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Upregulation of Interleukin-6 Gene Expression in Iraqi Patients with Metabolic Syndrome

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Abstract

Background: Metabolic syndrome (MetS) is a cluster of metabolic disorder, including insulin resistance, central obesity, hyperlipidemia, and hypertension which all these conditions promote the risk of cardiovascular disease and type 2 diabetes Miletus. Chronic low-grade inflammation is the feature of MetS, in which IL-6 is the key pro-inflammatory marker responsible for pathogenesis. Il-6 secreted by many cells' types, especially adipose tissue. Its production stimulated by the IL-1β and TNF-α, as well as through Toll-like receptor activation, prostaglandins, and adipokines. Il-6 and CRP are the main factors responsible for obesity and insulin resistance. The persistent elevated level of IL-6 cause insulin resistance through suppressing the expression of GLUT-4 and IRS-1 via activation of the JAK-STAT signaling pathway and upregulation of SOCS3.

Methodology: In this case-control study, blood samples were obtained from 45 MetS Iraqi patients, that fit three or all the inclusion criteria. Also, the study included control group consist of 45 healthy individuals, the estimation of IL-6 expression was achieved via quantitative real time polymerase chain reaction (qRT-PCR), while evaluation of biochemical tests was done by using automatically Abbott Architect c4000 Chemistry Analyzer.

Results: the final result show that measurement of IL-6 expression in patient group was significantly higher than control group, it was increased about seven folds compared to control group ($p < 0.001$). waist circumference, BMI, systolic, and diastolic blood pressure was significant elevated in patent than control group ($p < 0.001$) for all. Biochemical tests (FBG, Triglycerides, and HbA1c) in patient group was highly elevated than control group ($p < 0.001$) for all. Sex has non-significant to link with metabolic syndrome.

Conclusion: Over all, these results emphasize the pivotal involvement of IL-6-driven inflammatory pathways in the development and progression of MetS, and point to the promising utility of IL-6 gene expression as a highly sensitive and distinguishing diagnostic biomarker for MetS within the Iraqi population.

التعبير الجيني عن السيتوكينات المُحرِّضة للالتهاب (إنترلوكين-6) في المرضى العراقيين المصابين بالمتلازمة الأيضية

ياسر محمد غازي ومحمد علي الكعبي

الخلاصة

المقدمة: المتلازمة الأيضية هي مجموعة من الاضطرابات الأيضية المترابطة، تشمل مقاومة الأنسولين، والسمنة المركزية، وفرط شحميات الدم، وارتفاع ضغط الدم، وتُشكّل هذه الاضطرابات مجتمعةً خطراً متزايداً للإصابة بأمراض القلب والأوعية الدموية وداء السكري من النوع الثاني. يُعدّ الالتهاب المزمن المنخفض الدرجة سمةً رئيسية للمتلازمة الأيضية، إذ يُمثّل الإنترلوكين- 6 أحد أبرز الوسطاء الالتهابية المرتبطة بتطور هذه المتلازمة. حيث يُفرز من أنواع متعددة من الخلايا، وبشكل رئيسي من الأنسجة الدهنية، وتُحفّز إنتاجَه كلٌّ من إنترلوكين-1 بيتا وعامل نخر الورم ألفا، فضلاً عن مسارات أخرى. يُسهم الإنترلوكين- 6 وبروتين سي التفاعلي في تعزيز السمنة ومقاومة الأنسولين.

العينات وطرق العمل: في هذه الدراسة (مريض – سليم) تم جمع عينات الدم من 45 مريض عراقي مصاب بالمتلازمة الايضية حيث تم اخذ العينات من المريض الذي يطابق كل او ثلاثة من معايير الاشتمال. كذلك الدراسة شملت مجموعة ضابطة (أصحاء) حيث تم قياس التعبير الجيني للانترلوكين-6 باستخدام جهاز تفاعل البوليميراز المتسلسل بالزمن الحقيقي / الكمي بينما تم عمل الفحوصات الكيميائية بواسطة جهاز الكيمياء الاوتوماتيكي من عينات مصل الدم.

النتائج: أظهرت النتائج النهائية أن قياس تعبير الانترلوكين-6 في مجموعة المرضى كان أعلى بشكل ملحوظ مقارنةً بمجموعة الاصحاء، إذ ارتفع بمقدار سبعة أضعاف تقريبًا مقارنةً بمجموعة الاصحاء ($p < 0.001$). كما كان محيط الخصر، ومؤشر كتلة الجسم، وضغط الدم الانقباضي والانبساطي مرتفعةً بشكل ملحوظ لدى المرضى مقارنةً بمجموعة الاصحاء ($p < 0.001$) لجميع هذه المتغيرات. وأظهرت الاختبارات البيوكيميائية (سكر الدم الصائم، والدهون الثلاثية، والهيموغلوبين الغليكوزيلاتي) ارتفاعًا ملحوظًا جدًا في مجموعة المرضى مقارنةً بمجموعة الاصحاء ($p < 0.001$) لجميعها. في حين لم يكن للجنس تأثير ذو دلالة إحصائية في ارتباطه بمتلازمة الأيض.

الاستنتاج: بشكل عام، تؤكد هذه النتائج الدور المحوري للمسارات الالتهابية التي يقودها الانترلوكين-6 في تطور ومسار متلازمة الأيض، وتشير إلى الفائدة الواعدة لتعبير جين الانترلوكين-6 بوصفه واصمًا تشخيصيًا بالغ الحساسية وذا قدرة تمييزية عالية لمتلازمة الأيض في السكان العراقيين.

1. Introduction

Metabolic syndrome (MetS) includes a group of metabolic disorder, involve insulin resistance, hyperlipidemia, central obesity and hypertension (Fahed et al., 2022). The first definition of metabolic syndrome introduced by the World Health Organization (WHO) in 1999, highlighting the insulin resistance and hyperglycemia as the primary diagnostic criteria of the condition (Rus et al., 2023). According to the world Conesus of metabolic syndrome, the main causes are abdominal obesity and insulin resistance, in which both conditions may also be linked to other clinical disorders including, atherosclerosis, overweight and typer 2 diabetes (Regufe et al., 2020). Chronic low-grade inflammation is well recognizing feature of metabolic syndrome, in which the key inflammatory markers are interleukin-6 (IL-6) and high sensitivity C-reactive protein (CRP) that contribute to obesity and insulin resistance (Zahedi et al., 2023). Among the cytokines involve in the pathogenesis of metabolic syndrome, IL-6 emerges as a pleiotropic mediator involved in inflammation regulation, host defense and tissue injury response. It is secreted by many immune cells, fibroblasts, endothelial cells and adipose tissue — it has been recognized as a clinically significant biological marker of metabolic dysfunction. Adipose tissue alone responsible for an estimated 15-35% of total systemic IL-6 in vivo (Gupta et al., 2023). The production of IL-6 is simulated by interleukin 1 β (IL-1β) and tumor necrosis factor (TNF-α); additional pathways also contribute to it is upregulation, including Toll-like receptor (TLR) activation, prostaglandins, adipokines, cellular stress response, and a variety of other cytokines (Grebenciucova & VanHaerents, 2023). Persistently elevated IL-6 in obesity induces insulin resistance by suppressing the expression of both glucose transporter-4 (GLUT-4) and insulin receptor substrate-1 (IRS-1), effects that are mediated through the activation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway and the consequent upregulation of suppressor of cytokine signaling-3 (SOCS3) (Chen et al., 2015a). This study aimed to evaluate the expression of IL-6 as an inflammatory biomarker in Iraqi patient with metabolic syndrome, to better characterize its contribution to metabolic dysfunction in this population.

2. Materials and Methods

2.1. Study Subjects

The study involving 90 adults, the population was divided into two groups, including 45 subjects, - males (51.1%) and - females (48.9%), who were already diagnosed with MetS. The remaining 45 as apparently healthy controls, - males (51.1%) and - females (58.9%). The study protocol followed the institutional guidelines established by the Medical College of Wasit University. Upon receiving consent from all the participants, those who provided affirmative consent were included in the study. Furthermore, the study was carried out in accordance with scientific and ethical principles at both Al-Zahraa General Hospital and AI-Karama Teaching Hospital, Wasit Province, Iraq.

2.2. Inclusion Criteria

Waist circumference measurement (Men: > 102 cm, Women: > 88 cm), HDL cholesterol (Men: < 40 mg/dL, Women: < 50 mg/dL), Triglycerides ≥ 150 mg/dL, Blood pressure ≥ 130/85 mmHg, Fasting blood glucose (FBG) ≥ 100 mg/dl or diagnosis of diabetes, the presence of at least three of these criteria is required. Both sexes were included; the males to females' ratio is nearly 1:1; they were aged from 18 to 65 years.

2.3. Exclusion criteria

Any patient who does not meet the inclusion criteria is excluded from this study.

2.4. Control group

The control group was similar to the case group in terms of age, sex, and other relevant factors, except for the outcome of interest MetS.

2.5. Obesity Detection

Obesity was assessed using two anthropometric measures

1- Body mass index (BMI) Body weight and height were measured to calculate the BMI using the formula:

BMI (kg/m²) = weight (kg) / height² (m²). Participants were classified as underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), or obese (≥30 kg/m²).

2- Waist circumference (WC) was measured directly on the skin using a flexible inelastic tape, with participants standing upright and breathing normally. Two measurements were recorded at each site, and a third was taken if the difference exceeded 1 cm, with the final result recorded as the average. The optimal WC cutoff thresholds for diagnosing metabolic syndrome in the Iraqi population were 91 cm for males and 82.5 cm for females.

2.6. Sample Collection

The study required the collection of 5 ml of venous blood from each participant, 3ml of blood kept in EDTA tube for molecular analysis and 2ml of blood put in gel tube for serum extraction.

2.7. Laboratory Investigation

2.7.1. Estimation Of FBG, HDL, and Triglycerides

put the sample at room normal temperature for clotting after it has been collected. Usually, this spends fifteen min. then Centrifuge at 3,000-4000 rpm to 15 minutes to obtain clear serum and separate the clot. The gel tube containing serum was entered to the equipment and analyzed automatically Abbott Architech c4000 Chemistry Analyzer from Abbott Diagnostics is used to detect FBG, HDL and Triglycerides.

2.7.1. IL-6 Gene Expression

Two hundred and fifty microliters of blood were obtained from each subject and it was put into 750 µl of trizol preservation for RNA extraction using RNA purification kit (Promega/USA). Estimation of RNA concentration and purity was done using nanodrop (Bioneer/Korea). Expression of IL-6 gene was estimated by using the GoTaq® 1-Step RT-qPCR System, which combines GoScript™ Reverse Transcriptase and GoTaq® qPCR Master Mix in a single-step real-time amplification reaction. The system utilizes BRYT Green® dye as a proprietary fluorescent DNA-binding dye for detection.

the specific primers provided by Macrogen (Korea) Table1 were used. The PCR amplification was done by using RT-qPCR (Analytik jena/ Germany) according to the program which clarified in Table2. The glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene was used as a reference gene.

Table1: Primers of IL-6 and GAPDH Reference Gene

Primers	Sequences 5-3`	References
IL-6 F	GCCACTCACCTCTTCAGAACGAAT	(Ahmadi et al., 2025)
IL-6 R	GCCTCTTTGCTGCTTTTCACACAT	
GAPDH F	GAAATCCCATCACCATCTTCCAGG	
GAPDH R	GAGCCCCAGCCTTCTCCATG	

Table2: Thermocycler Protocol for IL-6 Gene Expression.

qPCR step	Temperature	Time	cycles
RT	37°C	15 min	1
RT inactivation	95 °C	10 min	1
Steps qPCR			
Denaturation	95 °C	15 sec	45
Annealing	58 °C	30 sec	
Extension	72 °C	30 sec	
Dissociation	60-95°C		1

2.7.2. Statistical Analysis

Data collected for this study were checked, coded, and analyzed using the Statistical Package for the Social Sciences (SPSS) version 26. The independent samples t-test was used to compare the mean differences between two independent groups. The Chi-square test or Fisher's Exact Test was applied to assess associations between categorical variables. Pearson's correlation coefficient (r) was used to determine the strength and direction of correlations between quantitative variables.

3. Results

3.1.Demographic Features

This case-control study included forty-five Iraqi patients with metabolic syndrome and forty-five healthy control. The clinical presentations of MetS patient and control group are shown in Table3. The MetS patient age ranged between (20-70) years. The percentage age for the studied groups was 35.6% (20-44), 64.4% (45-70), 82.2% (20-44) and 17.8% (45-70) respectively. This result showed a significant difference in the ages among the studied groups ($p<0.001$).

Table3: Frequency Distribution of Demographic Features Among the Study Participants (N=90)

Variable	Category	Patients No. (%)	Controls No. (%)	Total No. (%)	P-value
Sex	Male	23 (51.1%)	23 (51.1%)	46 (51.1%)	1.000
	Female	22 (48.9%)	22 (48.9%)	44 (48.9%)	
Age group (years)	20–44	16 (35.6%)	37 (82.2%)	53 (58.9%)	<0.001
	45–70	29 (64.4%)	8 (17.8%)	37 (41.1%)	
Age, (Year) Mean ± SD	—	48.93 ± 14.31	35.44 ± 8.41	42.19 ± 13.50	<0.001

3.2. The comparison of anthropometric and clinical characteristics between patients and healthy controls

Patients demonstrated significantly higher waist circumference compared with controls (101.31 ± 6.97 cm vs. 79.62 ± 8.13 cm, $p < 0.001$). Likewise, the mean body mass index (BMI) was markedly elevated among patients relative to controls (32.66 ± 2.35 kg/m² vs. 22.68 ± 1.44 kg/m², $p < 0.001$). Regarding blood pressure measurements, both systolic and diastolic blood pressures were significantly increased in patients compared with controls. The mean systolic blood pressure was 133.18 ± 7.77 mmHg in patients versus 111.24 ± 4.76 mmHg in controls ($p < 0.001$). Similarly, the mean diastolic blood pressure was higher among patients than controls (86.69 ± 4.70 mmHg vs. 73.20 ± 5.15 mmHg, $p < 0.001$), are demonstrated in Table4.

Table4: Anthropometric and Clinical Characteristics of Study Participants (N = 90)

Variable	Patients	Controls	P-value
	Mean ± SD	Mean ± SD	
Waist circumference (cm)	101.31 ± 6.97	79.62 ± 8.13	<0.001
BMI (kg/m²)	32.66 ± 2.35	22.68 ± 1.44	<0.001
Systolic blood pressure (mmHg)	133.18 ± 7.77	111.24 ± 4.76	<0.001
Diastolic blood pressure (mmHg)	86.69 ± 4.70	73.20 ± 5.15	<0.001

3.3. The Comparison of Biochemical Parameters Between Patients and Controls

The biochemical parameters of patients and healthy controls are presented in Table5. Patients demonstrated significantly higher fasting blood sugar (FBS) levels compared with controls (116.60 ± 11.44 vs. 88.58 ± 4.76 mg/dL, $p < 0.001$). Similarly, the mean glycated hemoglobin (HbA1c) level was significantly elevated in patients relative to controls (5.90 ± 0.68% vs. 5.08 ± 0.26%, $p < 0.001$). Serum triglyceride levels were markedly increased in patients compared with controls (235.27 ± 71.14 vs. 112.20 ± 17.93 mg/dL, $p < 0.001$). In contrast, high-density lipoprotein (HDL) levels were significantly lower among patients than controls (34.58 ± 4.97 vs. 57.49 ± 9.03 mg/dL, $p < 0.001$), are demonstrated in Table5.

Table5: Comparison of Biochemical Parameters Between Patients and Controls (N = 90)

Biochemical Parameter	Patients	Controls	P-value
	Mean ± SD	Mean ± SD	
FBS (mg/dL)	116.60 ± 11.44	88.58 ± 4.76	<0.001
HbA1c (%)	5.90 ± 0.68	5.08 ± 0.26	<0.001
Triglycerides (mg/dL)	235.27 ± 71.14	112.20 ± 17.93	<0.001
HDL (mg/dL)	34.58 ± 4.97	57.49 ± 9.03	<0.001
FBS: Fasting Blood Sugar; HbA1c: Glycated Hemoglobin; HDL: High-Density Lipoprotein			

3.4. Interleukin-6 (IL-6) Gene Expression Level Between Patients and Controls

Patients with metabolic disorders showed significantly elevated levels of inflammatory biomarkers compared with healthy controls. The gene expression of interleukin-6 (IL-6) is presented in Table6. IL-6 levels were markedly increased in the patient group compared with healthy controls (7.67 ± 1.89 vs. 1.03 ± 0.28, $p < 0.001$).

Table6: Comparison of Interleukin-6 (IL-6) Gene Expression Level Between Patients and Controls

Biomarker	Patients (Mean ± SD)	Controls (Mean ± SD)	P-value
IL-6	7.67 ± 1.89	1.03 ± 0.28	<0.001

3.5. Receiver operating characteristic (ROC) curve analysis

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of inflammatory IL-6 biomarkers in distinguishing patients from healthy controls. IL-6 showed the highest diagnostic performance in distinguishing patients from controls, as shown in Fig.1.

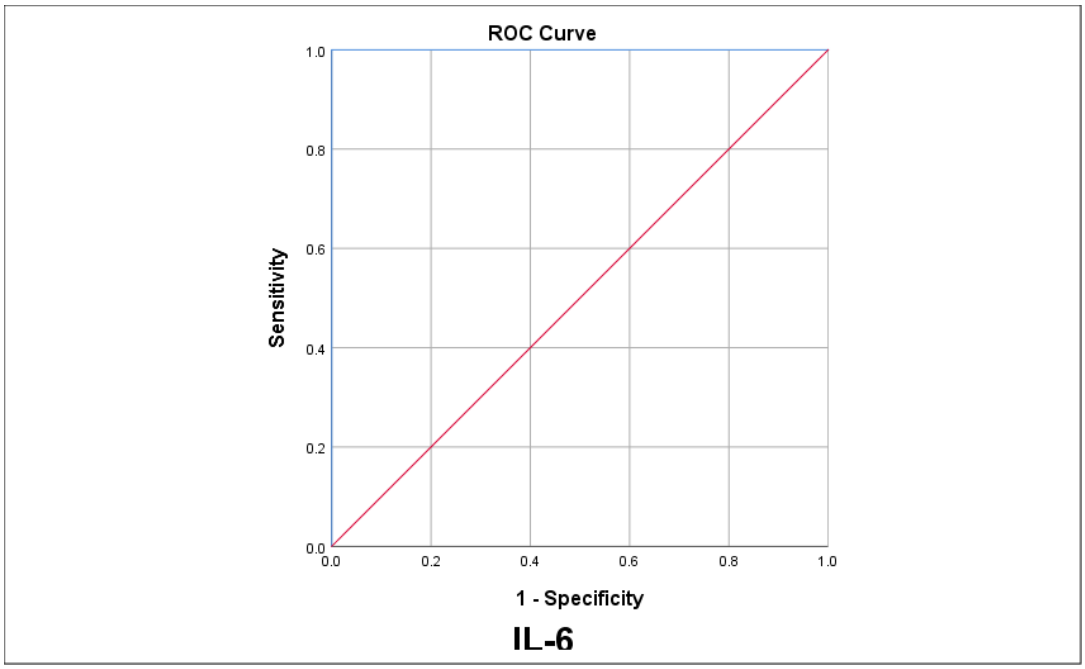

Figure1: ROC Curve Analysis Of IL-6 Ratio in Differentiating Patients from Controls.

4. Discussion

This case-control study investigates IL-6 gene expression in Iraqi patient diagnosis with metabolic syndrome (MetS), beside a comprehensive estimation of demographical, anthropometric, clinical and biochemical parameters. The study results show significant differences between the patient and control groups across all the measured variables, which explain the role of IL-6 upregulation in pathophysiology of MetS. The demographic distribution of the study population, show significant difference in age distribution between patient and control ($p < 0.001$). the mean age of patients was 48.93 ± 14.31 years, compared to 35.44 ± 8.41 years in the control group. The most of patients (64.4%) fall within the 45-70 age group, whereas most controls (82.2%) fall in younger 20-44 age group. MetS prevalence increase with advancing age due to hormonal change, physical inactivity and decrease metabolic efficiency, This finding agreement with (Meligi et al., 2024; Palmer & Jensen, 2022). In contrast, sex distribution was equal between patients and controls, with 51.1% males and 48.9% females in both groups ($p = 1.000$), this means the sex not confounding variable in subsequent comparisons. MetS patients showed significantly higher waist circumference (101.31 ± 6.97 vs. 79.62 ± 8.13 cm, $p < 0.001$) and BMI (32.66 ± 2.35 vs. 22.68 ± 1.44 kg/m², $p < 0.001$), consistent with central obesity as a hallmark of MetS. Visceral adipose tissue is metabolically active and a major source of pro-inflammatory cytokines, including IL-6, which enhance insulin resistance, that agree with (Gupta et al., 2023) and (Al-Jabory et al., 2025). Both systolic (133.18 ± 7.77 vs. 111.24 ± 4.76 mmHg) and diastolic (86.69 ± 4.70 vs. 73.20 ± 5.15 mmHg) blood pressure were significantly elevated in patients ($p < 0.001$), according to (Mohamed et al., 2023; Rus et al., 2023), further reflecting the vascular consequences of systemic inflammation and insulin resistance characteristic of MetS. Biochemical analysis confirmed the expected metabolic derangements of MetS. Patients had significantly higher FBS (116.60 ± 11.44 vs. 88.58 ± 4.76 mg/dL), HbA1c (5.90 ± 0.68% vs. 5.08 ± 0.26%), and triglycerides (235.27 ± 71.14 vs. 112.20 ± 17.93 mg/dL), alongside significantly reduced

HDL (34.58 ± 4.97 vs. 57.49 ± 9.03 mg/dL), all with $p < 0.001$. This pattern of atherogenic dyslipidemia and impaired glycemic control is a well-recognized biochemical signature of insulin resistance and is consistent with findings from comparable regional populations (Regufe et al., 2020; Zahedi et al., 2023). The primary finding of this study was the approximately 7-fold upregulation of IL-6 gene expression in MetS patients compared to healthy controls (7.67 ± 1.89 vs. 1.03 ± 0.28, $p < 0.001$). This marked elevation is mechanistically consistent with the increased visceral adiposity observed in patients, as adipose tissue accounts for an estimated 15–35% of total systemic IL-6 in vivo (Gupta et al., 2023). According to (Chen et al., 2015b; Pedersen & Febbraio, 2007), chronically elevated IL-6 promotes insulin resistance by suppressing GLUT-4 and IRS-1 expression via JAK-STAT pathway activation and SOCS3 upregulation, thereby impairing insulin signaling and worsening the metabolic dysregulation central to MetS. ROC curve analysis further confirmed the strong diagnostic utility of IL-6 gene expression in distinguishing patients from controls, supporting its potential as a sensitive biomarker for MetS in the Iraqi population. These results are in agreement with previous studies consistently reporting elevated IL-6 in MetS across diverse populations (Gupta et al., 2023; Zahedi et al., 2023).

Conclusion

This study demonstrates a significant upregulation of IL-6 gene expression in Iraqi patients with metabolic syndrome, accompanied by marked elevations in waist circumference, BMI, blood pressure, fasting blood glucose, HbA1c, and triglycerides, as well as a significant reduction in HDL cholesterol. These findings collectively underscore the central role of IL-6-mediated inflammation in the pathogenesis of MetS and highlight the potential of IL-6 gene expression as a sensitive and discriminative biomarker for MetS in the Iraqi population. Targeting IL-6 signaling pathways may represent a promising therapeutic avenue for mitigating the systemic inflammatory burden associated with MetS and reducing the risk of its cardiovascular and metabolic complications.

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