Research Article

High-intensity interval training modulates thrombotic susceptibility in metabolic syndrome: Attenuation of plasma PAI-1 and fibrinogen via ameliorated metabolic dysfunction

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Abstract

Metabolic syndrome (MetS) elevates thrombotic risk through dysregulated coagulation factors, including plasminogen activator inhibitor-1 (PAI-1) and fibrinogen, driven by visceral adiposity and metabolic dysfunction. High-intensity interval training (HIIT) improves cardiometabolic health, but its effects on hemostatic markers in MetS remain underexplored. Twenty-four men with MetS (ATP-III criteria; age 44.4 ± 5.4 years, BMI 31.7 ± 2.3 kg·m^{-2}) were randomized to HIIT (n=12) or control (n=12). HIIT comprised 3 sessions/week for 8 weeks (4 × 4-min intervals at 90% HRmax, interspersed with 3-min active recovery at 70% HRmax). Fasting plasma PAI-1, fibrinogen, insulin resistance (HOMA-IR), body composition, and lipid profiles were assessed pre/post-intervention. HIIT significantly reduced PAI-1 (−30.7%, p<0.001) and fibrinogen (−21.8%, p<0.001) versus controls. Concurrent improvements occurred in HOMA-IR (−20.6%, p<0.001), body fat (−3.8%, p<0.05), systolic/diastolic BP (−7.5%/−5.2%, p<0.05), LDL-c (−5.6%), triglycerides (−9.4%), and HDL-c (+3.0%; all p<0.05). Control group exhibited no significant changes. HIIT attenuates prothrombotic risk in MetS, evidenced by reductions in PAI-1 and fibrinogen. These hemostatic improvements are mechanistically linked to ameliorated metabolic dysfunction, highlighting HIIT's role in modulating adipose tissue–vascular cross talk.

Key Words: High-intensity interval training, Metabolic syndrome, PAI-1, Fibrinogen, Thrombotic risk, Hemostasis, Insulin resistance, Visceral adiposity, Exercise prescription

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Introduction

Metabolic syndrome (MetS) represents a pathophysiological cluster of dysregulated cardiometabolic risk factors—central adiposity, dysglycemia, hypertension, and atherogenic dyslipidemia—that collectively elevate susceptibility to cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) (Ahima, 2024). Globally, obesity-driven metabolic dysfunction underpins this epidemic, with visceral adipose tissue (VAT) serving as a critical endocrine organ that secretes bioactive adipokines (Galic et al., 2010). Dysregulated adipokine production, particularly from hypertrophied VAT, establishes a chronic pro-inflammatory milieu and ectopic lipid deposition, driving insulin resistance (IR) and endothelial dysfunction (Rosen & Spiegelman, 2006).

Notably, VAT is a primary source of plasminogen activator inhibitor-1 (PAI-1), a key regulator of hemostasis that suppresses fibrinolysis by inhibiting tissue plasminogen activator (tPA) (Bruno et al., 2022). Elevated plasma PAI-1—a hallmark of MetS—directly promotes a prothrombotic phenotype by impeding clot dissolution, thereby accelerating atherothrombotic events (Nawaz & Siddiqui, 2022). Concomitantly, fibrinogen, an acute-phase hepatic glycoprotein integral to coagulation cascade amplification and platelet aggregation, is frequently elevated in MetS, further exacerbating thrombotic risk (Frischmuth et al., 2022). This dysregulation establishes a mechanistic nexus between metabolic dysfunction and hemostatic imbalance, positioning PAI-1 and fibrinogen as pivotal mediators of the MetS-thrombosis axis.

Exercise interventions are established countermeasures against VAT accumulation and metabolic dysregulation (Chang et al., 2021). High-intensity interval training (HIIT), characterized by brief, supramaximal efforts interspersed with active recovery, demonstrates superior time efficiency and efficacy in improving VAT reduction, IR, and lipid metabolism compared to moderate-intensity continuous training (MICT) in MetS cohort (Atakan et al., 2021; Sanca-Valeriano et al., 2023).

HIIT-induced metabolic adaptations are postulated to modulate adipose tissue–vascular cross talk, yet its specific impact on thrombotic susceptibility via hemostatic markers remains underexplored.

While HIIT's cardiometabolic benefits are well-documented, its influence on PAI-1 and fibrinogen dynamics in MetS—despite their established roles in thrombogenesis—remains ambiguous. This knowledge gap impedes the optimization of exercise prescriptions targeting thrombotic risk attenuation. Accordingly, this study investigated the effects of an 8-week HIIT protocol on plasma PAI-1 and fibrinogen levels in men with MetS, hypothesizing that HIIT-mediated metabolic improvements would concomitantly attenuate prothrombotic hemostatic dysregulation.

Materials and methods

Study design and ethical oversight

This randomized controlled trial employed a parallel-group design to investigate the effects of high-intensity interval training (HIIT) on thrombotic susceptibility biomarkers in metabolic syndrome (MetS). Twenty-four males meeting ≥3 National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for MetS were recruited from community fitness centers. The institutional review board approved all procedures (Protocol #JEOCT-2506-1158), and written informed consent was obtained prior to participation. The study conformed to the Declaration of Helsinki.

Participant selection and randomization

Eligible participants (age 44.4 ± 5.4 years; BMI 31.7 ± 2.3 kg·m^{-2}) exhibited central obesity (waist circumference >102 cm), fasting triglycerides ≥1.7 mmol/L, HDL-c <1.0 mmol/L, blood pressure ≥135/85 mmHg or antihypertensive use, and fasting glucose ≥6.1 mmol/L. Exclusion criteria encompassed cardiovascular disease (except hypertension), malignancy, insulin therapy, structured exercise (>1 session/week) within 2 years, alcohol consumption, or contraindications to vigorous exercise. Computer-generated block randomization (block size=4) allocated participants to HIIT (n=12) or control (n=12) groups, with allocation concealment maintained via sequentially numbered opaque envelopes.

Exercise intervention protocol

The HIIT group completed 24 supervised treadmill sessions (h/p/cosmos pulsar 4.0, Germany) over 8 weeks, attending 3 sessions per week with at least 48 hours of recovery between sessions. Each session included a warm-up of 10 minutes at 70% HRmax, followed by intervals consisting of four 4-minute bouts at 90% HRmax, interspersed with 3-minute active recovery periods at 70% HRmax between intervals, and concluded with a 5-minute cool-down at 50% HRmax. Individual HRmax was determined beforehand via symptom-limited graded exercise testing using the COSMED Quark CPET (Italy) with 12-lead ECG monitoring. During the sessions, exercise intensity was regulated in real-time using Polar H10 telemetry (Polar Electro, Finland). Adherence to the protocol exceeded 95%, and any missed sessions were rescheduled within 72 hours.

Control group and activity monitoring

Control participants maintained habitual physical activity. Triaxial accelerometry objectively quantified activity patterns during waking hours (≥10h/day for 7 consecutive days at baseline and week 8). No significant changes occurred in moderate-to-vigorous physical activity (MVPA: 28.3 ± 5.1 vs. 29.7 ± 6.2 min/day, p=0.41).

Outcome assessments

Anthropometrics and hemodynamics

Anthropometrics and hemodynamics were assessed using standardized measurements obtained after a 12-hour fasting period. Body composition was evaluated via bioimpedance analysis (BOCA-X1, Jawon Medical, South Korea; CV <0.8%). Resting blood pressure was measured using an automated sphygmomanometer (Omron HEM-7322, Japan), with triplicate readings taken after participants had rested in a seated position for 10 minutes. Waist and hip circumferences were recorded following an ISO 20685-compliant protocol.

Biochemical analyses

Biochemical analyses were performed using fasted venous blood samples collected both pre-intervention and 48 hours post-final exercise session to exclude acute exercise effects. Plasma was isolated from EDTA-anticoagulated blood via centrifugation (3000 × g for 10 minutes at 4°C), aliquoted, and stored at -80°C until analysis. Assays included: PAI-1 measured by quantitative ELISA (RayBiotech ELH-PAI1-1, USA; sensitivity 35 pg/mL, interassay CV 6.8%); fibrinogen assessed via sandwich ELISA (Abcam ab108841, UK; CV 4.7%); insulin analyzed using chemiluminescent immunoassay (RayBiotech ELH-Insulin-1, USA; sensitivity 4 μIU/mL, CV 6.2%); and lipids/glucose quantified through enzymatic assays (Pars Azmoon, Iran; CV <3%). Additionally, HOMA-IR was derived as [glucose (mmol/L) × insulin (μIU/mL)]/22.5.

Statistical analysis

The Shapiro-Wilk test was used to assess the normality of data distribution, which indicate that the data were normally distributed

. Therefore, analysis of covariance (ANCOVA) was employed to determine the significance of differences between the study groups. Data analysis was performed using SPSS version 24, and the significance level was set at $p < 0.05$.

Results

For statistical analysis, data from all participants were included, and none of the participants were excluded from the study. The values of BMI, body fat percentage, cholesterol, triglycerides, HDL-c, LDL-c, systolic blood pressure, diastolic blood pressure, insulin resistance, and waist-to-hip ratio (WHR) in the HIIT and control groups at both pre-test and post-test stages are presented as mean ± standard deviation in Table 1.

The present findings showed that BMI, body fat percentage, cholesterol, triglycerides, LDL-c, insulin resistance (HOMA-IR), systolic and diastolic blood pressure, and waist-to-hip ratio (WHR) significantly decreased in the HIIT group compared to the control group ($p<0.05$). Additionally, HDL-c levels in the HIIT group significantly increased compared to the control group ($p=0.013$). Furthermore, plasma PAI-1 levels significantly decreased in the HIIT group compared to the control group ($p < 0.001$). According to the present results, the percentage change of PAI-1 from pre-test to post-test was -30.67% in the HIIT group and -3.82% in the control group. Fibrinogen levels showed a 21.8% decrease in the HIIT group from pre-test to post-test, whereas a 1.4% increase was observed in the control group.

Table 1. Investigated variables in the Control and HIIT groups (Mean ± Standard Deviation).

Variable		Control	HIIT
Age (years)		45.3 ± 4.60	46.9 ± 4.76
BMI (kg/m^2)	Pre-test	31.12 ± 1.94	31.44 ± 2.44
	Post-test	31.17 ± 2.0	30.84 ± 2.29*
Body fat (%)	Pre-test	32.44 ± 3.95	32.79 ± 4.40
	Post-test	32.67 ± 4.07	31.54 ± 3.93*
Cholesterol (mg/dl)	Pre-test	212.1 ± 25.96	197.8 ± 18.56
	Post-test	207.5 ± 19.79	179.6 ± 15.88*
Triglycerides (mg/dl)	Pre-test	135.8 ± 9.27	141.2 ± 11.77
	Post-test	137.5 ± 10.29	127.9 ± 8.57*
HDL-c (mg/dl)	Pre-test	39.83 ± 2.69	41.08 ± 3.20
	Post-test	40.08 ± 2.32	42.33 ± 3.14*
LDL-c (mg/dl)	Pre-test	153.3 ± 12.27	149.4 ± 14.69
	Post-test	155.4 ± 14.90	141.08 ± 11.55*
IR (HOMA-IR)	Pre-test	2.58 ± 0.65	2.47 ± 0.64
	Post-test	2.61 ± 0.75	1.96 ± 0.34*
SBP (mmHg)	Pre-test	136.9 ± 9.29	140.16 ± 8.29
	Post-test	138.4 ± 8.84	129.6 ± 5.82*
DBP (mmHg)	Pre-test	88.8 ± 3.15	87.7 ± 3.62
	Post-test	87.9 ± 2.57	83.1 ± 3.43*
WHR	Pre-test	0.98 ± 0.05	0.99 ± 0.07
	Post-test	0.98 ± 0.06	0.97 ± 0.07*

Statistical significance compared to the control group is indicated by an asterisk (*) where $p < 0.05$. The following acronyms are used: IR (Insulin Resistance), SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), and WHR (Waist-to-Hip Ratio).

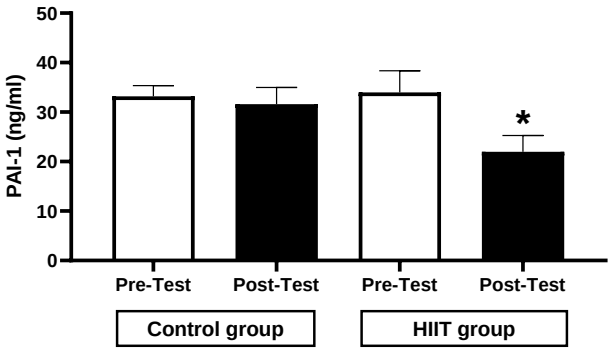

Figure 1. Changes in PAI-1 levels at two groups of study. Data were shown as mean ± SD. Asterisk (*) Indicates a significant decrease compared to the control group.

Based on the findings, fibrinogen significantly decreased in the HIIT group compared to the control group ($p < 0.001$). Changes in PAI-1 levels are presented in Figure 1, and changes in fibrinogen levels are shown in Figure 2.

Discussion

The aim of the present study was to investigate the effect of eight weeks of high-intensity interval training (HIIT) on plasma levels of PAI-1 and fibrinogen in men with metabolic syndrome. The main finding of this study was that eight weeks of HIIT resulted in a significant decrease in coagulation factors, including PAI-1 and fibrinogen ($p < 0.001$).PAI-1 is the primary and rapid inhibitor of fibrinolysis, and since fibrinolysis plays a crucial role in preventing cardiovascular diseases by removing thrombi from the vascular system, elevated levels of PAI-1 can be considered a risk factor (Hoekstra et al., 2004). Among inflammatory and coagulation components, PAI-1 is one of the main elements of metabolic syndrome, which becomes upregulated in individuals with this condition (Mertens et al., 2006). Supporting the association between elevated levels of the examined factors in this study and development of cardiovascular diseases, it has been stated that

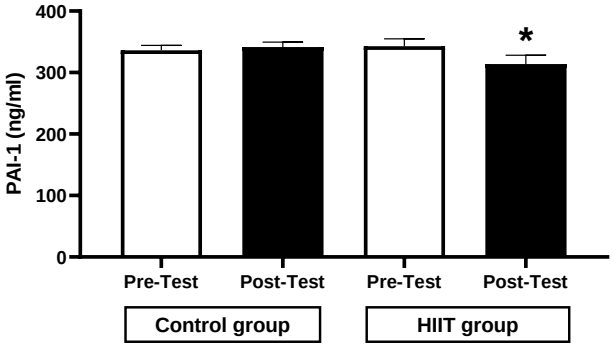

Figure 2. Changes in Fibrinogen levels at two groups of study. Data were shown as mean ± SD. Asterisk (*) Indicates a significant decrease compared to the control group.

increased circulating levels of PAI-1 and tPA serve as independent markers for cardiovascular diseases (Thögersen et al., 1998). On the other hand, researchers have highlighted the beneficial role of physical exercise in modulating and reducing circulating levels of PAI-1 (Keating et al., 2013). High-Intensity Interval Training (HIIT) has been introduced as an alternative to moderate-intensity continuous exercise, and its positive effects have been reported in numerous studies. In the present study as well, the modulatory effects of HIIT on PAI-1 and fibrinogen levels were observed.

Consistent with the results of the present study, Hemmatinefar et al. (2013) reported that six weeks of high-intensity interval training (HIIT) in inactive young men led to a significant reduction in plasma PAI-1 levels (Hemati Nafar et al., 2013). Despite the similar findings, their study involved healthy young individuals, whereas the present study was conducted on men with metabolic syndrome. In another study, Dekker et al. (2007) found that resting PAI-1 levels were significantly higher in obese individuals compared to the lean group. In the diabetic group, PAI-1 levels were lower than in the obese group but higher than in the lean group; however, these differences were not statistically significant. Moreover, consistent with the current findings, they demonstrated that 12 weeks of endurance training led to reductions in PAI-1 levels by 6.3%, 24.7%, and 7.4% in lean, obese, and type 2 diabetic individuals, respectively (Dekker et al., 2007).

According to the findings of Dekker et al. (2007), it can be concluded that there is a positive correlation between body fat mass and PAI-1 levels. In that study, the greatest reduction in body fat was observed in the obese group, which also showed the largest decrease in PAI-1 levels. Supporting the association between body adipose tissue and PAI-1 levels—particularly in patients with metabolic syndrome—it has been reported that PAI-1 is primarily produced by adipose tissue, and its levels are elevated in obese individuals with metabolic syndrome as well as in patients with type 2 diabetes. Moreover, the more severe the metabolic syndrome, the higher the plasma levels of PAI-1. Researchers have identified infiltrating macrophages in adipose tissue as the main source of PAI-1 production in individuals with metabolic syndrome (Alessi & Juhan-Vague, 2006). Therefore, the reduction of adipose tissue mass as a result of various interventions, including exercise training, can be considered one of the primary mechanisms responsible for the decrease in PAI-1 levels. In the present study as well, a significant reduction in body fat percentage was observed after eight weeks of HIIT, which was accompanied by decreased PAI-1 levels. In contrast to the current findings, Bodary et al. (2003) did not report a significant change in PAI-1 levels following a short-term aerobic exercise program (10 consecutive days) in overweight and obese women (Bodary et al., 2003). One possible explanation for the lack of significant change in PAI-1 levels in their study—aside from differences in the type, intensity, and duration of exercise sessions—could be the shorter intervention period compared to the current study. These results highlight the importance of exercise duration in achieving physiological adaptations and emphasize that significant changes in the measured variables may not occur over the short term.

Regarding the reduction in fibrinogen levels, Sobhani et al. (2016) reported that eight weeks of HIIT led to a decrease in fibrinogen levels, though statistically non-significant (Sobhani et al., 2016). The discrepancy with our findings likely stems from two key factors: differences in HIIT protocols and, crucially, divergent participant health statuses. First, Sobhani et al. utilized 3–8 bouts of 35-second intervals, representing lower exercise volume per session than our protocol (16 minutes of high-intensity exercise). This suggests training volume may influence coagulation marker responses. Second, and critically, while our cohort consisted of men with metabolic syndrome (MetS)—a population with inherent prothrombotic dysregulation—Sobhani et al. studied healthy, normal-weight individuals. Given that MetS elevates baseline fibrinogen and alters hemostatic responsiveness, this fundamental difference in participant phenotype is a major confounder likely contributing to the divergent outcomes.One of our study's primary limitations, beyond dietary and physical activity controls, was the small sample size, which constrains the strength of our conclusions. Future research should employ larger samples to enhance reliability and generalizability.

In addition to the reductions in PAI-1 and fibrinogen levels, the present results demonstrated that eight weeks of HIIT led to significant decreases in systolic and diastolic blood pressure, improvements in lipid profile (including reduced levels of cholesterol, triglycerides, and LDL-c, and increased HDL-c), and ultimately a reduction in insulin resistance, compared to the control group. These findings suggest that HIIT plays an effective role in improving the metabolic profile in individuals with metabolic syndrome. Consistent with the present findings, a study comparing the effects of HIIT and moderate-intensity continuous training (MICT) in patients with metabolic syndrome reported significant reductions in BMI, systolic blood pressure, cholesterol, triglycerides, and LDL-c, along with a significant increase in HDL-c. However, a significant reduction in waist circumference was observed only in the HIIT group (Drigny et al., 2013), highlighting the greater impact of this training modality. Despite the similarities in findings and training protocols between that study and the present one, it is important to note that the duration of the intervention in the former was longer (nine months). Supporting the importance of training intensity for physiological adaptations in patients with metabolic syndrome, results by Aloulou et al. (2006) showed that eight weeks of low-intensity endurance training did not lead to significant changes in

lipid profile or fibrinogen levels in individuals with metabolic syndrome (Aloulou et al., 2006). Recently, Steckling et al. (2019) also confirmed the present findings regarding the positive effects of HIIT in patients with metabolic syndrome. These researchers demonstrated that 12 weeks of HIIT in women with metabolic syndrome significantly reduced body fat percentage, waist circumference, and waist-to-hip ratio (WHR). In addition, consistent with the current findings, they reported significant reductions in systolic and diastolic blood pressure, glucose levels, and insulin resistance in the HIIT group. Regarding the lipid profile, they observed a significant increase in HDL-c, although no significant changes were found in LDL-c, cholesterol, or triglyceride levels. This lack of change may be attributed to the participants' lower baseline levels of LDL-c and cholesterol compared to those in the present study.

It is worth noting that unlike the current study, which included both HIIT and control groups and compared post-test changes relative to the control group, Steckling et al. (2019) used a single-group design and only compared pre- and post-test values within the HIIT group (Steckling et al., 2019). Overall, the existing evidence highlights the beneficial effects of exercise training in improving the metabolic profile of patients with metabolic syndrome. However, it appears that to achieve significant changes over short-term interventions, the exercise intensity must be sufficiently high. In the present study, clear evidence was provided for the positive effects of HIIT in reducing coagulation and inflammatory factors such as PAI-1 and fibrinogen. Moreover, eight weeks of HIIT led to improvements in other cardiometabolic risk factors, including insulin resistance, systolic and diastolic blood pressure, and lipid profile.

Several limitations of this study warrant consideration. First, the modest sample size (n=12 per group) increases the risk of Type II error, potentially limiting our ability to detect smaller but biologically relevant treatment effects. Second, the absence of dietary control represents a significant confounding factor, as nutritional intake directly modulates both coagulation parameters (e.g., fibrinogen) and metabolic pathways; this limitation precludes definitive causal attribution of observed changes solely to the exercise intervention. Third, our exclusively male cohort restricts generalizability to females, who exhibit distinct thrombotic risk profiles influenced by hormonal factors. Future investigations should prioritize larger participant cohorts, standardized dietary monitoring/control, and inclusion of female populations to validate these findings.

Conclusion

Based on the current findings, it can be concluded that HIIT, like other forms of exercise, can serve as an effective training method for modulating risk factors in patients with metabolic syndrome. However, given the limited number of studies investigating the effects of high-intensity interval training on PAI-1 and fibrinogen levels—especially in patients with metabolic syndrome—further research is warranted to better understand the impact of exercise on these factors and to address the many outstanding questions in this area.

What is already known on this subject?

Dysregulated adipokine production, particularly from hypertrophied VAT, establishes a chronic pro-inflammatory milieu and ectopic lipid deposition, driving insulin resistance (IR) and endothelial dysfunction.

What this study adds?

The HIIT can serve as an effective training method for modulating risk factors in patients with metabolic syndrome.

Organ Cross-Talk Tips:

- These hemostatic improvements are mechanistically linked to ameliorated metabolic dysfunction, highlighting HIIT's role in modulating adipose tissue–vascular cross talk.

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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 they have no conflict of interest.

Ethical approval The institutional review board approved all procedures (Protocol #JEOCT-2506-1158), and written informed consent was obtained prior to participation. The study conformed to the Declaration of Helsinki.

Informed consent Participants signed an informed consent form prior to participation in the study

Author contributions

Conceptualization: N.Gh., A.R.; Methodology: A.A., D.B.; Software: E.R.M., M.R.M.; Validation: MS.RK., A.A. Formal analysisS.RK.; Investigation: N.Gh.; Resources: A.A.; Data curation: A.R.; Writing - original draft: A.R.; Writing–review & editing

editing: E.R.M.; Visualization: D.B.; Supervision: A.R.; Project administration: A.R.; Funding acquisition: A.R.

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