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Circulating Irisin as a Potential Diagnostic and Vascular Protective Biomarker in Patients with Metabolic Syndrome

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Annotation: Background & Aims: Metabolic syndrome (MetS) is a multifaceted metabolic disorder characterized by an increased cardiovascular risk and endothelial dysfunction. Recently, it has become increasingly apparent that myokines from skeletal muscle may have profound effects on metabolism and vascular tone. The aim of the present study is to assess the diagnostic potential of circulating Irisin and its association with oxidative stress, vascular function and metabolic profile in MetS.

Materials and Methods: One hundred fifty-six subjects were included, consisting of 78 patients with MetS and 78 age-matched healthy control subjects. The anthropometric measurements and blood pressure were also measured. Plasma contents of Irisin, Myostatin, FGF-21, malondialdehyde (MDA) and nitric oxide (NO) were assayed ELISA methods. HOMA-IR was used to evaluate the extent of insulin resistance.

Results: MetS patients had significantly higher BMI (31.8 ± 4.5 vs 23.4 ±

2.1 kg/m²), waist circumference (104.5 ± 9.2 vs 84.2 ±6.1 cm) and blood pressure (p <0..05). Serum Irisin was significantly lower in MetS patients (6.2 ± 1.5 vs. 12.4 ± 2.8 ng/mL; p <0.001), whereas serum Myostatin and FGF-21 were higher than in controls. Oxidative stress was also augmented as observed by higher MDA concentrations (4.2 ± 0.9 vs 1.8 ± 0.4 μmol/L) and decreased availability of NO (18.4 ± 3.1 vs 35.8 ± 5,2 μmol/L, p < 0,001). Irisin was found to be significantly negatively correlated with BMI (r = −0.425), HOMA-IR (r = −0.512) and MDA (r = −0.621) and positively with NO (r= 0.582, p < 0.001). ROC analysis showed that the diagnostic performance of Irisin for MetS was excellent (AUC = 0.89, sensitivity = 85.9%, specificity = 82.1%).

Conclusions: Low circulating Irisin levels are strongly related to metabolic disarrangement, oxidative stress and endothelial dysfunction in MetS. Irisin might be taken as a potential diagnostic and protective biomarker of metabolic syndrome.

Keywords: Irisin, Metabolic Syndrome, Oxidative Stress, Endothelial Function.

Introduction

Metabolic Syndrome (MetS) is one of the most pressing public health threats of the 21stSt century, defined by a complex constellation of clinical disturbances: central obesity, insulin resistance, dyslipidemia and systemic hypertension [1]. The physiologic basis of MetS is strongly associated with chronic, low-grade inflammation and cellular stress [2]. Of the many tissues implicated, skeletal muscle emerges as a major metabolic engine that accounts for most glucose disposal and fatty acid oxidation [3]. In the recent evolution of molecular physiology, we have realized that skeletal muscle function is governed by the condition of its mitochondria. Defected mitochondrial function, characterized by abnormal oxidative phosphorylation and overproduction of reactive oxygen species (ROS), is a new indication for metabolic deterioration [4, 5]. The identification of benchimar-ker Irisin, a myokine that is the product of proteolysis of fibroblast growth factor domain-containing protein 5 (FNDC5), in 2012 marked the beginning of a new era

in muscle-endocrine communication [6]. Physiologically, Irisin is produced during physical exercise and serves as a powerful modulator of energy balance [7]. It increases the "browning" of white adipose tissue and stimulates up-regulation of UCP1, resulting in an increase in thermogenesis and metabolic rate [8]. In addition to being thermoactive, Irisin is an essential factor to sustain mitochondrial biogenesis in skeletal myocytes by activating PGC-1α/TFAM signaling pathway that increases the cell's power of energy expenditure [10–12]. But in the case of Metabolic Syndrome, Irisin's role as a regulator is disturbed. New evidence indicates that circulating Irisin concentration is considerably changed in patients with insulin resistance and obesity, however currently there are intense physiological discussions concerning the direction of this change [11, 12]. The cross-talk between Irisin and other metabolic regulators, such as FGF-21 and the muscle-growth inhibitor Myostatin forms a sophisticated network that leads to overall metabolic phenotype [13]. In addition, cardioprotection due to Irisin against oxidative stress, particularly its role in reducing lipid peroxidation and increasing nitric oxide bioavailability, is an important untapped area in cardiovascular physiology [14, 15]. However, several fundamental questions concerning Irisin are not yet answered: The systemic levels of this myokine in relation to the interaction between Myostatin and FGF-21 as well as certain oxidative stress markers have so far not been reported, to explain mitochondrial damage apparent in MetS patients. The aim of this study is to analyze serum Irisin levels in relation to certain biomarkers (FGF-21, Myostatin, MDA, and NO), such as those related to metabolism/metabolism or mitochondria and their usefulness as therapeutic targets in Metabolic Syndrome.

Materials and Methods

Study Design and Setting

This case control study was designed to assess the physiological role of Irisin and its relationship with mitochondrial and metabolic parameters.

Patients and Methods

The clinical phase of the study was conducted at Azadi Teaching Hospital in Kirkuk, Iraq. The data and sampling were performed from April to August 2024. The study protocol was approved by the Ethics Committee of our local healthcare area, and all enrolled subjects signed an informed consent learning agreement form.

Study Population

A total of 156 volunteers were enrolled and assigned into two main groups:

- Patient Group (n= 78): Patients met the criteria of Metabolic Syndrome (MetS) defined by International Diabetes Federation (IDF).
- Control (n = 78): Healthy, not otherwise specified; no previous diagnoses of metabolic or chronic inflammatory diseases.

Blood Sampling and Processing

Venous blood (5 mL) was taken in fasting condition (10-12 hours overnight). After centrifugation at 3000 g for 15 min, the separated serum was stored at -80°C until analysis.

Specialized Physiological Assays

The serum Irisin, Myostatin, FGF-21 and MDA were measured by high-sensitivity Enzyme-Linked Immunosorbent Assay (ELISA) kit (Sunlong Biotech Co.,LTD, Zhejiang, China). All measurements were made based on the microplate reader and washer (Biobase Group, Shandong, China). Serum NO was also measured by the same ELISA method.

Routine Biochemical Analysis

Fasting Blood Glucose (FBG) and Lipid Profile parameters were determined on a full Automatic Biochemistry Analyzer (Biobase, China) Assay-specific reagents and kits were obtained from

Mindray Medical International Limited (Shenzhen-China).

Statistical Analysis

Data were processed using SPSS 26.0 edition. Data were presented as Mean ± SD. Comparisons between groups were made by the Independent Student's t-test, and correlations were analysed by Pearson's coefficient. A p value less than 0.05 was considered statistically significant [16,17].

Results

Anthropometric and Clinical Characteristics

The anthropometric and clinical baseline characteristics of the study subjects are summarized in Table 1. Patients with MetS showed significantly greater body mass index (BMI), waist circumference, systolic and diastolic blood pressure than controls ($p < 0.05$). No significant difference was observed between the two groups for age.

Table 1. Baseline anthropometric and clinical characteristics of the study groups

Parameter	Control (n = 78)	MetS Patients (n = 78)	P-value
Age (years)	42.5 ± 5.2	43.1 ± 6.4	0.524
BMI (kg/m²)	23.4 ± 2.1	31.8 ± 4.5	0.001*
Waist Circumference (cm)	84.2 ± 6.1	104.5 ± 9.2	0.001*
Systolic BP (mmHg)	118 ± 8	142 ± 12	0.012*
Diastolic BP (mmHg)	76 ± 6	92 ± 8	0.015*

* Statistically significant ($p < 0.05$)

Serum Myokines, Oxidative Stress, and Vascular Markers

According to Table 2, MetS patients had significantly lower levels of serum Irisin than controls ($p < 0.001$). On the other hand, serum Myostatin and FGF-21 were significantly higher in MetS group ($p < 0.05$). Furthermore, patients of MetS manifested a significantly higher levels of malondialdehyde (MDA) and decreased NO bioavailability- features suggestive of increased oxidative stress and endothelial dysfunction.

Table 2. Comparison of serum myokines, oxidative stress, and vascular markers between groups

Parameter	Control (n = 78)	MetS Patients (n = 78)	P-value
Irisin (ng/mL)	12.4 ± 2.8	6.2 ± 1.5	0.001*
Myostatin (pg/mL)	145.2 ± 22.4	210.5 ± 35.8	0.001*
FGF-21 (pg/mL)	112.5 ± 15.4	185.2 ± 28.6	0.005*
MDA (µmol/L)	1.8 ± 0.4	4.2 ± 0.9	0.001*
Nitric Oxide (µmol/L)	35.8 ± 5.2	18.4 ± 3.1	0.001*

* Statistically significant ($p < 0.05$)

Correlation Analysis

Within the MetS group was shown to be negatively correlated with BMI, HOMA-IR, Myostatin, and MDA levels (Table 3). In parallel, a strong positive correlation was found between Irisin and nitric oxide ($r = 0.582$, $p < 0.001$), indicating the protective effect of Irisin against oxidative stress and vascular dysfunction.

Table 3. Correlation between serum Irisin and studied parameters in MetS patients

Parameter	Correlation Coefficient (r)	P-value
BMI	−0.425	0.01*
HOMA-IR	−0.512	0.001*

Myostatin	−0.384	0.05*
MDA	−0.621	0.001*
Nitric Oxide	+0.582	0.001*

* Statistically significant ($p < 0.05$)

Receiver Operating Characteristic (ROC) Curve Analysis

The diagnostic value of serum Irisin, Myostatin, and FGF-21 for discrimination between MetS patients and healthy subjects We used the ROC curve analysis to evaluate the diagnostic performance of serum Irisin, Myostatin, and FGF-21 for identifying patients with MetS from healthy individuals. Table 4 and figure 1 Diagnostic performance of Irisin yielded an AUC of 0.89 (95% CI: 0.83–0.94, p < 0.001). At the 8.1 ng/mL cut-off of Irisin, it reached sensitivity and specificity to be estimated as being high (85.9%) and (82.1%), respectively. Myostatin and FGF-21 were strongly associated with diagnostic accuracy, but their prediction was less than that of Irisin.

Table 4. ROC curve analysis of serum biomarkers for MetS diagnosis

Biomarker	AUC	95% CI	Cut-off Value	Sensitivity (%)	Specificity (%)	P-value
Irisin (ng/mL)	0.89	0.83–0.94	≤ 8.1	85.9	82.1	0.001*
Myostatin (pg/mL)	0.84	0.77–0.90	≥ 178.5	80.3	76.9	0.001*
FGF-21 (pg/mL)	0.81	0.74–0.88	≥ 150.2	78.2	74.4	0.001*

* Statistically significant ($p < 0.05$)

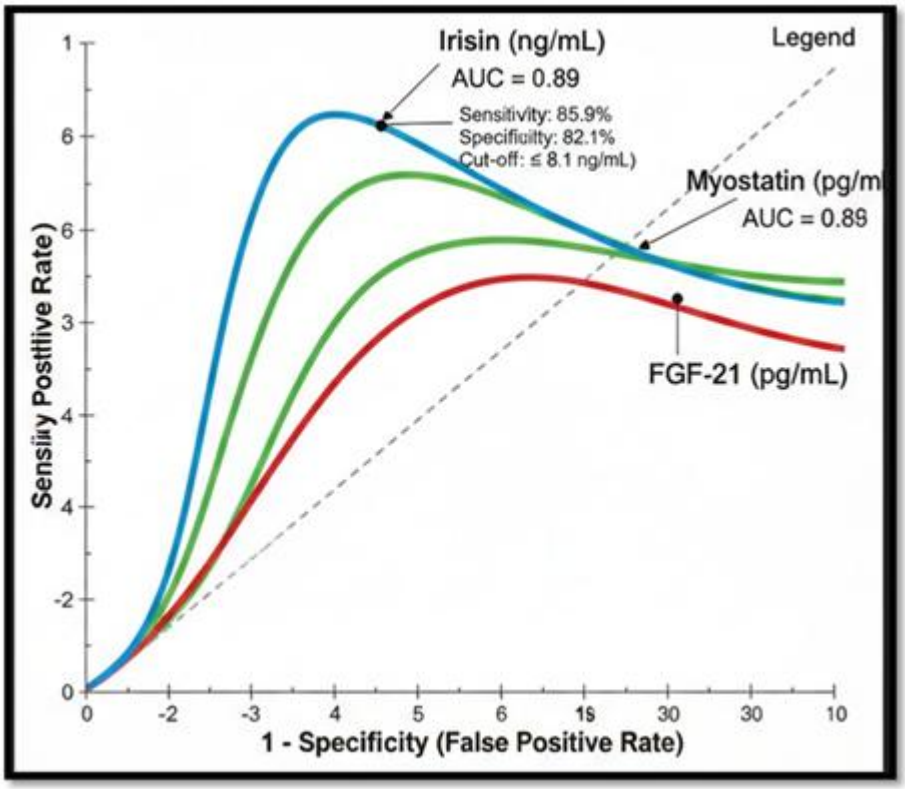

Figure 1. Receiver Operating Characteristic (ROC) curves of serum Irisin, Myostatin, and FGF-21 for discrimination between MetS patients and control subjects.

Discussion

In the present study, we detected lower levels of circulating Irisin in MetS patients than in healthy

subjects; meanwhile, Myostatin and FGF-21 were increased, oxidative stress indices (MDA) were significantly elevated and nitric oxide bioavailability was reduced. These findings are supported by studies, which have described a low level of Irisin in subjects with metabolic conditions, suggesting its protective role as a myokine implicated in metabolic and vascular homeostasis [18,19]. Irisin induces white adipose tissue browning and increases energy spending, promotes glucose uptake, improves insulin sensitivity through PGC-1α/FNDC5 signaling completion; its decrease in the presence of MetS might increase IR (insulin resistance) as well as adiposity [20,21]. The negative associations of Irisin with BMI, HOMA-IR and MDA in our sample are consistent with previous data indicating that low Irisin levels reflect disrupted metabolic equilibrium and heightened oxidative stress [22,23]. In relation to vascular action, Irisin improves the endothelial function by stimulation of one hand AMPK-eNOS and leading to increase in nitric oxide (NO) production and decreased oxidative/nitrative stress factors involved in NO levels suppression as observed in our MetS group [24,25]. Conversely, paradoxical rises in circulating Irisin levels under certain circumstances have also been documented, as perhaps indicative of adaptive processes in initial and mild metabolic derangement [26]. The enhanced FGF-21 that we observe in our patients is compatible with FGF-21's function as stress-triggered mitokine induced in the metabolic syndrome and possibly represents an adaptive metabolic response [18,27]. In addition, the increase in Myostatin itself, as a negative regulator of muscle growth and positive regulator of fat deposition [19,20], may have been responsible for insulin resistance and adiposity. Collectively, our results demonstrate the intricate relationship among Irisin, Myostatin, FGF-21 and oxidative/vascular markers in MetS. The bulk of evidence argues that low Irisin is associated with more unfavorable metabolic profiles and impaired vascular endothelial function, indicating its prospect as a biomarker and therapeutic target.

Conclusions

The present data indicate a central role for Irisin in the pathophysiology of MS, connecting skeletal muscle with metabolic and vascular health. The high diagnostic value of Irisin suggests that it is a possible candidate for early diagnosis of MetS and CVD complications.

Limitations

This study is cross-sectional in nature and as such causation cannot be determined. The sample size is relatively small and the lack of repeated measures may compromise generalizability. Large-scale prospective studies are needed in the future to confirm these findings and investigate mechanistic pathways by which Irisin might exert its protective effects.

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