Original Article

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The effects of circuit resistance training on plasma progranulin level, insulin resistance and body composition in obese men

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Abstract:
Background: Progranulin (PGRN) is implicated in obesity and insulin resistance (IR). The aim of this study was to evaluate the effects of 8 weeks of circuit resistance training (CRT) on plasma PGRN, IR and body composition in obese men.
Materials and methods: Twenty-eight healthy obese men [age: 36 ± 7.7 years, body weight (BW): 96.4 ± 15.6 kg, body mass index (BMI): 32.4 ± 4.5 kg/m^2] completed the study. Subjects were randomly assigned to two groups of control and training. Subjects in the training group underwent training for 8 weeks, 3 times a week. Blood samples and anthropometric characteristics were taken before the commencement of the exercise protocol and 72 h after the last training session. The homeostatic model assessment of insulin resistance (HOMA-IR) was used to measure IR.
Results: BW, BF%, BMI, waist-hip ratio (WHR), HOMA-IR and plasma PGRN levels except lean body mass (LBM) were significantly reduced in the training group ($p < 0.05$). Additionally, except for LBM, subjects in the training group had significantly decreased BW, BF%, BMI, WHR, HOMA-IR and plasma PGRN levels compared to changes in those in the control group ($p < 0.05$). Significant correlations were found between the changes in plasma PGRN and the changes in insulin, HOMA-IR and BMI ($p < 0.05$).
Conclusions: The findings showed that 8 weeks of CRT improved body composition and IR which were accompanied by reduced plasma PGRN levels. This study suggests that CRT has the potential for obese individuals to counteract obesity-associated health impairments.

Keywords: body composition, circuit resistance training (CRT), insulin resistance, obesity, progranulin (PGRN)
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Introduction

Obesity creates a chronic systemic low-grade inflammation, which is considered as one of the pathogenic factors for insulin resistance (IR) [1]. During obesity, adipose tissue (AT) as a metabolically active endocrine organ is accounted for the pathogenesis of IR [2]. AT-derived hormones collectively called adipokines are involved in the development of IR [3]. Progranulin (PGRN), a novel inflammatory adipokine, is implicated in obesity and IR. PGRN is an obesity-induced inflammatory adipokine contributing to AT IR. Moreover, hyperprogranulinemia is involved in the pathogenesis of systemic obesity-associated IR [4]. Therefore, excess AT reduction and the improvement in abnormal adipokine secretion seem to be important strategies for the prevention of obesity-related diseases. Regular exercise training has long been shown to reduce low-grade inflammation and to improve IR [5]. Exercise training primarily improves IR through decreases in adipocyte size (AT) induced by an increase in AT lipolysis. Moreover, a reduced (smaller) AT is known to have a reduced secretome of inflammatory adipokines [6]. Studies regarding the effects of chronic resistance exercise training on AT secretome in humans, obese individuals in particular, are under-studied. Available evidence shows the potential of chronic resistance training for alleviating obesity-induced systemic low-grade inflammation by reducing two major

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pro-inflammatory adipokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in obese individuals [7]. However, there are other adipokines which has not yet been investigated in this context. Although being implicated in obesity, yet, PGRN response to a weight-loss exercise program has not been elucidated in obese individuals. Obese people are often prescribed aerobic programs with little regard to resistance training (RT), whereas RT is a major component in a weight-loss program [8]. RT has been shown to provide many benefits including body composition and IR to obese people [9]. Circuit resistance training (CRT), which keeps the heart rate elevated during the training session [10], has been reported to have concomitant effects on LBT and body fat mass (FM) [11], [12] and is also known as a time-efficient exercise modality, is highly recommended for weight management and weight loss in obese individuals [12]. Given that circulating PGRN concentration is increased in obesity and hyperprogranulinemia is involved in the pathogenesis of obesity-associated IR, we hypothesized that CRT-induced possible improvements in body composition and IR would be accompanied by improvements in plasma PGRN levels in obese men. So, this study was conducted to evaluate the effects of 8 weeks of CRT on plasma PGRN, body composition and IR index [homeostatic model assessment of insulin resistance (HOMA-IR)] in response to a weight-loss training program in obese men.

Materials and methods

Participants and study design

This study was approved by the Ethics Committee of the University of Mazandaran with the code IR.UMZ.REC.1398.007 on the date 17/06/2019. The date cited in the code is in terms of solar calendar which is equivalent to the date of 17/06/2019. The participants were gathered through the distribution of announcements at both university and dormitory. Sixty male college students enrolled for the study. Based on health/medical questionnaire, 28 healthy subjects [age: 36 ± 7.7 years, body weight (BW): 96.4 ± 15.6 kg, body mass index (BMI): 32.4 ± 4.5 kg/m^2] had the medical qualifications to fulfill the study. All the participants were included in the study after taking their informed signed consent and filling out their questionnaire of health records. To qualify for the study, the participants had to meet some criteria, including no records of regular physical activity over the past 6 months, having no symptoms of metabolic and cardiovascular diseases and following no specific diet or weight-loss program over the past 3 months. The participants were also not allowed to smoke and take drugs during the study. After doing a general assessment, the participants were assigned to two equal groups of control (C, n = 14) and CRT (n = 14). They were required to stick to their typical diet throughout the study. The control group did not undergo any training in the entire study, and was simply assessed at pre-and post-training periods. They were also required not to take part in any regular physical activity in the period of study. The study was of 8 weeks' duration. The variables of the study were measured at two time points, once before the onset of the study and once at the end of the 8-week period.

Training protocol

A one-session familiarization course was taken for the subjects of the training group at the gym to get familiarized with exercise equipment and to practice correct exercise techniques in order to prevent possible injuries. The CRT was of 8 weeks' duration, 3 times a week. The participants had to complete three circuits in each session, with 12 stations (exercises) per circuit and 8–10 repetitions per station (exercise). The training intensity was considered 50% of one repetition maximum (1-RM) in the first week. In the next weeks, the training intensity was gradually increased by 85% of 1-RM (a weekly increase by 5–10% 1-RM). In the last 3 weeks, training intensity was fixed, with 80–85% of 1-RM. The rest intervals between stations and circuits were 30–60 s and 2–3 min, respectively. The stations, in order, were chest press, leg extension, leg flexion, seated cable row, military press, barbell curl, seated triceps press, leg press, dumbbell flyes, sit-up, barbell squat and barbell incline bench press. The participants had a 15-min warm-up and a 10-min cool down in each training session. Each training session lasted nearly 80 min. The Brzycki regression equation was used to calculate a 1-RM, where 1-RM = weight lifted during an RM/[1.0278 − 0.0278 (n)]. To adjust the training load for each exercise, the 1-RM test was repeated in the onset of both the 4th and 8th weeks.

Anthropometric testing and blood analyses

BMI was calculated by dividing BW in kilograms by height in square meters. Body fat percent (BF%) was also calculated using Jackson and Pollock's three-point equation via measuring skin folds at three points (triceps

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brachii, abdomen and thigh). The lean body mass (LBM) was calculated by subtracting FM from BW (LBM = BW − FM). Waist-hip ratio (WHR) measurement was calculated as waist measurement divided by hip measurement. Blood samples were taken from the antecubital vein in a 10-h fasting state at two time points: once 2–3 days prior to the first exercise session (pre-training) and once 72 h after the last exercise session (post-training). The taken blood samples were centrifuged at 4 °C and the resultant plasma samples were stored at −20 °C for analysis. Plasma PGRN concentrations were measured using an enzyme-linked immunosorbent assay (ELISA; Cusabio Inc., China). The PGRN kit sensitivity was 1.7 ng/mL, and its coefficient of variation was 3.44%. Plasma insulin concentrations were also determined by ELISA (Mercodia Inc., Sweden). The insulin kit sensitivity was 1 μU/mL, with a coefficient of variation of 1.2%. Plasma glucose concentrations were measured using the glucose oxidase method (Pars Azmun Inc., Iran). Hematocrit values were measured using an automatic cell counter machine (K 1000 model, USA). Plasma volume variations (PVV% or %ΔPV) were calculated using hematocrit values according to Van Beaumont's formula: %ΔPV = 100 × [(Ht1 − Ht2)/(Ht2 × (100 − Ht1)] [13]. Also, the corrected plasma PGRN (PGRNc) variations were calculated using the formula: PGRNc = (PGRN × 100) ÷ (100 − ΔPV) [13]. Insulin resistance was measured via the formula: fasting plasma glucose (mmol/L) × fasting serum insulin (μU/mL)/22.5.

Statistical analysis

The normalcy of data was tested using the Kolmogorov-Smirnov test. Within- and inter-group changes were tested using a paired t-test and analysis of covariance (ANCOVA), respectively. Statistical analyses were done using the SPSS software version 16. The significance level was set at $\alpha \leq 0.05$. Data are presented as mean ± standard deviation (SD).

Results

The anthropometric characteristics of both groups are summarized in Table 1. A paired t-test was conducted to compare the pre- and post-training values of the variables in each group. Except for LBM (p = 0.17, Δ + 0.5%), BW (p = 0.025, Δ − 2.25%), BF% (p = 0.011, Δ − 4.45%), body mass index (BMI) (p = 0.018, Δ − 2.25%) and WHR (p = 0.014, Δ − 3.16%) were significantly reduced in the training group. Additionally, a one-way ANCOVA was conducted to compare the effectiveness of training whilst controlling for pre-training values of variables. Levene's test and normality checks were carried out and the assumptions met for all the variables. One-way ANCOVA results showed that there are significant differences for BW [F(1, 25) = 6.82, p = 0.016], BF% [F(1, 25) = 10.96, p = 0.003], BMI [F(1, 25) = 8.73, p = 0.010] and WHR [F(1, 25) = 5.563, p = 0.005] between the groups.

Table 1: Anthropometric changes over an 8-week training period in the control and training groups.

Variables	Groups	Pre-training	Post-training	%Δ[a]	p-Values[b]	p-Values[c]	ES[d]
BW, kg	Control	99.8 ± 20	99 ± 19.3	−0.8%	0.75	0.016[f]	0.21
	Training	93 ± 8.80	90.9 ± 8[e]	−2.25%	0.025[e]		
BMI, kg/m^2	Control	33.7 ± 5.8	33.4 ± 5.5	−0.9%	0.28	0.010[f]	0.24
	Training	31 ± 2.20	30.3 ± 2.0[e]	−2.25%	0.018[e]		
BF%	Control	30.2 ± 5.4	30.1 ± 5.3	−0.33%	0.33	0.003[f]	0.31
	Training	27 ± 3.0	25.8 ± 2.9 [e]	−4.45%	0.011[e]		
LBM, kg	Control	67.24 ± 2.9	66.93 ± 2.8	−0.45%	0.25	0.11	0.17
	Training	67.85 ± 2.1	68.20 ± 2.4	+0.5%	0.36		
WHR	Control	0.98 ± 0.07	0.99 ± 0.09	+1%	0.14	0.005[f]	0.29
	Training	0.95 ± 0.11	0.92 ± 0.06 [e]	−3.16%	0.014[e]		

BW, body weight; BMI, body weight index; BF%, body fat percentage; LBM, lean body mass; WHR, waist-hip ratio.
[a]Δ, post-training vs. pre-training values (%).
[b]Paired t-test.
[c]ANCOVA test (between-group differences).
[d]Size effect.
[e]p < 0.05 compared post- and pre-training values (paired t-test).
[f]p< 0.05 compared between-group differences controlling for pre-training values (ANCOVA test).

Table 2 shows the metabolic, hematological and plasmatic variations of variables. The t-test results showed significant differences between pre- and post-training values for insulin (p = 0.001, Δ − 18.7%), HOMA-IR (p

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= 0.008, Δ − 14.1%) index, hematocrit (p = 0.009, Δ + 2.3%) and PGRN (p = 0.002, Δ − 19.4%) in the training group. Also, the one-way ANCOVA results showed significant differences for insulin [F(1, 25) = 7.62, p = 0.011], HOMA-IR [F(1, 25) = 6.30, p = 0.019] and PGRN [F(1, 25) = 4.70, p = 0.040].

Table 2: Metabolic, hematological and plasmatic changes over an 8-week training period in the control and training groups.

Variables	Groups	Pre-training	Post-training	%Δ[a]	p-Values[b]	p-Values[c]	ES[d]
Glucose, mmol/L	Control	4.15 ± 0.53	4.21 ± 0.57	1.44%	0.680	0.639	0.009
	Training	4.06 ± 0.27	4.18 ± 0.26	2.95%	0.720		
Insulin, μU/mL	Control	8.50 ± 0.29	8.90 ± 3.2	4.7%	0.069	0.011[f]	0.24
	Training	9.10 ± 3.20	7.40 ± 3.5[e]	−18.7%	0.001[e]		
HOMA-IR	Control	1.59 ± 0.61	1.74 ± 0.63	9.4%	0.076	0.019[f]	0.20
	Training	1.63 ± 0.56	1.40 ± 0.67[e]	−14.1%	0.008[e]		
Hematocrit, %	Control	46.07 ± 2.88	46.43 ± 3.29	0.78%	0.519	0.30	0.043
	Training	45.94 ± 2.11	47.0 ± 2.43[e]	2.3%	0.009[e]		
PVV, %	Control				−0.014%	0.273	0.046
	Training				−0.042%		
PGRN, ng/mL	Control	242.22 ± 86.57	239.11 ± 80.42	−1.28%	0.855	0.040[f]	0.16
	Training	256.17 ± 60.92	206.46 ± 55.18	−19.40%	0.002[e]		
PGRNc, ng/mL	Control	239.07 ± 81.95	−1.30%	0.855	0.040[f]	0.06	
	Training	206.50 ± 49.84	−19.38%	0.002[g]			

PVV, plasma volume variation; PGRN, progranulin; PGRNc, corrected progranulin for PVV.
[a]Δ, post-training vs. pre-training values (%).
[b]Paired t-test.
[c]ANCOVA test (between-group differences).
[d]Size effect.
[e]p < 0.05 compared post- and pre-training values (paired t-test).
[f]p < 0.05 compared between-group differences (ANCOVA test).
[g]p< 0.05 compared PGRNc and pre-training PGRN values (paired t-test).

Moreover, having been suggested to take into account when comparing the changes in blood measurements [13], plasma volume variations (ΔPV%/PVV%) were taken into account using hematocrit changes in each group. PVV% showed insignificantly decreased volumes for both the control (−0.014% ≈ zero percentage) and training (−0.042% ≈ zero percentage) groups. As the PGRN variable was the major variable in this study, we assessed its within- and inter-changes controlling for ΔPV% as a new variable called corrected PGRN (PGRNc). The PGRNc values were almost the same as the post-training PGRN values in each group, and were not statistically different (Table 2). Moreover, we assessed the associations of PGRN with anthropometric, metabolic and ΔPV% using the Pearson correlation test. Significant and positive correlations between the changes in plasma PGRN, HOMA-IR and BMI were observed (Table 3).

Table 3: Association of PGRN's changes with metabolic, anthropometric and plasma volume changes.

	Control (n = 14)	Training (n = 14)	Total (n = 28)
Fasting glucose			
r	0.044	0.349	0.172
p	0.882	0.222	0.381
Fasting insulin			
r	0.084	**0.773[a]**	**0.821[a]**
p	0.775	**0.044**	**0.021**
HOMA-IR			
r	0.057	**0.738[a]**	**0.854[a]**
p	0.847	**0.044**	**0.037**
BMI			

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r	0.044	**0.841[a]**	**0.911[a]**
p	0.881	**0.018**	**0.011**
BF%			
r	0.052	0.450	0.057
p	0.860	0.106	0.772
Lean body mass (LBM)			
r	0.068	0.060	0.058
p	0.712	0.580	0.452
PVV%			
r	0.211	−0.110	0.096
p	0.469	0.709	0.628
WHR			
r	0.054	0.249	0.182
p	0.782	0.122	0.487

Bolded values indicate on statistical significance.
[a] Correlation is significant at the 0.05 level (two tailed).

Discussion

The present study assessed the effects of 8 weeks of CRT on the plasmatic levels of adipokine PGRN, IR index and body composition components in obese men. The findings showed that 8 weeks of CRT decrease the circulating PGRN levels and improve IR and body composition in obese men. Considering white adipose tissue (WAT) as a metabolically active endocrine organ, it secretes substances, collectively called adipokines, whose expression and secretion are dysregulated in the expanded WAT during obesity [14]. Obesity-induced dysregulated adipokine production has been shown to cause IR, which is the pathogenesis of diabetes [14]. It is established that there is an inverse relationship between physical activity and pro-inflammatory adipokine secretion in obesity [15]. One of the mechanisms through which exercise training exerts its anti-inflammatory effects is to decrease the secretion of pro-inflammatory adipokine secretion [16], [17], [18]. Contrary to a single bout of RT, chronic resistance exercise training due to adaptation to training leads to reduced plasma pro-inflammatory adipokines at rest and as a response to exercise [19]. In the study by El-Kader, 12 weeks of RT (3 times per week, 60–80% 1-RM) significantly reduced circulating IL-6 and TNF-α in obese individuals with type 2 diabetes [20]. In another study, 16 weeks of RT (3 times per week, 60–85% 1-RM) significantly reduced plasma IL-6 and TNF-α in obese adolescents [7]. Regarding PGRN, to the best of our knowledge, the response of PGRN to a weight-loss resistance exercise training has not been elucidated in obese individuals. A study by Youn et al. reported that 4 weeks of an intensive combined exercise training significantly reduced serum PGRN levels in type 2 diabetes subjects [21]. Our result also showed that 8 weeks of chronic circuit resistance exercise training (3 times per week, 50–85% 1-RM) significantly decreased plasma PGRN levels in obese men. Altogether, these findings propose that chronic RT has the potential to alleviate obesity-induced systemic inflammation. Despite the differences in study samples (e.g., age, diseases, adipokines), type of RT protocols (e.g., traditional, circuit) and various protocol components (e.g., intensity, volume, duration of intervention), CRT seems to be a good strategy to combat obesity-related inflammation.

Additionally, we evaluated the effects of 8 weeks of CRT on two other variables, e.g. body composition components and IR index in obese men. CRT is one form of RT in which a subject moves from exercise to exercise with little rest, which leads to an elevated heart rate, increased physiological stress and a time-efficient modality of exercise [10]. Body composition represents human body features such as BW, BMI, BF% and LBM. Data regarding the effects of CRT in obese individuals are sparse. The study by Kolahdouzi et al. reported that 8 weeks of CRT improved body composition by significantly decreasing BW, BMI and WHR in obese men [22]. However, in the study by Franklin et al., it was reported that 8 weeks of CRT had no effect on BW, BMI, WHR and BF% in obese women [23]. In the study by Miller et al., 4 weeks of high-intensity CRT improved body composition parameters via significant reductions in BF%, fat tissue% and increases in LBM% in sedentary obese men [24]. Several meta-analysis studies represent that circuit training effectively decreases BW and BMI in overweight and obese individuals [25], [26]. The problem with those studies is that different circuit training, including circuit aerobic, interval and combined (aerobic plus resistance) training, had been analyzed in overweight and obese individuals than CRT alone. Our circuit training also showed that 8 weeks of CRT improve body composition via significantly decreasing BW, BMI, WHR and BF% in obese men. Due to limited literature in this context, more studies are needed to confirm these findings in obese individuals.

Additionally, RT is known for increasing muscle mass (LBM), which is a key factor in weight reduction and improving body composition [27]. In our study, 8 weeks of CRT had no effect on LBM in obese men. This result

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is in line with the study by Kim et al., who reported that 12 weeks of regular CRT had no effect on LBM in obese people [28]. However, Liao et al.'s study showed that exercise could significantly increase LBM in obese people [29]. Recently, Schonfeld et al. showed that training volume (sets × reps × load) is a vital factor in promoting muscle mass and suggested a clear dose-response relationship between number of sets and hypertrophy [27]. Therefore, training volume implemented in our study might have a contributing role in not increasing LBM. In addition to training volume, these different findings might be due to the other components of CRT including duration, intensity and interval rests.

As RT has been shown to exert positive effects on body composition (increase in muscle mass and decrease in body fat), it might affect the anti-inflammatory effects of exercise and might contribute to interpretation of the anti-inflammatory effects of RT [30], [31]. In this regard, previous studies have reported positive correlations between circulating PGRN levels, BMI and BF% [21], [32], [33], [34]. Youn et al. reported that 4 weeks of a weight-loss combined exercise program significantly reduced serum PGRN levels in type 2 diabetes subjects [21]. In that study, the authors claimed that the decreased circulating PGRN levels are regulated by improvements in body composition in individuals with type 2 diabetes. Recently, the study by Kolahdouzi et al. also underlined that CRT could affect adipokine secretion via improvements in body composition in obese individuals [22]. In our study, we also found significant correlations between changes in plasma PGRN levels and changes in BMI ($r = 0.911$, $p = 0.011$, Table 3) in obese men. These data may suggest that the exercise training-induced inflammation improvement in obese individuals might be interpreted by exercise training-induced body composition improvements.

Another variable measured in this study was the IR index in obese men. There is evidence indicating that RT has the potential to counteract metabolic dysfunction in obese individuals [35], [36]. Previous findings suggest that 2–3 weekly RT for 8–26 weeks improve insulin sensitivity by 10–48% [37], [38], [39]. In line with those studies, our study also suggests that 8 weeks of CRT improve IR by 14% in obese men. In the present study, the IR index (HOMA-IR) improved in response to 8 weeks of CRT by means of reducing fasting insulin levels, while fasting glucose levels were not changed in response to 8 weeks of CRT in obese men. Nikseresht et al. reported that 12 weeks of RT reduced fasting HOMA-IR via reductions in fasting insulin levels in sedentary obese, middle-aged individuals [40]. In the study by Miller et al., 4 weeks of high-intensity RT improved HOMA-IR via significantly reducing fasting insulin levels, whereas had no effect on fasting glucose levels in sedentary obese males [24]. Exercise-induced increased insulin sensitivity is attributed to the increased glucose transporter type 4 (GLUT4) and other signaling proteins [41]. RT has also been reported to improve IR by promoting the concentration, activity and/or sensitivity of GLUT4, insulin receptors and signaling proteins [42]. In addition, increases in LBM from RT may contribute to the improved IR because skeletal muscle is responsible for the uptake of glucose to produce energy needed during exercise [42]. However, mechanisms by which RT increases glucose uptake are attributed to RT-induced intramuscular adaptations including increased GLUT4 and other signaling proteins and/or RT induced-increased LBM [43]. Molsted et al. [44] reported improvements in fasting insulin in patients with type 2 diabetes who had no increase in muscle mass, while Mavros et al. [45] reported that the improvements in HOMA-IR in older patients with type 2 diabetes were associated with changes in skeletal muscle mass. In our study, RT-induced improvements in HOMA-IR were accompanied by reductions in fasting insulin levels in obese men who had no increased LBM. Therefore, the influence of changes in muscle mass in improving IR through resistance exercise requires further elucidation.

Obesity-induced inflammatory alterations in AT, caused by dysregulated expression of inflammation-related adipokines, contribute to the development of IR [14]. Upregulation of PGRN during obesity contributes to local and systemic IR [46]. Significant correlations between circulating PGRN levels and HOMA-IR have been reported in obese and diabetic individuals [32], [33], [47]. Animal studies also show that PGRN-deficient mice have smaller adipocyte size, lower insulin concentrations and better glucose tolerance [48]. These data indicate that PGRN contributes to obesity and obesity-associated IR. In the present study, we found positive and significant correlations between the changes in plasma PGRN and those in fasting insulin levels ($r = 0.773$, $p = 0.044$, Table 3) and HOMA-IR ($r = 0.738$, $p = 0.044$, Table 3) in response to 8 weeks of training. It seems that circuit exercise training like CRT is an apt strategy to counteract obesity-induced inflammation in obese subjects.

There are some limitations to be considered in the current research. There are limited data regarding the adipokine PGRN in response to exercise interventions that emphasizes the necessity for more researches into this adipokine. Furthermore, given that PGRN is also regulated by dietary interventions, it makes it necessary to compare the effects of a weight-loss exercise intervention with a dietary intervention on PGRN in obese individuals. In the present study, the dietary intakes of the participants were not monitored, and they were simply asked to have their routine dietary regimens. Additionally, it was not possible for us to fully control the amount of physical activity levels of the participants in the control group. Nevertheless, they were required not to participate in any exercise training and to have only their daily routine activities as much as possible. Finally, future studies should measure physical performance-related factors including maximal oxygen consumption (VO_{2max}) and muscle strength to more effectively confirm the training effect in obese individuals.

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Conclusion

In conclusion, the findings showed that 8 weeks of CRT improved body composition and IR which were accompanied by reduced plasma PGRN levels. This study suggests that CRT has the potential for obese individuals to counteract obesity-associated health impairments. This study might also underline that improving obesity-associated complications like adipokines' abnormal secretion and IR could be ameliorated by improvements in body composition.

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Author statement

Ethical approval: This study was approved by the Ethics Committee of the University of Mazandaran with the code IR.UMZ.REC.1398.007.

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Informed consent: The written informed consent about volunteering was received from all the participants.

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