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Original Article

Associations of Irisin with Blood Pressure, Central Obesity, and Hypertension Duration

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ABSTRACT

Background: Irisin is a myokine recently linked to blood pressure and fat metabolism. However, its role in essential hypertension without comorbidities and its relationship with body fat and hypertension duration remain inadequately defined.

Objectives: This study aims to investigate the association between serum irisin and blood pressure, waist-to-height ratio (WHtR), and hypertension duration in otherwise healthy, middle-aged hypertensive adults.

Methods: A cross-sectional study was conducted on 95 adults aged 40–65 with hypertension, excluding those with comorbidities. Blood pressure, anthropometric data, medication use, and physical activity were assessed. Serum irisin was measured using ELISA. Correlation and regression analyses were performed; a P-value of ≤ 0.05 was considered significant.

Results: Serum irisin levels showed no significant differences by age ($p = 0.865$), sex ($p = 0.735$), physical activity ($p = 0.584$), or hypertension duration ($p = 0.567$). In the early middle-age group, irisin was a significant negative predictor of systolic (SBP: $\beta = –0.380$, $p = 0.008$) and diastolic blood pressure (DBP: $\beta = –0.332$, $p = 0.032$), and positively associated with waist-to-hight ratio (WHtR: $\beta = 0.341$, $p = 0.022$), which was the only significant predictor of serum irisin. Males in the late middle-aged group had higher irisin levels than females. Among younger participants, irisin ($\beta = –0.380$, $p = 0.008$) and waist circumference ($\beta = 0.408$, $p = 0.005$) were significant predictors of blood pressure.

Conclusions: Serum irisin is inversely associated with blood pressure (BP), and positively with WHtR, independent of hypertension duration and physical activity, highlighting its potential role in cardiovascular risk modulation among hypertensive adults.

Keywords: Irisin, Blood Pressure, Waist-Height ratio, Middle-Aged Adults, Hypertension Duration..

1 Introduction

According to the European guidelines, hypertension occurs when systolic blood pressure (SBP) reaches 140 mmHg or higher, and/or diastolic pressure (DBP) exceeds 90 mmHg [1]. It remains a major and growing global health issue, currently affecting approximately 1.13 billion people worldwide, with projections indicating a 15–20% rise by 2025 [2]. Elevated blood pressure is a major contributor to the development of cardiovascular conditions and often occurs alongside other CVD risk factors and unhealthy lifestyle habits, such as smoking, diabetes, dyslipidemia, being overweight, sedentary lifestyles, and poor dietary patterns [3]. Similar trends have been observed regionally, with overweight and obesity being highly common among Iraqi adults and strongly linked to hypertension and cardiovascular risk [4,5]. Recently, emerging evidence indicated that irisin may be involved in the regulation of blood pressure [6-10].

Irisin is a myokine cleaved from fibronectin type III domain-containing protein 5 (FNDC5) in skeletal muscle during exercise, acting as a hormone-like peptide that regulates energy metabolism and thermogenesis [11-14]. It promotes the browning of white adipose tissue and aids in improving metabolic function and regulation of obesity [15-18]. In addition, irisin enhances endothelial nitric oxide (NO) production through activation of endothelial enzymes [15,19]. However, findings regarding its association with blood pressure remain inconsistent, with positive, negative, and null correlations reported [6-10]. Therefore, this study aimed to investigate the association between serum irisin concentrations and blood pressure parameters in otherwise healthy hypertensive adults, while considering the influence of central obesity (waist-to-height ratio), physical activity, and duration of hypertension.

2 Methods and Materials

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2.1 Study Design and Ethical Approval

This descriptive cross-sectional investigation included hypertensive individuals aged between 40 and 65 years. Ethical clearance was obtained from the Institutional Review Board of the College of Medicine, University of Sulaimani (Approval No. 21, dated September 22, 2024). Informed written consent was secured from each participant prior to data collection.

2.2 Sample Size and Participants

Sample size estimation was derived from an earlier study that reported a mean serum irisin concentration of 34 ± 14 pg/mL [20]. Assuming a moderate correlation (r = 0.3), a minimum of 95 subjects was required, accounting for a 5% attrition rate. Participants were consecutively recruited from Anwar Sheikha Medical City, provided they had no other comorbid conditions, as confirmed by their specialist physicians and clinical medical history, and met all inclusion and exclusion criteria. All participants had a prior diagnosis of hypertension, defined by SBP of ≥ 140 and DBP of ≥ 90 mmHg, following 2-3 office visits at a few-week intervals [21] , and were on standard antihypertensive therapy. Their medical records were reviewed to exclude individuals with a history of metabolic, systemic, or chronic diseases.

2.3 Inclusion and Exclusion Criteria

Inclusion criteria involved hypertensive individuals aged 40–65 years old, clinically confirmed to have no systemic or metabolic comorbidities, and who were willing to provide informed written consent.

Exclusion criteria include individuals with heart failure, secondary hypertension, heart disease, arrhythmias or other systemic or cardiac diseases; were pregnant or lactating; had a diagnosis of malignancy, autoimmune or inflammatory disorders; had used lipid-lowering medications or other drugs affecting blood pressure outside of standard antihypertensive therapy; or reported significant lifestyle changes, including new diet or exercise routines or significant weight fluctuations in the preceding four weeks were excluded.

Data were collected through face-to-face interviews with every individual using a structured questionnaire, which documented sociodemographic characteristics, medical and family histories, medication use, lifestyle behaviors, and hypertension-related information, including duration and type of therapy. Physical activity classification followed the American Heart Association (AHA) recommendations [22,23], with ≥150 minutes of moderate or 75 minutes of vigorous weekly activity considered physically fit.

2.4 Anthropometric and Blood Pressure Measurements

Anthropometric measurements included height, weight, and waist circumference. Height was measured to the nearest 0.1 cm with participants standing barefoot, upright, and looking straight ahead. Weight was recorded to the nearest 0.1 kg using a calibrated scale, with participants in light clothing and without shoes. Waist circumference was measured midway between the lowest rib and the iliac crest at the end of normal expiration using a flexible measuring tape. and the Waist-to-height ratio (WHtR) was calculated by dividing waist circumference (cm) by height (cm), both measured to the nearest 0.1 cm. To minimize any influence on blood pressure readings, all participants were confirmed to have abstained from caffeinated beverages and smoking for at least four hours prior to measurements. Furthermore, each participant remained seated and rested for a minimum of 20 minutes before any blood pressure measurement was performed. During this time, they completed the questionnaire to relax and make good use of the waiting period.

Blood pressure was measured with the participant seated in a comfortable and relaxed position, maintaining proper posture: back supported, feet flat on the floor, and arms aligned with the heart level. Blood pressure was measured three times from the same arm (left arm) using a manual sphygmomanometer. Each measurement was preceded by at least 10 minutes of rest before the next reading, with 30-minute intervals between the first and third measurements. The average of the second and third readings was used for analysis. Care was taken to ensure the participant remained still and refrained from talking during the process.

2.5 Blood Sampling and Biochemical Analysis

Venous blood was drawn and subsequently centrifuged. The serum was then divided into labeled Eppendorf tubes and preserved at –80°C for subsequent analysis.

Serum irisin levels were measured using a quantitative sandwich ELISA kit (Elabscience®, Cat. No. E-EL-H5573, 96T), following the manufacturer's protocol. The assay employed a double-antibody sandwich format, where a pre-coated capture antibody binds irisin in the sample. A biotinylated detection antibody specific to irisin was then added, followed by HRP-conjugated streptavidin. After washing, a substrate solution was added to produce a color reaction, which was stopped and measured spectrophotometrically at 450 nm. The detection range of the kit was 781.3–50,000 pg/mL, with a detection sensitivity of 46.88 pg/mL and an intra-assay coefficient of variation maintained below 10%. All samples were measured in duplicate, and the average optical density was used to calculate concentrations using a four-parameter logistic (4-PL) standard curve. Serum samples were stored at –80°C until analysis of serum irisin levels, and all reagents were brought to room temperature prior to use. The results were interpreted in accordance with the standard curve generated using the kit's calibrators.

2.6 Statistical Analysis

The data were analyzed using SPSS (version 26). Normality was assessed for all variables, and skewed data, such as serum irisin, were log-transformed before analysis. Normally distributed data were expressed as mean ± SD. Participants were categorized into two age groups (40–51 and 52–65 years) and three hypertension-duration groups (<1 year, 1–5 years, and >5 years). Group comparisons were performed using the Student's t-test or one-

way ANOVA, and the Mann–Whitney U test was used for comparing non-normally distributed data, as appropriate. Correlations between variables were assessed using Pearson's or Spearman's coefficients for parametric and non-parametric data, respectively. Multiple linear regression analyses were conducted to identify independent predictors of SBP, DBP, mean BP, and log-transformed irisin levels, with statistical significance set at $P \leq 0.05$.

3 Results and Discussion

3.1 Baseline Characteristics of Participants

Among the 95 individuals diagnosed with hypertension, the mean age was 52.4 (7.02), with 53 males and 42 females. There was no statistically significant variation in age, sex, and BMI between the hypertensive and control groups. The general characteristics of the participants have been summarized below for clarity (Table 1).

Table 1: Basic characteristics of the study participants.

Variables	Hypertensives Mean±SD or Number (%)	Control Mean±SD or Number (%)	P-value
Age (year)	52.4 ± 7.02	52.51 ± 5.19	0.920
Sex			
Male	53 (55.8%)	29 (52.7%)	0.735
Female	42 (44.2%)	26 (47.3%)	
BMI (Kg/m^2)	30.46 ± 3.24	29.07 ± 3.68	0.022
Waist circumference (cm)	103.48 ± 8.72	99.69 ± 8.17	0.01
WHtR	0.622 ± 0.053	0.603 ± 0.052	0.032
Smoker			
No	64 (67.4%)	38 (69.1%)	0.297
Yes	31 (32.6%)	17 (30.91%)	
Exercise			
No	68 (71.6%)	19 (34.5%)	0.584
Yes	27 (28.4%)	36 (65.5%)	
Type of exercise			
Aerobic	26 (96.3%)	19 (100%)	0.596
Exercise Intensity			
Mild	13 (48.1%)	8 (42.1%)	0.013
Moderate	7 (25.9%)	11 (57.9%)	
Heavy	7 (25.9%)	0 (0.0%)	
Activity duration (min/week) *	210.0 (10-1080)	180.0 (25-2100)	0.589
Fitness level			
Fit	7 (7.6%)	5 (9.3%)	0.557
Not fit	85 (92.4%)	49 (90.7%)	
Hypertension duration groups			
< 1year	39 (41.1%)		
1-5 years	33 (34.7%)		
> 5 years	23 (24.2%)		

*Activity duration is demonstrated in Median (range) as it is not normally distributed.

3.2 Comparison Between Age Groups

To illustrate the differences between age groups, Table 2 shows the means of serum irisin and blood pressure parameters (SBP, DBP, Mean BP, and Pulse pressure) across the two hypertensive age groups.

Table 2: Mean serum irisin and blood pressure measurements between the two age groups.

Variables	Early Middle Age group N= 42 Mean ±SD	Late Middle Age group N = 53 Mean ±SD	P-Value
Log serum Irisin (pg/ml)[a]	3.35 ± 0.35	3.37 ± 0.38	0.865
SBP (mmHg)	144.54 ± 14.27	143.05 ± 16.05	0.639
DBP (mmHg)	90.98 ± 11.98	85.15± 10.37	0.013
Mean BP (mmHg)	108.83 ± 11.57	104.45± 10.80	0.06
Pulse pressure (mmHg)	53.56 ± 11.56	57.90 ± 13.54	0.102

All means (SD) of parameters (normally distributed) between groups were compared using the Student T-test.
[a]Log transformed mean serum irisin level was used for comparison via parametric analysis.

3.3 Serum Irisin and Blood Pressure Across Age Groups

The median irisin level did not differ significantly between early and late middle-aged groups (2232.15 vs. 2909.30 pg/ml; P = 0.865). However, DBP and mean BP were higher in the early middle-aged group (P = 0.013 and 0.06, respectively; Table 2).

To visualize these findings in context, Figure 1 compares irisin and blood pressure profiles across sex and age categories.

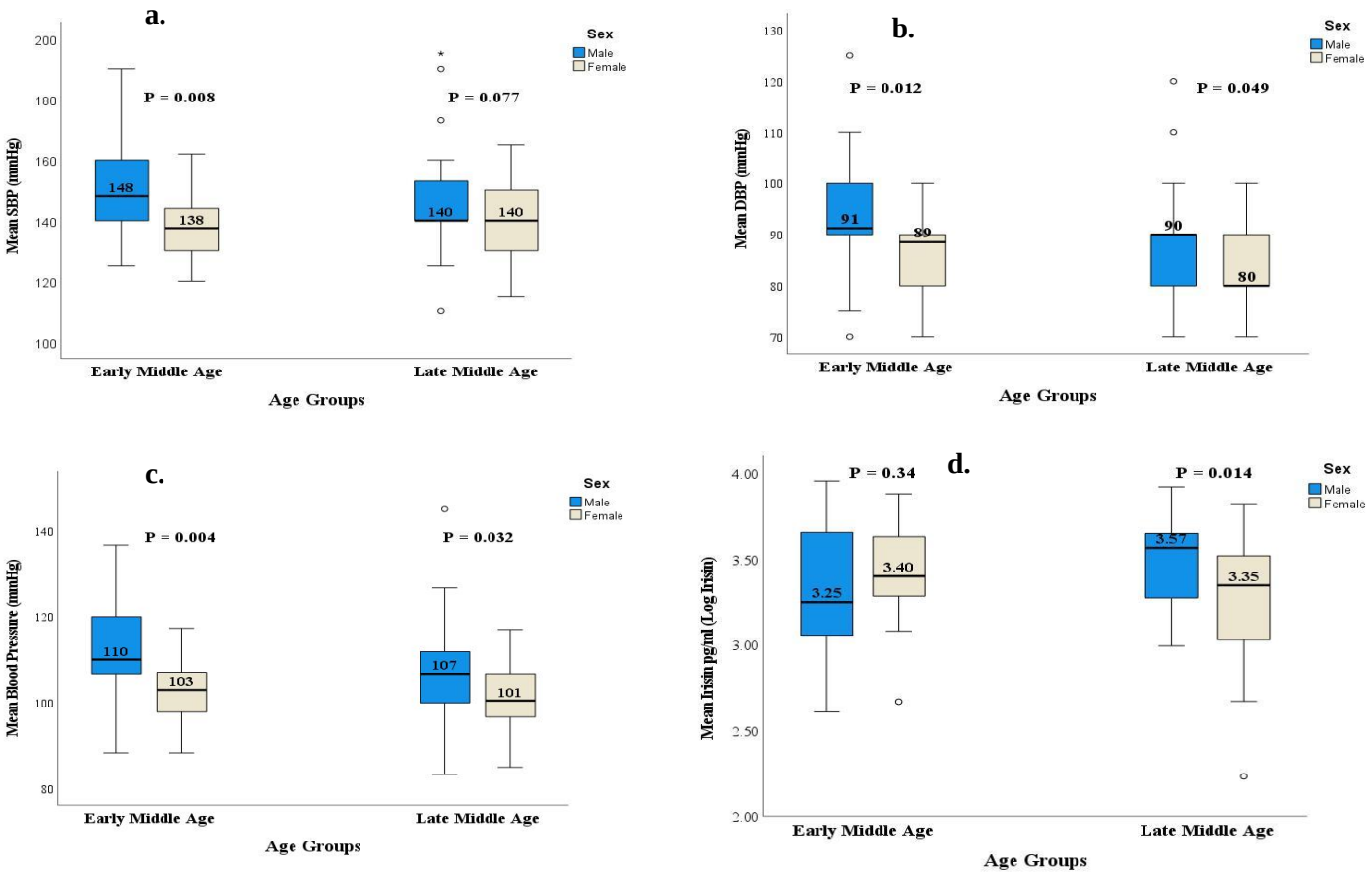

Figure 1: Sex-based comparison of blood pressure and irisin levels across different age groups. (a) Mean systolic blood pressure (SBP). (b) Mean diastolic blood pressure (DBP). (c) Mean blood pressure (BP). (d) Mean serum irisin levels. Data were presented as mean ± SD. Comparisons between males and females were performed using the Student's t-test. $p < 0.05$ was considered statistically significant.

3.4 Association of Irisin with Central Adiposity and Blood Pressure

The current study is among the few to assess the relationship between serum irisin levels, blood pressure parameters, and

central adiposity exclusively in otherwise healthy individuals with uncomplicated hypertension. Previous investigations often included patients with comorbidities such as metabolic syndrome [7], CKD [7,9], or diabetes, which can confound the observed associations. This study highlights the inverse relationship between irisin and blood pressure parameters, as well as a positive association with WHtR, particularly in the early middle-aged group.

3.5 Relationship Between Irisin, Physical Activity, and Hypertension Duration

Mean serum irisin did not differ significantly between individuals who did or did not engage in exercise (P = 0.592). Although irisin levels in physically fit individuals were higher compared to non-fit individuals, the difference was not significant (P = 0.373; Supplementary Figure 1). No significant differences were observed across activity type or intensity (P = 0.510 and 0.095). Similarly, comparisons among the three hypertension duration groups showed no significant differences in serum irisin or blood pressure. A summary of these comparisons is presented below (Table 3).

Table 3: Mean serum irisin and blood pressure measurements between different HTN duration groups.

Variables	Hypertension duration groups			P-Value
	< 1 year N = 39 Mean ±SD	1-5 years N= 33 Mean ±SD	>5 years N = 23 Mean ±SD	
Age (years)	52.41 ± 6.80	50.58 ± 7.02	55.0 ± 6.84	0.315
HTN duration in years	2 ± 0.0	2.29 ± 1.43	13.78 ± 7.40	0.077
HTN duration in days	59.18 ± 118.29	834.06 ± 521.05	5030.65 ± 2702.34	< 0.001
Log serum Irisin (pg/ml)[a]	3.35 ± 0.37	3.43 ± 0.35	3.28 ± 0.38	0.567
SBP (mmHg)	145.38 ± 13.58	144.58 ± 18.26	139.61 ± 12.78	0.307
DBP (mmHg)	88.38 ± 10.29	89.88 ± 13.47	83.52 ± 9.19	0.078
Mean BP (mmHg)	107.38 ± 9.69	108.11 ± 13.93	102.22 ± 8.70	0.106
Pulse pressure (mmHg)	57.0 ± 13.15	54.7 ± 13.08	56.09 ± 12.27	0.768

All means (SD) of parameters (normally distributed) between groups are compared using the ANOVA test.
[a]Log-transformed mean serum irisin level was used for comparison via parametric analysis.

Despite irisin's established association with exercise, our study found neither significant differences in serum irisin levels between physically active and inactive individuals, nor any correlation between irisin and weekly exercise frequency or duration. One possible explanation is that participants were at rest for several hours prior to blood sampling to prevent the confounding effect of short-term exercise on the association between irisin and blood pressure levels, which may have prevented the detection of any acute exercise-induced spikes in irisin. While irisin levels can be elevated after acute exercise, this increase is transient and returns to baseline within approximately one hour after exercise ends [24,25]. In contrast, chronic exercise, especially resistance training, appears to have the most pronounced cumulative effect on increasing irisin levels compared to aerobic exercise [26]. Additionally, studies have claimed that the intensity of exercise is key to raising irisin levels, as high-intensity exercise may promote a greater increase in irisin levels [26,27]. Other studies have shown that the type of exercise can affect irisin levels, as resistance exercise generally induces a greater irisin response than endurance exercise [25,26,28]. The majority of our participants performed aerobic, rather than resistance exercise, and only a small percentage were classified as physically fit. This may explain the lack of association.

3.6 Sex-Related Differences in Irisin and Blood Pressure Parameters

A comparative assessment of mean irisin concentrations and blood pressure indices across male and female subjects is demonstrated in Figure 1. In the late middle-aged group, males had significantly higher mean serum irisin levels compared to females (P = 0.014), whereas no sex-related differences were observed in the early middle-aged group. All blood pressure parameters, SBP, DBP, and Mean BP, were also higher in males than in females (P < 0.05).

This sex-related difference in irisin levels is consistent with prior studies attributing higher circulating irisin to greater skeletal muscle mass in males, as irisin is primarily secreted by skeletal muscle [24,29]. Studies have shown higher irisin levels in healthy males [29]. Another study suggested that middle-aged women had noticeably lower average circulating irisin levels compared to younger women, whereas no such age-related difference was found among men [30].

Figure 2 demonstrates the group-wise comparison between hypertensive and normotensive individuals.

3.7 Comparison Between Hypertensive and Normotensive Individuals

When serum irisin, SBP, DBP, and MBP were compared between the hypertensive and control groups, serum irisin did not differ significantly between the groups. In contrast, all blood pressure

parameters were significantly elevated in hypertensive individuals compared to the control group, as shown in Figure 2.

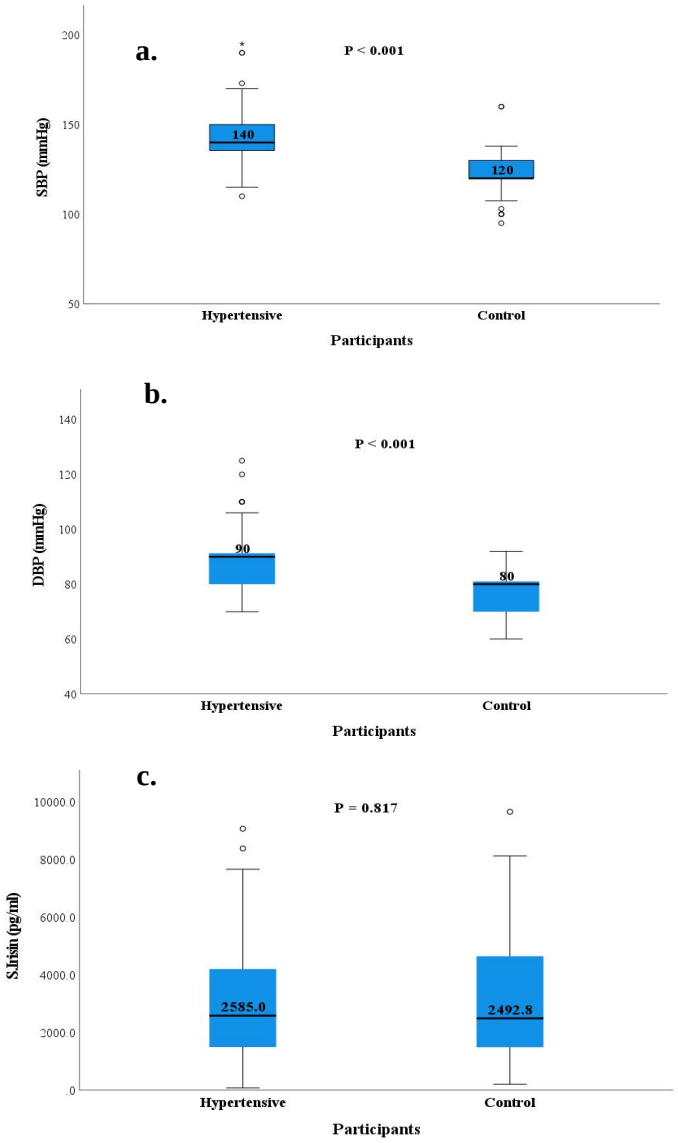

Figure 2: Comparison of blood pressure and serum irisin level between control and hypertensive groups. (a) Mean systolic blood pressure (SBP). (b) Mean diastolic blood pressure (DBP). (c) Mean serum irisin levels. Data are presented as mean ± SD. Comparisons between males and females were performed using the Student's t-test. $p < 0.05$ was considered statistically significant.

The relationship between circulating irisin and blood pressure remains a topic of debate in humans. In animal models, irisin has been shown to reduce BP via enhancement of endothelial nitric oxide synthase (eNOS) phosphorylation and increased NO production, supporting its potential vasodilatory effects [6]. In Zucker diabetic rats, it also lowered BP by reducing renal inflammation, oxidative stress, and angiotensin II type 1 receptor expression, partly via NF-κB pathway inhibition [31]. In humans, however, the findings are inconsistent. Some studies, including those conducted in dialysis patients, have shown an inverse relationship between irisin and blood pressure [9], Conversely, other studies have reported positive correlations with both systolic and diastolic pressures [7,8].

Such discrepancies may stem from differences in study populations, comorbidity profiles, and methodologies. Notably, many previous studies included patients with metabolic or renal comorbidities, or even children [7] potentially confounding the irisin–BP relationship. In contrast, the current study uniquely focused on otherwise healthy individuals with uncomplicated hypertension, which may explain our consistent inverse associations between irisin and multiple BP indices.

3.8 Correlation Analyses of Irisin, Hypertension Duration, and Adiposity

Linear correlation revealed no significant association between irisin and activity variables (days/weeks, minutes/day), or activity duration (min/week); q=-0.071, -0.243, -0.012, P=0.725, 0.222, 0.953, respectively.

A negative, though nonsignificant, correlation was observed between mean serum irisin and hypertension duration (q = -0.225, P=0.093**,** Figure 3.a).

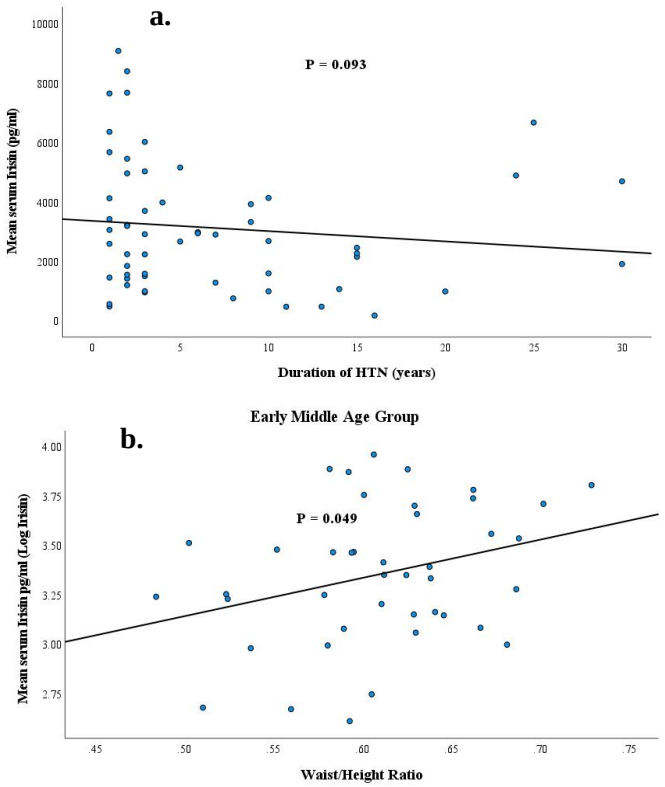

Figure 3: Correlation of serum irisin levels with (a) duration of hypertension in all participants and (b) waist-to-height ratio in the early middle-aged group. Data were analyzed using Pearson's correlation test. $p < 0.05$ was considered statistically significant.

Although the correlation between hypertension duration and irisin was not significant, a weak inverse trend was observed. This may reflect progressive endothelial dysfunction or metabolic

adaptation over time; however, larger longitudinal studies are needed to clarify this relationship.

In the early middle-aged group, irisin correlated positively with WHtR (Figure 3.b), and negatively with SBP, DBP, and Mean BP (Figure 4). In the late middle-aged group, age correlated positively with pulse pressure (r = 0.333; P = 0.015).

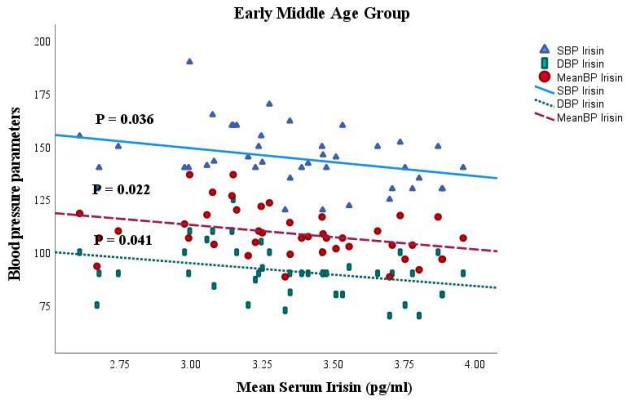

Figure 4: Significant correlations between serum irisin levels and systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (BP) in the early middle-aged hypertensive group. Data were analysed using Pearson's correlation test. $p < 0.05$ was considered statistically significant. Each regression line is shown in a different colour as indicated in the figure.

A novel and important finding was the significant positive relationship between irisin and WHtR among early middle-aged participants. Irisin is known to regulate adipose tissue metabolism and maintain glucose balance by stimulating the conversion of white to brown adipose tissue [32,33]. However, the connection between circulating irisin levels and obesity has not yet been clearly established [34].

Several studies have reported a positive correlation between irisin and adiposity indices. For example, circulating irisin was positively associated with WHtR in T2DM males [35]. Similar findings were observed in the study by Alzoughool et al. [36]. Bodybuilders also showed a positive correlation between serum irisin concentration and overall body composition [37]. Other research has shown higher irisin levels in obese individuals, possibly resulting from altered metabolic signaling [38]. Evidence in hypertensive patients, however, remains limited, which makes our findings especially significant.

3.9 Regression Analysis of Independent Predictors

Multiple regression analysis identified serum irisin and waist circumference as independent predictors of SBP and mean BP, while irisin alone predicted DBP. WHtR was the only significant predictor of serum irisin ($P \leq 0.05$; Table 4). To clarify these relationships, Table 4 summarizes the regression models and the strength of each association.

Table 4: Multiple linear regression analysis of independent predictors for each of the SBP, DBP, Mean BP, and log serum Irisin as outcome variables.

Model	Unstandardized Coefficients B	S.E	Standardized Coefficients Beta	P-value	95% C.I for B Lower Bound	Upper Bound
Dependent: SBP						
Irisin[a]	-0.002	0.01	-0.380	0.008	-0.004	-0.001
Waist circumf.	0.641	0.213	0.408	0.005	0.210	1.072
Dependent: DBP						
Irisin[a]	-0.002	0.01	-0.332	0.032	-0.003	0.000
Dependent: Mean BP						
Irisin[a]	-0.002	0.01	-0.403	0.005	-0.003	-.001
Waist circumf.	0.501	0.172	0.394	0.006	0.153	0.849
Dependent: Mean Irisin[a]						
SBP	-0.007	0.005	-0.268	0.151	-0.016	0.003
DBP	-0.005	0.005	-0.156	0.396	-0.015	0.006
WHtR	2.162	0.905	0.341	0.022	0.330	3.994

[a]Log transformed mean serum irisin level is used for multiple regression.

Regression models reinforce irisin's potential physiological role in cardiovascular regulation. In early middle-aged participants, irisin independently predicted diastolic BP and contributed to the prediction of SBP and Mean BP alongside waist circumference. WHtR was the only independent predictor of irisin levels, further supporting a link between central adiposity and irisin dynamics. Notably, these associations were not observed in the late middle-aged group, possibly due to age-related changes in vascular or metabolic responsiveness.

4 Study Limitations

While this study provides valuable insights, it also has some limitations. Although the sample size was appropriate for examining overall patterns, it might not have been large enough to fully capture differences within smaller subgroups. Additionally, some important factors that can influence irisin levels, such as physical activity, muscle mass, and diet, were not measured in detail, which could have affected the results. Finally, measuring irisin using ELISA kits remains a debated topic in the research field, as different kits can yield varying results.

Conclusion

In conclusion, this study demonstrated that lower serum irisin levels are associated with higher blood pressure, particularly among early middle-aged hypertensive individuals with central obesity. At the same time, no association was found with hypertension duration or physical activity. These findings suggest that irisin may serve as an early biomarker of cardiovascular dysfunction, highlighting the clinical relevance of the waist-to-height ratio as a simple indicator of central adiposity and cardiovascular risk in hypertensive adults.

Data Availability statements

The data used in this study are available from the corresponding author upon reasonable request.

Ethical consideration

The research proposal was approved by the ethical committee of the College of Medicine University of Sulaimani, with research no. 21, on 22-9-2024. Written informed consent was obtained from all participants.

Disclosure statements

Conflict of Interest: The authors declare no conflicts of interest and have received no funding or grants for this study.

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Author's contribution

The concept and design of the research is by DA. RM did the patient interview and data collection for anthropometric, BP assessment, and laboratory measures. DA did a statistical analysis and data interpretation. RM wrote the first draft of the manuscript DA had revised it for intellectual content. All authors, RM and DA, reviewed the final draft of the manuscript.

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