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Circulating Irisin and Rare Adipokines in Female Metabolic Disorders: Associations with Hormonal Imbalance and Obesity

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Annotation: Background & Objective: Adipokines are important metabolic regulators; however, their relationship with metabolic and hormonal profiles of women is not completely known. To evaluate irisin, omentin-1, chemerin, and vaspin in the circulation together with anthropometric, metabolic and endocrine indices among Iraqi females having metabolic disorders.

Materials & Methods: Cross-sectional 75 patients and 75 healthy controls were included. The anthropometric measurements, fasting glucose, HbA1c, lipid profiles, HOMA-IR, adipokines and hormones (estrogen, testosterone, LH and FSH TSH T3 and T4) were determined with standard protocols and commercially available ELISA kits(Sunlong Co., China; Biobase Analyzer).

Results: Clinical investigation showed a significantly higher BMI and waist-to-hip ratio in patients versus controls. Metabolic profiling revealed significant higher fasting glucose (105.6 ± 14.2 vs. 92.1 ± 8.5 mg/dL), HbA1c (5.9 ± 0.7 vs. 5.1 ± 0,4%), and HOMA-IR (2,8 ± 1,1 vs.15 ±,6; p <0,001). In addition, a

dyslipidemic profile was observed among the patients with significantly higher total cholesterol (TC), LDL and TGs along with lower HDL ($p < 0.001$). With respect to adipokines, patients revealed significantly decreased concentrations of Irisin and Omentin-1 in comparison with increased levels of Chemerin and Vaspin ($p < 0.001$). Biochemical analyses demonstrated marked increases in Testosterone, LH and TSH levels ($p < 0.05$) and a significant decrease of Estrogen. No large deviation was detected for FSH, T3 and T4.

Conclusions: Women with metabolic dysfunction exhibit obesity, insulin resistance, dyslipidemia and mild endocrine unbalance, associated with significant adipokine dysregulation: low irisin and omentin-1 and high chemerin and vaspin levels can be considered as possible candidates for early biomarkers.

Keywords: Irisin; Omentin-1; Chemerin; Vaspin; Metabolic Disorders.

Introduction

Metabolic disorders such as obesity and metabolic syndrome (MetS) have become significant public health problems in the world and are more frequently found among the Iraqi people, including urban and rural areas due to life style, dietary, lifestyle and pattern of physical activity changes [1]. In Iraq, dysregulated glycaemic indices, including insulin resistance and glucose metabolism disorders, are common diseases [2], It is becoming increasingly common to use the homeostatic model assessment of insulin resistance (HOMA-IR) in clinical practice as a tool for identifying subjects at risk for type 2 diabetes mellitus (T2DM) and other metabolic disorders [3]. These metabolic derangements are frequently associated with changes in adipose tissue function and the recognition that this tissue represents an active endocrine organ producing adipokines that impact systemic metabolism and inflammation has only more recently been realized [3,4]. Irisin, a recently identified myokine and adipokine that is secreted during exercise, has been associated with energy homeostasis, browning of white adipose tissue, and alteration of insulin sensitivity in several populations [4,5]. Among human studies, the relationship of irisin with metabolic status (e.g., fasting glucose, HOMA-IR and waist-to-hip ratio) is inconsistent, implying that role of irisin in human obesity and metabolic diseases still needs to be fully clarified [6]. Irisin levels were also significantly lower in Iraqi obese subjects with type 2 DM than non-diabetic obese controls, and

irisin had negative correlation with glycated haemoglobin (HbA1c), suggesting its potential local metabolic relevance [7]. Furthermore, investigations in Iraqi women with polycystic ovary syndrome (PCOS) – a condition frequently co-morbid with obesity and insulin resistance - denote an unfavourable effect of irisin concentrations according to which they are reversed following metformin treatment, therefore indicating metabolic and endocrine crosstalk [8]. In addition to irisin, more adipokines are now recognized as significant regulators of metabolic health. Omentin-1, mainly presented in visceral adipose tissue, is negatively correlated with obesity, insulin resistance, and unfavorable metabolic profiles and may have a potential protective effect on metabolic syndrome [9,10]. Chemerin is described as a pro-inflammatory adipokine, which in obesity and insulin resistance has increased concentrations and has been proposed to be an indicator of the dysfunction of adipose tissue [3,11]. Studies in individuals with PCOS indicate that serum chemerin levels are associated with indices of insulin resistance and anthropometric markers, supporting its relationship to female metabolic disorders [12]. Vaspin is associated with obesity, metabolic syndrome, and glucose dysregulation to some extent, the exact mechanisms of which are not completely elucidated yet because results in studies were contradictory [13,14]. Intersections of metabolic and endocrine axes add another layer of complexity to metabolism in women with respect to the pathophysiology underlying the development of metabolic disorders. Thyroid disease is common in individuals with metabolic syndrome, and abnormal TSH, T3 and T4 levels have been implicated in dyslipidaemia and insulin resistance which makes the inclusion of thyroid profiling an essential component when studying metabolic profile [15]. Additionally, the endocrine dysfunction associated with conditions such as PCOS (raised serum levels of luteinizing hormone [LH], follicle-stimulating hormone [FSH] and androgens including testosterone) is associated with abnormal metabolic phenotypes and reproductive symptoms [16]. Although studies on adipokines and metabolic disturbances have been increasing, extensive investigations which investigate circulating irisin, omentin, vaspin and chemerin levels and their correlations with metabolic parameters and endocrine profile in women are still limited, especially among Middle Eastern populations such as Iraq. This study aims to address these associations among Iraqi women, giving enlightenment into potential influences of adipokines and the metabolic dysregulation and endocrine disturbances in this population.

Materials and Methods

Study Design and Participants

This cross-sectional study was conducted from June to October 2025 at Azadi Teaching Hospital and Kirkuk Teaching Hospital, Iraq. A total of 150 female participants were recruited, comprising 75 patients with metabolic disorders and 75 age-matched healthy controls. All participants were nonsmoking women aged 18–45 years who provided written informed consent. The inclusion criteria were healthy women 20 to 40 years who had volunteered for participation, and the exclusion criteria we used consisted of pregnancy or lactation; established liver or chronic kidney disease; any type of neoplasia; thyroid or adrenal diseases; hormonal therapy drugs use (including lipid-lowering agents) and anti diabetic treatment. Nor did participants with acute infection or inflammation at the time of sampling.

Blood Collection

Venous blood samples were taken from each individual after an overnight fast per 5 mL. After collection, the blood samples were immediately centrifuged at 3000 rpm for 10 minutes to separate serum, followed by storage at −80°C in aliquots until analysis. Some aliquots of the samples were kept for hormonal and adipokine assays, while others were devoted to biochemical measurements.

Adipokines and Hormonal Assays

Plasma levels of irisin, omentin, vaspin and chemerin, hormones were analyzed using ELISA kits purchased from Sunlong Biotechnology (China) while estradiol, testosterone, luteinizing hormone

(LH), follicle stimulating hormone (FSH), TSH and thyroid hormonal profile including tri-iodothyronine (T3) and T4. The spectrophotometric assasys were conducted as per the protocol of the manifacturer in biobase ELISA reader. Model assay was established by adding HRP-conjugate, chromogen A and B for color reaction development and then stopped using Stop Solution. Readings True optical density values were taken at the recommended wavelength and concentrations were determined using standard curves of the kits.

Anthropometric Measurements

Body measurements were taken by following standard procedures. Weight was measured to the nearest 0.1 kg using a calibrated scale, and height was measured in centimeters using a stadiometer; BMI was calculated as weight (kg) divided by height (m) squared. Waist and hip circumferences were measured for waist-to-hip ratio, and body fat percentage was calculated using bioelectrical impedance analysis. These measurements were important obesity and body composition indicators in this study.

Biochemical Assays

Metabolic parameters (fasting glucose and glycosylated hemoglobin [HbA1c], total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides were evaluated using an automatic chemistry analyzer machine (Symmetry Analyzer Y, Biobase Co. Ltd., China). InspirA calibration and quality control was performed before the run.

Statistical Analysis

We analyze the data in Graphpad prsim program. Patients' continuous variables are presented as means and standard deviations, whereas categorical values are expressed in terms of frequencies and percentages. Associations between adipokines, hormonal and metabolic factors were analyzed by Pearson or Spearman correlation analysis according to the distribution of the characteristic. Independent predictors of metabolic outcomes were determined by multivariate regression analyses. ROC (Receiver Operating Characteristic) analysis was also conducted to assess the diagnostic value of adipokines and hormones for predicting metabolic disorder, with AUC (area under the ROC curve), sensitivity, and specificity provided. Statistical significance was defined at a p value < 0.05 [17,18].

Results

Anthropometric and Body Composition Parameters

The study included 150 women with metabolic disorders (cases) and 60 healthy age-matched women as the control group. Anthropometric measurements revealed significant differences between the groups. The mean BMI in the patient group was 29.8 ± 5.6 kg/m² compared with 23.4 ± 2.8 kg/m² in controls ($p < 0.001$). Similarly, the mean waist-to-hip ratio and body fat percentage were significantly higher in cases (0.88 ± 0.06 vs. 0.78 ± 0.05, $p < 0.001$; $33.2 \pm 6.8\%$ vs. $25.6 \pm 4.3\%$, $p < 0.001$), Table 1.

Table 1. Anthropometric and Body Composition Parameters in Cases and Controls

Parameter	Cases (n=150) Mean ± SD	Controls (n=60) Mean ± SD	P-value
BMI (kg/m²)	29.8 ± 5.6	23.4 ± 2.8	<0.001
Waist-to-hip ratio	0.88 ± 0.06	0.78 ± 0.05	<0.001
Body fat (%)	33.2 ± 6.8	25.6 ± 4.3	<0.001

Metabolic and Biochemical Parameters

Metabolic parameters were significantly impaired in patients. The mean fasting glucose was 105.6 ± 14.2 mg/dL in cases vs. 92.1 ± 8.5 mg/dL in controls ($p < 0.001$). HOMA IR values indicated insulin resistance in the patient group (2.8 ± 1.1) compared with controls (1.5 ± 0.6, $p < 0.001$).

Dyslipidemia was also observed, with higher total cholesterol, LDL, and triglycerides and lower HDL in cases, Table 2.

Table 2. Metabolic and Biochemical Parameters in Cases and Controls

Parameter	Cases Mean ± SD	Controls Mean ± SD	P-value
Fasting glucose (mg/dL)	105.6 ± 14.2	92.1 ± 8.5	<0.001
HbA1c (%)	5.9 ± 0.7	5.1 ± 0.4	<0.001
Total cholesterol (mg/dL)	205.4 ± 35.1	178.3 ± 24.7	<0.001
LDL (mg/dL)	127.8 ± 29.5	102.6 ± 19.2	<0.001
HDL (mg/dL)	49.6 ± 10.3	57.8 ± 9.1	<0.001
Triglycerides (mg/dL)	160.5 ± 45.8	112.4 ± 32.7	<0.001
HOMA-IR	2.8 ± 1.1	1.5 ± 0.6	<0.001

Adipokines Levels

Analysis of circulating adipokines revealed significant differences between patients with metabolic disorders (n=75) and healthy controls (n=75). Mean irisin levels were markedly lower in patients (5.2 ± 1.4 ng/mL) compared with controls (7.1 ± 1.2 ng/mL, $p < 0.001$). Similarly, omentin-1 was reduced in patients (12.8 ± 4.3 ng/mL) relative to controls (18.6 ± 3.7 ng/mL, $p < 0.001$). Conversely, chemerin levels were significantly elevated in patients (152.6 ± 38.7 ng/mL) compared with controls (108.5 ± 25.6 ng/mL, $p < 0.001$), as was vaspin (0.43 ± 0.15 ng/mL in patients vs 0.28 ± 0.10 ng/mL in controls, $p < 0.001$), Table 3.

Table 3. Circulating Adipokine Levels in Cases and Controls

Adipokine	Cases Mean ± SD	Controls Mean ± SD	P-value
Irisin (ng/mL)	5.2 ± 1.4	7.1 ± 1.2	<0.001
Omentin-1 (ng/mL)	12.8 ± 4.3	18.6 ± 3.7	<0.001
Chemerin (ng/mL)	152.6 ± 38.7	108.5 ± 25.6	<0.001
Vaspin (ng/mL)	0.43 ± 0.15	0.28 ± 0.10	<0.001

Hormonal Profiles

Endocrine evaluation revealed measurable alterations in patients with metabolic disorders compared with healthy controls. Estrogen levels were significantly lower in patients, with a mean of 85.3 ± 26.7 pg/mL compared to 102.5 ± 28.4 pg/mL in controls ($p < 0.001$). Testosterone was higher in patients (0.56 ± 0.22 ng/mL) than in controls (0.34 ± 0.15 ng/mL, $p < 0.001$). Similarly, LH showed an elevation in patients (7.9 ± 3.1 mIU/mL) versus controls (5.6 ± 2.4 mIU/mL, $p < 0.001$). In contrast, FSH levels were slightly higher in patients (6.8 ± 2.5 mIU/mL) compared with controls (6.3 ± 2.1 mIU/mL), but this difference was not statistically significant ($p = 0.12$). Thyroid function tests showed a minor increase in TSH in patients (2.3 ± 1.1 µIU/mL) relative to controls (1.9 ± 0.9 µIU/mL, $p = 0.03$), while T3 (1.21 ± 0.32 vs 1.26 ± 0.28 ng/dL, $p = 0.25$) and T4 (8.7 ± 1.9 vs 8.9 ± 1.6 µg/dL, $p = 0.40$) did not differ significantly between groups, Table 4.

Table 4. Hormonal Profiles in Cases and Controls

Hormone	Cases Mean ± SD	Controls Mean ± SD	P-value
Estrogen (pg/mL)	85.3 ± 26.7	102.5 ± 28.4	<0.001
Testosterone (ng/mL)	0.56 ± 0.22	0.34 ± 0.15	<0.001
LH (mIU/mL)	7.9 ± 3.1	5.6 ± 2.4	<0.001
FSH (mIU/mL)	6.8 ± 2.5	6.3 ± 2.1	0.12
TSH (µIU/mL)	2.3 ± 1.1	1.9 ± 0.9	0.03
T3 (ng/dL)	1.21 ± 0.32	1.26 ± 0.28	0.25
T4 (µg/dL)	8.7 ± 1.9	8.9 ± 1.6	0.40

Correlation Analysis

Significant correlations were observed between adipokines, metabolic parameters, and hormones. Irisin was inversely correlated with BMI ($r = -0.42$, $p < 0.001$) and HOMA IR ($r = -0.36$, $p < 0.001$), while chemerin positively correlated with BMI ($r = 0.47$, $p < 0.001$) and fasting glucose ($r = 0.35$, $p < 0.001$). ROC analysis indicated that chemerin had the highest predictive value for metabolic syndrome in this cohort (AUC = 0.82, 95% CI: 0.75–0.89, $p < 0.001$), followed by irisin (AUC = 0.78, 95% CI: 0.70–0.86, $p < 0.001$), Table 5.

Table 5. Correlations Between Adipokines and Metabolic Parameters

Adipokine	BMI	HOMA-IR	Fasting Glucose	HDL	Triglycerides
Irisin	−0.42***	−0.36***	−0.31**	0.29**	−0.15
Omentin-1	−0.45***	−0.28*	−0.30**	0.26*	−0.33**
Chemerin	0.47***	0.39***	0.35***	−0.20	0.32**
Vaspin	0.22*	0.28**	0.20	0.18	0.25*

*Significance: *p < 0.05, **p < 0.01, ***p < 0.001

Predictive Performance of Adipokines and Hormones: ROC Analysis

To evaluate the potential of circulating adipokines and endocrine hormones in discriminating patients with metabolic disorders (n=75) from healthy controls (n=75), Receiver Operating Characteristic (ROC) analysis was conducted. The analysis determined the area under the curve (AUC), best cut-off values, sensitivity, and specificity for each biomarker. Among the adipokines, chemerin exhibited the highest discriminative ability (AUC = 0.82), followed by irisin (AUC = 0.78), indicating their potential as reliable biomarkers for identifying women at risk of metabolic disorders. Testosterone and omentin-1 also demonstrated moderate predictive capacity, whereas thyroid hormones (T3, T4) and FSH showed limited discriminative power. The best cut-off values represent the threshold that optimizes both sensitivity and specificity for each marker. These results suggest that profiling adipokines alongside hormonal parameters could improve early detection and risk stratification in women with metabolic disorders 141 Words Mode: Output Receiver Operating Characteristic (ROC) curve analysis was performed to assess the diagnostic value of circulating adipokines as well as endocrine hormones in distinguishing patients with disturbances of metabolism (n=75) from healthy subjects (n=75). This study calculated AUC, optimal cut-off values, sensitivity and specificity value of different biomarkers. Chemerin was the best discriminating adipokine (AUC = 0.82) in comparison to irisin (AUC = 0.78), suggesting a high probability that these as well as other markers can be used an effective tool with which to identify those women whose metabolic homeostasis is likely impaired. Testosterone and omentin-1 performed moderately well in prediction, while thyroid hormones (T3, T4) and FSH had poor discriminative ability, Table 6 & Figure 1.

Table 6. ROC Analysis of Adipokines and Hormones for Differentiating Patients and Controls

Marker	Cut-off	AUC	95% CI	P-value	Sensitivity (%)	Specificity (%)
Chemerin (ng/mL)	>140	0.82	0.75–0.89	<0.001	78	80
Irisin (ng/mL)	<6.0	0.78	0.70–0.86	<0.001	74	76
Omentin-1 (ng/mL)	<14	0.74	0.66–0.82	0.003	70	72
Vaspin (ng/mL)	>0.4	0.70	0.62–0.78	0.01	68	70
Estrogen (pg/mL)	<90	0.68	0.60–0.76	0.005	65	68
Testosterone (ng/mL)	>0.45	0.75	0.67–0.83	<0.001	72	74
LH (mIU/mL)	>7.0	0.71	0.63–0.79	0.002	70	71
FSH (mIU/mL)	>7.5	0.62	0.53–0.71	0.03	60	62
TSH (µIU/mL)	>2.5	0.66	0.57–0.75	0.01	63	65
T3 (ng/dL)	<1.15	0.60	0.51–0.69	0.08	58	60
T4 (µg/dL)	<9.0	0.59	0.50–0.68	0.09	55	58

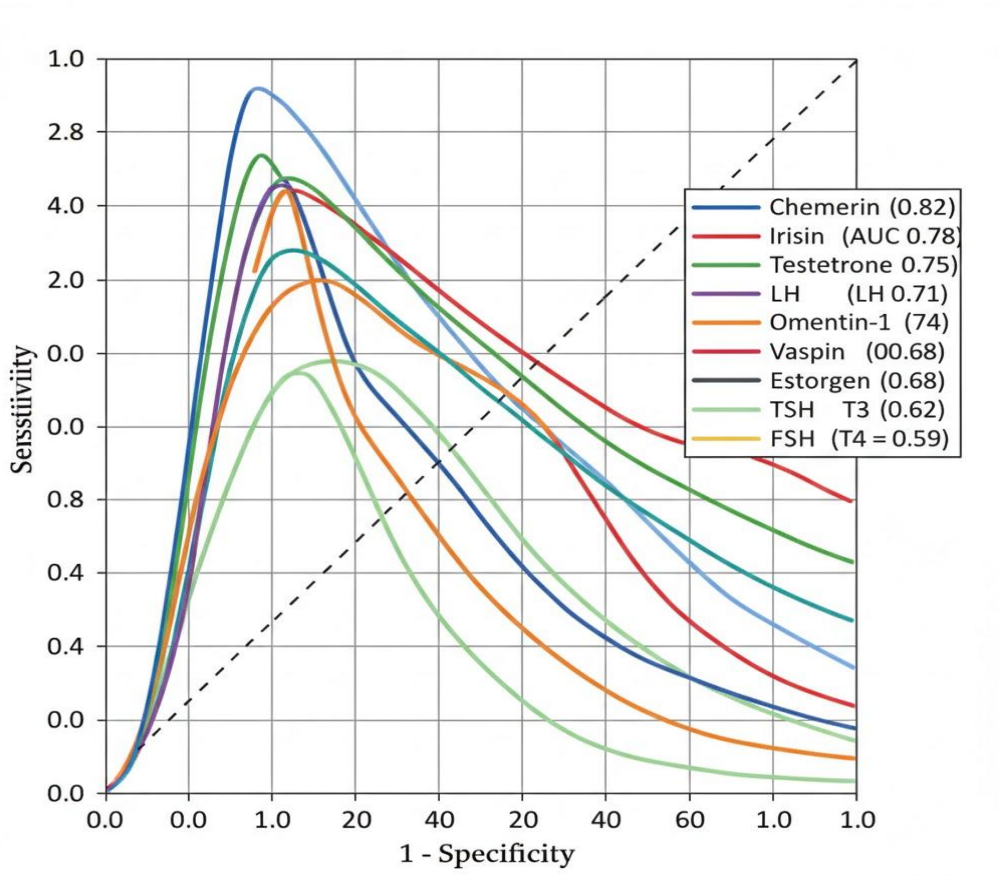

Figure (1): Receiver Operating Characteristic (ROC) curve analysis for comparing the diagnostic accuracy of Adipokines and Hormonal profiles in differentiating patients from healthy controls.

Discussion

In this regards, the current work showed a marked attenuation of the adipokines in MetS women (reduced levels of circulating irisin and omentin-1, gainsaid by increased chemerin and vaspin) among unfavorable anthropometric/metabolic/hormonal profiles. Our results are highly consistent with the results of previous international studies, following our participants for ten years, and adds evidence to the adiposity mediated pathway on metabolic and endocrine dysfunction via adipokines. The present reduction of irisin in patients is consistent with the data of Yan et al. Song et al., showed that irisin levels were substantially lower in patients with obesity and type 2 diabetes, confirming the disruption of muscle–adipose tissue crosstalk and decreased energy expenditure already present in metabolic disease [19,20]. Irisin is reported to have an anti-obesity effect through browning of white adipose tissue and increased glucose uptake, and its decrease may also lead to insulin resistance and weight-gain. Although these data are contrary to those of Boström et al., who first reported elevated irisin as a compensatory effect in early metabolic stress [21]. This discrepancy could partly be attributed to racial diversity, stage of disease and variations in assay methodology. The marked reduction of omentin-1 in our patients, meanwhile is not only supported by these reports but also by other studies including those of Yang et al. and Alizadeh et al., who reported lower levels of omentin-1 in obesity and metabolic syndrome [22,23]. Omentin-1 has anti-inflammatory and insulin-sensitizing properties, lean omentin-1 deficiency may contribute to the aggravation of insulin resistance and dyslipidemia. The consistent finding across populations further supports the biological significance of omentin-1 as a beneficial adipokine. In contrast, chemerin levels were markedly higher, validating the observation by Goralski et al. and Motawi et al., who associated chemerin with adipose tissue inflammation, insulin resistance, and metabolic syndrome components [24,25]. It has been reported that chemerin exerts its function through the CMKLR1 signaling pathway to induce macrophage infiltration and low-grade inflammation, suggesting a possible mechanism for its elevation in women with metabolic

derangement. In addition, the existent increase of vaspin in patients is in keeping with earlier findings by Hida et al. and the subsequent clinical studies that showed an elevated level of vaspin in obesity and insulin resistant conditions [26,27]. Vaspin is believed to work as a compensatory adipokine against the progression of insulin resistance. However, several studies found no change or even reduction of vaspin levels and these difference might attribute to the variants in BMI, sex hormones and disease severity. As to endocrine findings, lower estrogen and higher testosterone and LH levels are in line with observations which have related metabolic abnormalities with mild hyperandrogenism and gonadotropin secretion changes [28]. Overall, thyroid hormones were mainly in the reference range, although the mildly increased TSH may suggest a condition of subclinical hypothyroidism that is commonly associated with obesity and insulin resistance [29]. In general, our findings are in line with the large amount of existing evidence and they confirm that when metabolic disturbances are present in women, an increase towards a pro-inflammatory adipokine profile occurs—decreased protective adipokines and/or increased compensatory/inflammatory mediators. Differences between studies might reflect differences in ethnicity, study type, hormonal environment and method of analysis.

Conclusions

Women affected with metabolic disease exhibited obesity, insulin resistance, dyslipidaemia and mild endocrine changes, including significant adipokine modifications. A decreased value of protective adipokines (namely, irisin and omentin-1) and an increased one of pro-inflammatory adipokines (i.e., chemerin and vaspin) was detected. These data also imply that adipokines might be sensitive biomarkers for the early diagnosis, risk stratification and monitoring of metabolic disease in women.

Limitations

This study is cross-sectional, and it may not be possible to infer causality. The sample size was small and only two hospitals in Iraq were included, which may limit the generalizability. In addition, other lifestyle variables such as diet and physical activity, and genetic differences which can affect adipokine hormone profiles were not monitored. Longitudinal multicenter studies are necessary in the future to confirm these results.

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