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The Effect of Eight Weeks of Resistance Training on Serum Levels of Myostatin, Interleukin-1 Beta, Vascular Endothelial Growth Factor, and Nitrotyrosine-3, and Its Association with Inflammatory-Myokine Changes and Glycemic Control in Middle-Aged Women with Type 2 Diabetes

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Abstract

Background and Aim: Type 2 diabetes is a prevalent metabolic disorder. Resistance training has been proposed as an effective non-pharmacological intervention; however, its underlying molecular mechanisms in middle-aged women remain poorly understood. The present study was therefore conducted to investigate the effects of eight weeks of resistance training on serum levels of myostatin, interleukin-1 beta, vascular endothelial growth factor, and nitrotyrosine-3, and to examine its association with inflammatory myokine changes and glycemic control in middle-aged women with type 2 diabetes.

Materials and Methods: In this quasi-experimental study, 14 middle-aged diabetic women were randomly divided into two groups: resistance training (8 weeks, 3 sessions per week, 40–75% of one repetition maximum) and control. Serum levels of variables were measured at pre-test and 48 hours after the last training session. Paired t-test, ANCOVA, and Pearson correlation tests were used for data analysis.

Results: Resistance training significantly decreased myostatin and IL-1β ($P = 0.001$) and significantly increased VEGF and NT-3 ($P = 0.001$). Additionally, a significant reduction in HbA1c was observed in the training group ($P = 0.012$), while changes in fasting blood sugar and albumin were not significant. Correlation analysis revealed that decreased IL-1β was associated with increased albumin ($r = -0.853$, $P = 0.015$), and decreased myostatin was associated with decreased fasting blood sugar ($r = -0.802$, $P = 0.030$).

Conclusion: Eight weeks of resistance training, by modulating myostatin, IL-1β, VEGF, and NT-3 and reducing HbA1c, may serve as an effective strategy in managing type 2 diabetes in middle-aged women. The observed correlations support the interplay between inflammatory, muscular, and metabolic systems in response to resistance training.

Trial registration: This trial was registered in the Iranian Registry of Clinical Trials (IRCT20241001063236N1) on 2024-10-11. (http://www.irct.ir/)

Keywords: Resistance Training, Type 2 Diabetes, Myostatin, Interleukin-1 Beta, Vascular Endothelial Growth Factor, Nitrotyrosine 3

Introduction

Type 2 diabetes is one of the most prevalent metabolic disorders worldwide, characterized by chronic hyperglycemia, insulin resistance, and impaired insulin secretion (1). According to the International Diabetes Federation, approximately 537 million adults were living with diabetes in 2021, and this number is projected to rise to 783 million by 2045 (2). Beyond its substantial economic burden, type 2 diabetes is associated with serious complications, including cardiovascular disease, nephropathy, retinopathy, and neuropathy, all of which significantly impair patients' quality of life (3). Therefore, identifying effective non-pharmacological strategies to manage this disease and mitigate its complications is of paramount importance.

Regular physical activity is widely recognized as one of the most effective non-pharmacological approaches for managing type 2 diabetes (4). In recent years, resistance training has garnered considerable attention due to its positive effects on increasing muscle mass, improving insulin sensitivity, and reducing fasting blood glucose (5). Unlike aerobic exercise, which primarily targets the cardiovascular system, resistance training enhances muscle protein synthesis and improves the metabolic function of skeletal muscle, positioning it as a promising strategy for glycemic control in type 2 diabetes (6). However, the precise molecular mechanisms underlying these beneficial effects remain to be fully elucidated.

Among the key molecules involved in the response to resistance training is myostatin, a member of the transforming growth factor-beta (TGF-β) superfamily, which acts as a potent negative regulator of skeletal muscle growth (7). This myokine is predominantly expressed in skeletal muscle and, through binding to the activin receptor type IIB (ACTRIIB) and subsequent activation of the Smad2.3 signaling cascade, inhibits satellite cell proliferation and differentiation, ultimately suppressing muscle hypertrophy (8). Elevated myostatin levels have been observed in diabetic patients and are associated with insulin resistance, reduced muscle mass, and exacerbated systemic inflammation (9). Conversely, resistance training has been shown to reduce circulating myostatin levels, thereby promoting muscle hypertrophy and enhancing insulin sensitivity (10). Nevertheless, the precise relationship between changes in myostatin and glycemic control indices in middle-aged women with type 2 diabetes remains underexplored.

In parallel with myostatin, interleukin-1 beta (IL-1β) serves as a key pro-inflammatory cytokine with a pivotal role in the pathogenesis of type 2 diabetes (11). Elevated IL-1β levels in diabetic patients activate intracellular inflammatory pathways, impair insulin signaling, and reduce glucose uptake by skeletal muscle cells (12). Regular physical activity, particularly resistance training, can attenuate systemic inflammation by reducing IL-1β levels, thereby improving insulin sensitivity (13). Exercise-induced reduction in inflammation appears to be a primary mechanism underlying improved glycemic control in type 2 diabetes. The crosstalk between myostatin and IL-1β—termed the inflammation-myokine axis—may represent a critical pathway in the adaptive response to resistance training, whereby their concurrent reduction leads to substantial metabolic improvements in diabetic patients.

Beyond myostatin and IL-1β, other biochemical markers, including vascular endothelial growth factor (VEGF) and nitrotyrosine-3 (NT-3), are also modulated by exercise. VEGF is a key factor in angiogenesis and vascular repair, and its circulating levels are altered in diabetic patients due to tissue hypoxia and inflammation (14). Increased VEGF in response to resistance training may reflect improved blood flow and tissue oxygenation (15). Nitrotyrosine-3, on the other hand, is a biomarker of oxidative and nitrosative stress, formed via the nitration of tyrosine residues in proteins by peroxynitrite—a potent pro-oxidant generated from the interaction between superoxide anion and nitric oxide (16). Elevated 3-NT levels are associated with various diabetic complications, including endothelial dysfunction, enhanced endothelial apoptosis, and accelerated atherosclerosis (17). In patients with type 2 diabetes, 3-NT levels are significantly higher than in non-diabetic individuals and correlate with insulin resistance and vascular complications (18). The response of 3-NT to exercise appears to be dependent on the type, intensity, and

duration of training (19). Despite its established role as a biomarker in diabetes, the impact of resistance training on 3-NT levels in middle-aged women with type 2 diabetes has not been adequately investigated. Furthermore, the influence of resistance training on VEGF and 3-NT, and their association with other inflammatory and muscular variables in this population, warrants further study.

Albumin, the most abundant plasma protein, serves as a nutritional and inflammatory marker in diabetic patients (20). In uncontrolled diabetes, glycation of albumin occurs, leading to reduced albumin levels, which are associated with an increased risk of renal and cardiovascular complications (21). Moreover, IL-1β, as a pro-inflammatory cytokine, inhibits hepatic albumin synthesis (22). Therefore, the anti-inflammatory effect of resistance training may be accompanied by an increase in serum albumin. However, previous studies have reported conflicting results regarding the effect of resistance training on albumin, with some showing an increase (23) and others reporting no significant changes (24). Nevertheless, the relationship between alterations in IL-1β and albumin in response to resistance training in diabetic women has received limited attention.

Despite substantial evidence supporting the positive effects of resistance training on glycemic control (25) and inflammation, many aspects of the relationship between myokine (particularly myostatin) and pro-inflammatory cytokine (such as IL-1β) changes and clinical indices of diabetes (fasting blood glucose, HbA1c, and albumin) remain poorly understood. Similarly, the role of VEGF and NT-3 as vascular markers in response to resistance training in middle-aged women with type 2 diabetes has been scarcely investigated. Examining the correlations among these biomarkers could enhance our understanding of the interplay between inflammatory, muscular, vascular, and metabolic systems in response to resistance training. In other words, it remains unclear whether resistance training-induced changes in myostatin and IL-1β are associated with improved glycemic control and vascular parameters. Ultimately, exercise and physical activity may serve as an appropriate strategy for the management and control of diabetes.

Accordingly, the primary hypothesis of the present study was that eight weeks of resistance training, through reducing myostatin and IL-1β, would be associated with changes in glycemic control indices (fasting blood glucose and HbA1c) and albumin levels. Therefore, this study was conducted to investigate the effects of eight weeks of resistance training on serum levels of myostatin, interleukin-1 beta, vascular endothelial growth factor, and nitrotyrosine-3, and its association with inflammatory myokine changes and glycemic control in middle-aged women with type 2 diabetes.

Materials and Methods

Study Design and Participants

This study was conducted on women with type 2 diabetes referred to hospitals and the Diabetes Association of Ardabil. Inclusion criteria comprised a physician-confirmed diagnosis of type 2 diabetes for more than one year, age between 35 and 60 years, body mass index (BMI) between 27 and 32 kg.m², and a sedentary lifestyle (defined as less than 20 minutes of structured exercise per week). Exclusion criteria included hypertension, elevated fasting triglycerides, history of cardiovascular disease, thyroid disorders, cancer, endocrine disorders (other than diabetes), severe renal or hepatic disease, history of surgery, and use of tobacco, narcotics, or alcohol. Participants were permitted to use only oral hypoglycemic agents (e.g., metformin and glybenclamide) and were instructed not to alter their medication regimen throughout the study period.

From an initial pool of 80 women assessed for eligibility, 14 met the inclusion criteria. Following an orientation session and provision of written informed consent, participants were randomly allocated into two groups of seven: a resistance training group and a control group (25, 26). Although the sample size was

relatively small, the homogeneity of the participants, strict adherence to eligibility criteria, and random allocation supported the internal validity of the study. Randomization was performed by an individual independent of the exercise intervention, in accordance with the CONSORT guidelines (27).

Experimental Procedures

Seventy-two hours prior to the intervention, anthropometric measurements were obtained, and 48 hours later, participants underwent medical examination by a physician and were referred to the laboratory for baseline blood sampling. The experimental group visited the university wellness center for familiarization with the exercise protocol, while the control group was instructed to refrain from any physical activity throughout the study period. Forty-eight hours after the final training session, all anthropometric and blood measurements were repeated.

This study was conducted as an 8-week clinical trial at the University of Mohaghegh Ardabili, registered with the Iranian Registry of Clinical Trials (IRCT20241001063236N1) and performed in accordance with the CONSORT reporting standards. The study protocol was approved by the Ethics Committee of the University of Mohaghegh Ardabili (IR.UMA.REC.1403.055).

Pre-intervention Procedures

Prior to the intervention, all participants attended informational sessions covering the study objectives, procedures, and exercise equipment. Baseline assessments, including anthropometric measurements and blood pressure, were conducted during this phase. Fasting blood samples were collected between 8:00 and 10:00 a.m. at the laboratory by a trained specialist.

Resistance Training Protocol

The resistance training program was performed for 8 weeks, with three sessions per week. Each session initially lasted 45 minutes and gradually increased to 60 minutes by the eighth week. To prevent hypoglycemia during sessions exceeding 30 minutes, participants received 15–30 grams of carbohydrates (in the form of dates) at 30- to 60-minute intervals.

Each resistance training session consisted of a 10-minute aerobic warm-up, a main segment comprising six resistance exercises, and a 5-minute cool-down with light stretching exercises. Exercise intensity was prescribed as a percentage of one-repetition maximum (1RM) and progressively increased according to the principle of overload. During weeks 1 and 2, participants performed two sets of 10–12 repetitions at 40% of 1RM. Intensity was increased to 45% in week 3, 50% in week 4, 60% in week 5, and 70% in week 6, with three sets of 10 repetitions during these weeks. In weeks 7 and 8, participants performed three sets of eight repetitions at 75% of 1RM.

To determine initial training loads and monitor progression, 1RM was assessed using the Brzycki formula (28):

$$1RM\ (kg) = \text{Lifted Weight (kg)} \div [1.0278 - (0.0278 \times \text{Number of Repetitions})]$$

All physiological measurements and blood sampling were repeated 48 hours after the final training session, following the same procedures as the pre-test. The exercise protocol was designed based on the American College of Sports Medicine guidelines for clinical and elderly populations and is summarized in Table 1 (29).

Table 1. Resistance Training Program

Week	1	2	3	4	5	6	7	8
Warm-up	**10 minutes**							
Barbell Chest Press	2 × 10–12	3 × 10					3 × 8	**3 × 8**
Leg Extension	2 × 10–12	3 × 10					3 × 8	**3 × 8**
Leg Curl	2 × 10–12	3 × 10					3 × 8	**3 × 8**
Dumbbell Shoulder Press	2 × 10–12	3 × 10					3 × 8	**3 × 8**
Barbell Biceps Curl	2 × 10–12	3 × 10					3 × 8	**3 × 8**
Single-Arm Dumbbell Triceps Extension	2 × 10–12	3 × 10					3 × 8	**3 × 8**
Intensity (% of 1RM)	40	40	45	50	60	70	75	**75**
Rest between sets	60 s	60 s	90 s	90 s	90 s	120 s	120 s	**120 s**
Rest between exercises	90 s	90 s	120 s	120 s	120 s	180 s	180 s	**180 s**
Cool-down	**5 minutes**							

Measurements and Data Analysis

Anthropometric and Body Composition Measurements

Anthropometric parameters and body composition indices, including body mass index (BMI), body fat percentage (BF%), and skeletal muscle mass (SMM), were measured 72 hours before the intervention and again upon completion of the training period. Body composition was assessed using the X-Contact 356 bioelectrical impedance analysis device (Jawon Medical, South Korea). Height (without shoes) and weight were measured using standard equipment and a calibrated Seca scale (Germany), respectively. Waist circumference was measured at the midpoint between the iliac crest and the lower border of the ribs, and hip circumference at the most prominent point of the buttocks from a lateral view, both recorded to the nearest 0.1 cm. The waist-to-hip ratio (WHR) was calculated by dividing waist circumference by hip circumference (30). BMI was calculated as body weight in kilograms divided by height in meters squared ($kg.m^2$).

Blood Sampling and Biochemical Analyses

Blood samples were collected on two occasions: 48 hours before the intervention and 48 hours after the final training session, at the Ardabil University of Medical Sciences Laboratory. Participants attended the laboratory between 8:00 and 10:00 a.m. after a minimum 12-hour fast. Approximately 10 mL of blood was drawn from the antecubital vein by a trained laboratory technician while participants were seated and at rest. Serum was separated by centrifugation using a Universal 18-centrifuge (Iran) at 3000 rpm for 5 minutes. The extracted serum was aliquoted into sterile microtubes and stored at -80°C until analysis.

Serum levels of myostatin were measured using an ELISA kit (R&D Systems, USA) with a sensitivity range of 0.922–5.32 ng.mL and reported in ng.mL. VEGF concentrations were determined using ELISA kits (Boster, USA) with a sensitivity of 1 pg.mL. Serum 3-NT levels were measured using commercially available ELISA kits according to the manufacturer's instructions, with final concentrations calculated from standard curves and expressed as pg.mL. Serum IL-1β levels were quantified using a commercial ELISA kit (BioVendor, Austria), with a detection range of 1.25–80 pg.mL and a sensitivity of 0.4 pg.mL. Serum albumin was measured using the bromocresol green method with a kit from Bairc Fars (model ml500, product code BXC0222A) at the Saray Tabriz Laboratory, with a normal reference range of 3.5–5.2 g.dL.

Statistical Analysis

Data normality was assessed using the Shapiro-Wilk test, and homogeneity of variances was evaluated using Levene's test. To examine the effect of the exercise intervention on serum myostatin and body composition indices, a one-way analysis of covariance (ANCOVA) was employed for between-group

comparisons, and paired t-tests were used for within-group comparisons. Given the primary study objective of elucidating the relationship between the inflammatory-muscular axis (IL-1β and myostatin) and glycemic control indices (fasting blood glucose, HbA1c, and albumin), correlation analysis using Pearson's test was focused exclusively on these variables. VEGF and 3-NT, being secondary markers with longer-term responses, were excluded from the correlation matrix to prevent table congestion and thematic dispersion. Statistical significance was set at $P < 0.05$ for all analyses. All statistical procedures were performed using SPSS version 26.

Results

Baseline Characteristics

Baseline characteristics of the participants are presented in Table 2. Independent t-tests revealed no significant differences between the resistance training and control groups in pre-test values for age, height, weight, WHR, or BMI, confirming initial homogeneity between the groups.

Table 2. Baseline Characteristics of Participants

Variables	Group	Mean ± SD	Range (Min–Max)	P
Age (years)	Resistance Control	51.14 ± 4.59 46.40 ± 5.15	46 - 58 37 - 54	0.095
Height (m)	Resistance Control	157.57 ± 6.34 154.85 ± 6.66	148 - 166 145 - 163	0.450
Weight (kg)	Resistance Control	75.67 ± 11.66 70.93 ± 7.80	58.50 – 92.10 56.80 – 80.70	0.389
WHR	Resistance Control	0.88 ± 0.04 0.86 ± 0.03	0.84 – 0.95 0.82 – 0.90	0.506
BMI	Resistance Control	30.41 ± 3.80 30.01 ± 3.89	29.94 ± 3.43 29.82 ± 4.11	0.867

Data are presented as mean ± standard deviation (SD).
WHR: Waist-to-hip ratio.
P-value derived from independent t-test for pre-test comparisons between groups.

Data Distribution and Statistical Analysis

The distribution of data for all study variables was normal in both pre-test and post-test phases across the study groups, as confirmed by the Shapiro-Wilk test. Additionally, Levene's test confirmed the homogeneity of variances for all variables ($P > 0.05$). To evaluate the effect of the eight-week resistance training program and compare between-group changes, analysis of covariance (ANCOVA) was employed, with pre-test scores entered as covariates. The assumption of homogeneity of regression slopes was met for all analyses. Paired t-tests were also used for within-group comparisons. The results of these analyses are presented in Table 3 (for glycemic indices) and Table 4 (for primary outcome variables).

Between-Group Changes in Glycemic Indices

The between-group changes in glycemic indices related to diabetes are summarized in Table 3 and Figure 1. Following ANCOVA, which controlled for baseline values, no significant between-group differences were observed in any of the glycemic variables in the post-test phase ($P > 0.05$). Specifically, the resistance training group did not show statistically significant differences compared to the control group in fasting blood glucose ($F = 1.850$, $P = 0.188$), HbA1c ($F = 2.458$, $P = 0.115$), or albumin ($F = 0.260$, $P = 0.620$).

Table 3. Effect of Exercise Training on Glycemic Variables

Variables	Group		Mean ± SD	t-value	P-value*	ANCOVA		Effect Size (ES)
						F	P-value†	
Fasting Blood Sugar (mg.dL)	Resistance	Pre-test	149.14 ± 26.32	2.427	0.051	1.850	0.188	**0.179**
		Post-test	136.28 ± 15.62					
	Control	Pre-test	194.28 ± 37.79	1.082	0.321			
		Post-test	178.14 ± 32.61					
HbA1c (%)	Resistance	Pre-test	8.04 ± 1.40	3.532	0.012*	2.458	0.115	**0.224**
		Post-test	7.00 ± 1.90					
	Control	Pre-test	7.68 ± 0.97	0.727	0.490			
		Post-test	7.44 ± 0.84					
Albumin (g.dL)	Resistance	Pre-test	4.25 ± 0.46	-1.992	0.052	0.260	0.620	**0.023**
		Post-test	4.39 ± 0.39					
	Control	Pre-test	4.04 ± 0.54	-2.414	0.093			
		Post-test	4.31 ± 0.45					

Data are presented as mean ± standard deviation (SD).
P-value*: Paired t-test for within-group comparisons (pre-test vs. post-test).
P-value†: ANCOVA for between-group comparisons (post-test values adjusted for pre-test covariates).
Significant at $P < 0.05$.

Within-Group Changes in Glycemic Indices

The within-group changes in glycemic indices, as determined by paired t-tests (summarized in Table 3 and Figure 1), revealed that the resistance training group exhibited a significant reduction only in HbA1c from pre-test to post-test ($P = 0.012$). No significant changes were observed in fasting blood glucose or albumin levels within the resistance training group.

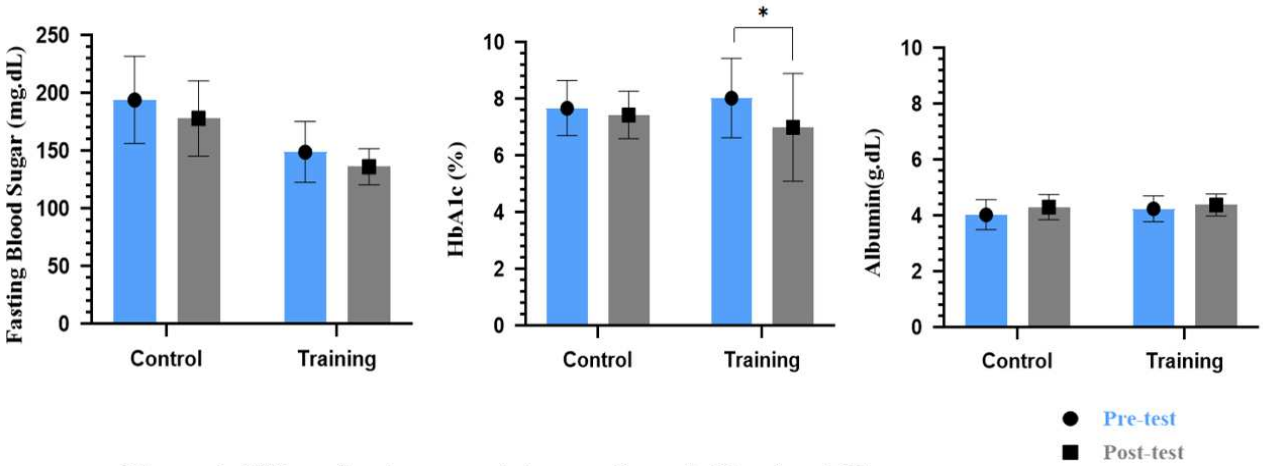


Figure 1: Effect of resistance training on glycemic blood variables
* Significant difference in post-test compared to pre-test in the training group by paired t-test

Between-Group Changes in Primary Outcome Variables

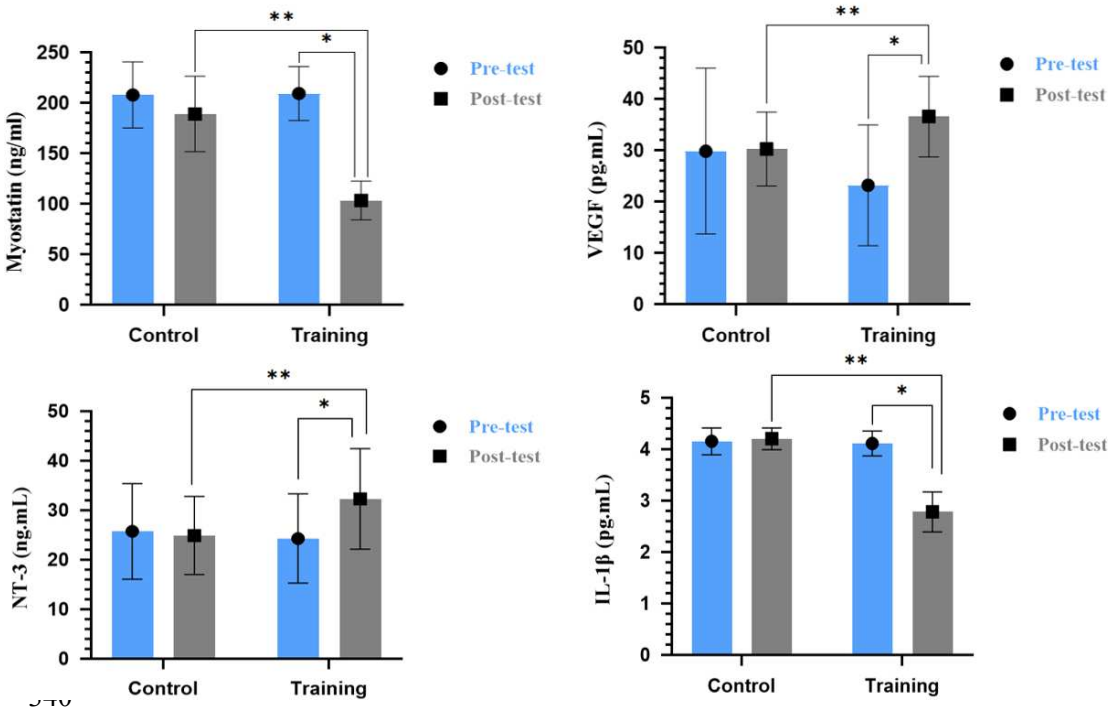
The between-group changes in the primary outcome variables are summarized in Table 4 and Figure 2. Following ANCOVA, which controlled for baseline values, significant between-group differences were observed for all primary variables in the post-test phase ($P < 0.05$). Specifically, the resistance training group demonstrated a significant decrease in serum myostatin ($F = 36.170$, $P = 0.001$) and interleukin-1 beta ($F = 852.988$, $P = 0.001$), as well as a significant increase in VEGF ($F = 5.526$, $P = 0.024$) and 3-NT ($F = 21.353$, $P = 0.001$) compared to the control group.

The within-group changes in the primary outcome variables, as determined by paired t-tests (summarized in Table 4 and Figure 2), revealed that the resistance training group exhibited significant reductions in serum myostatin and IL-1β levels from pre-test to post-test ($P = 0.001$ for both), as well as significant increases in VEGF and 3-NT levels ($P = 0.001$ for both). These findings indicate that eight weeks of resistance training effectively modulated key inflammatory-myokine and vascular markers in middle-aged women with type 2 diabetes.

Table 4. Effect of Resistance Training on Primary ELISA Variables

Variables	Group		Mean ± SD	t-value	P-value*	ANCOVA		Effect Size (ES)
						F	P-value†	
Myostatin (ng.mL)	Resistance	Pre-test	209.60 ± 66.81	7.674	0.001*	36.170	0.001*	**0.767**
		Post-test	103.62 ± 19.24					
	Control	Pre-test	208.24 ± 32.77	2.371	0.055			
		Post-test	189.35 ± 37.34					
VEGF (pg.mL)	Resistance	Pre-test	23.25 ± 11.77	-13.376	0.001*	5.526	0.024*	**0.334**
		Post-test	36.63 ± 7.86					
	Control	Pre-test	29.91 ± 16.14	-0.047	0.964			
		Post-test	30.31 ± 7.22					
NT-3 (ng.mL)	Resistance	Pre-test	24.29 ± 9.03	-7.780	0.001*	21.353	0.001*	**0.660**
		Post-test	32.26 ± 16.10					
	Control	Pre-test	25.71 ± 9.66	0.542	0.607			
		Post-test	24.87 ± 7.90					
IL-1β (pg.mL)	Resistance	Pre-test	4.11 ± 0.24	31.591	0.001*	852.988	0.001*	**0.987**
		Post-test	2.78 ± 0.17					
	Control	Pre-test	4.15 ± 0.26	-1.000	0.356			
		Post-test	4.20 ± 0.21					

Data are presented as mean ± standard deviation (SD).
P-value*: Paired t-test for within-group comparisons (pre-test vs. post-test).
P-value†: ANCOVA for between-group comparisons (post-test values adjusted for pre-test covariates).
Significant at $P < 0.05$.
Abbreviations: ES, Effect Size; VEGF, Vascular Endothelial Growth Factor; NT-3, Nitrotyrosine-3; IL-1β, Interleukin-1 beta; SD, Standard Deviation.



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Figure 2. Myostatin, VEGF, NT-3, IL-1β changes in the study groups
*Significant difference compared to the pre-test stage (P = 0.001)
**Significant difference compared to the control group (P = 0.001)

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Correlation Analysis

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To examine the relationships between changes (Δ = post-test − pre-test) in inflammatory-metabolic variables in response to eight weeks of resistance training, Pearson's correlation test was employed. The results of this analysis are summarized in Table 5. The findings revealed a significant negative correlation between Δ IL-1β and Δ serum albumin (r = -0.853, P = 0.015), indicating that reductions in IL-1β levels were associated with increases in albumin. Additionally, a significant negative correlation was observed between Δ myostatin and Δ fasting blood glucose (r = -0.802, P = 0.030), suggesting that decreased myostatin levels were associated with improved glycemic control.

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Table5. Correlation Matrix of Changes in Study Variables in the Resistance Training Group

			Myostatin	IL-1β	FBS	Hba1c	ALB
Mean difference values	Myostatin	Correlation coefficient	1	-0.204	-0.802*	-0.207	0.375
		Sig (2-tailed)		0.660	0.030**	0.656	0.408
	IL-1β	Correlation coefficient	-0.204	1	0.398	0.088	-0.853*
		Sig (2-tailed)	0.660		0.376	0.851	0.015**
	FBS	Correlation coefficient	-0.802*	0.398	1	-0.003	-0.451
		Sig (2-tailed)	0.030**	0.376		0.994	0.310
	Hba1c	Correlation coefficient	-0.207	0.088	-0.003	1	0.261
		Sig (2-tailed)	0.656	0.851	0.994		0.572
	ALB	Correlation coefficient	0.375	-0.853*	-0.451	0.261	1
		Sig (2-tailed)	0.408	0.015**	0.310	0.572	

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

It is noteworthy that although VEGF and 3-NT were measured as dependent variables, the primary focus of the present study was on the relationship between changes in IL-1β and myostatin—as representatives of the inflammation-myokine axis—and metabolic indices. Therefore, to maintain internal coherence and avoid potentially misleading interpretations arising from the small sample size, correlation analyses were concentrated on these key variables.

Discussion

The present study aimed to investigate the effects of eight weeks of resistance training on serum levels of myostatin, interleukin-1 beta, vascular endothelial growth factor, and nitrotyrosine-3, and its association with inflammatory myokine changes and glycemic control in middle-aged women with type 2 diabetes. The findings demonstrated that resistance training significantly reduced myostatin and IL-1β and significantly increased VEGF and 3-NT. Additionally, a significant reduction in HbA1c was observed in the training group, although changes in fasting blood glucose and albumin were not significant. Correlation analyses revealed that decreased IL-1β was associated with increased albumin, and decreased myostatin was associated with reduced fasting blood glucose.

Myostatin

The finding that resistance training significantly reduced serum myostatin levels in diabetic women aligns with previous research. Shabkhiz et al. (2021) demonstrated that resistance training significantly reduced circulating myostatin and improved insulin resistance in elderly men with type 2 diabetes (10). Similarly, Asadpour et al. (2026) reported reduced myostatin levels in the gastrocnemius muscle of aged female rats following resistance training (31). Jeong et al. (2026) found that combined resistance exercise with essential amino acid intake enhanced the follistatin-to-myostatin ratio in older women (32). A comprehensive meta-analysis by Zhang et al. (2025) confirmed that exercise, particularly resistance training, reduces myostatin expression through activation of the Wnt.GSK-3β.β-catenin pathway and is the most effective intervention for reducing myostatin across various populations (33). The mechanisms underlying myostatin reduction include increased follistatin (a myostatin antagonist), reduced inflammation, and activation of the AKT.mTOR pathway (7). Given that elevated myostatin is associated with insulin resistance and reduced muscle mass in diabetic patients, the training-induced reduction observed in this study represents a positive adaptation toward improved metabolic health.

Interleukin-1 Beta

The significant reduction in IL-1β following resistance training is consistent with the systematic review and meta-analysis by Kadoglou et al. (2025), which demonstrated that resistance training reduces inflammatory burden in diabetic patients (34). In agreement with Katbi et al. (2022), the present study found a significant decrease in IL-1β after eight weeks of resistance training. In their study, the reduction in IL-1β in the combined training group (aerobic + resistance) was accompanied by decreased lipocalin-2, indicating a synergistic effect of exercise in modulating systemic inflammation (35). Furthermore, Dobre et al. (2025) emphasized the role of myokines in the inflammation-insulin resistance crosstalk, demonstrating that muscle contractions reduce pro-inflammatory cytokines including IL-1β through AMPK activation and increased IL-10 and IL-1Ra (36). The mechanisms underlying IL-1β reduction may be attributed to decreased visceral adipose tissue, reduced reactive oxygen species (ROS), and increased anti-inflammatory cytokines. Given the pivotal role of IL-1β in the pathogenesis of diabetes through induction of insulin

resistance, its reduction through resistance training represents an important mechanism for improving metabolic status (37).

Vascular Endothelial Growth Factor

The significant increase in VEGF following eight weeks of resistance training in middle-aged women with type 2 diabetes is consistent with the findings of Yari et al. (2024) and Kim et al. (2023) (38, 39). Razavi Dehkordi et al. (2024) also reported increased VEGF gene expression following combined training (40). Tan et al. (2022) demonstrated that resistance training improves capillary angiogenesis through activation of the VEGF-PI3K-Akt-eNOS pathway. Increased blood flow, shear stress, and HIF-1α activation are additional mechanisms contributing to VEGF elevation (39, 41). In contrast, Behjati et al. (2015) reported a decrease in VEGF following resistance training in older women, which may be attributed to differences in baseline metabolic status (42). Overall, resistance training-induced VEGF elevation may serve as a protective mechanism against diabetic vascular complications.

Nitrotyrosine-3

The finding that eight weeks of resistance training significantly increased 3-NT in diabetic women is consistent with the results of Gutiérrez-Camacho et al. (2020) (19). The mechanism underlying this increase may be attributed to elevated production of reactive oxygen and nitrogen species (ROS.RNS) in response to muscle contractions during resistance training, leading to increased peroxynitrite and subsequent tyrosine nitration (43). This transient increase acts as a hormetic stimulus, activating the antioxidant defense system (44). Considering the concurrent reductions in IL-1β and myostatin, the observed 3-NT elevation appears to be an adaptive and transient response occurring within a context of reduced inflammation.

Glycemic Control and Albumin

The present study found no significant effect of eight weeks of resistance training on fasting blood glucose, although a within-group reduction in HbA1c was observed. The meta-analysis by Bärg et al. (2025) indicated that resistance training can improve glycemic control (45). Regarding albumin, no significant change was observed, consistent with Nemati (2024) (24), but in contrast to Ramezani et al. (2026), who reported an increase in albumin (23).

Correlation Analyses

Pearson correlation analysis revealed significant negative correlations between changes in IL-1β and serum albumin ($r = -0.853$, $P = 0.015$), and between changes in myostatin and fasting blood glucose ($r = -0.802$, $P = 0.030$). These findings indicate that reduction in IL-1β, a pro-inflammatory cytokine, is associated with increased albumin, an acute-phase protein with antioxidant properties, while decreased myostatin, a muscle growth inhibitory myokine, correlates with improved glycemic control (reduced fasting blood glucose). Although direct correlation studies investigating the relationship between IL-1β and albumin in response to resistance training in diabetic women are lacking, mechanistic evidence supports an inverse relationship between these variables. Park et al. (2021) demonstrated in hepatic stellate cells that albumin increases IL-1β expression through retinoic acid sequestration, and this IL-1β elevation, in turn, exerts anti-fibrotic effects via inhibition of TGF-β-Smad3 signaling (46). Based on this mechanism, the negative correlation observed in the present study between reduced IL-1β and increased albumin may reflect a regulatory feedback loop wherein decreased inflammation facilitates increased albumin as an acute-phase protein with anti-inflammatory properties. However, given the paucity of correlation studies in this area, the relationship between IL-1β and albumin appears to be influenced by multiple factors, including tissue type, inflammation severity, and baseline metabolic conditions.

The negative correlation between changes in myostatin and fasting blood glucose aligns with previous findings. Liu et al. (2018) demonstrated that myostatin inhibits glucose uptake in muscle cells through suppression of insulin-dependent and -independent signaling pathways (47). Therefore, resistance training-induced myostatin reduction may contribute to decreased fasting blood glucose through enhanced glucose uptake by skeletal muscle. Previous studies have also established that elevated myostatin levels are directly associated with insulin resistance and type 2 diabetes, and its reduction can improve insulin sensitivity (10).

Conclusion

In summary, the findings of the present study indicate that eight weeks of resistance training, through modulation of myostatin, IL-1β, VEGF, and 3-NT, and reduction of HbA1c, may serve as an effective non-pharmacological strategy for managing type 2 diabetes in middle-aged women. The observed correlations between changes in IL-1β and albumin, and between myostatin and fasting blood glucose, support the interplay between inflammatory, muscular, and metabolic systems in response to resistance training. Resistance training appears to concurrently reduce IL-1β and myostatin, potentially facilitating improvements in metabolic and nutritional status in diabetic patients. Reduced IL-1β may contribute to increased albumin through decreased inhibition of hepatic albumin synthesis, while decreased myostatin may lower fasting blood glucose through enhanced skeletal muscle glucose uptake. However, given the relatively small sample size and the scarcity of similar correlation studies in this field, longitudinal studies with larger sample sizes are recommended to confirm these findings.

List of Abbreviations:

ANCOVA: Analysis of Covariance

BMI: Body Mass Index

ELISA: Enzyme-Linked Immunosorbent Assay

ES: Effect Size

FBS: Fasting Blood Sugar

HbA1c: Glycosylated Hemoglobin

IL-1β: Interleukin-1 beta

NT-3: Nitrotyrosine-3

1RM: One Repetition Maximum

SD: Standard Deviation

VEGF: Vascular Endothelial Growth Factor

WHR: Waist-to-Hip Ratio

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the University of Mohaghegh Ardabili (IR.UMA.REC.1403.055). All participants provided written informed consent prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form (including individual details, images or videos).

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AN: Conceptualization, methodology, data collection, formal analysis, writing—original draft. FS: Conceptualization, methodology, supervision, validation, writing—review & editing. All authors read and approved the final manuscript.

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