Research Article

# Effects of eight weeks of functional training with and without blood flow restriction on serum irisin, IGF-1, and lipid profile in elderly women: A randomized controlled clinical trial

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## Abstract

Aging in women accelerates declines in anabolic hormones and disrupts lipid homeostasis, increasing cardiometabolic risk. Whether combining blood flow restriction (BFR) with functional training provides greater benefits for irisin, IGF-1, and lipid indices than functional training alone remains unclear. This study examined the effects of 8 weeks of functional training with and without BFR on these outcomes in older women. Thirty-six older women (mean age, 63.41 years) were randomly assigned to functional training with BFR (FTBFR;20–55% 1RM), functional training (FT;40–75% 1RM), or control (CON). The exercise protocol included 10 functional movements performed three times weekly for 8 weeks. Fasting blood samples were collected before and 48 hours after the final session. Serum irisin and IGF-1 were measured by ELISA, and lipid indices (TC, TG, LDL, and HDL) were assessed using enzymatic assays. Data were analyzed using paired t-tests and ANCOVA ($P < 0.05$). Significant between-group differences were observed for irisin ($P = 0.0001$), IGF-1 ($P = 0.001$), and the LDL/HDL ratio ($P = 0.0001$). Both training groups increased irisin (FTBFR, 32.85%; FT, 23.98%) and IGF-1 (FTBFR, 14.03%; FT, 9.28%) and reduced the LDL/HDL ratio (FTBFR, 25.09%; FT, 18.39%), whereas no changes occurred in CON. FTBFR produced a greater improvement in the LDL/HDL ratio than FT ($P=0.025$). Eight weeks of functional training improved endocrine and lipid-related biomarkers in older women. Adding BFR may enhance lipid-related adaptations during low-load functional training, although its independent contribution requires further investigation.

*Key Words:* Sarcopenia, Blood flow restriction, Functional training, Irisin, Elderly, Women

## Introduction

Population ageing has become one of the defining demographic transitions of the twenty-first century; the proportion of the world's population aged 60 years and over is projected to nearly double, rising from approximately 12% to 22% between 2015 and 2050 (World Health Organization, 2015). This transition is accompanied by a progressive decline in neuromuscular function, most notably the age-related loss of skeletal muscle mass, strength, and quality—collectively defined as sarcopenia—which independently predicts frailty, disability, and all-cause mortality in older adults (Cruz-Jentoft et al., 2019). In women, these processes are accelerated by the menopausal transition. Specifically, the withdrawal of ovarian estrogen hastens the loss of lean mass and increases central adiposity. Furthermore, this period induces an atherogenic shift in the blood lipid profile, characterized by elevated total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL), alongside reduced high-density lipoprotein cholesterol (HDL) (Ko & Kim, 2020). Older women therefore represent a population at disproportionate risk of both sarcopenia and cardiometabolic disease, underscoring the need for interventions that concurrently target musculoskeletal and metabolic health. In parallel with these structural and metabolic changes, ageing is characterized by a reduced concentration and bioactivity of anabolic and metabolically active myokines and hormones. Irisin, a myokine cleaved from the membrane protein FNDC5 under the transcriptional control of PGC-1α, has attracted considerable attention as a molecular link between physical activity and whole-body metabolism (Boström et al., 2012). Irisin promotes the browning of white adipose tissue, enhances thermogenesis, and is associated with favourable glucose and lipid regulation (Perakakis et al., 2017). Although circulating irisin declines with age and physical inactivity, and lower levels have been linked to dyslipidemia in older populations (Chang et al., 2017), the quantification of human iri-

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-sin remains methodologically debated. Owing to early concerns regarding antibody specificity and ELISA validity, irisin data should be interpreted with appropriate analytical caution (Albrecht et al., 2015).

Insulin-like growth factor-1 (IGF-1), the principal mediator of growth hormone action, further supports this system by driving skeletal muscle protein synthesis and tissue repair through the PI3K/Akt/mTOR signalling pathway (Bian et al., 2020). As levels of IGF-1 decline steadily with advancing age—a process often termed “somatopause”—this attenuation contributes not only to muscle atrophy but also to impaired lipid metabolism (Perrini et al., 2010). Given that both irisin and IGF-1 are responsive to muscular contraction, they represent biologically plausible mediators through which exercise may exert its anabolic and metabolic benefits in older women. Exercise training, and resistance training in particular, is a well-established countermeasure against age-related declines in muscle mass and metabolic function (Fragala et al., 2019). Conventional resistance training, however, typically requires intensities of at least 70% of one-repetition maximum (1RM) to elicit meaningful adaptations. Such heavy mechanical loading is often poorly tolerated by older adults due to pre-existing joint degeneration, osteoporosis, and cardiovascular risk (Csapo & Alegre, 2016). This limitation has generated growing interest in low-load resistance training combined with blood flow restriction (BFR). By utilizing an inflatable cuff to produce partial venous occlusion, BFR enables substantial gains in muscle size and strength at significantly lower intensities (20–40% of 1RM) (Loenneke et al., 2012). Proposed mechanisms include metabolite accumulation, cell swelling, and augmented anabolic signalling; indeed, several studies have reported acute increases in growth hormone and IGF-1 following BFR exercise (Takarada et al., 2000). Although much of the myokine evidence to date derives from acute responses, chronic BFR training has also been shown to be effective. Notably, eight weeks of functional training with BFR significantly increased circulating irisin in older men, indicating that the ischaemic–metabolic milieu induced by BFR may specifically potentiate the myokine response over the longer term (Pazokian et al., 2022). Given its low mechanical load and favourable safety profile, BFR represents a particularly attractive modality for frail or previously untrained older women.

Concurrently, functional training—which emphasizes multi-joint, task-specific movements that reproduce the demands of daily activities—has been shown to improve mobility and independence in older adults more effectively than isolated strengthening exercises (Liu et al., 2014). Combining functional training with BFR is therefore conceptually compelling, as it may integrate the neuromuscular benefits of functional movement with the potent anabolic stimulus of BFR at loads that are safe for this population. While emerging evidence suggests that such combined approaches can enhance strength and functional capacity (Centner et al., 2019), the evidence base concerning functional training combined with BFR in older women remains limited.

Most existing BFR studies have focused on isolated single-joint exercises, younger populations, or a narrow range of functional outcomes, and few have concurrently assessed anabolic–metabolic markers alongside lipid indices. Crucially, it remains unclear whether adding BFR to a functional training programme confers superior benefits for circulating irisin, IGF-1, and the lipid profile compared with functional training performed at conventional loads, particularly as previous findings have been generated predominantly in men (Pazokian et al., 2022). Clarifying this question is clinically relevant, as it could inform the design of time-efficient, low-load, and well-tolerated exercise prescriptions. Therefore, the present randomized controlled trial aimed to determine the effects of eight weeks of functional training, with (FTBFR) and without (FT) blood flow restriction, compared with a non-exercising control group (CON), on serum irisin, IGF-1, and lipid indices in older women.

## Materials and Methods

### Study design

This study was conducted as a randomized, assessor-blinded, controlled clinical trial with a pretest–posttest design. Participants were randomly assigned to one of three groups: the functional training with blood flow restriction (FTBFR) group, the functional training (FT) group, or the control (CON) group. The study was designed following the SPIRIT 2025 guidelines, and results were reported in accordance with the CONSORT 2025 guidelines. All interventions were described following the TIDieR checklist. A flowchart illustrating the study design is presented in Table 1.

### Trial registration and ethics

Ethical approval was granted by the Research Committee of Alzahra University (Reference No: IR.ALZAHRA.REC.1404.021). The study was registered with the Iranian Registry of Clinical Trials (IRCT ID: IRCT20250424065464N1). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

### Participants and sample size calculation

This study was conducted on community-dwelling older women

**Table 1**. Flow diagram of the study design, participant allocation, intervention procedures, and pretest-posttest assessments in the FTBFR, FT, and CON groups.

| | TRIAL PERIOD | | | | |
|---|---|---|---|---|---|
| | ENROLLMENT | ALLOCATION | BASELINE | AFTER 8 WEEKS | |
| TIMEPOINT[b] | $-t_i$ | 0 | $Pr_1$ | $Po_1$ | Po2 |
| **ENROLLMENT:** | | | | | |
| Eligibility screen | X | | | | |
| Informed consent | X | | | | |
| socio-demographic and clinical profile | X | | | | |
| Randomization | | X | | | |
| Allocation | | X | | | |
| **INTERVENTION/ COMPARATOR:** | | | | | |
| FTBFR | | X → | → | → | X |
| FT | | X → | → | → | X |
| CON | | X → | → | → | X |
| **ASSESSMENTS:** | | | | | |
| Health questionnaire | X | | | | |
| BMI (Body Mass Index) | X | | | | X |
| Serum Irisin | X | | | | X |
| Serum IGF-1 | X | | | | X |
| lipid indices (TC, TG, LDL, and HDL) | X | | | | X |

Abbreviation: FBFR: Functional Training with blood flow restriction group, FT: functional training without blood flow restriction group CON: Control group, $-t_1$: pre pre-allocation time point, Pr1: Pre-test, Po1: Post-test, Po2: Post-test (48 h After 8 Weeks), TC: total cholesterol, TG: Triglycerides, LDL: Low-Density Lipoprotein Cholesterol, HDL: High-Density Lipoprotein Cholesterol.

aged 60 years and above residing in Tehran. The sample size was calculated using G*Power software (version 3.1.9.6) based on analysis of variance (ANOVA). The input parameters included a significance level (alpha) of 0.05, a statistical power of 0.90, and an effect size of 0.65. The effect size was determined based on findings from a previous randomized controlled trial (Pazokian et al., 2022) that examined the effect of an intervention on Irisin levels in older adults and reported an effect size of 0.65 (6). Based on these calculations, the required sample size was estimated at 36 participants, who were randomly allocated into three equal groups, with 12 participants in each group (Figure 1).

## Randomization, allocation concealment and blinding

Participants were randomly allocated in equal proportions to one of three study groups: functional training with blood flow restriction (FTBFR), functional training without blood flow restriction (FT), or the non-exercising control group (CON). Randomization was performed using a web-based randomization tool (randomizer.org), with a 1:1:1 allocation ratio. The random allocation sequence was generated by a member of the research

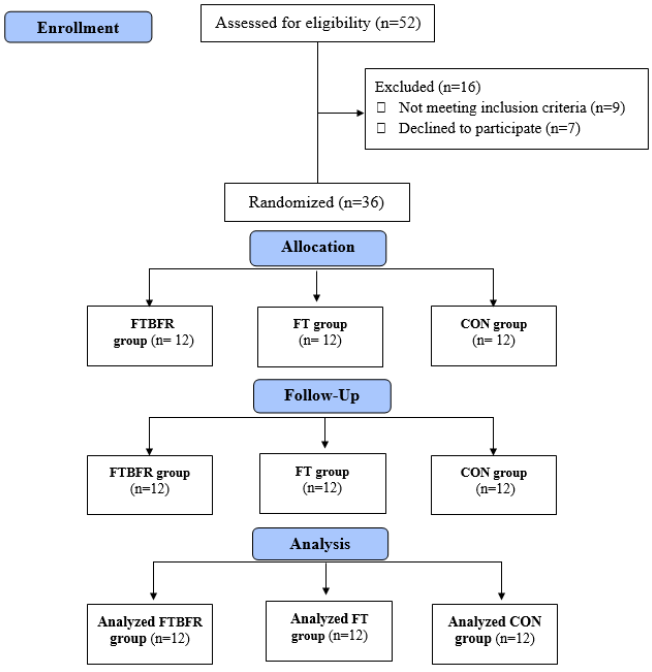


**Figure 1.** CONSORT flow diagram of the study

team who was not involved in participant recruitment or assessment. Allocation concealment was maintained using opaque, sealed, consecutively numbered envelopes, which were opened only after each participant had been enrolled in the study.

The trial was conducted as an assessor-blinded randomized controlled study. Because of the visible and perceptible nature of the inflatable blood-flow-restriction cuffs, and because sham cuffs were not used in the functional-training group, complete participant blinding was not feasible. Participants in different groups were asked not to discuss their training procedures with one another. Outcome assessors responsible for clinical and functional measurements were not involved in the randomization process or intervention delivery and remained unaware of group assignments throughout data collection. Laboratory personnel analyzed coded blood samples and were blinded to participants' group assignments.

## Participants: inclusion and exclusion criteria

Participants were community-dwelling elderly women (aged ≥60 years) residing in Tehran. The inclusion criteria were as follows: (a) healthy status; (b) age ≥60 years; no history of smoking; (d) no cardiovascular disease; (e) no metabolic or kidney disorders; (f) no use of blood pressure medications; (g) no neurological, muscular, or skeletal disorders; (h) no regular functional training in the two years prior to the study; (i) no adherence to a weight-loss diet; (j) no use of medications or supplements affecting study outcomes in the three months prior to the study; and (k) provision of written informed consent. Exclusion criteria included: (a) significant changes in physical condition during the study; (b) diagnosis of any medical, psychological, or behavioral disorder; missing two consecutive or four total intervention sessions; (d) failure to complete baseline assessments; or (e) withdrawal of consent.

## Procedure

Participants were recruited through announcements at local senior centers, sports facilities, and social media. One week before the intervention, participants attended a familiarization session during which the study procedures were explained and competency in performing the functional exercises was ensured. During this session, blood samples were also collected to assess irisin, IGF-1, and lipid indices. Participants were screened for psychological conditions using the General Health Questionnaire (GHQ) and were evaluated by a specialist physician to confirm eligibility. A total of 36 participants were enrolled and randomly allocated to the FTBFR, FT, or CON groups, with 12 participants in each group.

## Intervention description

The FTBFR group performed functional training with blood flow restriction three times per week for 8 weeks, whereas the FT group performed the same functional training protocol over the same period without blood flow restriction. The CON group maintained their usual daily activities without receiving any intervention. All exercise sessions lasted 45 minutes and were supervised by an experienced coach at Barman Sport Club in Tehran. The functional training protocol consisted of a 5-minute warm-up, a 10-station circuit, and a 5-minute cool-down. Stations included: (1) Wall squat with a Swiss ball; (2) Dumbbell fly on a Swiss ball; (3) Deadlift with dumbbells; (4) Triceps extension on a Swiss ball; (5) Crunches with a Medicine ball; (6) Bench push-ups; (7) Shoulder press on a Bosu ball; (8) Farmer's walk; (9) Medicine ball hyperextension; and (10) Standing biceps curl on a Bosu ball (Figure 2).

Details of the training protocol, including exercise intensity, repetitions, and sets, are presented in Table 2. Exercise intensity was determined as follows: for stations 1–4, 6–8, and 10, intensity was expressed as a percentage of one-repetition maximum (%1RM), whereas for stations 5 and 9, intensity was based on the weight of the medicine ball. The 1RM was estimated using the Brzycki formula (Brzycki, 1993).

$$1RM = Weight / [1.0278 - (0.0278 \times Repetitions)]$$

The difference in external training load between the FT and FTBFR groups was intentional and reflected the conventional application of BFR training. The training load was set at 40% of 1RM for the FT group and 20% of 1RM for the FTBFR group during the first week, increasing by 5% weekly until the eighth week, resulting in final loads of 75% of 1RM in the FT group and

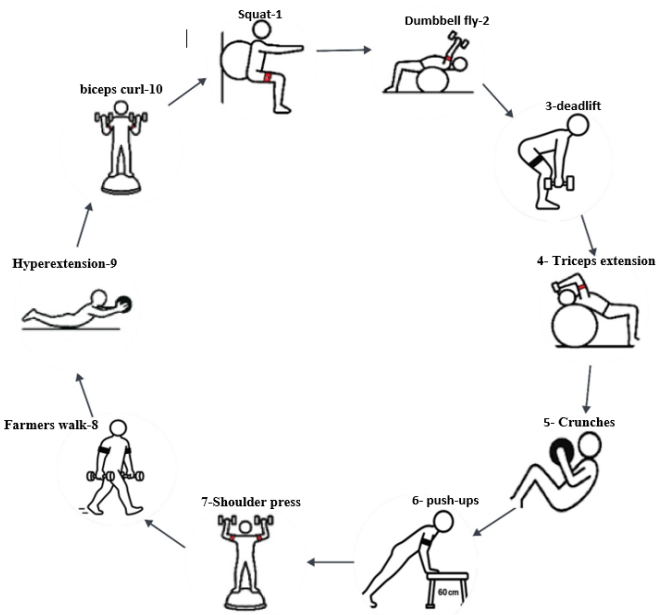


**Figure 2.** Functional circuit training.

55% of 1RM in the FTBFR group, respectively (Table 2). Thus, the FT group performed functional training with moderate-to-high external loads, whereas the FTBFR group performed the same functional training protocol with relatively low external loads while BFR was applied. This load prescription was selected because BFR is typically combined with relatively low external loads to increase metabolic stress and neuromuscular demands while limiting the need for high mechanical loading. Accordingly, the present study was designed to compare two practically relevant training protocols and was not intended as a load-matched comparison.

## Blood flow restriction (BFR) protocol

In the FTBFR group, 5-cm-wide elastic cuffs (Ghamat Pouyan Co., Iran) were applied bilaterally to the most proximal region of the exercising limbs, including the upper arms during upper-body exercises and the upper thighs during lower-body exercises. Arterial occlusion pressure (AOP) was estimated individually for each participant using regression equations reported by Pazokian et al. (2022). These equations were based on limb circumference and resting blood pressure variables and were developed using the same type of BFR cuffs manufactured by Ghamat Pouyan Co., Iran, in an Iranian sample (Pazokian et al., 2022). For the upper limbs, AOP was calculated using the following equation:

Upper-limb AOP (mmHg)=(1.461xarm circumference) + (0.514x systolic blood pressure) + (0.339xdiastolic blood pressure) + 17.236

For the lower limbs, the following equation was used:

Lower-limb AOP (mmHg)=(5.893xthigh circumference)+(0.912 x systolic blood pressure)+(0.734xdiastolic blood pressure)-220.046

During the intervention, cuff pressure was prescribed at 60% to 80% of the individually estimated AOP. The cuffs remained inflated throughout each exercise set and were released during the inter-set rest periods as well as immediately after the completion of the training session, in accordance with established safety recommendations for blood flow restriction exercise. All training sessions were directly supervised by the research team to ensure correct execution of the exercises, compliance with the prescribed training intensity, and participant safety Table 2.

## Concomitant care and adverse effects

Participants were prohibited from using other supplements or engaging in structured exercise during the study. Mild, temporary muscle soreness was anticipated as a possible response to exercise. During each training session, a physician monitored participants for adverse events and exercise-related symptoms, including excessive pain or discomfort, dizziness, light-headedness, unusual fatigue, muscle cramping, numbness, tingling, bruising, swelling, and skin discoloration. Participants were also instructed to report any unusual symptoms occurring during or after the sessions. If concerning symptoms had occurred, the exercise session would have been stopped and the participant would have been medically evaluated. However, no adverse events or symptoms requiring discontinuation of the intervention were documented during the eight-week study period.

## Anthropometric and biochemical measurements

Anthropometric and biochemical measurements were performed at baseline and after the 8-week intervention. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer, and body mass was recorded to the nearest 0.1 kg using a calibrated digital scale. All measurements were obtained under standardized conditions, with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated by dividing body mass in kilograms by height in meters squared (kg/m²).

Venous blood samples were collected after a 10–12 h overnight fast, 24 h before the first training session and 48 h after the final training session. To minimize the effects of circadian variation, pre- and post-intervention blood samples were collected at approximately the same time of day. The samples were centrifuged to separate the serum, and serum aliquots were stored at −80°C until biochemical analysis.

**Table 2.** Functional training protocol with or without BFR

| Variables | intensity | | | | Sets (N) | Repetitions (N) | Rest between sets (min) |
|---|---|---|---|---|---|---|---|
| | Cuff pressure (AOP%) | 1RM with BFR | 1RM without BFR | Medicine ball (kg) | | | |
| **Week 1** | 50% AOP | 20% 1RM | 40% 1RM | 2 | 2 | 10 | 1 |
| **Week 2** | 55% AOP | 25% 1RM | 45% 1RM | | | | |
| **Week 3** | 60% AOP | 30% 1RM | 50% 1RM | 3 | 3 | 10 | 1 |
| **Week 4** | 65% AOP | 35% 1RM | 55% 1RM | | | | |
| **Week 5** | 70% AOP | 40% 1RM | 60% 1RM | 4 | 3 | 10 | 1 |
| **Week 6** | 75% AOP | 45% 1RM | 65% 1RM | | | | |
| **Week 7** | 80% AOP | 50% 1RM | 70% 1RM | 5 | 3 | 10 | 1 |
| **Week 8** | 85% AOP | 55% 1RM | 75% 1RM | | | | |

**Figure 3**. Baseline anthropometric characteristics of participants (mean ± SD).

| Variable | FBFR (n = 12) | F (n = 12) | CON (n = 12) | P-value |
|---|---|---|---|---|
| **Age (years)** | 63.5 ± 2.8 | 62.7 ± 3.3 | 64.1 ± 2.9 | 0.51 |
| **Body mass (kg)** | 68.4 ± 8.1 | 67.3 ± 7.5 | 65.3 ± 7.9 | 0.63 |
| **Height (cm)** | 159.3 ± 5.2 | 158.9 ± 4.8 | 159.5 ± 5.1 | 0.94 |
| **BMI (kg/m²)** | 26.7 ± 2.6 | 26.8 ± 2.7 | 25.8 ± 2.5 | 0.58 |

Serum irisin and insulin-like growth factor 1 (IGF-1) concentrations were measured using enzyme-linked immunosorbent assay (ELISA) kits supplied by ZellBio GmbH (Germany), in accordance with the manufacturer's instructions. The serum lipid profile, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), was determined using enzymatic colorimetric assays according to the manufacturer's protocols. All biochemical measurements were performed in duplicate, and the pre- and post-intervention samples from each participant were analyzed in the same analytical batch to minimize inter-assay variability. The LDL-C/HDL-C ratio was calculated by dividing the serum LDL-C concentration by the serum HDL-C concentration.

### Statistical analysis

All statistical analyses were performed using SPSS version 25, and figures were generated in Excel 2023. Data were reported as mean ± standard deviation. The assumptions of normality, homogeneity of variance, and homogeneity of regression slopes for ANCOVA were assessed before conducting the main analyses. Normality was examined using the Shapiro–Wilk test, and homogeneity of variance was evaluated using Levene's test. The homogeneity of regression slopes assumption was tested by examining the interaction between baseline values and group allocation for each dependent variable. These assumptions were met for the main ANCOVA models, indicating that ANCOVA was appropriate for evaluating adjusted post-intervention between-group differences. Between-group differences at post-test were examined using ANCOVA, with baseline values entered as covariates, and effect sizes were reported as partial eta squared. When significant group effects were observed, Bonferroni-adjusted post hoc comparisons were conducted to identify pairwise differences. Within-group changes were evaluated using paired-samples t-tests, and percentage changes in variables over the intervention period were calculated. The statistical significance level was set at $P < 0.05$ for all analyses.

## Results

All 36 participants completed the study, and no adverse events related to the training protocols or blood flow restriction were reported. Baseline demographic and anthropometric characteristics of the participants are presented in Table 3. There were no significant differences among the FTBFR, FT, and CON groups in age, body mass, height, or BMI at baseline ($P > 0.05$), indicating that the groups were comparable before the intervention. Descriptive statistics for the dependent variables, including mean ± standard deviation and percentage changes, are reported separately for each group.

### Between-group comparisons

### Serum irisin

After adjustment for baseline values, ANCOVA revealed a significant between-group difference in post-intervention serum irisin levels ($F(2,32)=20.03$, $P<0.001$, partial $\eta^2=0.494$). The baseline irisin value was also a significant covariate ($F(1,32)= 3.03$, $P=0.04$, partial $\eta^2=0.069$). Bonferroni-adjusted pairwise comparisons showed that both the FTBFR and FT groups had significantly higher post-intervention serum irisin levels than the CON group, whereas no significant difference was observed between the FTBFR and FT groups.

### IGF-1

For IGF-1, ANCOVA indicated a significant group effect after controlling for pre-intervention values ($F(2,32)=9.48$, $P=0.001$, partial $\eta^2=0.316$). In addition, the baseline IGF-1 value was a significant covariate ($F(1,32)=14.93$, $P<0.001$, partial $\eta^2=0.267$). Bonferroni-adjusted comparisons demonstrated that post-intervention IGF-1 levels were significantly higher in both the FTBFR and FT groups compared with the CON group, while no significant difference was found between the two training groups.

### LDL-C/HDL-C Ratio

A significant adjusted between-group difference was also observed for the LDL-C/HDL-C ratio following the intervention ($F(2,32)=67.19$, $P<0.001$, partial $\eta^2=0.766$). The baseline value of the ratio was also significant as a covariate ($F(1,32)=8.74$, $P = 0.05$, partial $\eta^2=0.176$). Bonferroni-adjusted pairwise comparisons showed significant differences among all three groups, including FTBFR versus FT, FTBFR versus CON, and FT versus CON.

### Within-group changes

### Serum Irisin

Paired-samples t-test revealed a significant increase in serum Irisin from pre-intervention to post-intervention in both the FTBFR

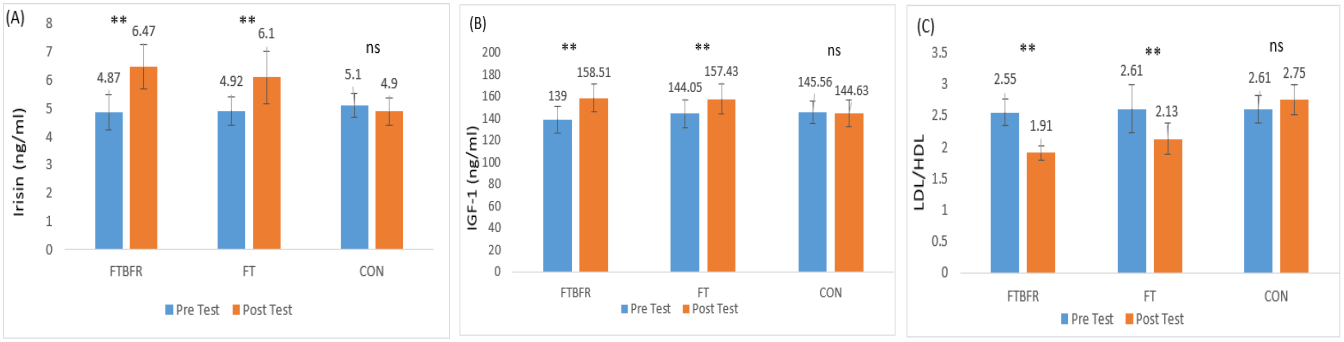


**Figure 3.** Pre- to post-intervention changes in (A) serum Irisin, (B) serum IGF-1, and (C) LDL/HDL ratio across the FTBFR, FT, and CON groups. Data are shown as mean ± SD. **P < 0.01 denotes significant within-group pre–post differences assessed by paired-samples t-tests; ns denotes non-significant differences.

group (4.87±0.64 vs. 6.47±0.78, t(11) = 6.057, P<0.001) and the FT group (4.92±0.51 vs. 6.10±0.91, t(11) = 5.274, P < 0.001). However, no significant within-group change was observed in the CON group (5.10±0.43 vs. 4.90±0.49, t(11)=2.176, P=0.06). As presented in Figure 3A, serum Irisin increased by 32.85% in the FTBFR group and by 23.98% in the FT group, whereas no significant change was found in the control group.

### IGF-1

Paired-samples t-test also showed a significant increase in IGF-1 levels from pre-intervention to post-intervention in the FTBFR group (139.00±12.20 vs. 158.51±13.92, t(11)=5.701, P<0.001) and the FT group (144.05±12.27 vs. 157.43±13.57, t(11)=3.742, P = 0.002). In contrast, the change in the CON group was not statistically significant (145.56±10.43 vs. 144.63±12.06, t(11) = 0.385, P=0.706). As shown in Figure 3B, IGF-1 increased by 14.03% in the FTBFR group and by 9.28% in the FT group, while no significant change was observed in the control group.

### LDL-C/HDL-C Ratio

For the LDL/HDL ratio, paired-samples t-test demonstrated a significant reduction from pre-intervention to post-intervention in both the FTBFR group (2.55±0.21 vs. 1.91±0.12, t(11)=16.389, P <0.001) and the FT group (2.61±0.38 vs. 2.13±0.25, t(11)= 4.114, P=0.001). However, no significant within-group change was found in the CON group (2.61±0.22 vs. 2.75±0.24, t(11)=1.158, P =0.27). According to Figure 3C, the LDL/HDL ratio decreased by 25.09% in the FTBFR group and by 18.39% in the FT group, whereas no significant change occurred in the control group.

## Discussion

The main findings of the present study indicate that an eight-week functional training program favorably modulated endocrine and cardiometabolic markers in older women, as reflected by increa-sed serum irisin and IGF-1 concentrations and an improved LDL/HDL ratio. Importantly, the integration of blood flow restriction (BFR) appeared to intensify these adaptations, with the BFR condition producing the most pronounced changes and showing a superior effect on the LDL/HDL ratio compared with functional training without BFR. These findings suggest that BFR may serve as a potential metabolic amplifier during low-load functional exercise, although this interpretation should be considered hypothesis-generating because the underlying molecular pathways were not directly assessed. This interpretation is consistent with the broader concept that skeletal muscle functions as an endocrine organ and releases exercise-responsive myokines that contribute to systemic metabolic regulation (Pedersen & Febbraio, 2012).

The observed increase in serum irisin is biologically plausible and may be partly related to activation of the PGC-1α/FNDC5/irisin pathway. Irisin is produced through cleavage of fibronectin type III domain-containing protein 5 (FNDC5), whose expression is regulated, at least in part, by peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α). The PGC-1α/FNDC5/irisin axis was originally proposed as an exercise-responsive mechanism linking skeletal muscle contraction to browning of white adipose tissue and thermogenic regulation (Boström et al., 2012). Repeated muscle contraction, increased energetic demand, calcium flux, mitochondrial stress, and metabolic perturbation during exercise could potentially stimulate PGC-1α-related signaling and thereby contribute to irisin release (Egan & Zierath, 2013). In older women, such an adaptation may be clinically meaningful because aging is commonly associated with impaired mitochondrial function, reduced skeletal muscle quality, anabolic resistance, and increased cardiometabolic risk. However, because PGC-1α, FNDC5, and related molecular markers were not measured in the present study, this proposed pathway should be regarded as a plausible explanation rather than a confirmed mechanism.

The functional characteristics of the training program may have contribute to the rise in circulating irisin. Functional training differs

from isolated single-joint resistance exercise because it typically involves multi-joint, weight-bearing, and task-oriented movements that require coordinated activation of large muscle groups, postural control, balance, and repeated transitions between concentric, eccentric, and stabilizing contractions. These features may increase the total recruited muscle mass and cumulative metabolic demand, both of which are important potential stimuli for contraction-induced myokine secretion. Previous evidence suggests that irisin responses to exercise may depend on exercise intensity, recruited muscle mass, training modality, and participant characteristics (Huh et al., 2014). Therefore, the increase in irisin observed in the present study may reflect the integrated neuromuscular and metabolic stimulus created by functional movement patterns rather than only isolated muscle contraction. This interpretation remains tentative because muscle recruitment and intramuscular signaling were not directly assessed. The greater irisin response observed in the BFR-integrated condition may be explained by the specific physiological environment created by partial vascular restriction. BFR partially restricts venous return while maintaining arterial inflow, which may contribute to local hypoxia, metabolite accumulation, increased intramuscular acidosis, and accelerated fatigue (Patterson et al., 2019). These conditions may promote earlier recruitment of higher-threshold motor units, particularly type II muscle fibers, even when the external load is relatively low. From a molecular perspective, the metabolic stress induced by BFR could plausibly influence exercise-sensitive signaling pathways, including AMPK, p38 MAPK, CaMK, HIF-1α-related responses, and PGC-1α-mediated mitochondrial signaling (Egan & Zierath, 2013; Patterson et al., 2019). Although these pathways were not directly measured in the present study, they represent plausible biological explanations for the enhanced irisin response in the BFR group and should be tested directly in future mechanistic studies.

The increase in IGF-1 after the intervention further supports the possible anabolic effects of functional training in older women. IGF-1 is a key regulator of skeletal muscle remodeling and may contributes to protein synthesis, satellite-cell activation, muscle repair, and hypertrophic adaptation, primarily through the PI3K/Akt/mTOR pathway (Glass, 2005). Exercise-induced activation of anabolic signaling may help counteract age-related anabolic resistance and support the preservation of muscle mass and function. This is particularly relevant in older women, who are at increased risk of sarcopenia, frailty, and reductions in functional independence. Therefore, the observed increase in IGF-1 may indicate a favorable endocrine adaptation with potential implications for musculoskeletal health and healthy aging. Nevertheless, the present findings do not establish that the PI3K/Akt/mTOR pathway was activated, because this pathway was not directly measured.

Although the BFR group demonstrated the largest absolute increase in IGF-1, this finding should be interpreted cautiously. Functional training alone may provide sufficient mechanical and neuromuscular stimulation to increase systemic IGF-1, whereas BFR may provide an additional metabolic stimulus rather than producing a completely distinct endocrine response. Previous evidence indicates that low-load resistance exercise combined with BFR can induce hypertrophic and strength-related adaptations comparable to those achieved with traditional higher-load resistance training (Slysz et al., 2016). Moreover, BFR exercise has been shown to stimulate muscle protein synthesis and mTORC1 signaling in older adults, supporting its potential role in promoting anabolic adaptations under low-load conditions (Fry et al., 2010). Thus, the present findings are consistent with the possibility that BFR may enhance the efficiency or magnitude of the anabolic response to functional training, particularly in populations for whom high mechanical loading may not be feasible. This proposed interpretation requires confirmation through direct assessment of anabolic signaling and muscle protein synthesis. From a practical perspective, the approximately 14% increase in IGF-1 observed in the FTBFR group may indicate a potentially favorable endocrine environment for maintaining muscle health and functional independence in older women. However, because muscle strength, physical performance, and activities of daily living were not directly assessed, the clinical translation of this biomarker change remains uncertain.

The improvement in the LDL/HDL ratio, especially the superior response observed in the BFR group, may be one of the most clinically relevant cardiometabolic outcomes of this study. The LDL/HDL ratio reflects the balance between atherogenic and anti-atherogenic lipoprotein fractions and is commonly considered an informative marker of lipid-related cardiovascular risk. Exercise training may improve lipid profile through several mechanisms, including increased skeletal muscle lipoprotein lipase activity, enhanced clearance of triglyceride-rich lipoproteins, improved hepatic lipid metabolism, increased fat oxidation, and stimulation of reverse cholesterol transport (Wang & Xu, 2017). Functional training could contribute to these adaptations by increasing total energy expenditure and improving skeletal muscle oxidative capacity. The additional improvement observed with BFR may be related to a stronger metabolic challenge at relatively low workloads, which could partly explain the greater improvement in the LDL/HDL ratio in the BFR condition. However, because lipid-metabolism pathways and vascular function were not directly assessed, these mechanistic interpretations remain speculative.

A possible mechanistic link between the endocrine and lipid findings is the interaction between irisin and AMPK-mediated lipid metabolism. Irisin has been reported to be associated with adipose tissue browning, increased thermogenic gene

expression, improved glucose uptake, and enhanced fatty acid oxidation (Boström et al., 2012; Huh et al., 2014). AMPK activation may also promote fatty acid oxidation and inhibit lipid synthesis-related pathways, thereby contributing to improved metabolic homeostasis (Egan & Zierath, 2013). Therefore, the concurrent increase in irisin and improvement in the LDL/HDL ratio observed in the present study could be consistent with an integrated exercise-induced response involving skeletal muscle–adipose tissue–liver cross-talk. In this context, BFR may plausibly strengthen the metabolic signal generated by functional training and could potentially contribute to adaptations related to both myokine secretion and lipid handling. Because AMPK activity, adipose-tissue browning, and tissue-specific metabolic signaling were not measured, this explanation should be viewed as a plausible hypothesis generated by the present findings rather than as evidence of a confirmed causal pathway.

Overall, the present findings suggest that the combination of functional training and BFR may provide a potentially effective metabolic stimulus in older women while maintaining a low-load training structure. The concurrent increases in irisin and IGF-1, together with the improvement in the LDL/HDL ratio, may reflect an integrated adaptation involving skeletal muscle endocrine activity, anabolic signaling, and lipid metabolism. Nevertheless, the mechanistic interpretation should remain cautious, as molecular pathways such as PGC-1α/FNDC5, AMPK, and PI3K/Akt/mTOR were not directly measured. Future studies using longer interventions, direct molecular assessments, body-composition analysis, vascular-function measurements, and post-intervention follow-up are needed to clarify whether these proposed pathways contribute causally to the observed adaptations and to determine their durability.

## Conclusion

The present study demonstrated that eight weeks of functional training improved serum irisin, IGF-1, and the LDL/HDL ratio in older women, with the most pronounced overall responses observed in the BFR-integrated training condition. Although both exercise protocols increased irisin and IGF-1, BFR-integrated functional training produced a superior improvement in the LDL/HDL ratio compared with functional training alone. These findings suggest that adding BFR to functional training may be an effective low-load strategy for enhancing endocrine and cardiometabolic adaptations in older women. The mechanisms underlying these responses remain to be confirmed, and further studies incorporating direct molecular assessments are warranted.

### Limitations and future directions

Despite the strengths of this study, several limitations should be acknowledged. First, the study was conducted in older women; therefore, the findings may not be directly generalizable to older men, younger populations, or individuals with clinically diagnosed metabolic or musculoskeletal disorders. Second, although circulating irisin, IGF-1, and lipid-related indices provide valuable insight into endocrine and cardiometabolic adaptations, the absence of direct molecular assessments, such as skeletal muscle PGC-1α/FNDC5 expression, AMPK activation, or PI3K/Akt/mTOR signaling, limits the ability to confirm the underlying mechanistic pathways and requires the mechanistic interpretations presented in the Discussion to be considered hypothesis-generating. Third, the intervention period was limited to eight weeks, which may be sufficient to detect short-term physiological adaptations but does not clarify whether these responses are sustained after detraining or over longer follow-up periods. Fourth, complete participant blinding was not feasible due to the perceptible and visible nature of BFR application and the non-use of sham cuffs in the functional training group, although outcome assessors and laboratory personnel were strictly blinded to group allocation. Finally, dietary intake and habitual physical activity outside the supervised sessions may have influenced metabolic outcomes. Although participants were instructed to maintain their usual lifestyle throughout the study, physical activity and daily habits in the control group were not objectively monitored throughout the intervention; therefore, unrecognized changes in activity patterns cannot be completely excluded.

Future studies should examine whether similar responses occur in broader clinical and demographic groups, including older adults with sarcopenia, obesity, type 2 diabetes, or dyslipidemia. Longer interventions with follow-up assessments are also needed to determine the durability of BFR-induced adaptations. In addition, integrating molecular analyses, body composition imaging, vascular function assessments, and functional performance outcomes would provide a more comprehensive understanding of how BFR-integrated functional training influences endocrine, metabolic, and musculoskeletal health in aging populations.

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speed, chair-rise performance, balance, activities of daily living, and health-related quality of life, to determine whether biomarker changes translate into tangible benefits for older women.

## What is already known on this subject?

• Functional training can improve physical function and cardiometabolic health in older adults.

• Exercise-induced myokines, particularly irisin, are involved in skeletal muscle–adipose tissue communication and metabolic regulation.

• IGF-1 plays an important role in muscle remodeling, protein synthesis, and healthy aging.

• Blood flow restriction training can induce metabolic and neuromuscular adaptations with relatively low external loads.

## What this study adds?

• To our knowledge, few studies have simultaneously examined the effects of functional training with and without blood flow restriction on irisin, IGF-1, and lipid profile markers in older women.

• This study shows that both functional training protocols increased serum irisin and IGF-1 levels, while the greatest overall changes were observed when functional training was combined with blood flow restriction.

• BFR-integrated functional training produced a significantly greater improvement in the LDL/HDL ratio compared with functional training alone.

**Organ Cross-Talk Tips:**

- Eight weeks of functional training, particularly when combined with blood flow restriction, increased circulating irisin and improved the LDL/HDL ratio, suggesting enhanced skeletal muscle–adipose tissue–liver cross-talk potentially mediated by AMPK-related metabolic signaling.

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## Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest in the present research.

Ethical approval The study protocol was reviewed and approved by the Research Ethics Committee of Alzahra University (Approval ID: IR.ALZAHRA.REC.1404.021). The trial was also registered in the Iranian Registry of Clinical Trials under the registration number IRCT20250424065464N1. All participants provided written informed consent before enrollment, and all study procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Informed consent Written informed consent was obtained from all participants before their enrollment in the study. The participants were informed about the study objectives, procedures, potential benefits, and possible risks, and were free to withdraw from the study at any time without consequences.

## Author contributions

Conceptualization: E.S. and F.K.; Methodology: E.S., K.R., and G.A.; Software: F.K.; Formal analysis: F.K., E.S., and K.R.; Investigation: F.K.; Resources: E.S., K.R., and G.A.; Data curation: F.K.; Writing – original draft: F.K., E.S., K.R., and G.A.; Writing – review and editing: F.K., E.S., K.R., and G.A.; Visualization: F.K. and E.S.; Supervision: E.S.; Project administration: E.S. All authors have read and agreed to the published version of the manuscript.; Funding acquisition: E.S.

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