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Effect of Different Intensities of Aerobic Exercise Combined with Resistance Exercise and Consumption of Cinnamon on Meteorin-like protein (METRNL) and Irisin in Diabetic Women

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Abstract

Objective: Studies show that exercise and herbal supplements help improves type 2 diabetes. The aim of this study was to investigate the effect of different intensities aerobic exercise with resistance training and cinnamon on the levels of METRNL and irisin in diabetic women.

Materials and Methods: In this clinical trial study, 54 diabetic women (age 41.73± 4.05) were selected from Nowshahr and randomly allocated into six groups; Control (C), Resistance and Moderate Aerobic Exercise (RME, 50% VO2max, 200 kcal), Resistance and Vigorous Aerobic Exercise (RVE, 80% VO2max, 200 kcal), Cinnamon (Ci, 1000 mg/day), Resistance and Moderate Aerobic Exercise+Cinnamon (RMECi), Resistance and Vigorous Aerobic Exercise+Cinnamon (RVECi). Data were analyzed using an independent t-test and ANCOVA ($P< 0.05$).

Results: It was observed a significant increase in Metrnl, irisin in the RME ($P= 0.041$ and $P= 0.004$, respectively), RVE ($P= 0.0001$ and $P= 0.0001$, respectively), Ci ($P= 0.006$ and $P= 0.0001$, respectively), RMECi ($P= 0.00$ and $P= 0.0001$, respectively) and RVECi ($P= 0.001$ and $P= 0.0001$, respectively) compared to group C. The increase in Metrnl and irisin was significant in RVE compared to RME ($P= 0.045$, and $P= 0.028$, respectively); RMECi relative to RME ($P= 0.004$) and Ci ($P= 0.0001$); RVECi compared to RME ($P= 0.0001$), RVE and Ci ($P= 0.0001$). It was also observed a significant decrease in HOMA-IR in the RME ($P= 0.014$), RVE ($P= 0.001$), Ci ($P= 0.044$), RMECi ($P= 0.0001$), and RVECi ($P= 0.0001$) compared to group C.

Conclusion: Combining exercise with cinnamon may help prevent or delay T2D complications. RVE exercise showed greater improvements in irisin and HOMA-IR than RME.

Keywords: Cinnamomum, Diabetes mellitus, Exercise, FNDC5 protein, Irisin, Metrnl protein

QR Code:

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Introduction

According to the latest estimate by the International Diabetes Federation (IDF), nearly half of all patients (240 million) with diabetes mellitus (DM) are unaware of their condition and remain undiagnosed. However, the number of diagnosed cases of DM in 2021 was 537 million, and it is projected to rise to 643 million by 2030 and 783 million by 2045, respectively (1). Improving Insulin resistance (IR) is a crucial area of research in the treatment of T2D and metabolic syndrome, particularly given the need for new insulin-sensitizing therapies.

Metrnl is an immunoregulatory adipomyokine released from white adipose tissue, activated monocytes, macrophages, and skeletal muscle, and it plays an essential role in maintaining glucose homeostasis and regulating energy metabolism. Metrnl can increase energy expenditure and enhance insulin sensitivity, stimulating gene expression related to thermogenesis and the browning of white adipose tissue, while also promoting the production of anti-inflammatory cytokines (2). These functions have led to Metrnl being recognized as one of the effective adipomyokines involved in the pathophysiological mechanisms of metabolic disorders, including T2D. Nevertheless, research on patients with T2D has yielded conflicting results (3,4).

Irisin is a proteolytic derivative of fibronectin type III domain-containing muscle protein 5 (FNDC5) that is released into the bloodstream. Increased levels of FNDC5/irisin lead to greater energy consumption, improved glucose and fat metabolic disorders, changes in adipose tissue phenotype, and reduced insulin resistance (5). These studies highlight the significance of Metrnl and FNDC5/irisin as effective strategies for reducing metabolic disorders and insulin resistance in T2D. Additionally, studies have shown a strong correlation between Metrnl and irisin (4). Engaging in exercise training is one effective method for managing T2D. The increase in Metrnl generated by muscle is released into the bloodstream and subsequently influences other tissues, such as the liver and adipose tissue (2). Engaging in physical activity, particularly a combination of aerobic and resistance training, offers numerous benefits for patients with T2D, including enhanced body composition (6), improved insulin sensitivity (6), better lipid profiles, and decreased systemic low-grade inflammation. However, sports parameters such as the duration and intensity of training may influence these benefits in different ways. Meta-analyses have demonstrated that high-intensity exercise serves as an effective exercise strategy for individuals with T2D (7). However, it has been stated that high-intensity, low-volume training is similar to moderate-intensity continuous training (MICT), due to the greater shear stress on the cardiovascular system during intense training, such as increased heart rate and cardiac output (8).

In addition, the combination of resistance training with aerobic training, besides increasing lean mass and muscle strength, can alter body fat, fat profiles, and levels of adipokines, as well as factors affecting T2D. According to ACSM's recommendations, an energy consumption of 400 kcal per day through exercise can positively affect fat profile, insulin levels, blood sugar, and certain adipokines (9). Another strategy used in the treatment of metabolic diseases is the use of natural extracts such as cinnamon. The effect of cinnamon on regulating glucose metabolism is superior to that of many other plants. Studies have shown that cinnamon can improve markers of browning in adipose tissue and reduce insulin resistance (10). It also indirectly influences Metrnl expression by affecting PPARγ (11). Therefore, in this research, we have investigated the effect of two different intensities of aerobic exercise combined with resistance exercises (while maintaining an equal caloric intake) and cinnamon on Metrnl and Irisin in women with T2D.

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Materials and Methods

In randomized clinical trial, 134 women with T2D from Nowshahr city, aged between 35 and 50 years (41.73 ± 4.05), were purposefully selected in coordination with the Nowshahr Diabetes Association. The sampling among women with type 2 diabetes was done voluntarily, purposefully, and through availability. At the beginning of the study, the purpose of the research, benefits, and potential risks of participating were explained to the participants. The inclusion criteria for this study include: confirmation of T2D by a specialist doctor, the use of oral antidiabetic medications, an HbA1C level above 6.5, no foot ulcers, no diabetic eye complications (such as retinopathy), no cardiovascular diseases or peripheral nerve disorders, and consent to participate in the study. The exclusion criteria also encompass: not taking supplements or exercising, having an allergy to cinnamon, using other medicinal plants, a diagnosis of other underlying diseases during the study protocol (such as fatty liver, liver cirrhosis, or heart or respiratory failure), insulin use, concerns about the risks associated with exercising or taking supplements, and the absence of contact from the researcher for follow-up. F Following initial telephone screening, volunteer interviews, and obtaining informed consent one week prior to study commencement, 54 participants were randomly selected from a pool of 134 eligible individuals using a simple randomization technique. The sample was then evenly allocated into six groups: Control (C), Resistance and Moderate Aerobic Exercise (RME), Resistance and Vigorous Aerobic Exercise (RVE), Cinnamon (Ci), Resistance and Moderate Aerobic Exercise+Cinnamon (RMECi), Resistance and Vigorous Aerobic Exercise+Cinnamon (RVECi). Randomization was performed by writing participants' names on individual slips of paper, which were placed into a container. Names were drawn at random to assign participants to the respective intervention or placebo groups.

Exercise protocol

To estimate VO2max, a 1-mile (1609 m) walk was performed by the participants wearing a heart rate monitor; VO2max of the subjects was estimated before starting the exercise with the following formula:

VO2max (ml/min/kg)= 132.853− (0.1692× body mass in kg)− (0.3877× age)+ (6.315× sex)− (3.2649× time in min)− (0.1565× HR)

Sex: man= 1, woman= 0; HR: Heart rate immediately after the end of walking.

The exercise program used in this study is shown in Table 1 and was performed five times a week by each group. Energy consumption was measured using the smart watches to measure 400 kcal from when the target intensity was reached (daily energy expenditure of 400 kcal per day by the ACSMs recommendation). After a 10-15-min warm-up under expert supervision, the participants ran on a treadmill at 50% VO2max in the RME group and 80% VO2max in the RVE group to reach a 200-kcal expenditure. Thereafter, total body resistance exercise (TRX) was performed.

The TRX exercises comprised the use of resistance bands to perform various upper body, lower body, and abdominal exercises (Table 1).

Table 1. Exercise program.

Exercise Type		Exercise Program	Expenditure Calorie
Warming up		Stretching (10-15 min)	
Main exercise	**RME**	Treadmill (50% VO2max) + TRX	Resistance: 200 kcal
		TRX program—push up, standing row, Kneeling triceps extension, biceps curl, jump squat, lunge, leg curl, ab slide, reverse lying knee pull	Aerobic: 200 kcal
	RVE	Treadmill (80% VO2max) + TRX	Resistance: 200 kcal
		TRX program—push up, standing row, Kneeling triceps extension, biceps curl, jump squat, lunge, leg curl, ab slide, reverse lying knee pull	Aerobic: 200 kcal
Cool down		Stretching (10 min)	

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TRX was performed for a further 200-kcal expenditure (12). At the end, cooling down was done for 10 minutes.

Cinnamon consumption

Cinnamon tree bark was purchased, and after receiving approval from the herbalist, it was washed, dried, and powdered before being placed into 500 mg capsules. Participants in the supplement group took one capsule of either the supplement or a placebo (1000 mg/day) twice daily, after breakfast and lunch (13).

Blood sampling and analysis

Two days before and after the training period (to eliminate the acute effect of the last training session and supplement consumption) Blood samples were obtained from the antecubital vein after a 12-h fast. Metrnl and Irisin serum levels were measured using the human kit of R&D Systems by ELISA method. After estimating the amount of glucose and fasting insulin, the HOMA-IR index was utilized to assess insulin resistance (6).

HOMA-IR= [glucose (mmol/l)× insulin (µU/ml)]/ 22.5

Statistical methods

The sample size for the present study was determined based on the results of previous research, using a significance level of 5% (Type I error) and a statistical power of 95% (Type II error), calculated via the sample size formula for studies with a pre-test and post-test design. The required sample size was approximately 54 participants (9 participants per group), as shown below.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (S)^2}{(\mu_1 - \mu_2)^2}$$

In this formula, the mean level of HbA1c, considered as the primary indicator related to diabetes, was assumed to be approximately 8.5% with a standard deviation of 2.5%, based on previous literature. Furthermore, the clinically significant reduction in HbA1c was estimated to be around 20%.

$$n = \frac{(1.96 + 1.96)^2 (2.5)^2}{(1.7)^2} = 54.25$$

Shapiro-Wilk test was used to evaluate the normality of the data and Paired T-test and Analysis of Covariance (ANCOVA) were applied for within-group comparisons (pre-test and post-test scores of each group) and for between-group comparisons, respectively. Data comparison was performed at a significance level of $P< 0.05$ in SPSS23 software.

Ethical considerations

This study was approved by the Research Ethics Committee of the Islamic Azad University, Ayatollah Amoli Branch, with the code IR.IAU.AMOL.REC.1403.099 and was registered in the Clinical Trial Center under the number IRCT20140415017288N12.

All the participants provided their informed written consent for participation in the present study.

Results

The results of the one-way ANOVA test showed that at the baseline, there were no significant differences between the groups in terms of mean age (*P*= 0.860), height (*P*= 0.663), weight (*P*= 0.138), body mass index (*P*= 0.518), body fat percentage (*P*= 0.307), VO_2 max (*P*= 0.718), Metrnl (*P*= 0.885), irisin (*P*= 0.748), and HOMA-IR (*P*= 0.864) (Table 2).

The descriptive characteristics of the subjects, along with the statistical results for some variables, are presented in Table 3.

Data analysis using ANCOVA showed that there is a significant difference in Metrnl level between different groups (*P*= 0.0001, *F*= 37.317).

The results of Benferroni's post hoc test showed a significant increase of Metrnl in RME (*P*= 0.041), RVE (*P*= 0.0001), Ci (*P*= 0.006), RMECi (*P*= 0.0001) and RVECi (*P*= 0.001) compared to group C; RVE compared to RME (*P*= 0.045); RMECi compared to RME (*P*= 0.004) and Ci (*P*= 0.033); RVECi compared to RME (*P*= 0.0001), RVE (*P*= 0.0001), Ci (*P*= 0.001) and RMECi (*P*= 0.0001).

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The results of intra-group comparison showed a significant increase in Metrnl levels in RME (*P*= 0.0001), RVE (*P*= 0.0001), Ci (*P*= 0.0001), RMECi (*P*= 0.0001), and RVECi (*P*= 0.001) (Figure 1).

Also, data analysis using ANCOVA showed that there is a significant difference in Irisin level between different groups (*P*= 0.0001, F= 34.720). The results of Benferroni's post hoc test showed a significant increase in irisin levels in RME (*P*= 0.041), RVE (*P*= 0.0001), Ci (*P*= 0.0001), RMECi (*P*= 0.0001), and RVECi (*P*= 0.0001) compared to group C; RVE compared to RME (*P*= 0.028) and Ci (*P*= 0.026); RMECi

Table 2. Baseline comparison of variables between groups using one-way ANOVA

Variable	C	RME	RVE	Ci	RMECi	REVCi	Sig.
Age (years)	41.57 (± 4.39)	41.88 (± 4.12)	40.25 (± 2.96)	43.13 (± 4.05)	41.71 (± 4.15)	41.86 (± 5.39)	0.860
Height (M)	1.57 (± 0.03)	1.59 (± 0.03)	1.6 (± 0.06)	1.56 (± 0.11)	1.62 (± 0.05)	1.59 (± 0.05)	0.663
Weight (kg)	65.14 (± 4.59)	69.25 (± 8.9)	73 (± 8.35)	70.5 (± 4.2)	72.57 (± 5.62)	66.86 (± 3.13)	0.138
Body mass index	26.27 (± 2.27)	27.17 (± 2.92)	28.52 (± 3.78)	29.17 (± 5.45)	27.5 (± 1.8)	26.47 (± 2)	0.518
Body fat (%)	37.15 (± 4.12)	38.43 (± 4.15)	35.5 (± 5.27)	38.17 (± 5.43)	33.33 (± 4.16)	36.12 (± 4.38)	0.307
Vo2max (ml/kg/min)	23.35 (± 3.44)	21.91 (± 3.9)	24.44 (± 2.13)	23.09 (± 2.86)	22.96 (± 4.35)	22.14 (± 2.99)	0.718
Metrnl (pg/ml)	583.29 (±69.85)	579.13 (±78.85)	583.63 (±86.58)	609.38 (±50.17)	566.86 (± 37)	599 (± 86.36)	0.885
Irisin (ng/ml)	236.14 (±18.7)	246.63 (±19.06)	246.25 (±2.43)	240.5 (± 19.79)	252.14 (± 14.26)	243.71 (± 27.81)	0.748
HOMA-IR	4.49 (± 1.64)	4.25 (± 1.61)	5.05 (± 1.51)	4.24 (± 078)	4.57 (± 1.58)	4.43 (± 0.72)	0.864

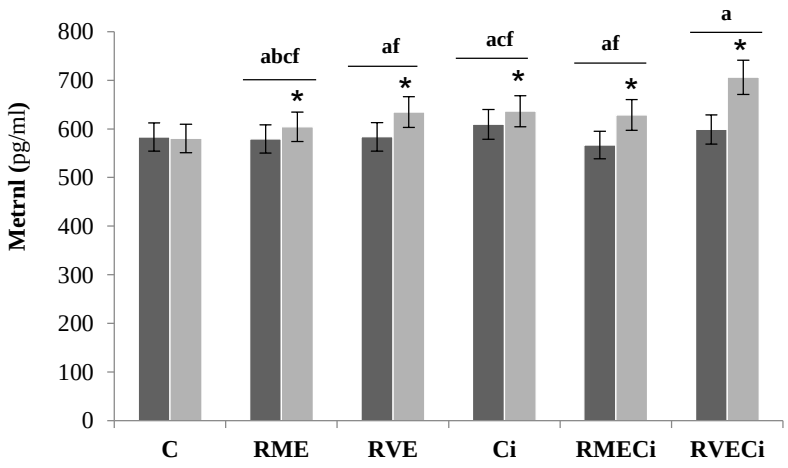

Figure 1. Metrnl serum levels by dependent t and ANCOVA test (at *P*< 0.05).
***Difference with pre-test, a difference with C, b difference with RVE, c difference with RMECi, f difference with RVECi.**
C (Control), RME (Resistance and Moderate Aerobic Exercise), RVE (Resistance and Vigorous Aerobic Exercise), Ci (Cinnamon), RMECi (Resistance and Moderate Aerobic Exercise+Cinnamon), RVECi (Resistance and Vigorous Aerobic Exercise+Cinnamon).

Table 3. The average height, weight, BMI, Body fat and Vo2max of the groups

Groups		C	RME	RVE	Ci	RMECi	RVECi
Age (years)	**pre-test**	41.57 (± 4.39)	41.88 (± 4.12)	40.25 (± 2.96)	43.13 (± 4.05)	41.71 (± 4.15)	41.86 (± 5.39)
Height (M)	**pre-test**	1.57 (± 0.03)	1.59 (± 0.03)	1.6 (± 0.06)	1.56 (± 0.11)	1.62 (± 0.05)	1.59 (± 0.05)
	pre-test	65.14 (± 4.59)	69.25 (± 8.9)	73 (± 8.35)	70.5 (± 4.2)	72.57 (± 5.62)	66.86 (± 3.13)
Weight (kg)	**post-test**	65.86 (± 1.4)	65 (± 9)[a]	66.25 (± 6.96)[a]	67.38(± 4.5)[acf]	67.43 (± 4.35)[a]	60.71 (± 3.7)[a]
	intragroup p	0.220	0.0001*	0.0001*	0.0001*	0.002*	0.001*
	pre-test	26.27 (± 2.27)	27.17 (± 2.92)	28.52 (± 3.78)	29.17 (± 5.45)	27.5 (± 1.8)	26.47 (± 2)
Body mass index	**post-test**	26.56 (± 1.2)	25.48 (± 2.89)[a]	25.9 (± 3.31)[a]	27.89 (± 5.5)[ad]	25.58 (± 1.74)[a]	24.05 (± 2.23)[a]
	intragroup p	0.230	0.0001[a]	0.0001*	0.0001*	0.002*	0.0001*
	pre-test	37.15 (± 4.12)	38.43 (± 4.15)	35.5 (± 5.27)	38.17 (± 5.43)	33.33 (± 4.16)	36.12 (± 4.38)
Body fat (%)	**post-test**	37.25 (± 3.69)	35.69 (± 4.1)[a]	32.79 (± 5.69)[a]	35.36 (± 6.17)[a]	29.86 (± 3.65)[a]	31.72 (± 3.60)[a]
	intragroup p	0.701	0.006*	0.0001*	0.001*	0.006*	0.001*
	pre-test	23.35 (± 3.44)	21.91 (± 3.9)	24.44 (± 2.13)	23.09 (± 2.86)	22.96 (± 4.35)	22.14 (± 2.99)
Vo2max (ml/kg/min)	**post-test**	22.19 (± 4.81)	26.27 (± 4.45)[a]	27.56 (± 3.66)[a]	23.58 (± 2.82)[d]	26.6 (± 5.76)[a]	25.53 (± 3.36)[a]
	intragroup p	0.218	0.003*	0.009*	0.056	0.009*	0.009*

*Difference with pre-test, a difference with C, b difference with RVE, d difference with RME, c difference with RMECi, f difference with RVECi.

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compared to RME (*P*= 0.0001) and Ci (*P*= 0.0001); RVECi compared to RME (*P*= 0.0001), RVE (*P*= 0.039) and Ci (*P*= 0.0001). The results of intra-group comparison showed a significant increase in Irisin levels in RME (*P*= 0.0001), RVE (*P*= 0.0001), Ci (*P*= 0.002), RMECi (*P*= 0.0001), and RVECi (*P*= 0.001) (Figure 2).

In addition, data analysis using ANCOVA showed that there is a significant difference in HOMA-IR between different groups (*P*= 0.0001, F=16.939). The results of post hoc test showed a significant decrease in HOMA-IR in RME (*P*= 0.014), RVE (*P*= 0.001), Ci (*P*= 0.044), RMECi (*P*= 0.0001), and RVECi (*P*= 0.0001) compared to C; RMECi compared to RME (*P*= 0.013), Ci (*P*= 0.004); RVECi compared to RME (*P*=0.001), RVE (*P*=0.023) and Ci (*P*= 0.0001) (Figure 3).

The results of intra-group comparison showed a significant decrease in the mean levels of HOMA-IR in RME (*P*= 0.016), RVE (*P*= 0.008), Ci (*P*= 0.011), RMECi (*P*= 0.006) and RVECi (*P*= 0.0001) (Figure 3).

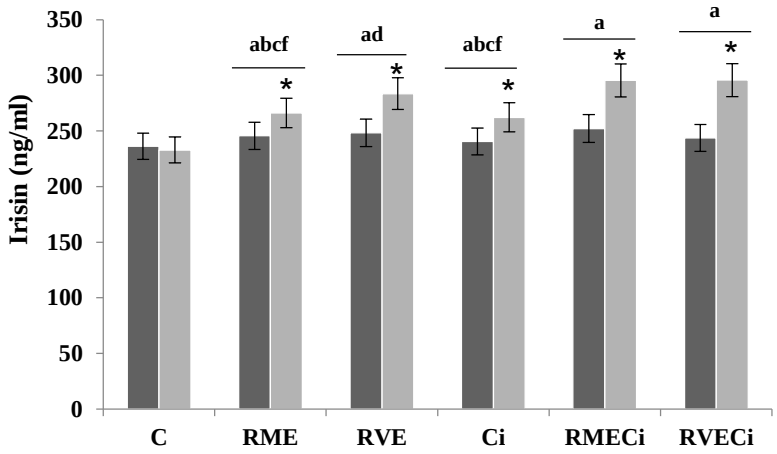

Figure 2. Irisain serum levels by dependent t and ANCOVA test (at *P*< 0.05).
***Difference with pre-test, a difference with C, b difference with RVE, c difference with RMECi, f difference with RVECi.**

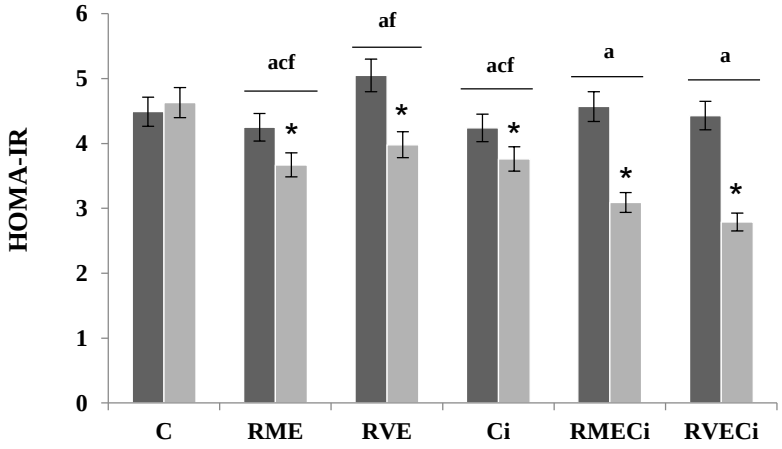

Figure 3. HOMA-IR levels by dependent t and ANCOVA test (at *P*< 0.05).
***Difference with pre-test, a difference with C, b difference with RVE, c difference with RMECi, f difference with RVECi.**
C (Control), RME (Resistance and Moderate Aerobic Exercise), RVE (Resistance and Vigorous Aerobic Exercise), Ci (Cinnamon), RMECi (Resistance and Moderate Aerobic Exercise+Cinnamon), RVECi (Resistance and Vigorous Aerobic Exercise+Cinnamon).

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Discussion

The results of the present study indicated that both training methods led to a significant increase in serum levels of Metrnl and Irisin in women with T2D. Additionally, the HOMA-IR index showed a significant decrease following both training methods. In this context, Tayibi et al. (2023) found that eight weeks of circuit resistance training at varying intensities could elevate resting Metrnl levels in men with TD2, correlating with improvements in fasting blood glucose levels and insulin resistance (14). Liu et al. (2023) also reported an increase in serum levels of Metrnl after exercise in the skeletal muscles of patients with coronary artery disease (CAD) (15). Rao et al. (2014) documented an increase in Metrnl levels following a period of combined endurance and resistance training (2). In the present study, the increase in Metrnl was linked to a rise in irisin in T2D. Research has indicated a strong correlation between Metrnl and irisin (4). An increase in irisin was also noted in T2D men (16) and women (17) following exercise. Studies have demonstrated that exercise training promotes mitochondrial biogenesis and the release of Metrnl through the upregulation of PGC-1α, thereby reducing adipocyte dysfunction and insulin resistance. Lee et al. (2020) stated that the increase in Metrnl due to exercise-induced contractions, through stimulating AMPK phosphorylation and increasing the expression of GLUT4 in the cell membrane, enhances glucose uptake and improves glucose tolerance (18). Additionally, the increase of PGC-1α resulting from exercise activity leads to the upregulation of the conversion of FNDC5 to irisin. Both proteins play a role in stimulating the browning of white adipose tissue, increasing glucose absorption, and enhancing the function of pancreatic β cells (19). Metrnl can improve glucose tolerance and increase GLUT4 transcription via an AMPKα2-dependent pathway in HFD-induced obese-diabetic rats (3). Based on this, increasing the levels of these proteins may contribute to improving the insulin resistance index (HOMA-IR) in women with T2D in the present study. However, some studies have indicated that exercise does not significantly affect Metrnl and Irisin. Mu et al. (2023) conducted a study examining the effects of cold-water training on Metrnl levels and found that such training does not significantly impact Metrnl in swimmers (20). In another study on overweight teenage boys, it was found that six weeks of resistance training did not influence serum levels of Metrnl, insulin resistance index, or body composition (21). Variations in findings may result from the type, intensity of exercise, or the exercise environment. Additionally, differences among subjects regarding the type of disease can affect the outcomes. Another outcome of the current study was a significant increase in Metrnl and irisin in the RVE group compared to the RME group. In the study by Riahy et al. (2024), which examined the effects of HIIT and MICT on FGF21, irisin, and myostatin in men with T2D, it was observed that while both training types improved insulin resistance, body composition, and VO2max, only HIIT led to significant increases in irisin (16). Furthermore, in the study by Da Silva et al. (2020), found that higher intensity exercises produced better outcomes for insulin, LDL, and HOMA-IR (22). Numerous studies have demonstrated the effectiveness of high-intensity aerobic exercise over moderate and low-intensity exercise in improving insulin levels. It seems that high-intensity exercise increases the phosphorylation of insulin receptor substrates in adipose and muscle tissues, and these changes are linked to a reduction in fatty acid intake and a decrease in lipogenesis in adipose tissues through a decrease in the activity of fatty acid transporters and fatty acid synthesis (23). More intense exercise can more strongly stimulate the signaling pathways activated by exercise in cells due to a greater increase in energy metabolism compared to low-intensity exercises (24). Previous findings suggest that exercise intensity may influence FNDC5/Irisin signaling pathways, indicating that low-intensity exercise may (25) not be sufficient to activate these signaling pathways.

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Among the other results of this study, there was a significant increase in serum levels of Metrnl and irisin, along with a decrease in the HOMA-IR index following the consumption of cinnamon in women with T2D. The effect of cinnamon on improving irisin, insulin resistance, and fasting insulin in overweight individuals was also confirmed. Kwan et al. (2017) also noted that cinnamon extract enhances the expression of UCP1 and markers indicative of adipose tissue browning in subcutaneous fat cells and 3T3-L1 adipocytes (26). However, Mirshfahi et al. (2023) demonstrated that, despite the upregulation of UCP1 expression in visceral adipose tissue and a reduction in insulin resistance following cinnamon consumption in insulin-resistant mice, cinnamon consumption alone did not have a significant effect on the expression of irisin and FNDC5 (10). Evidence suggests that cinnamon may enhance PPARγ activity and lipid metabolism (11), potentially influencing Metrnl. In adipocytes, the application of PPARγ inhibitors resulted in decreased Metrnl expression, suggesting that PPARγ is one of the signaling pathways for Metrnl that regulates adipose tissue phenotype (27). By modulating AMPK and subsequently increasing the phosphorylation of PGC-1α, cinnamon promotes mitochondrial metabolism and biogenesis (28). As previously mentioned, PGC-1α elevates FNDC5 expression and subsequently boosts the levels of irisin. Research has indicated that cinnamon can lower blood glucose levels and enhance insulin sensitivity. Cinnamon diminishes the activity of insulin phosphatase receptors, and by activating insulin kinase receptors, it results in increased insulin sensitivity and decreased insulin resistance (29). In addition, cinnamon increases adrenergic receptors, particularly β3-AR (30), which can activate factors such as UCP1 and PGC-1α, thereby enhancing thermogenesis and boosting fat and carbohydrate metabolism (31).

The results of the present study indicated that both training methods, combined with cinnamon consumption, significantly elevated the serum levels of Metrnl and Irisin in women with T2D, with a notable increase compared to the RME and Ci groups. The levels of HOMA-IR significantly decreased in both training methods alongside cinnamon consumption in comparison to the RME and Ci groups. The simultaneous effects of exercise and cinnamon supplementation on Metrnl were also corroborated by other studies. In this context, Tayibi et al. (2024) demonstrated that the combination of swimming training and cinnamon extract consumption resulted in a significant increase in serum levels of Metrnl and a reduction in fasting blood sugar levels in diabetic rats (32). Another study observed that the combination of exercise and cinnamon upregulated the expression of FNDC5 and UCP1 in visceral fat tissue and reduced insulin resistance in mice fed a high-fructose diet (10). Delshad et al. (2022) also reported that combining aerobic training with TRX and cinnamon supplementation led to decreased serum concentrations of insulin and HOMA-IR, while also increasing irisin levels (33). A crucial cellular pathway for transitioning adipose tissue phenotype from white adipose tissue (WAT) to brown adipose tissue (BAT) is the PGC-1α signaling pathway, which ultimately elevates irisin levels. Studies have shown that both aerobic exercise (34) and cinnamon (35) have a synergistic effect by influencing PGC-1α, consequently enhancing thermogenesis-related genes and potentially converting WAT to BAT. In addition, it has been observed that the combination of exercise and cinnamon increases the expression of β3-AR and ERK2 genes, which play an important role in regulating white adipose tissue (WAT) metabolism and in converting WAT into brown fat tissue (30). Another interesting finding of this study was the significant increase in serum levels of Metrnl in the RVECi group compared to the RMECi group. As mentioned earlier, the difference in exercise intensity is one of the effective factors influencing the activation of PGC-1α and subsequently Metrnl, which may explain this difference.

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Conclusions

Based on the findings of this study, both types of exercise positively affected indicators of fat tissue browning, such as Metrnl and Irisin, and improved the insulin resistance index in diabetic women. However, the effect of RVE exercise was superior to RME regarding irisin and the HOMA-IR index. Furthermore, the consumption of cinnamon supplement enhanced the effect of exercise on indicators that influence the browning of white adipose tissue and glucose homeostasis. Therefore, employing a combined exercise program (aerobic + resistance) alongside cinnamon consumption may help prevent or delay complications associated with T2D, serving as an effective treatment method for women.

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Conflict of Interest

The authors declare that they have no competing interests

Authors' contribution

Designing the study: A.A and A.B. Experimental work: A.A and M.Gh. Data analysis: Kh.JD. Writing the manuscript: A.A and M.Gh.

All the authors critically revised the manuscript, agree to be fully accountable for the integrity and accuracy of the study, and read and approved the final manuscript.

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