval resistance training in non-athlete men with obesity caused a significant decrease in leptin levels and a significant increase in Nrg4 and adiponectin. Interval training showed superior effects on all study outcomes followed by circular and traditional training, respectively. Considering the benefits that changes in circulating adipokines can have on health conditions, it is recommended that obese people use such resistance training, especially interval resistance training as a non-invasive, low-cost method with no side effects in order to promote health and weight loss.

Acknowledgments

This work has been written based on the results obtained from Mona Alizadeh's Master thesis at Tarbiat Modares University.

Conflict of interest

The authors do not declare any conflict of interests.

Ethical standard

Study protocol and procedures were approved by the ethics committee of Faculty of Medicine, Tarbiat Modares University (Ethical code: IR.MODARES.REC.1398.178); informed consent was obtained and signed by all subjects on the day of testing.

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