



Contents lists available at ScienceDirect

Journal of Exercise Science & Fitness

journal homepage: www.elsevier.com/locate/jesf

The effects of aerobic, resistance, and combined exercises on the plasma irisin levels, HOMA-IR, and lipid profiles in women with metabolic syndrome: A randomized controlled trial

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ARTICLE INFO

Article history:

Received 13 May 2020

Received in revised form

16 June 2020

Accepted 17 June 2020

Available online 20 June 2020

Keywords:

Metabolic syndrome

Irisin

HOMA-IR

Exercise program

Insulin

Aerobic

Resistance

ABSTRACT

Background/objective: Irisin is suggested to be an exercise beneficial effects mediator. This study aimed to examine the effects of the aerobic exercise (AE), resistance exercise (RE), and combined exercise (CE) on the plasma levels of irisin and some metabolic and anthropometric indices.

Methods: Sixty overweight women with metabolic syndrome were assigned equally into four groups: AE, RE, CE, and control. The study variables were measured before and 24 h after the intervention period.

Results: None of the study groups showed statistically significant changes in the serum irisin. However, muscle mass significantly increased in the RE and CE groups. Also, a significant decrease was observed in the body fat percentage in all groups. In addition, compared with the control group, the homeostatic model assessment of insulin resistance in the AE ($p = 0.021$), RE ($p = 0.039$), and in the CE ($p = 0.003$) groups reduced significantly. According to the analysis of indices' changes, serum irisin was significantly correlated with the body fat percentage ($r = 0.532$) and HOMA-IR ($r = 0.424$).

Conclusions: The systematic exercise program for 8-weeks did not change circulating irisin and no statistically significant difference was observed between the exercise methods. Also, serum irisin seemed to be associated with the glycemic status, body fat and weight independent of exercise activity.

RCT registration code: IRCT20180806040721N2.

Registry name: Iranian Registry of Clinical Trials.

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Introduction

Despite the unquestionable health beneficial effects of regular exercise, little is known about underlying molecular pathways that

regulate these effects.¹ There are several signal peptides termed myokines, which have been introduced in recent years as key regulators.² Myokines are secreted from skeletal contracting muscles, the largest organ in the human body, and are known to have endocrine effects on other organs. Irisin is one of the newest myokines described by Boström et al. in 2012.³ Irisin is an exercise-induced myokine and has been suggested to increase energy expenditure through the browning of adipose tissue.² It has been suggested that the browning process of adipose tissue via irisin may be a body response to the cold environment and physical activity.⁴ The upregulation of the peroxisome proliferator-activated

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receptor gamma coactivator 1-alpha (PGC-1 α), as a transcript activator, due to physical activity enhances the expression of fibronectin type III domain-containing protein 5 (FNDC5) gene. FNDC5 gene encodes the precursor protein for irisin production.³

Previous research on irisin secretion has shown that muscle tissue plays an important role in raising the blood level of irisin following exercise.^{5,6} Serum irisin levels rise and peak immediately and last shortly after the exercise session.⁷ It has been reported that elevated irisin levels in response to exercise may reduce weight in obese individuals and insulin resistance in patients with diabetes.^{8–10} In addition, serum irisin has been found to have an inverse correlation with glucose intolerance.¹¹ However, it is not clear whether exercise can increase the baseline serum irisin. As shown in population studies, high serum irisin levels reduce the risk of BMI enhancement and coronary atherosclerosis.^{12,13} Moreover, a short-term increase in serum irisin due to exercise is responsible for some beneficial metabolic changes.^{14,15} This becomes more complicated when we find that the lipid tissue is responsible for the baseline level of irisin in the blood among obese individuals.¹⁶ Furthermore, the serum irisin level is positively correlated with higher waist circumference, body fat mass, and unfavorable lipid profile.^{17,18}

Putting aside the conflicting results, physical activity is regularly prescribed in patients with different metabolic diseases including diabetes,¹ dyslipidemia and metabolic syndrome (MetS). MetS, as a cluster of health-related conditions including glucose intolerance, hypertension, dyslipidemia and central obesity, is an overwhelming health problem across the globe.¹⁹ Regardless of the molecular pathways, regular exercise, especially a program with a combination of aerobic and resistance training can improve MetS indices.²⁰

To the best of our knowledge, the effects of a variant exercise program on serum irisin using a well-controlled clinical trial have not been studied yet. Therefore, this study aimed to examine two hypotheses: (i) whether different exercise regimens including aerobic, resistance, and a combination of aerobic and resistance, could increase the serum irisin and, (ii) whether changes in the serum irisin levels are associated with changes in other metabolic parameters in women with MetS.

Materials and methods

Participants

This randomized controlled trial was performed on the basis of the CONSORT 2010 flow diagram (Fig. 1) to examine the effects of aerobic exercise (AE), resistant exercise (RE), and combined exercise (CE) on the levels of plasma irisin, fasting blood sugar (FBS), insulin, insulin resistance (HOMA-IR), lipid profile, and body composition in obese women with MetS. The primary hypothesis of this study was that a significant change in the irisin level would be observed after the exercise program compared to that at the baseline measurements. The second hypothesis was that statistically significant changes would be observed in the plasma levels of HOMA-IR and lipid profiles. MetS was confirmed when at least three of the following conditions were met: abdominal obesity (waist circumference greater than 88 cm in women and 102 in men), triglyceride ≥ 150 mg/dL, HDL-cholesterol ≤ 40 mg/dL in men and ≤ 50 mg/dL in women, hypertension (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg), and increased FBS (≥ 100 mg/dL).²¹ Inclusion criteria for subjects were as follows: having at least three diagnostic criteria of MetS, aged between 46 and 60 years and being at the pre-menopausal period, non-smoker, no history of cancer, no history of cardiovascular and musculoskeletal disorders, no use of dietary or ergogenic supplements, and willingness to take part in the study. Exclusion criteria were unwillingness to continue with

the intervention, missing more than 10% of the exercise sessions, pregnancy and starting a specific dietary regimen. The Ethics Committee affiliated with Shiraz University of Medical Sciences approved the research proposal and corroborated its ethical considerations throughout the study (decree code: IR.SUMS.REC.1397.279).

Study design

The study protocol was registered on the Iranian Registry of Clinical Trials (IRCT) under registration code of IRCT20180806040721N2. The study was conducted from February to April 2018 on 60 overweight/obese women with MetS selected from women visiting a public clinic affiliated with Shiraz University of Medical Sciences, Iran. Block randomization with the block size of four was used for assigning the subjects into four groups: (I) AE, (II) RE, (III) CE, and (IV) control group. Each group consisted of 15 women who were not blind to group assignments due to the nature of interventions. However, neither the laboratory staff nor the data collectors or the biostatistician were aware of group assignments. The eligible women were contacted by a nurse to participate in the study. The women were informed of the study method and objectives and were asked to sign the informed consent form before the initiation of the study. They were examined by a general practitioner before commencing the study to ensure that the interventions would not jeopardize their health condition.

Intervention: the exercises program

The control group were advised not to change their physical activity during the study. Also, their compliance with the interventions was monitored every other week via phone calls.

Aerobic exercise (AE) consisted of running on the treadmill (Cosmuse/hp model Saturn,® Germany) three times per week on non-consecutive days. In the group-based training sessions, the exercise time was increased gradually from 30 min to 60 min in each session after two weeks. Each 60-minute session consisted of stretching exercises (10 min), treadmill walking and stationary cycling (40 min), and balance exercises (10 min). They were allowed to have a 5- to 10-minute rest during each session. The exercise intensity was based on the maximum heart rate; it started at 60% and was gradually elevated to 75% during the exercise. The heart rate was monitored using the wristband heart rate monitor. The accuracy of the wristband heart rate monitor was approved through comparing the results with those collected via electrocardiography. The target heart rate was calculated using the Karvonen formula: (HR Target = HR Rest + [(%Desired intensity) QUOTE QUOTE \times (HR Max - HR Rest)]).²²

Resistance training (RE): The exercise techniques were instructed to the women and their performance was supervised by professional trainers in group-based training sessions. The exercise was performed for 2 sessions per week (each session 60 min) during the first two weeks and was increased to 3 sessions on non-consecutive days per week. Similar to the aerobic exercise, each resistance session was started with 10 min of stretching exercises followed by 40 min of strength exercises and 10 min of balance exercises. Strength training consisted of 2 sets of 10 different exercises, including bench press, seated row, shoulder press, chest press, lateral pull-down, abdominal crunches, leg press, leg extension, triceps pushdown, and seated bicep curls, for upper and lower parts of the body.²³ The subjects had 8–10 repetitions for each exercise and 5–10 min of rest between each set. For the first two weeks of training, the intensity of the exercises was 60% one repetition maximum (1RM) and was elevated to 75–80% 1RM from the 3rd week on. One repetition maximum was calculated based on the

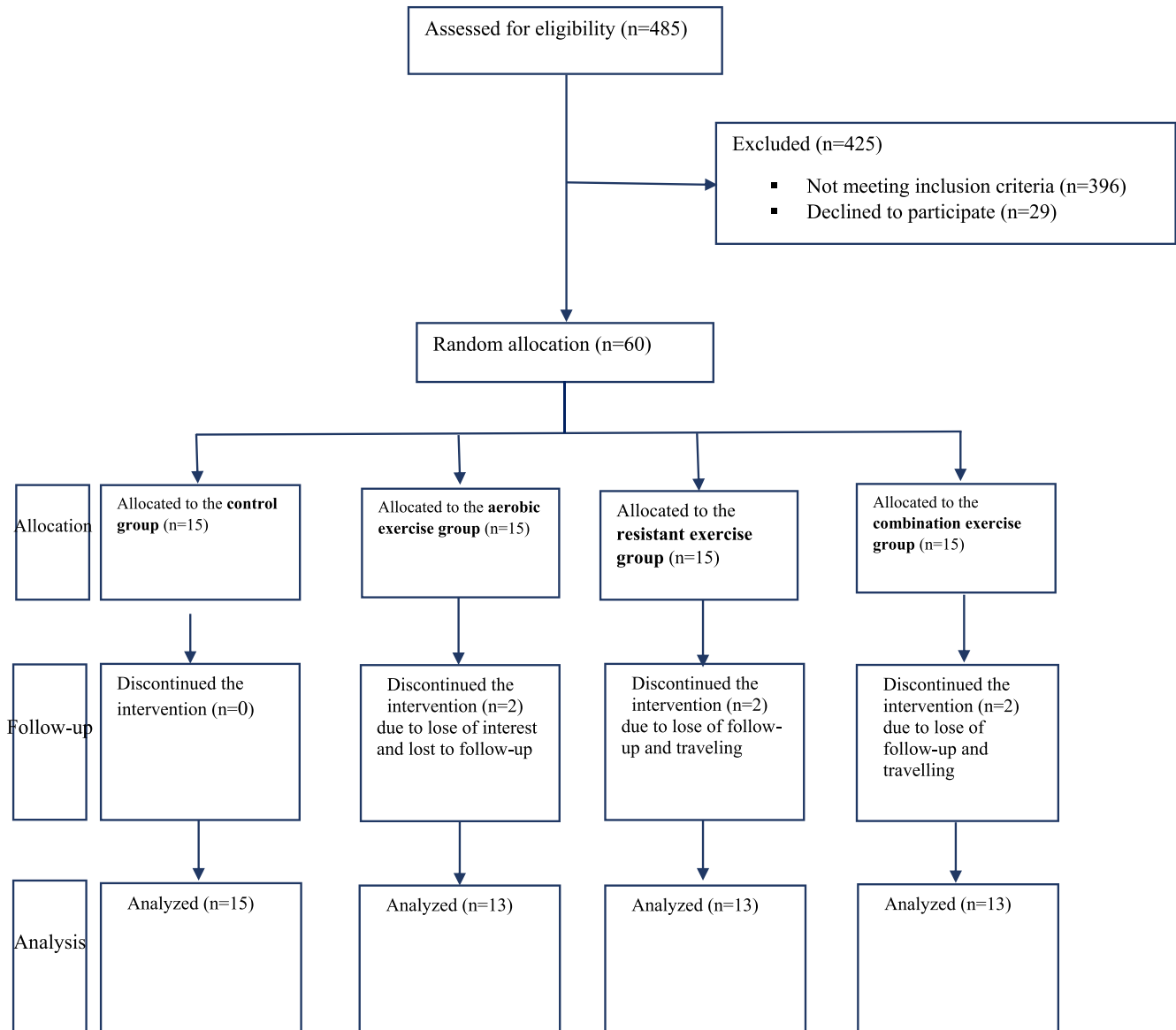


Fig. 1. Study flow diagram.

Brzycki formula:

$$1RM = \frac{\text{Amount of displaced weight (kg)}}{(1.0278 - (0.0278 \times \text{count of repetitions}))}$$

Combined exercise (CE): This group also participated in group-based training sessions, so that they performed both AE and RE simultaneously in one session. The CE group performed exercise two sessions a week for the first two weeks and three sessions for the rest of the intervention period. Each session was started with 10 min stretching exercises and 20 min walking on a treadmill, followed by 5 min rest and one set of strength training, consisting of 10 different exercises similar to the RE exercise program. The sessions were ended with 10 min balance exercises. The intensities of the aerobic and strength exercises were gradually increased according to the AE and RE protocols, respectively.

Nutrition and supplements

Dietary intake was evaluated using a 24-hour dietary recall

before and after the intervention. The subjects were also asked not to change their dietary habits during the intervention. They were contacted every other week by a nutritionist to ensure that no dietary changes occurred. A 24-hour dietary recall questionnaire was used to collect data on dietary energy and macronutrient content. Data were entered into Nutritionist IV software (First Databank® Inc., Hearst Corp., San Bruno, CA) for analysis.

Measurement

Demographic data were collected before the intervention. The anthropometric parameters, including body weight, height circumference, waist circumference, and hip circumference, were measured in the morning without shoes and with minimal clothing according to the WHO guideline.²⁴ The body mass index (BMI) and waist-to-hip ratio (WHR) were calculated. Body composition parameters, including body fat percentage (%BF) and skeletal muscle mass (SMM), were measured using the bioelectric impedance analysis (InBody 720; BioSpace®, Co., Korea) with patients in the

standing position, in the normal hydration status, and no vigorous exercise session for at least 6 h before the measurement. Blood pressure was measured in the seated position after 5 min rest, and the average of the two consecutive measurements was recorded.

Before the intervention, 5 mL of venous blood was taken from each participant in the morning after 12 h of fasting. The samples were incubated for 15 min in the room temperature for clotting and then centrifuged for 10 min in 4000 rpm to separate serum. The serum was frozen at -70°C until the time of laboratory analysis. In the second stage, the blood samples were collected 24 h after the last exercise bout of the eighth week of the intervention and all processes on blood samples were repeated.

Fasting serum glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride were measured by commercial kits (Pars Azmoon®, Tehran, Iran) and using the photometric and enzymatic methods and an autoanalyzer (Biotechnica instrument®, Rome, Italy). The serum fasting insulin and serum irisin levels were assessed by the enzyme-linked immunosorbent assay (ELISA) method and using the human insulin kit (ZellBio®, Ulm, Germany) and human irisin kit (Phoenix Pharmaceuticals®, Burlingame, USA). HOMA-IR was calculated using the following formula: $\text{HOMA-IR} = [\text{fasting glucose (mg/dL)} \times \text{fasting insulin (mU/L)}] / 405$. An overview of the study protocol is presented in Fig. 2.

Statistical analysis

The sample size was calculated to detect at least a 1.5 ng/ml (SD = 1.3) difference between the groups in terms of the plasma irisin level after the interventions. In addition, the alpha and power were set at 0.05 and 80%, respectively. Accordingly, the sample size was estimated as 15 participants per group.^{25,26} The extracted data were entered into the SPSS software for analysis. The Kolmogorov-Smirnov test was used to assess the normal distribution of data. The

baseline status of the individuals was compared using the ANOVA test. The paired sample *t*-test and the Mann-Whitney *U* test were used to compare differences in the means of parametric and non-parametric variables, respectively, before and after the intervention period. The effectiveness of exercise programs was examined through comparing the mean difference of changes in each variable using the ANCOVA test, adjusted for the baseline body weight as a covariate, followed by the Bonferroni post hoc test. The significance level was set as $p < 0.05$, and the data analysis was performed using the IBM SPSS Statistics 25 (Armonk, NY: IBM Corp).

Results

Participant characteristics

The data were collected from 54 women (control group: $n = 15$; AE group: $n = 13$; RE group: $n = 13$; CE group: $n = 13$). Six women (AE group: $n = 2$; RE group: $n = 2$; CE group: $n = 2$) were excluded because of failure to complete more than 90% of the exercise sessions or traveling (full analysis set; Fig. 1). The participants' mean age was 53.47 (SD = 6.53) years, and 40 (60%) participants had minimal or no formal education. Age and education showed no statistically significant difference between the study groups.

Baseline in terms of anthropometric, dietary recall, and biochemical characteristics

As shown in Table 1, except body weight, no statistically significant differences were observed between the groups at the baseline in terms of anthropometric and biochemical characteristics. About 23% of the participants were diagnosed with diabetes. According to the dietary recall, as summarized in Table 2, energy, macronutrient, and fiber intakes at the end of the study had no

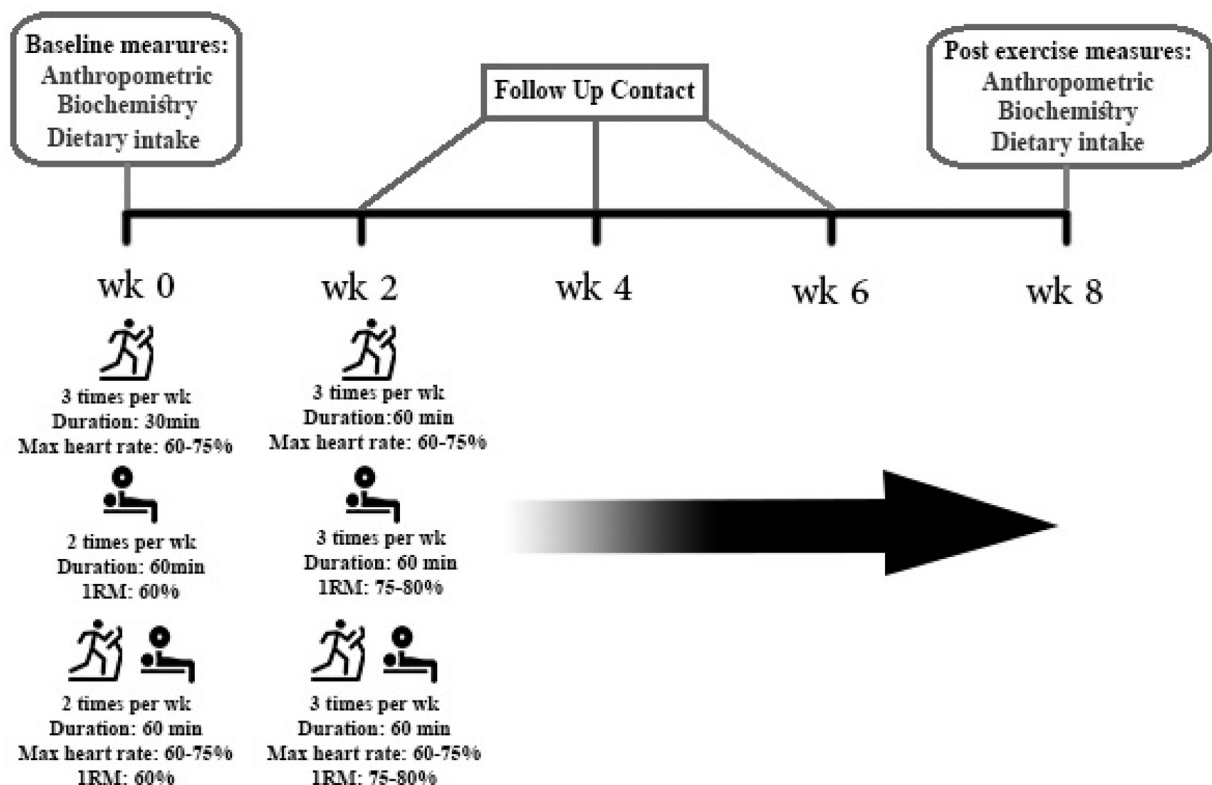


Fig. 2. An overview of study protocol.

Table 1
The baseline characteristics of the women in the groups.

Characteristic	Control (n = 15)	Aerobic (n = 15)	Resistance (n = 15)	Combination (n = 15)	P-value ^a
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Height, cm	157.69 ± 8.25	160.00 ± 10.29	159.08 ± 7.39	156.83 ± 7.82	0.802
Weight, kg	75.61 ± 9.36	73.25 ± 12.28	74.75 ± 11.68	76.83 ± 8.96	0.036
BMI, kg.cm ²	30.41 ± 3.83	28.61 ± 3.46	29.54 ± 2.95	31.23 ± 3.40	0.051
Body fat, %	35.15 ± 7.77	34.86 ± 4.15	35.40 ± 9.95	33.84 ± 7.09	0.239
Muscle, Kg	39.07 ± 8.41	42.83 ± 11.76	41.83 ± 7.76	42.08 ± 6.84	0.775
SBP, mmHg	133.08 ± 11.12	136.40 ± 15.21	131.17 ± 9.68	131.68 ± 11.47	0.184
DBP mmHg	87.31 ± 9.14	91.02 ± 10.11	93.55 ± 8.99	89.21 ± 10.19	0.323
FBS, mg. dL	119.07 ± 8.94	128.91 ± 31.65	115.50 ± 12.76	130.66 ± 9.49	0.186
Insulin, μIU. mL	10.15 ± 1.60	11.57 ± 1.04	10.58 ± 1.55	10.72 ± 1.38	0.894
HOMA-IR	2.98 ± 0.35	3.37 ± 0.49	3.02 ± 0.65	3.46 ± 0.48	0.604
TG, mg/dl	160.53 ± 11.70	154.41 ± 12.08	155.41 ± 11.27	155.41 ± 12.68	0.567
LDL, mg/dl	136.61 ± 12.37	131.58 ± 11.96	129.58 ± 11.98	122.41 ± 11.03	0.098
HDL, mg/dl	51.84 ± 9.59	51.91 ± 9.26	58.16 ± 13.24	47.25 ± 8.40	0.092
Chol, mg/dl	152.23 ± 8.47	161.25 ± 10.12	169.25 ± 14.55	153.41 ± 13.05	0.531
Irisin, ng/mL	9.14 ± 1.32	8.81 ± 1.07	9.42 ± 0.81	8.64 ± 0.98	0.304

Values are presented as mean ± standard deviation.

BMI: Body mass index; FBS: Fasting blood sugar; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; TG: Triglyceride; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

^a Analysis of variance (ANOVA).

Table 2
Dietary intake at baseline and at the end of the interventions in the groups.

Marker	Control			Aerobic			Resistance			Combination		
	Pre	Post	p-value ^a	Pre	Post	p-value ^a	Pre	Post	p-value ^a	Pre	Post	p-value ^a
Energy (kcal)	2245 ± 183	2298 ± 93	0.651	2214 ± 209	2301 ± 216	0.391	2188 ± 119	2243 ± 232	0.083	2147 ± 154	2287 ± 127	0.411
Protein (g)	84.74 ± 11.9	87.31 ± 9.3	0.401	81.91 ± 17.5	82.66 ± 13.3	0.683	79.92 ± 10.1	82.47 ± 8.1	0.432	85.80 ± 9.3	85.66 ± 12	0.762
Total fat (g)	67.35 ± 8.2	66.34 ± 9.2	0.514	65.43 ± 8.5	62.88 ± 10.1	0.184	67.58 ± 5.9	64.19 ± 5.5	0.214	68.22 ± 11.6	67.08 ± 7.5	0.452
Saturated fat (g)	14.2 ± 3.1	12.9 ± 5.2	0.213	19.06 ± 6.9	18.74 ± 8.3	0.444	16.09 ± 4.4	16.24 ± 5.2	0.782	15.4 ± 6.8	15.9 ± 4.4	0.691
Monounsaturated fat (g)	26.18 ± 6.5	29.03 ± 5.3	0.153	23.57 ± 6.7	24.10 ± 8.3	0.383	26.26 ± 11.3	27.88 ± 10.6	0.611	27.44 ± 12.7	26.85 ± 10.8	0.473
Polyunsaturated fat (g)	26.96 ± 7.0	24.42 ± 8.2	0.282	22.81 ± 9.1	20.04 ± 7.2	0.172	25.23 ± 9.1	20.07 ± 6.0	0.072	25.38 ± 7.4	24.33 ± 8.8	0.492
Carbohydrate (g)	324.96 ± 35.0	337.94 ± 43.2	0.424	346.12 ± 61.2	351.11 ± 38.29	0.272	315.02 ± 59.8	333.85 ± 41.1	0.063	297.45 ± 58.5	335.16 ± 48.3	0.051
Dietary fiber (g)	19.0 ± 7.0	19.3 ± 5.0	0.491	15.3 ± 4.0	16.10	0.141	15.8 ± 6.1	16.20	0.333	17.1 ± 4.0	17.90	0.361

^a p-value from the paired sample t-test comparing pre- and post-intervention dietary intakes in each group.

differences significantly with those at the baseline.

Intergroup comparison

After the interventions, a significant reduction was observed in the women's weight, body fat percentage, and BMI in the AE and CE groups (Table 3). In addition, resistance and combined exercise groups gained significant skeletal muscle mass (1.67 Kg and 1.33 Kg, respectively) after the exercise period. All the intervention groups exhibited improvements in the insulin resistance index compared to the baseline. However, the RE group did not reach a significant level. Fasting serum triglyceride levels in the intervention groups declined significantly. However, changes in other lipid profiles were not significant, except for the total cholesterol in the AE ($p = 0.033$) and CE ($p = 0.022$) groups, in which a decline from the baseline values was observed. The serum level of irisin after eight weeks of the intervention did not change significantly in the AE ($p = 0.221$), RE ($p = 0.152$) and CE ($p = 0.303$) groups from the baseline measurements (7% increase, 3% decrease, and 3% increase, respectively).

Intragroup comparison

Fig. 3 shows changes in each parameter and the intragroup comparisons after the interventions in the study groups. Body weight decreased significantly in the AE and CE groups in

comparison with that of the control group ($p = 0.026$ and $p = 0.019$, respectively). In addition, body fat percentage decreased significantly in all intervention groups. However, only the RE and CE groups developed greater skeletal muscle masses.

On the other hand, irrespective of the type of exercise, the interventions induced a significant reduction in fasting glucose ($p = 0.013$), HOMA-IR ($p < 0.001$), and triglyceride ($p = 0.020$) in comparison to those of the control group. At the eighth week of follow-up, comparing the changes in serum irisin showed no statistically significant differences between the groups ($p = 0.117$).

Table 4 represents correlations between the changes in the irisin level and other variables. The changes in serum irisin were statistically correlated with the changes in the body weight ($r = -0.357$, $p = 0.01$), body fat percentage ($r = 0.532$, $p = 0.01$), and HOMA-IR ($r = 0.424$, $p = 0.02$). Also, Irisin was inversely correlated with cholesterol ($r = -0.637$, $p = 0.01$) in the AE group.

Discussion

This study aimed to compare the effects of eight weeks of aerobic, resistance, and a combination of aerobic and resistance exercises on the serum levels of irisin, glycemic indices, and lipid profiles in women with MetS. The main finding of this randomized controlled trial was that serum irisin levels did not change after exercise compared with those before the intervention. In addition,

Table 3
Laboratory values and anthropometric measures in the groups at baseline and after 8 weeks of the interventions.

Marker	Control (n = 15)			Aerobic (n = 13)			Resistance (n = 13)			Combination (n = 13)			P Value ^b
	Pre	Post	P value ^a	Pre	Post	P value ^a	Pre	Post	P value ^a	Pre	Post	P value ^a	
Weight (Kg)	75.61 ± 9.36	75.84 ± 9.50	0.193	73.25 ± 12.28	71.73 ± 6.91	0.031	74.75 ± 11.68	74.21 ± 9.74	0.112	76.83 ± 8.96	74.02 ± 9.09	0.011	0.001
BMI (kg/cm ²)	30.41 ± 3.83	30.51 ± 3.85	0.182	28.61 ± 3.46	28.01 ± 3.61	0.033	29.54 ± 2.95	29.33 ± 2.98	0.104	31.23 ± 3.40	30.08 ± 3.04	0.014	0.001
Body fat (%)	35.15 ± 7.77	34.92 ± 8.06	0.642	34.86 ± 4.15	30.82 ± 5.38	0.014	35.40 ± 9.95	33.93 ± 9.46	0.083	33.84 ± 7.09	31.50 ± 8.26	0.013	0.011
Muscle (Kg)	39.07 ± 8.41	39.15 ± 7.72	0.101	42.83 ± 11.76	43.16 ± 10.70	0.102	41.83 ± 7.76	43.50 ± 10.75	0.012	42.08 ± 6.84	43.41 ± 8.69	0.033	0.013
SBP (mmHg)	133.08 ± 11.12	135.12 ± 11.09	0.893	136.40 ± 15.21	131.22 ± 10.30	0.214	131.17 ± 9.68	131.78 ± 13.59	0.781	131.68 ± 11.47	127.65 ± 10.05	0.141	0.234
DBP (mmHg)	87.31 ± 9.14	88.06 ± 7.5	0.452	91.02 ± 10.11	88.50 ± 6.48	0.191	93.55 ± 8.99	90.04 ± 10.10	0.243	89.21 ± 10.19	86.87 ± 8.92	0.172	0.411
Glucose (mg/dL)	119.07 ± 8.94	122.38 ± 9.05	0.102	128.91 ± 31.65	105.08 ± 28.13	0.011	115.50 ± 12.76	113.25 ± 12.96	0.111	130.66 ± 9.49	111.14 ± 9.93	0.022	0.010
Insulin (μ U/mL)	10.15 ± 1.60	9.98 ± 1.61	0.283	11.57 ± 1.04	10.50 ± 1.09	0.084	10.58 ± 1.55	9.32 ± 1.52	0.042	10.72 ± 1.38	8.45 ± 1.62	0.022	0.007
HOMA-IR	2.98 ± 0.35	3.01 ± 0.54	0.451	3.37 ± 0.49	2.72 ± 0.51	0.035	3.02 ± 0.65	2.60 ± 0.64	0.050	3.46 ± 0.48	2.31 ± 0.55	0.001	0.001
TG (mg/dL)	160.53 ± 11.70	160.00 ± 13.44	0.593	154.41 ± 12.08	140.75 ± 12.67	0.011	155.41 ± 11.27	148.66 ± 10.94	0.022	155.41 ± 12.68	142.75 ± 8.33	0.011	0.020
LDL (mg/dL)	136.61 ± 12.37	137.30 ± 11.75	0.121	131.58 ± 11.96	129.50 ± 12.74	0.232	129.58 ± 11.98	126.33 ± 12.04	0.173	122.41 ± 11.03	117.25 ± 11.29	0.061	0.060
HDL (mg/dL)	51.84 ± 9.59	52.00 ± 10.97	0.781	51.91 ± 9.26	51.08 ± 9.03	0.222	58.16 ± 13.24	58.83 ± 14.07	0.121	47.25 ± 8.40	50.08 ± 8.45	0.050	0.264
Cholesterol (mg/dL)	152.23 ± 8.47	151.11 ± 9.85	0.762	161.25 ± 10.12	157.00 ± 9.12	0.033	169.25 ± 14.55	167.33 ± 12.85	0.101	153.41 ± 13.05	147.83 ± 13.20	0.022	0.284
Irisin (ng/mL)	9.14 ± 1.32	9.02 ± 1.33	0.249	8.81 ± 1.07	9.04 ± 1.15	0.221	9.42 ± 0.81	9.31 ± 0.97	0.152	8.64 ± 0.98	8.78 ± 1.33	0.303	0.117

Values are presented as mean ± standard deviation.

BMI: Body mass index; FBS: Fasting blood sugar; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; TG: Triglyceride; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure. Paired sample t-test is based on the analysis of variance, comparing the groups for exact changes (pre- and post-intervention measures); P < 0.05 for all comparisons.

^a Paired sample t-test.^b Based on the ANCOVA for comparing the groups (pre- and post-intervention measures).

none of the AE, RE or CE groups exhibited a different pattern of irisin secretion due to the exercise interventions compared with that of the control group. The effectiveness of the exercise regimens was confirmed based on the significant reductions of body fat in the AE, RE, and CE groups and greater skeletal muscle masses in the RE and CE groups.

Several studies have explored the effects of different exercise regimens on serum irisin. Nonetheless, their results have not been consistent enough to warrant a firm conclusion. This study found no significant change in circulating irisin due to the exercise intervention, but Huh et al.²⁵ showed that regardless of the participants' age, fitness level, or health status, different exercise regimens, including high-intensity swimming, treadmill, and resistance exercise, increased the level of circulating irisin. Similarly, Daskalopoulou et al.²⁷ showed that three different exercise protocols significantly increased serum irisin, especially after a maximal exercise workload. These discrepant results could be due to differences in study designs. Huh et al. measured serum irisin during and minutes after an acute exercise session, but the subjects in the present study were evaluated after several weeks of training and in the resting state. Norheim et al. reported that the plasma levels of irisin increased right after 45 min of ergometer cycling and dropped 2 h post exercise. Since the production of irisin is dependent on PGC-1 α activity and FNDC5 transcription, during acute exercise, the sharp increase in serum irisin could be due to FNDC5 mRNA translation rather than FNDC5 transcription.⁴ The study of Norheim et al. showed that PGC-1 α transcription and FNDC5 mRNA expression increased significantly after 12 weeks of systematic exercise, but these increases did not translate to higher concentrations of serum irisin, which was consistent with our results. Likewise, Hecksteden et al.²⁸ reported that 26 weeks of aerobic or strength training did not induce an increase in irisin production while it significantly improved maximal performance.

In addition to acute or chronic exercise intervention, patients' anthropometric and health status may also affect the results. In this study, the subjects were overweight/obese and were diagnosed with MetS. Similarly, the participants in Norheim et al.'s study were obese and prediabetic volunteers, but the Pekkala et al.'s²⁹ study focused on healthy man, and their findings did not confirm the effects of AE, RE, and CE in inducing PGC-1 α and FNDC5 expression or irisin in healthy men. Timmons et al. (2012) studied the effects of endurance and resistance exercise on 205 healthy individuals and those with type II diabetes for 6 weeks. The results showed a greater expression of fibronectin type III domain-containing protein 5 (FNDC5) in the intervention group compared to that of the control group.⁵

Recently, Osella et al.³⁰ evaluated the effects of different diets on the serum irisin concentration and found that vegetable proteins and saturated fatty acids were positively associated with serum irisin. Unlike the studies reviewed above, the current study used a dietary regimen based on the pre-intervention dietary intake to adjust the effect of dietary components on serum irisin.

As expected, exercise interventions induced a positive change in glycemic indices, and the change was more significant in the CE group. Our results were similar to those of a previous study that evaluated the efficacy of different exercise regimens on serum omentin-1 in diabetic women.²⁰ The Pearson correlation test showed that changes in the HOMA-IR, body weight and body fat percentage were correlated positively with serum irisin in all participants. A positive relationship between serum irisin and metabolic disorders, such as obesity, diabetes, and cardiovascular diseases, has been reported in previous studies.^{31,32} Stengel et al.³³ showed that obese patients had a higher level of circulating irisin than normal-weight subjects. In addition, serum irisin was positively correlated with fat mass and insulin resistance. Our study

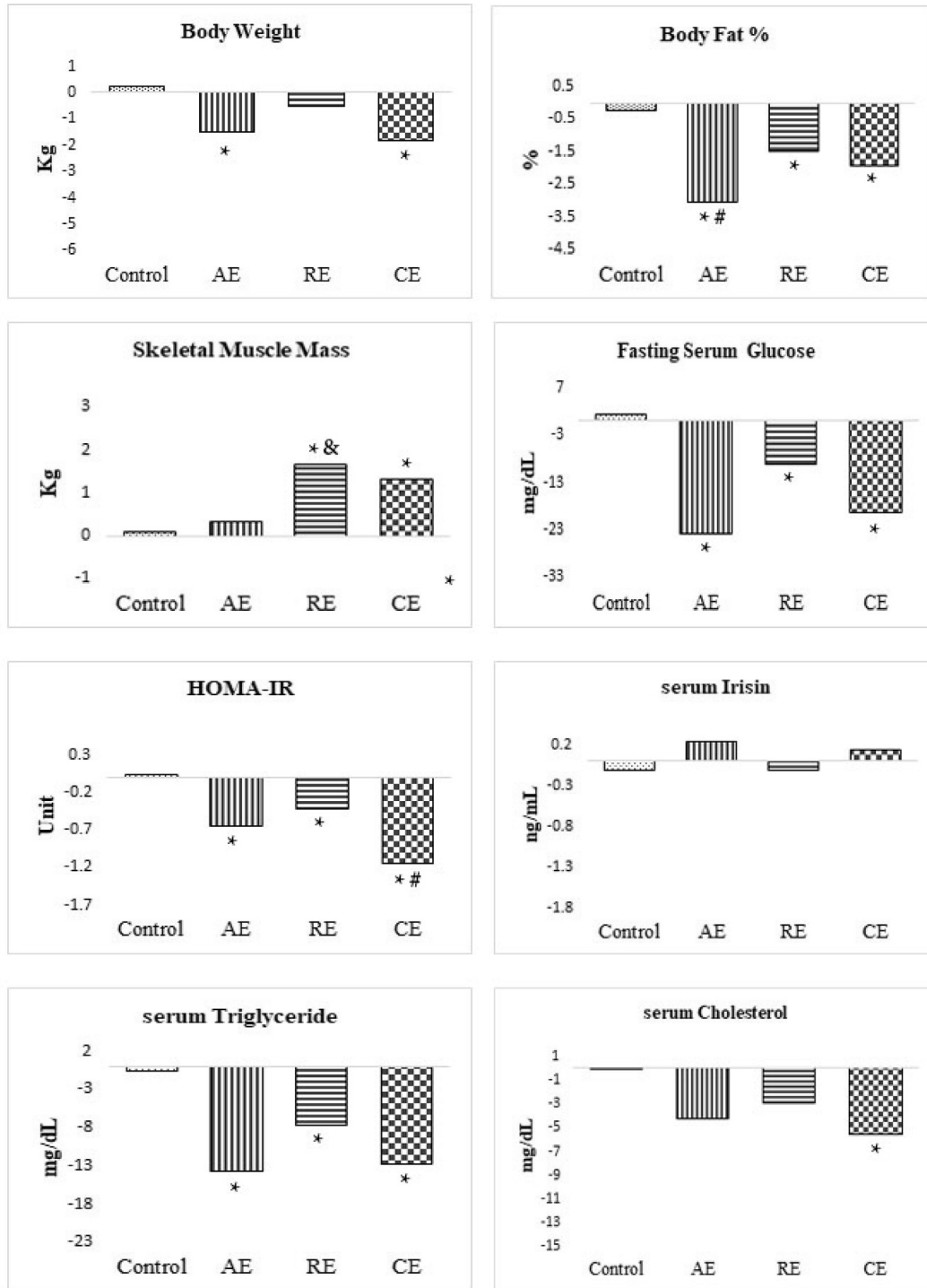


Fig. 3. Comparison of changes in anthropometric and biochemical indices between the groups.

*: Significant difference in comparison with the control group ($p < 0.05$).

&: Significant difference in comparison with the AE group ($p < 0.05$).

#: Significant difference in comparison with the RE group ($p < 0.05$).

showed that a reduction in insulin resistance or body fat percentage was associated with lower serum irisin. Contrariwise, Crujeiras et al.³⁴ reported that the circulating irisin increased proportionally to the weight regain after that patients underwent a calorie-restricted weight reduction diet.

There are two hypotheses to explain the underlying mechanism behind the association of serum irisin and weight gain. In the first

hypothesis, an increase in serum irisin is an adaptive response to weight gain and an increase in body fat. In recent years, the interaction between adipose tissue and muscle mass has been emphasized as it plays an important role in regulating body weight and improving metabolic risk factors.³⁵ Accordingly, the conversion of white fat tissue to brown adipose tissue can increase thermogenesis and energy consumption and, eventually, lead to weight loss

Table 4
Correlations between the variables.

Group: Irisin/Markers	Weight	BMI	Glucose	Insulin	HOMI-IR	Body fat	Muscle	HDL	LDL	TG	Cholesterol
All: Irisin	-0.357 ^a	0.307	0.381	0.319	0.424 ^a	0.532 ^a	-0.191	-0.064	0.089	0.266	0.178
Combination: Irisin	0.073	0.057	0.022	0.558	0.570	0.370	0.095	0.100	0.159	-0.413	0.066
Resistance: Irisin	-0.548	-0.535	0.058	-0.423	-0.308	0.016	0.326	-0.229	-0.051	-0.111	-0.637 ^a
Aerobic: Irisin	0.208	0.201	-0.243	0.247	0.044	0.076	-0.286	0.172	0.447	-0.343	0.137

BMI: Body mass index; HOMIIR: Homeostatic Model Assessment for Insulin Resistance; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; TG: Triglyceride.

^a Indicates that the correlation is statistically significant at the 0.05 level (2-tailed).

through myokine irisin.⁸ Irisin stimulates the expression and activity of uncoupling protein1 (UCP1) and causes the browning of the white adipose tissue. Therefore, it increases thermogenesis and total energy expenditure, which, in turn, can reduce obesity.^{36,37} This hypothesis was supported by the results of an animal study, in which irisin improved hyperinsulinemia and glucose tolerance in mice with a high-fat diet.³⁸ In the second hypothesis, an increase in serum irisin in adiposity suggests potential irisin resistance. Irisin is supposed to improve UCP1 production and promote the browning of white adipose tissues. However, it is contradictory that normal weight or anorexic patients have lower levels of circulating irisin than obese individuals. While adipose tissue itself secretes irisin, an increase in the body fat and irisin secretion does not lead to expected beneficial effects; for instance, it may lead to leptin resistance.³⁹ Leptin is an adipocyte hormone secreted in response to fat deposits and influences the central nervous system to suppress the appetite. Despite the anorexigenic effects of leptin and its high level in adiposity, obese patients often do not experience reduced appetite.⁴⁰

The results of this study also showed a significant reduction of fasting triglyceride in all groups and total cholesterol in the CE group compared to those of the control group. Nonetheless, no significant correlation was found between the changes in the lipid profile and serum irisin. Previous studies have shown a positive correlation between lipid profile and irisin concentration in adolescents and adults.^{41,42} Contrary to recent studies that used a cross-sectional design, in the present study, we conducted a randomized controlled trial to examine the correlation between the changes in irisin concentration and serum lipids. To the best of our knowledge, no other RCTs have investigated the relationship between irisin and lipid profile. Also, it must be added that changes in total cholesterol or triglycerides and irisin level were independent.

Study strengths and limitations

As a limitation, the inclusion of the expression of FND5 gene in skeletal muscle and fat mass could reveal the source of circulating irisin in the body. The process of evaluating the dietary intake before the intervention and using a dietary regimen based on the pre-intervention intake improved the quality of data collection and can be considered a strength of this study. Lastly, we recruited women aged 46–60 years that may influence the generalizability of our results to the whole population, so our results should be interpreted with caution when other age groups are considered.

Conclusions

All exercise groups experienced a significant positive change in anthropometric indices after eight weeks of training. In addition, fasting serum glucose and insulin resistance index decreased in the exercise groups in comparison with those of the control group. Despite no significant changes in serum irisin in the study groups, the changes in circulating irisin were positively correlated with the changes in the body weight, body fat percentage and HOMA-IR.

Aerobic, resistance, and combined exercises reduced serum triglyceride. Also, a combination of aerobic and resistance exercises effectively reduced LDL-cholesterol. Finally, no significant changes were observed in systolic and diastolic blood pressure after the interventions. Different exercise regimens did not lead to different results, but combined exercises had more beneficial effects on MetS risk factors. The contradictory results on the effect of exercise in serum irisin levels highlight the need for larger-scale RCTs on healthy and non-healthy participants.

Ethics approval and consent to participate

The research proposal was approved by the Ethics Committee affiliated with Shiraz University of Medical Sciences (decree code: 4500, IR.SUMS.REC. 1397.279). Also, the research protocol was registered on the Iranian clinical trial registration website under the code of IRCT20180806040721N2.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable requests.

Funding

This research was supported under a research grant (grant no.: 97-01-04-17589) from Shiraz University of Medical Sciences, Iran. The study funder had no role in study design, data collection, writing of the manuscript, and submission.

CRediT authorship contribution statement

Aria Dianatinasab: Conceptualization, Investigation, Methodology, Writing - original draft. **Roghayeh Koroni:** Data curation, Project administration, Software. **Mehrdad Bahramian:** Data curation, Visualization. **Mojtaba Vaismoradi:** Supervision, Validation, Writing - review & editing. **Mohammad Fararouei:** Formal analysis, Funding acquisition, Project administration, Validation, Writing - review & editing. **Sasan Amanat:** Conceptualization, Formal analysis, Resources.

Declaration of competing interest

The authors stated no conflict of interest.

Acknowledgments

The authors would like to thank the participation of the women in this study.

Abbreviations used

Mets	Metabolic Syndrome
AE	Aerobic Exercise
RE	Resistant Exercise
CE	Combined Exercise
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
FBS	Fasting Blood Sugar
SD	Standard Deviation
BMI	Body Mass Index
WHR	Waist-to-Hip Ratio
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
TG	Triglyceride
UCP1	Uncoupling Protein-1
FNDC5	Fibronectin Type III Domain-Containing Protein 5

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jesf.2020.06.004>.

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