Journal of Advances in Medical and Biomedical Research | ISSN:2676-6264

High-Intensity Interval Training Attenuates Dyslipidemia and Insulin Resistance via BMP-9 Signaling in Ovariectomized Rats

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Article Info

10.30699/jambr.34.1.76

Received: 2025/06/29;
Accepted: 2025/12/10;
Published Online: 28 Feb 2026;

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ABSTRACT

Background & Objective: Bone morphogenetic protein-9 (BMP-9) plays a pivotal role in regulating obesity, glucose homeostasis, and complications of metabolic syndrome (MetS), particularly in the context of estrogen deficiency. The aim of this study was to investigate the effects of eight weeks of high-intensity interval training on BMP-9 levels, insulin resistance (HOMA-IR), lipid profile, body composition, and components of metabolic syndrome in ovariectomized Wistar rats.

Materials & Methods: Twenty-one Wistar rats (200–220 g) were randomly assigned into three equal groups (n=7): ovariectomized sedentary (OVX+Sal), ovariectomized with HIIT (OVX+HIIT), and sham-operated (Sham). The HIIT group underwent eight weeks of training (three sessions/week). Body weight, BMI, waist circumference, visceral fat, lipid profile, HOMA-IR, and BMP-9 levels were measured 24 hours post-training.

Results: Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test, with significance set at $P < 0.05$. The HIIT intervention resulted in significant elevations in HDL and BMP-9 concentrations ($P = 0.001$) compared to the OVX+Sal group.

Conclusion: HIIT attenuates components of MetS in ovariectomized rats by increasing BMP-9 levels and improving insulin sensitivity, thereby suggesting a potential role for exercise in managing postmenopausal metabolic health.

Keywords: HIIT, HOMA-*IR,* Dyslipidemia, Metabolic Syndrome*, Ovariectomy*

How to Cite This Article:

Babaei P, Falahati S, Damirchi A, Bayat Z, Seyfi-Skishahr F, Sadeghi-Noghlebari F, et al. High-Intensity Interval Training Attenuates Dyslipidemia and Insulin Resistance via BMP-9 Signaling in Ovariectomized Rats. J Adv Med Biomed Res. 2026;34(1):76-84.

1. Introduction

Metabolic syndrome (MetS) is a multifaceted condition characterized by central obesity, insulin resistance (IR), dyslipidemia, elevated blood glucose levels, and hypertension (1). Given the evidence indicating an increasing incidence rate in the future and the deleterious consequences of MetS, such as progression to type 2 diabetes mellitus (T2DM) and cardiovascular disease (2), MetS represents one of the primary concerns for healthcare organizations (3).

Menopause increases the risk of metabolic and cardiovascular diseases due to reduced estrogen levels, which lead to fat redistribution and weight gain. It also exacerbates insulin resistance, commonly assessed using the HOMA-IR index **(2)**. In addition to weight gain, adipose tissue secretes various peptides, known as adipokines, which play pro-inflammatory and anti-inflammatory roles **(4)**.

BMP-9, mainly produced in the liver, regulates fat, glucose, and energy balance **(5, 6)**. Physical activity modulates hepatic enzymes related to lipid synthesis, stimulates pancreatic insulin release, inhibits gluconeogenesis in the liver, and facilitates brown adipose tissue development **(5, 7)**. Emerging evidence highlights a notable decline in serum BMP-9 levels among individuals recently diagnosed with T2DM **(8)** and individuals with obesity and IR **(9)**. Thus, BMP-9 contributes to improved glycemic regulation and enhanced insulin sensitivity in type 2 diabetes by regulating hepatic glucose metabolism **(10, 11)**. One hypothesis regarding the formation of MetS components involves combating radiotoxicity and anti-inflammatory adipokines **(12)**.

Currently, pharmacological options for effectively and safely mitigating adiposity and its complications remain limited. Non-pharmacological interventions, including calorie restriction and physical activity, play a significant role in preventing the progression of MetS to T2DM, particularly in menopausal women **(13, 14)**. HIIT, a widely used exercise protocol, is considered effective for reducing adiposity in menopausal women **(15)**. HIIT comprises brief, vigorous exercise bouts near anaerobic thresholds, alternated with intervals of lower-intensity recovery **(16)**. Due to its elevated intensity, HIIT offers a time-efficient approach by minimizing total exercise duration while maximizing physiological impact **(7)**. Recent studies indicate that HIIT reduces systemic inflammation and modulates hormonal patterns associated with metabolic dysfunction in postmenopausal individuals **(15)**. The present study hypothesizes that an eight-week HIIT protocol could alleviate key MetS indicators and elevate serum BMP-9 concentrations in ovariectomized rat models. While evidence supports the benefits of HIIT for MetS, its effects on BMP-9 levels in menopause models have not yet been investigated.

2. Materials and Methods

2.1 Animals

Twenty-one female Wistar rats, aged three months and weighing between 200 and 220 grams, were sourced from the Animal Breeding Center and housed in the Animal Exercise Physiology Laboratory. Animals were housed under standardized laboratory settings, including 22–24°C ambient temperature, 55–65% relative humidity, a 12-hour light/dark schedule, and unrestricted access to food and water **(17)**. All experimental protocols were reviewed and approved by the institutional ethics board, following established guidelines for the humane treatment of laboratory animals (Approval Code: IR.ARUMS.REC.1400.098). Daily food intake was recorded by allotting 20 grams per rat and calculating leftovers after 24 hours **(18)**. The sample size (n=7 per group) was established based on a power analysis, aiming for 80% power and a significance level of 0.05 to identify significant differences in BMP-9 levels.

2.2 Ovariectomy surgery

One week after acclimatization to their new environment, all animals underwent ovariectomy under general anesthesia, induced by an intraperitoneal injection of ketamine and xylazine (Alfasan, Holland) in a 4:1 ratio. After full anesthesia, ovariectomy was done through a midline abdominal cut. Sham-operated animals underwent identical surgical exposure, excluding ovary removal **(18)**.

2.3 Animals Groups

One month following ovariectomy, the animals were randomly assigned to 3 groups (n=7 per group): a sedentary group receiving saline (OVX+Sal), an exercise group (OVX+HIIT), and a sham group that underwent anesthesia and incision of the skin and muscles without undergoing ovariectomy. The experimental protocol is depicted in Figure 1.

2.4 Exercise protocol

Prior to the main intervention, rats in the HIIT group underwent a two-week treadmill familiarization period to ensure acclimatization to the training regimen. During the initial week, animals exercised on a flat treadmill at 10 m/min for 25 minutes per session, including warm-up and cool-down intervals. In the second week, the duration of each session was extended to 30 minutes, with exercise intensity set between 90% and 95% VO_2max, incorporating one-minute intervals of running at 50% VO_2max; this protocol persisted for 8 weeks **(19)**. VO_2max was determined through an incremental treadmill protocol, progressively increasing speed until animals reached exhaustion, indicated by three consecutive contacts with the treadmill's rear barrier. Subsequently, the speed was increased by 3 m/min every 3 minutes until the animal reached complete exhaustion, defined as the inability to continue running after three consecutive contacts with the treadmill's end within a 1-minute period (Table 1) **(19, 20)**.

2.5 Anthropometrical and biochemical assessments

24 hours after the completion of the last training session, the rats were subjected to a 12-hour fasting regimen. After achieving deep anesthesia, anthropometric data including body length, weight, and waist girth were collected. The abdominal cavity was then accessed, and blood specimens were drawn from the inferior vena cava. Serum separation was carried out by centrifugation (3,000 rpm, 15 min), and aliquots were stored at −80°C for subsequent analyses **(17, 18)**.

Post-blood collection, an investigator meticulously performed dissection and measured the weight of all intra-abdominal adipose tissues, comprising mesenteric, urogenital, and retroperitoneal fat pads, immediately after the procedure to avoid weight loss due to evaporation. The mesenteric fat pad included adipose tissue enveloping the gastrointestinal tract, extending from the gastroesophageal junction to the rectal region, with careful differentiation and exclusion of pancreatic cells. The urogenital fat pad surrounded the kidneys, ureters, bladder, ovaries, oviducts, and uterus, while the retroperitoneal fat pad was recognized as a specific accumulation located posterior to each kidney, proximate to the lumbar musculature (18).

Circulating BMP-9 levels were quantified using a standardized ELISA kit (Catalog No. LS-F1519; LifeSpan BioSciences, USA), which exhibits a detection limit of 0.059 ng/mL, intra-assay variability below 10%, and inter-assay variability under 12%. Circulating BMP-9 levels were quantified using a standardized ELISA kit (Catalog No. LS-F1519; LifeSpan BioSciences, USA), with a detectable range of 0.156 to 10 ng/mL. This assay kit presents an intra-assay variability of 4% and an inter-assay variability of 6.12%, with a measurable range extending to 40 mIU/L. Blood glucose measurements following fasting were acquired using a calibrated glucometer, suitable for rat models, designed to measure values from 10 to 600 mg/dL. The Insulin resistance was estimated via HOMA-IR index, applying the standard formula integrating fasting insulin and glucose values.

Triglyceride (TG) serum concentrations were ascertained by means of an enzymatic colorimetric assay (GOD-PAP, Catalog No. 132500, Pars Azmoun, Tehran, Iran). The assessment of total cholesterol (TC) concentrations was performed utilizing a distinct enzymatic colorimetric technique (GOD-PAP, Catalog No. DY3100-05, R&D Systems, USA), demonstrating an intra-assay coefficient of variation of 4% and an inter-assay coefficient of variation of 6.12%. High-density lipoprotein cholesterol (HDL-C) concentrations were quantified through an enzymatic colorimetric procedure (HDL Precitant, Catalog No. 111150, Pars Azmoun, Tehran, Iran). Low-density lipoprotein cholesterol (LDL-C) concentrations were approximated based on the Friedewald equation as described by Friedewald et al (21). Very-low-density lipoprotein cholesterol (VLDL-C) concentrations were quantified using an enzymatic colorimetric kit (Pars Azmoun, Tehran, Iran).

For all biochemical assays, blood samples were obtained from the inferior vena cava. Following collection, serum was isolated by centrifugation at 3,000 rpm for 15 minutes, then kept at -80°C until further analysis. Each assay was performed in duplicate, with outcomes expressed in relevant scientific units such as ng/mL, mIU/L, and mg/dL.

2.6 Statistical analysis

Data normality was confirmed through the Shapiro-Wilk test, with all variables meeting the $p > 0.05$ threshold. Group comparisons were carried out using one-way ANOVA, and significant findings were further explored using Tukey's post hoc analysis. Findings are reported as mean ± standard error (SE), with statistical significance set at a p-value ≤ 0.05. The sample size (n = 7 per group) was established through power analysis, based on a projected 20% variation in BMP-9 levels across groups, with 80% power and $\alpha = 0.05$, aligning with previous investigations in ovariectomized rat models.

Table 1. Protocol of experiment. High-intensity interval training protocol includes 8 weeks with three sessions per week, 4 minutes with intensity of 55% VO_2max: warming up and cooling down; HIIT: 9 one-minute intervals with intensity of 90 to 95% VO_2max and one-minute with the intensity of 50% VO_2max between intervals with zero-degree gradient.

			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
HIIT	Frequency	Days	3	3	3	3	3	3	3	3
	Inclination	Degrees	0	0	0	0	0	0	0	0
	Cycles	-	20	20	20	20	20	20	20	20
	Speed Exercise 90-95% VO2 max	Meter/ minute	28 /1min	30 /1min	32 /1min	34 /1min	36 /1min	38 /1min	40 /1min	42 /1min
Protocol	Speed Rest 50% VO2 max	Meter/ minute	17 /1min	18 /1min	19 /1min	20 /1min	21 /1min	22 /1min	23 /1min	24 /1min
	Speed Cooling down and Warming up 55% VO2 max	Meter / minute	16/ 4min	17/ 4min	18 /4min	19 /4min	20 /4min	21 /4min	22 /4min	23 /4min
	Duration	Minutes	25min	25min	25min	25min	25min	25min	25min	25min

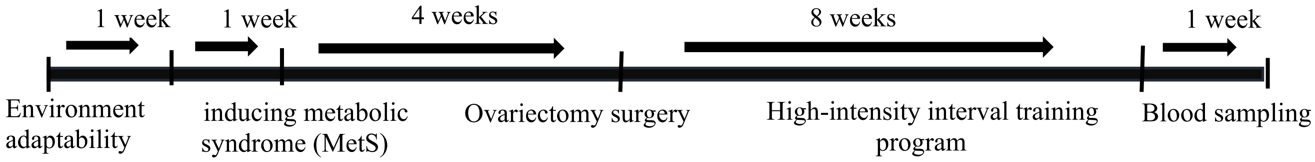

Figure 1. Study protocol: animals adapted for 1 week, underwent ovariectomy, completed 8-week HIIT (90–95% VO$_2$max, 3 times/week), and blood was collected 24 h after the final session (**Prepared by Authors, 2026**).

3. Result

Implementation of HIIT resulted in significant reductions in body mass, body mass index (BMI), waist circumference, and intra-abdominal fat in rats with menopause-related metabolic syndrome.

The results indicated significant differences among groups in body weight, waist circumference, visceral fat, BMI, lipid profile, BMP-9 levels, and HOMA-IR ($P < 0.002$). Tukey's post hoc analysis revealed that the OVX+Sal group exhibited significantly higher values for these parameters compared to the OVX+HIIT and Sham groups ($P = 0.001$ for all). Comprehensive measurements are detailed in Table 2 and Figures 2–4.

3.1 Effect of HIIT on Lipid Profile in a Menopausal Rat Model with MetS

The results conducted at the conclusion of week 8 demonstrated significant differences among groups regarding TG, TC, HDL, VLDL ($P=0.001$), and LDL ($P=0.002$). Results from the post hoc test indicated pronounced increases in TG and TC, alongside diminished HDL levels in the OVX+Sal group relative to others (Figure 3.a-e)

3.2 HII Training Alleviates IR in a Menopausal Rat Model with MetS

At the study's conclusion, statistical analysis confirmed substantial inter-group variation in HOMA-IR scores ($P < 0.002$). Additionally, Tukey's post hoc analysis revealed that the OVX+Sal group displayed a significantly elevated HOMA-IR (1.53 ± 0.63) compared to the OVX+HIIT group (0.12 ± 0.43) and the Sham group (0.07 ± 0.011) ($P = 0.001$).

3.3 V - HIIT Increased BMP-9 Levels in a Menopausal Rat Model of MetS

At the conclusion of the 8-weeks period, analysis revealed a significant divergence in serum BMP-9 values across groups, verified through one-way ANOVA ($P = 0.001$). Moreover, the Tukey post hoc test demonstrated a substantial decrease in serum BMP-9 levels in the OVX+Sal group compared to both the OVX+HIIT group and the Sham group ($P = 0.001$) (Figure 4).

Table 2. Anthropometric, Lipid Profile, and BMP-9 Measurements after 8 Weeks of HIIT in Ovariectomized Rats.

Parameter	OVX+Sal (Mean ± SE)	OVX+HIIT (Mean ± SE)	Sham (Mean ± SE)	P-value
Body Weight (g)	280 ± 10	240 ± 8	230 ± 7	0.001
Waist Circumference (cm)	18 ± 0.5	15 ± 0.4	14 ± 0.4	0.001
Visceral Fat (g)	15 ± 1.2	10 ± 0.8	9 ± 0.7	0.001
BMI (g/cm^2)	0.75 ± 0.03	0.65 ± 0.02	0.62 ± 0.02	0.001
Triglycerides (mg/dL)	150 ± 12	100 ± 8	95 ± 7	0.001
Total Cholesterol (mg/dL)	200 ± 15	140 ± 10	135 ± 9	0.001
HDL-C (mg/dL)	40 ± 4	60 ± 5	62 ± 5	0.001
LDL-C (mg/dL)	120 ± 10	80 ± 7	75 ± 6	0.002
VLDL (mg/dL)	30 ± 3	20 ± 2	19 ± 2	0.001
BMP-9 (ng/mL)	2.5 ± 0.2	4.0 ± 0.3	4.2 ± 0.3	0.001
HOMA-IR	1.53 ± 0.63	0.12 ± 0.43	0.07 ± 0.011	0.002

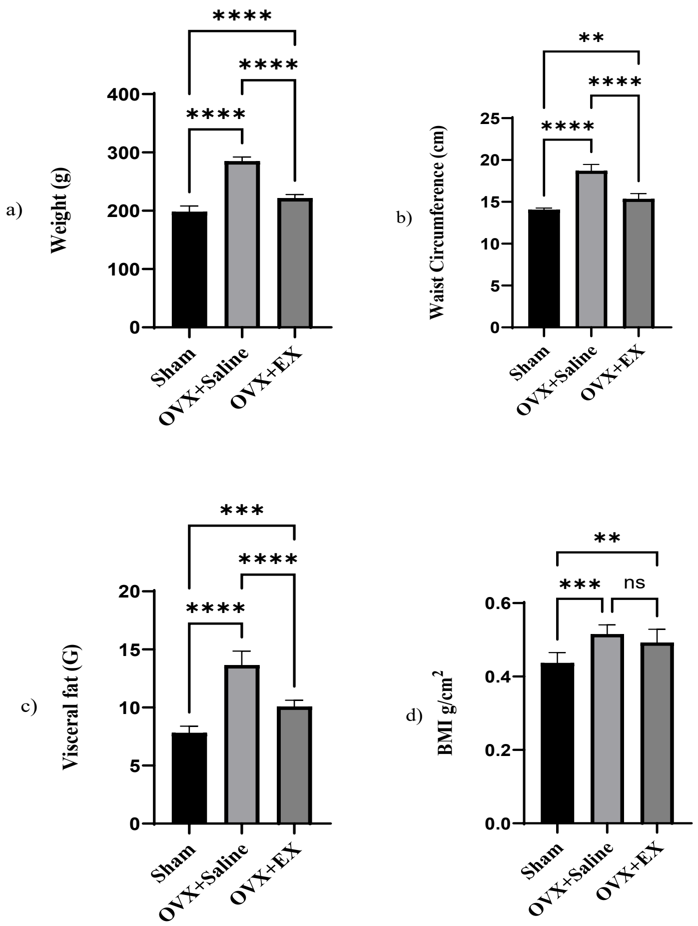

Figure 2. Body metrics: weight, waist size, and BMI were measured. OVX+Sal: saline-treated control; OVX+HIIT: trained group; Sham: surgical control. Data analyzed via ANOVA and Tukey's test, shown as mean ± SE (n=7). *P≤0.05, **P≤0.01, **P≤0.001 vs. OVX+Sal (Prepared by Authors, 2026).

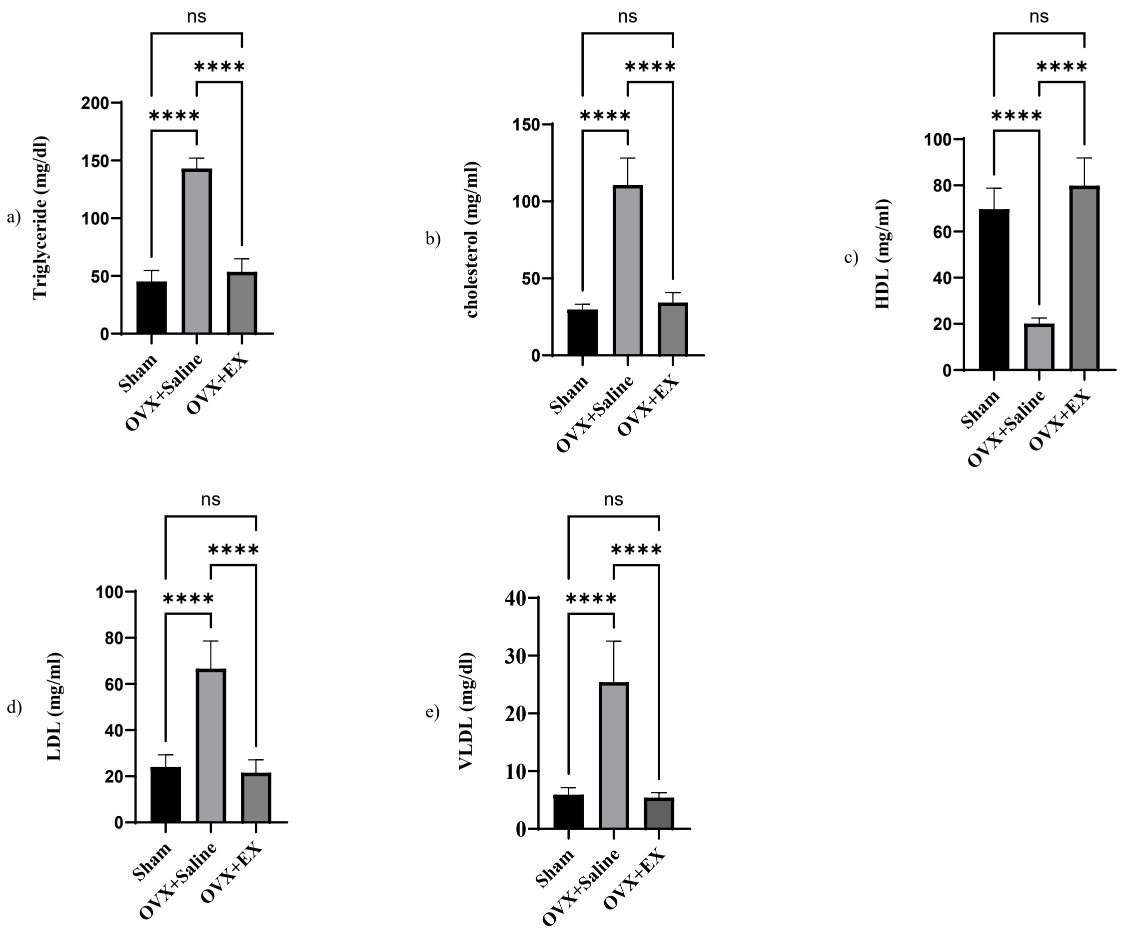

Figure 3. Lipid profile: TG, TC, HDL-C, LDL-C, and VLDL levels across groups. OVX+Sal: saline control; OVX+HIIT: trained group; Sham: non-ovariectomized control. Results shown as mean ± SE (n=7); analysis via ANOVA with Tukey's test. *P≤0.05, **P≤0.01, **P≤0.001 vs. OVX+Sal (**Prepared by Authors, 2026**).

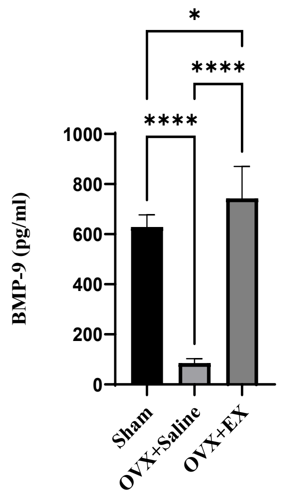

Figure 4. BMP-9 levels across groups: OVX+Sal (saline-treated), OVX+HIIT (training group), and Sham (non-ovariectomized). Data are expressed as mean ± SE (n=7). Statistical differences were identified by ANOVA followed by Tukey's test. *P≤0.05, **P≤0.01, **P≤0.001 vs. OVX+Sal (**Prepared by Authors, 2026**).

4. Discussion

This study aimed to investigate the impact of HIIT on serum BMP-9 concentrations and anthropometric measures in ovariectomized rats, aligning with prior research outcomes. Our results demonstrated a marked increase in body mass and abdominal fat accumulation one month following estrogen withdrawal (15, 18). The weight gain observed in OVX rats was not attributable to an increase in food intake, as this group showed no significant difference in energy consumption compared to the Sham rats. Three months post-ovariectomy, subjects developed notable dyslipidemic profiles and elevated insulin resistance, consistent with previous data (18, 22).

Here, we demonstrated a significant reduction in BMP-9 levels three months after ovariectomy. However, to our knowledge, our finding on BMP-9 in an animal model of ovariectomy is the first such report, and it aligns with recent human studies (6, 8) on T2DM patients, which indicate a negative association between MetS or diabetes and BMP-9 levels. The exact biological processes causing the BMP-9 drop after ovariectomy are not fully understood. It is postulated that BMP-9 influences metabolic homeostasis by inhibiting liver-based glucose production and supporting insulin-mediated pathways (6, 23) by suppressing hepatic gluconeogenesis, enhancing myogenic glucose synthesis, and promoting insulin secretion. These processes may contribute to a reduced blood lipid levels and improved IS. Additionally, BMP-9 appears to regulate lipid levels and reduce lipid accumulation in the liver, thus supporting glucose homeostasis and maintaining lipid balance in the body (6). Some studies suggest that BMP-9 may reduce food intake in animals (10, 24), but this effect was not assessed in the present study.

BMPs convey signals through interactions with two types of transmembrane serine-threonine kinase receptors: BMP type I and type II receptors (24). Studies suggest that BMP-9 interacts with both type I and II receptors, triggering downstream signaling via intermediates like TAK1. This interaction promotes the binding of receptors to the X-linked inhibitor of apoptosis (XIAP) and TGF-β-activated kinase 1/MAP3K7-binding protein 1. Following this, TAK1 triggers Mitogen-Activated Protein Kinases (MAPKs), facilitating signal transmission into cells and their nuclei. This process modulates the expression of target genes by either directly phosphorylating transcription factors or indirectly affecting other kinases that phosphorylate downstream genes (24).

Experimental models have shown that BMP-9 suppresses PEPCK transcription, enhances fatty acid synthesis, and activates AKT signaling (9, 25). In both normal and diabetic mice, BMP-9 has been shown to reduce glycemia (26). Furthermore, the decline in circulating BMP-9 levels in MetS may stem from either reduced synthesis or increased degradation in an insulin-resistant state (10). Additionally, in MetS patients, circulating BMP-9 levels exhibit a significant correlation with HDL and TG, indicating that extended hyperglycemia and hyperlipidemia in these individuals are associated with lower BMP-9 levels (25).

The present study demonstrates that eight weeks of HIIT reduces weight and visceral fat in aged ovariectomized rats, thereby confirming its efficacy in fat reduction. Furthermore, notable reductions in serum cholesterol, TG, LDL, and VLDL alongside increases in HDL, observed in conjunction with exercise may be ascribed to enhanced lipolysis and the mobilization of free fatty acids into the tricarboxylic acid cycle (19, 22). This process may also involve improvements in hepatic fatty acid oxidation and the inhibition of TG synthesis and FAS in the liver (27). Furthermore, this protocol elevated BMP-9 levels, suggesting that eight 8 weeks of HIIT promoted BMP synthesis in white adipose tissue and enhanced the metabotropic actions of BMP. The elimination of BMP-9 from liver ducts following HIIT further substantiates its regulatory role in lipid metabolism (24, 25).

The data also revealed a notable reduction in HOMA-IR in the OVX+HIIT group (0.12 ± 0.43) relative to OVX+Sal (1.53 ± 0.63; P=0.001), reflecting improved insulin sensitivity. This outcome is consistent with earlier reports indicating that physical activity enhances glucose uptake and insulin responsiveness via increased GLUT4 mobilization and AMPK activation in muscle tissue (8). Lower HOMA-IR supports HIIT's role in improving insulin function, likely linked to increase BMP-9, which modulates glucose regulation (28).

While this study did not examine the signaling mechanisms linked to BMP-9, (representing a limitation), in vitro studies indicate that BMP exerts an inhibitory role on PEPCK while promoting the activity of FAS and serine/threonine kinase AKT (24, 25). Other limitations encompass the relatively limited sample size and the 8-week experimental timeframe, which may not adequately reflect the prolonged effects of HIIT. This study did not measure the long-term effects of HIIT on BMP-9 levels, which limits our understanding of its sustained impact. The liver serves as the main organ for transforming surplus carbohydrates into fatty acids, which may then be stored as triglycerides or used by muscle tissue. Strict control of lipid metabolism and the preservation of stable serum free fatty acid concentrations are vital for maintaining lipid homeostasis. BMP may regulate two essential enzymes in hepatic fatty acid metabolism: ME and FAS (10, 24). The downstream signaling cascades of BMP-9 require additional research in forthcoming studies.

5. Conclusion

In summary, the increase in BMP-9 following HIIT may contribute to alleviating symptoms of metabolic syndrome. These outcomes highlight HIIT as a promising lifestyle-based strategy for addressing metabolic syndrome in postmenopausal contexts.

6. Declarations

6.1 Acknowledgments

This study is part of a Master's degree approved by the Ethics Committee of the University of Mohaghegh Ardabili. The authors received no specific funding for this research.

6.2 Ethical Considerations

This study was reviewed and approved by the Ethics Committee of the University of Mohaghegh Ardabili (Approval Code: IR.ARUMS.REC.1400.098). The experimental protocol adhered to the ARRIVE guidelines and the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978).

6.3 Authors' Contributions

Conceptualization: SF, BP, SF; Data curation: FS, BP, SF; Formal analysis: FS, SF; Funding acquisition: FS, BZ, SF; Investigation: FS, BP, DA, BZ, NM, SF; Methodology: FS, BP, SF; Project administration: DA, SF; Resources: FS; Software: FS, NM; Supervision: BP, SF; Validation: DA, SF; Visualization: BP, SF; Original draft preparation: FS, NM, SF; Review and editing: BP, DA, NM, SF. All authors reviewed, edited, and approved the final version of the manuscript.

6.4 Conflict of Interest

The authors declare that they have no conflicts of interest.

6.5 Fund or Financial Support

This research received no external funding.

6.6 Using Artificial Intelligence Tools (AI Tools)

During the preparation of this work, the authors used Grok to improve readability and language. After using this tool, the authors reviewed and edited the content and take full responsibility for the content of the publication.

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