DOI: https://doi.org/10.53350/pjmhs22166628

ORIGINAL ARTICLE

Irisin Level in Salah Adin's Insulin Resistance Syndrome Patients in View of Global Controversy

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ABSTRACT

Background: Metabolic syndrome (high blood pressure, hyperglycemia, dyslipidemia, and obesity) is now an international health problem that impacts about 20 per cent to 25 per cent of the total population and can be worsened in the developing world, particularly in the Middle East, which is roughly two out of every five Iraqis.

The metabolic syndrome has a direct link to many life-threatening diseases, such as cardiovascular disease, early onset of some cancers, such as colorectal cancer, Chronic liver illnesses, polycystic ovarian syndrome, and others.

Methodology: A case-control study on a total of ninety volunteers (46 males and 44 females), comprising sixty metabolic syndrome patients (25 males and 35 females), defined in terms of international diabetic federation criteria, and thirty controls, is to be conducted at Salah Alden general hospital. Adults men and women aged (24-to 65) years who attended Salah Alden's main hospital outpatient clinics in Tikrit\Iraq, from October 2021 to March 2022 were included in the research.

The levels (Irisin, and Insulin) in all research groups and controls are evaluated using an Enzyme-Linked Immune-sorbent Assay.

Results: Irisin level was significantly higher among controls with a mean of (6.84ng/ml), compared to metabolic syndrome patient mean (5.71 ng/ml), and significantly negatively correlated to triglycerides level, and non-significantly negatively correlated with (systolic blood pressure, fasting serum glucose, and waist circumference) and non-significantly positively correlated to high-density lipoprotein level.

Irisin levels were significantly different among treatment-based groups with the highest mean level among the treatment-free group (6.8450ng/ml±1.96052), followed by the antihypertensives taking group (5.3340ng/ml±2.99273), and the lowest mean level was recorded among diabetics (4.8916ng/ml±2.81952).

Conclusion: With the exception of HDL, a high level of Asprosin and a low level of Irisin are strongly linked to metabolic syndrome and its components. Irisin levels differ amongst metabolic syndrome patients with various therapy groups.

Keywords: Irisin, metabolic syndrome, Insulin Resistance.

INTRODUCTION

The deadly quartet of (hypertension, diabetes, dyslipidemia, and obesity) represents a global health problem that affects approximately 20%-25% of the population and can be increased in developing countries, especially in the middle east [1].

A high prevalence of metabolic syndrome was reported in a study conducted on 3703 participants in Iraq, and published in 2021, with a prevalence of 39.4% [2]. This study's findings have confirmed what was reported in previous data collected from Iraqi cities, Although the study groups were mostly cardiovascular disease patients or diabetics, except for Irbil study, the prevalence was high and correlated with the disease in patients who attended Bagdad medical city [3], and AL-Yarmouk medical center[4], Kirkuk "Baba Gur Gur Diabetic Center" [5], "Azadi Heart Center" in Duhok [6], "Coronary care unit in AL-Hussein teaching hospital" AL-Nasiriya city[4] and Erbil city [7].

The term metabolic syndrome, syndrome x, or insulin resistance syndrome joins (hypertension, diabetes, dyslipidemia, and obesity) in one condition that is defined by different criteria's "National Cholesterol Education Program ATP III"[8, 9], International diabetic federation 2005 [10], "American Association of Clinical Endocrinologists" (AACE) [11], and "World health organization" (WHO) in 1999[12], There are slight differences in the cut points for the definition criteria's for each of the four cornerstones, as based on the population it targets.

In this work IDF criteria would be used since it had been built to facilitate comparing results with other works, three of the cut-off points for components summarized in table 1-1 were diagnostic in this work. The importance of the condition is related to its direct association with many life-threatening diseases especially cardiovascular disease, to which, metabolic syndrome and a sedentary lifestyle are causative

factors [13], and the early onset of some types of cancers like colorectal cancer, are also associated with metabolic syndrome [14]. Chronic liver diseases, Fatty liver conditions like nonalcoholic fatty liver disease (NAFLD) and Metabolic associated fatty liver disease (MAFELD) [15], and metabolic syndrome, are also prevalent in women with polycystic ovary syndrome indicating an association with it [16].

Tissues like adipose tissue and muscles, besides their main function of storage, thermal conservation, posture maintaining, and movement, have been addressed with endocrine function, producing Adipokines and Myokines respectively. Adipokines, for instance, may contribute to biochemical abnormalities ranging from dyslipidemia, changes in lipid profile, and cardiovascular diseases, to insulin resistance and diabetes [17]. Myokines, on the other hand, secreted from the muscle fibers have an Autocrine and paracrine effect on muscle size and growth [18].

Based on the large muscle size standing for more than 30% of the body mass [19], changes in energy expenditure in muscles would have a potential effect on the metabolic status of the body, and perhaps it is the protective effect of the active lifestyle [20].

Estimation of the risk for metabolic disease and monitoring of conditions had been done so far, using the level of biochemical parameters, triglyceride, cholesterol, high-density lipoprotein and fasting serum glucose, and nonbiochemical, BMI and waist circumference, that also have rules in the risk assessment for cardiovascular diseases (especially central obesity) [21].

Targeting substances secreted from the muscles to evaluate the metabolic status and physical activity can give an alternative to the conventional parameters. A decade ago, when Irisin was discovered and defined for the first time by Pontus Bostro¨m in 2012 [22], as an exercise-induced metabolically active peptide that has effects on the energy expenditure and storage by adipose tissue leading to browning of the adipose tissue, increase in energy expenditure and thermogenesis [23].

Irisin is the product of the trance membrane glycoprotein FNDC5 "Fibronectin type III domain containing 5" cleavage, after gene stimulation by PGC1-α "Peroxisome proliferator-activated receptor-gamma coactivator" a family of cell metabolism regulators, and transcriptional co-activator that mediates metabolic reactions related to energy, leading to production and cleavage of FNDC5

producing Irisin [22]. Exercise induces the expression of genes embedded in the skeletal muscles to produce metabolically active peptides that have effects on energy expenditure and storage by adipose tissue [24].

Irisin has effects on the browning of the adipose tissue through stimulation of uncoupling protein1 transcription (UCP1) also named Thermogenin [22, 25].

An increase in brown adipose tissue means an increase in energy expenditure in thermogenesis which means the burning of fatty acids and emitting energy as heat [26]. In other words, the exercise stimulation of Irisin that involve browning of the adipose tissue and an increase in UCP1 would have the potential for protective effects against cardiologic and metabolic disorders [27].

Theoretical relevance of Irisin to metabolic syndrome: Different tissues release molecules that influence metabolic activity, Irisin is the product of the muscular tissue that occupies a large proportion of the body size, the skeletal muscle mass for instance, in normal-weight persons, represents more than 30% of the body [28], therefore the large size of skeletal muscle and their involvement in many physical activities reflects the amount of energy required to function properly and the impact that skeletal muscles exert on energy production and consumption which is the source of the protective effect of the active lifestyle [29].

Irisin is an exercise-induced hormone affecting fat metabolism and browning of the adipose tissue through stimulation of uncoupling protein1 transcription (UCP1) also named Thermogenin [22, 25].

Therefore, understanding the stimulatory and compensatory mechanisms that regulate the secretion of Irisin in metabolic illness patients may have implications for the prevention and management of obesity-related hazards.

Table 1: diagnostic cut-off points for metabolic syndrome

Component	Cut-off point	
	Male	Female
Waist circumference*	>94 cm	>80 cm
Fasting serum glucose	>100 mg/dl or specific treatment for DM	
serum triglycerides	>150mg/ dl	
HDL cholesterol	<40 mg/dl	<50mg/dl
Blood pressure	Systole > 130mm Hg, diastole >85mm Hg Or specific treatment for HT	

*European cut-off points were used according to IDF recommendations since no data for Arabic communities are available.

METHODOLOGY

Study Design: case-control research on a total of ninety volunteers, comprising sixty patients and thirty controls, to be conducted at Salah Alden general hospital. Adult men and females aged (24-to 65) years who attended Salah Alden's main hospital's outpatient clinics in Tikrit from October 2021 to March 2022 were included in the research.

Sampling: Blood samples of about 5ml were taken from each patient and controls, after overnight fasting and placed in a gel tube for 20 minutes, centrifuged for 20 minutes at 5000rpm. Then transferred

into two Eppendorf tubes, one had been used to measure (Fasting serum glucose, TGL, and HDL), and the other one was frozen at (-20C°) for measurement of Irisin and insulin levels by ELISA.

Calculation of Result: Draw the best fit curve across the points on the graph by plotting the mean OD for every standard on the vertical (Y) axis corresponding to the concentration on the horizontal (X) axis. These analyses are usually accomplished with machine curve-fitting systems, and regression analysis may be used to identify the optimal fit line.

Statistical Analysis: SPSS v26 (Statistical Package for Science Services), was used to perform computerized statistical analysis using Comparison, and this was carried out using; a T-test, one-way ANOVA, and Probability (P-value). The P-value ≤ 0.05 was considered statistically significant (S), less than 0.01 considered very significant (VS), and greater than 0.05 considered non-significant.

RESULTS

A high proportion of the study group was already on treatment for specific chronic diseases, as (88%) of the metabolic syndrome positive group were diagnosed with one or more of (diabetes, hypertension, or hyperlipidemia), figure (1).

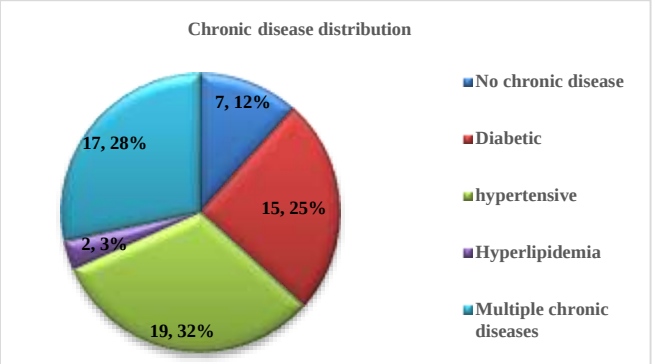

Figure 1: distribution based on the presence of chronic diseases.

Serum Irisin: Irisin level measured in (ng/ml) was significantly higher among controls with a mean of (6.84ng/ml), compared to metabolic syndrome patient mean (5.71 ng/ml) at P<0.05, as shown in figure (2).

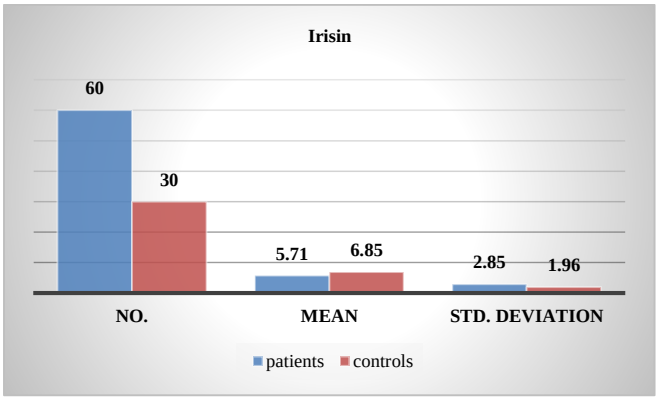

Figure 2: Irisin level mean difference, P <0.05.

There was no variation in the mean level of Irisin across age groups of individuals with metabolic syndrome.

In contrast, (diabetic and hypertensive) subgroups of metabolic syndrome patients had substantially lower Irisin levels than controls (p 0.05), figure (3).

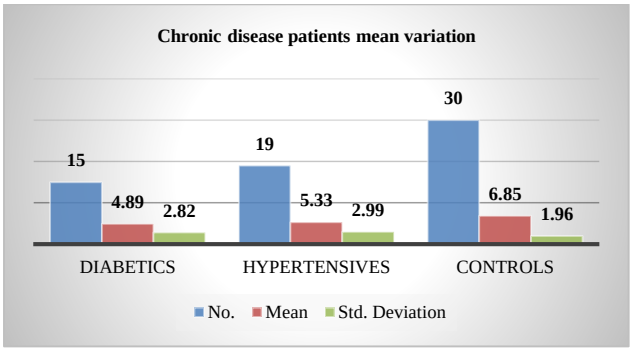

Figure 3: Irisin level mean difference in chronic disease patients, P<0.05.

Insulin resistance: HOMA-IR was determined using insulin levels obtained from ELISA data according to the following formula:

HOMA−IR ={insulin(u/ml)×serum glucose (mg/dl)}⁄405

As demonstrated in figure (4), insulin resistance was considerably greater in the study group, with a mean of 3.12, compared to 1.38 in the control group (p<0.05).

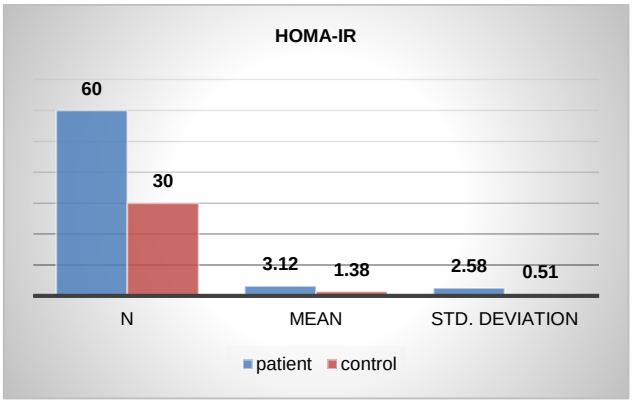

Figure 5: HOMA-IR mean difference between patients and controls at p<0.05.

Correlations of the Irisin with the measured parameters: There was a significant negative correlation between Irisin and triglycerides levels, a non-significant negative correlation with systolic blood pressure, waist circumference, and fasting serum glucose, and a non-significant positive correlation with HDL-cholesterol level.

In contrast, there was a highly significant positive correlation between HOMA-IR and waist circumference and significant positive correlation with triglycerides, and non-significant positive correlation with systolic blood pressure, and non-significant negative correlation with HOMA-IR, table (3).

Table 3: Correlations of the Irisin and HOMA-IR with the other parameters of metabolic syndrome

	HOMA-IR	Irisin
SBP	0.207	-0.028
WC	.305**	-0.146
TGL	.263*	-.228*
HDL	-0.192	0.199
FBS	.588**	-0.147

*p<0.05 or significant correlation, **P<0.01 or highly significant correlation

Table 2: summary of the measured parameters comparing patients and controls.

Parameter	Patients mean level	Controls mean level	p-value
Fasting serum glucose	157.46 mg/dl±79.99	84.25 mg/dl±7.94	<0.05
serum Triglycerides	177.9 mg/dl±106.23	92.15 mg/dl±30.08	<0.05
HDL-cholesterol	34.23 mg/dl±9.77	44.27 mg/dl±9.95	<0.05
Insulin level	7.98mIU/L±5.00	6.61±2.55	>0.05
HOMA-IR	3.12±2.58	1.38±0.51	<0.05
Irisin	5.71±2.85	6.85±2.63	<0.05

DISCUSSION

88 per cent of MetS patients were currently getting treatment for one or more chronic conditions. (diabetes, hypertension, hyperlipidemia), actuality, chronic disorders, particularly type 2 diabetes and hypertension, or specialized therapy for them are included in the IDF inclusion criteria for the diagnosis of metabolic syndrome [30], Consequently, it supports their significant incidence among individuals with metabolic syndrome. As determined by (M. Masriadia et al.) in 2022, Type2 DM and HT are regarded as determinants for the occurrence of metabolic syndrome [31].

There is no consensus regarding Irisin level in metabolic disease in general and metabolic syndrome in particular, as some studies have indicated an elevated level, such as (F. H. Rizk, 2016), which concluded that the serum Irisin level is elevated in metabolic syndrome patients and has a positive correlation with insulin resistance and triglycerides [32], Although (B. Osama et al., 2021) found a negative connection between insulin resistance and Irisin levels in metabolic syndrome patients, Irisin levels were lower in metabolic syndrome patients than in healthy controls [33], Unexpectedly, (C.-Z. Wu et al in 2021) in research of school-aged metabolic syndrome patients, no link was found between Irisin level and metabolic syndrome, while correlations with metabolic syndrome components in males and girls varied [34].

There have been several proposed causes for these variations, including:

- Different populations on whom research was conducted.
- Fat distribution in patients, regardless of whether they have central obesity or a high BMI.
- Some studies have small sample sizes, etc.

Under this experiment, Irisin level measured in (ng/ml) was significantly higher among controls with a mean of (6.84ng/ml), compared to metabolic syndrome patient mean (5.71 ng/ml) at P0.05, in conformity with the study results of (B. Yan, X. et al) from 2014, which were based on the outcomes of more than 1000 participants [35], (A. S. Huerta-Delgado, et al. in 2021) [36], and (B. Osama, et al. in 2021) [33].

A significantly lower mean level of Irisin reported in this study among diabetics compared to controls agreed with findings of a meta-analysis conducted by (R. Song, X. et al 2021) [37].

Hypertensive patients Irisin level mean was also significantly lower than that of the control group, disagreeing with (T. Miazgowski, et al.) findings in 2021, which claimed that the Irisin level is normal [38].

The source of this disagreement may be the lowering effect of the metabolic syndrome itself on the Irisin level as shown earlier by results of (B. Yan, X. et al) in 2014 [35], (B. Osama, et al. in 2021) [33], and findings of (A. S. Huerta-Delgado, et al. in 2021) [36], since all hypertensives included in this comparison was metabolic syndrome patients.

CONCLUSION

A low level of Irisin is associated with metabolic syndrome. The presence of Chronic diseases like T2DM and HT with metabolic syndrome may interfere with Irisin level and its correlations with metabolic syndrome components and can be the source of the global disagreement.

Recommendations: Further study for the effect of chronic disease or treatment for them taken by the metabolic syndrome patients on the Irisin level, and its correlation with the components of metabolic syndrome.

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