

Association Between Serum Interleukin-6 Level in Obese and Non-Obese Rheumatoid Arthritis

Nasreen Ghalib Obeaid¹; Fadhil Jawad Al-Tu'ma^{1,2,*} and Ali Mohammed Kadhim³

¹Department of Chemistry and Biochemistry, College of Medicine, University of Kerbala / Kerbala - Iraq.

²Medical Laboratories Techniques Department, College of Health and Medical Techniques, Al-Mustaqbal University, Babylon 51001, Iraq.

³Orthopedics, Department of Internal Medicine, College of Medicine, University of Karbala / Karbala-Iraq.

*Corresponding Author:

Fadhil Jawad Al-Tu'ma: fadhil.jawad.altuma@uomus.edu.iq.

Received: 10/07/2024

Accepted: 22/07/2024

Published: 31/12/2024

Keywords: Rheumatoid arthritis, inflammation, cytokines, interleukin-6, obesity.

DOI:10.62472.kjps.v15.i25.202-212



Abstract

Background: Rheumatoid arthritis (RA) is a chronic and progressive autoimmune disorder characterized by inflammation that affects every system in the body.

Objectives: A study aimed to investigate the association between serum interleukin-6 levels in sera of non-obese RA and compared with that in obese RA of Iraqi women.

Materials and Methods: A case-control study design was utilized to collect data from 130 participants between October 2023 and March 2024, aged 35 to 65. Five mL were withdrawn from patients who visited the joint consultation at Imam Hassan Al-Mujtaba Hospital. The SMART-120 chemical analyzer (AFLO/Germany, colorimetric enzymatic method) was utilized to quantify the amounts of total cholesterol (TC), triglycerides (TG), high-density cholesterol (HDL-C), and low-density cholesterol (LDL-C) in human serum. Additionally, the ELISA technique (UNO/HUMAN/Germany) was used to evaluate the levels of serum IL-6.

Results: The study found a significant increase in serum IL-6 levels in (obese and non-obese) RA patients when compared with control group (71.02 ± 11.39 pg/ml), (59.85 ± 14.50 pg/ml), and (5.87 ± 1.91 pg/ml, $P < 0.0001$) respectively. The receiver-operating curve (ROC) study for IL-6 in non-obese RA revealed a sensitivity of 69%, specificity of 73%, 95% confidence interval (CI) ranging from 0.684 to 0.887, and an area under the curve (AUC) of 0.785. The cut-off point was set at 51.52 pg/ml or above. In the obese RA group, IL-6 had AUC with a value of 0.945 [95% CI (confidence interval) = 0.899–0.991, Sensitivity = 91%, Specificity = 83%, Cut-off point = 54.35 pg /mL].

Conclusion: Elevated serum IL-6 levels in non-obese and obese RA patients suggest an important role in autoimmune disorders in RA and are considered as a biomarker for pro-inflammatory for assessing RA and obesity.

العلاقة بين مستوى الإنترلوكين 6 في الدم لدى مرضى السمنة وغير السمنة والتهاب المفاصل الروماتويدي

نسرین غالب عبید؛ فاضل جواد ال طعمة وعلي محمد كاظم

الخلاصة:

المقدمة: التهاب المفاصل الروماتويدي (RA) هو اضطراب المناعة الذاتية المزمن والتقدمي الذي يتميز بالالتهاب الذي يؤثر على كل نظام في الجسم.

الأهداف: هدفت دراسة إلى التحقق من العلاقة بين مستويات الإنترلوكين 6- في مصل الدم لدى مرضى التهاب المفاصل الروماتويدي غير المصابين بالسمنة ومقارنتها مع تلك الموجودة في مرض التهاب المفاصل الروماتويدي لدى النساء العراقيات البدينات.

المواد والطرق: تم استخدام تصميم دراسة الحالات والشواهد لجمع البيانات من 130 مشاركًا في الفترة ما بين أكتوبر 2023 ومارس 2024، والذين تتراوح أعمارهم بين 35 إلى 65 عامًا. وتم سحب خمسة مل من المصل من المرضى الذين زاروا الاستشارة المشتركة في مستشفى الإمام الحسن المجتبي. تم استخدام المحلل الكيميائي SMART-120 (AFLO/ألمانيا، الطريقة الأنزيمية اللونية) لتحديد كميات الكوليسترول الكلي (TC)، والدهون الثلاثية (TG)، والكوليسترول عالي الكثافة (HDL-C)، والكوليسترول منخفض الكثافة C- (LDL). في المصل البشري. بالإضافة إلى ذلك، تم استخدام تقنية ELISA (UNO/HUMAN/Germany) لتقييم مستويات IL-6 في المصل.

النتائج: وجدت الدراسة زيادة معنوية في مستويات IL-6 في مصل الدم لدى مرضى التهاب المفاصل الروماتويدي (السمنة وغير السمنة) بالمقارنة مع مجموعة السيطرة (11.39 ± 71.02 بيكوغرام / مل)، (14.50 ± 59.85 بيكوغرام / مل)، و (1.91 ± 0.0001 بيكوغرام / مل، $P < 0.0001$) على التوالي. كشفت دراسة منحنى تشغيل المستقبل (ROC) لـ IL-6 في التهاب المفاصل الروماتويدي غير المصاب بالسمنة عن حساسية بنسبة 69%، ونوعية بنسبة 73%، وفاصل ثقة 95% (CI) يتراوح من 0.684 إلى 0.887، ومنطقة أسفل المنحنى (AUC) من 0.785. تم تحديد نقطة القطع عند 51.52 بيكوغرام / مل أو أعلى. في مجموعة RA التي تعاني من السمنة المفرطة، كان لدى IL-6 مساحة تحت المنحنى بقيمة 0.945 [فاصل الثقة 95% (فاصل الثقة) = 0.899-0.991، الحساسية = 91%، النوعية = 83%، نقطة القطع = 54.35 بيكوغرام / مل].

الاستنتاج: تشير مستويات IL-6 المصلية المرتفعة لدى مرضى التهاب المفاصل الروماتويدي غير المصابين بالسمنة والسمنة إلى دور مهم في اضطرابات المناعة الذاتية في التهاب المفاصل الروماتويدي وتعتبر علامة حيوية للالتهابات لتقييم التهاب المفاصل الروماتويدي والسمنة.

1. Introduction

An autoimmune, inflammatory, progressive, chronic, and systemic disease, rheumatoid arthritis (RA) mostly affects the synovial joints and the surrounding tissues (Rufino *et al.*, 2024). The prevalence rate of RA is more than 1% worldwide, most of the patients are middle-aged and elderly, and the rate in females is higher than that in males (Xiang and Dai, 2009). Inflammation, swelling, pain, fatigue, and rigidity are some of the clinical signs of RA (Bautista-Molano *et al.*, 2024). There are wide variations in the disease's prevalence depending on genetic, environmental, and geographical factors as well as the urban and rural settings of a given global population (Mushtaq *et al.*, 2024). RA is common and continues to be an important issue for global public health over the past 30 years (Shi *et al.*, 2023).

The degeneration of bone and cartilage as well as ongoing inflammation of the synovial membranes are among the pathological features of RA (Zhou *et al.*, 2024). A complex network of different cytokines and cells play a role in the pathogenesis of RA (Kondo, Kuroda and Kobayashi, 2021). The network of cytokines can be divided into two groups, pro-inflammatory and anti-inflammatory cytokines (Werner and Wagner, 2023). The primary Pro-inflammatory mediator factors of RA, IL-1, IL-6, and TNF- α , are produced because of CD4⁺ T-cell activation, they cause bone erosion, which causes the synthesis of autoantibodies (Wang and He, 2020). Interleukin-6 (IL-6) is a cytokine that plays a vital role in the immune response and is produced by monocytes, macrophages, endothelial cells, and lymphoid cells. It has several biological activities (Pawłowska-Kamieniak, Krawiec and Pac-Kożuchowska, 2021). The release of IL-6 is triggered during the inflammatory response as a result of tissue injury or infection (Grebenciucova and VanHaerents, 2023). IL-6 is generated rapidly when infections or tissue damage affects homeostasis, by activating acute-phase and immunological responses, and supports the host's defense against stress (Tanaka, Narazaki and Kishimoto, 2018). Osteoporosis is a frequent systemic symptom of RA. Excessive production of IL-6 leads to osteopenia as a result of abnormal control of osteoclasts and osteoblasts (Hasanzad *et al.*, 2021). The functions in the pathogenesis of RA involve the activation and maturation of B and T cells, as well as the creation of autoantibodies (F. Wu *et al.*, 2021). In RA, Elevated levels of IL-6 in the bloodstream are linked to the degeneration of joints, maybe due to the role of IL-6 in facilitating the creation of osteoclasts (G. Wu *et al.*, 2021). Obesity is characterized as the abnormal or excessive accumulation of fat that poses a risk to health (Sandhu *et al.*, 2020). Adipokines have a crucial function in controlling adipogenesis, insulin secretion, and sensitivity. They exert an impact on several biological processes (Soliman *et al.*, 2022). Adipose tissue increase is linked with elevated pro-inflammatory molecule production that leads to the development of RA (Abdellatif *et al.*, 2024). A study aimed to investigate the association between serum interleukin-6 levels in sera of non-obese RA and compared with that in obese RA of Iraqi women.

2. Materials and Methods

A case-control study design was utilized to collect data from 130 participants (rheumatoid arthritis patients and healthy control) with matched ages ranging between 35 - 65 years. The rheumatoid arthritis out-patients were sub-grouped into 70 (obese and non-obese RA) out-patients who visited the consultant clinic of orthopedics at Al-Hassan Teaching Hospital, Kerbala Health Directorates / Kerbala – Iraq during Oct. 2023 to March 2024 and another 60 samples obtained from apparently healthy subjects as the control group with matched age ranged between (35-65 years). The SMART-120 chemical analyzer (AFLO/Germany, colorimetric enzymatic method) was utilized to quantify the amounts of total cholesterol (TC), triglycerides (TG), high-density cholesterol (HDL-C), and low-density cholesterol (LDL-C) in human serum. Sera withdrawn from patients and control were used for the determination of pro-inflammatory interleukin-6 levels using an enzyme-linked immunosorbent assay (ELISA) technique and other anthropometric markers required. The ELISA technique (UNO/HUMAN/Germany) was used to evaluate the levels

of IL-6 in serum. The formula below was used to calculate the body mass index (BMI) in kg/m² (Qiang, Lipscombe and Lega, 2020).

$$\text{Body Mass Index (BMI), kg/m}^2 = \text{Weight (kg)} / \text{Height (m}^2\text{)}$$

The BMI evaluation was conducted using the WHO classification. Normal BMI levels range from 20 to 24.9 kg/m², overweight BMI levels range from 25 to 29.9 kg/m², and a woman is considered obese if her BMI is 30 kg/m² or higher (Fendler *et al.*, 2021). A questionnaire was created for the study; participants were assured that their answers would remain private and anonymous to reduce the risk of influence from self-reported data. Additionally, a specialized physician assessed patients for joint issues by measuring their CRP, RF, and ESR levels. Demographic information such as age, gender, previous history of chronic diseases, family history, and length of sickness were all included in the questionnaire. Exclusion criteria included people with immune disease, diabetes, and other illnesses such as heart, liver, kidneys, cancer, and smokers.

2.1. Statistical Analysis

The data for this study was gathered and analyzed using IBM's Statistical Package for Social Sciences, version 22.0 (SPSS) in Chicago, Illinois, USA. Scale variables for normal data were presented as mean \pm standard deviation, while categorical variables were displayed using N (%) values. The data distribution was confirmed using the Shapiro-Wilk test. One ANOVA way and analysis of variance tables were used to compare the means of several groups for biomarkers. Analytical statistical tests were used to identify distinguishing factors between parameters with categorical variables. Statistical significance was established for all two-tailed hypothesis tests with p-values less than 0.05. Through the use of receiver operating characteristic (ROC) analysis, the ideal sensitivity and specificity threshold for critical cases was ascertained.

3. Results

Table 1 and Fig.1 and Fig.2. present the serum IL-6 levels in the study groups. The levels of IL-6 in obese individuals with RA were considerably higher compared to both non-obese RA patients and the control group, with a mean \pm standard deviation of (71.02 \pm 11.39 pg/ml) in obese RA, (59.85 \pm 14.50 pg/ml) in non-obese RA patients and (5.87 \pm 1.91 pg/ml) in the control group. In addition, the age of the control group is not statistically significant when compared to the RA group. Moreover, the body mass index (BMI) of both non-obese and obese individuals with rheumatoid arthritis (RA) exhibited a significant difference when compared to control groups. Furthermore, Table 1 displays significant changes in the levels of TC, TG, HDL-C, and LDL-C. Shown in Table 2 and Fig. 3 The analysis of the receiver operating curve (ROC) for IL-6 showed IL-6 had an AUC of 0.785 [95%CI (confidence interval) = 0.684-0.887, sensitivity = 69%, Specificity = 73%, Cut-off point =51.52ng/mL.

In the obese RA group, IL-6 had AUC with a value of 0.945 [95% CI (confidence interval) =0.899– 0.991, Sensitivity = 91%, Specificity = 83%, Cut-off point = 54.35 pg /mL], as presented in Table 2 and Fig.4.

Table 1: Comparison of Anthropometric and Proinflammatory Parameters Between the Two Groups of RA Patients and Controls

Groups	Mean \pm SD			P-value
	Non-Obese RA N=35	Obese RA N=35	Control N=60	
Age, (year)	48.61 \pm 6.52	45.07 \pm 7.89	46.17 \pm 7.99	0.102
BMI, (kg/m ²)	22.05 \pm 1.96	34.35 \pm 2.20	21.0 \pm 1.67	0.0001 [S]
TC, (mg/dl)	210.84 \pm 13.64	236.31 \pm 15.45	136.18 \pm 23.62	0.0001[S]
TG, (mg/dl)	145.18 \pm 18.23	186.08 \pm 21.14	92.97 \pm 19.11	0.0001[S]
HDL-C, (mg/dl)	39.47 \pm 4.71	37.54 \pm 2.84	57.35 \pm 7.02	0.0001[S]
LDL-C, (mg/dl)	156.37 \pm 24.75	160.57 \pm 29.59	97.0 \pm 13.44	0.0001[S]
IL-6, (pg/mL)	59.8 \pm 14.50	71.02 \pm 11.39	6.87 \pm 1.91	0.0001[S]

One-way ANOVA was significant at 0.05; SD: standard deviation, S: significant; RA: Rheumatoid Arthritis, TG: triglycerides, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TC: total cholesterol and BMI: body mass index.

Table 2: AUC, Optimal Threshold, Sensitivity, And Specificity Of IL-6 Obtained by ROC Curve In Patients With Non-Obese And Obese RA.

Parameters	Cut-off	Sensitivity	Specificity	AUC	P-value	95% CL	
IL-6, (pg/ml) (non-obese)	≥ 51.52	%69	%73	0.785	0.0001	0.684	0.887
IL-6, (pg/ml) (obese)	≥ 54.35	%91	%83	0.945	0.0001	0.899	0.991

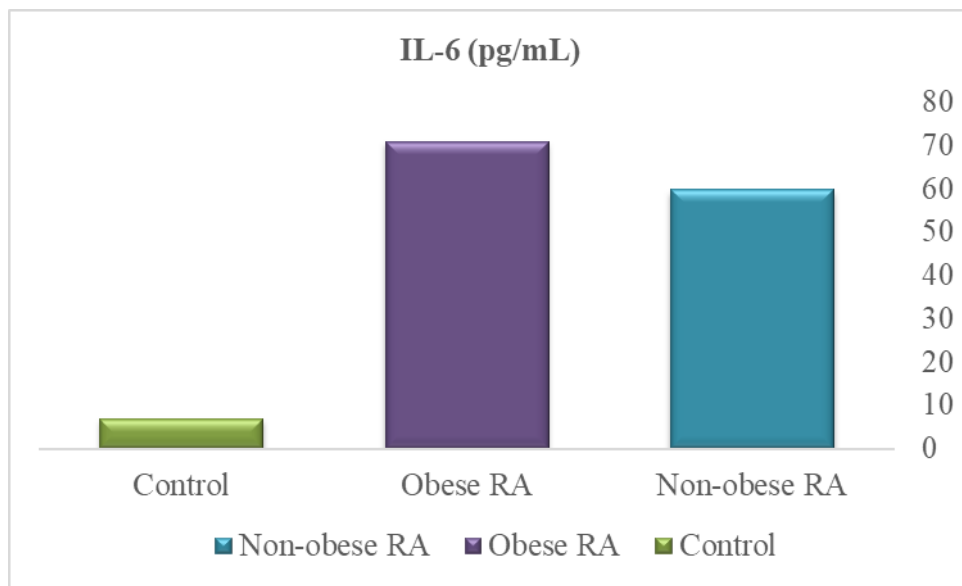


Figure 1: Displays the Variation in the IL-6 Levels Between the People with Non-Obese, Obese RA and The Control Groups.

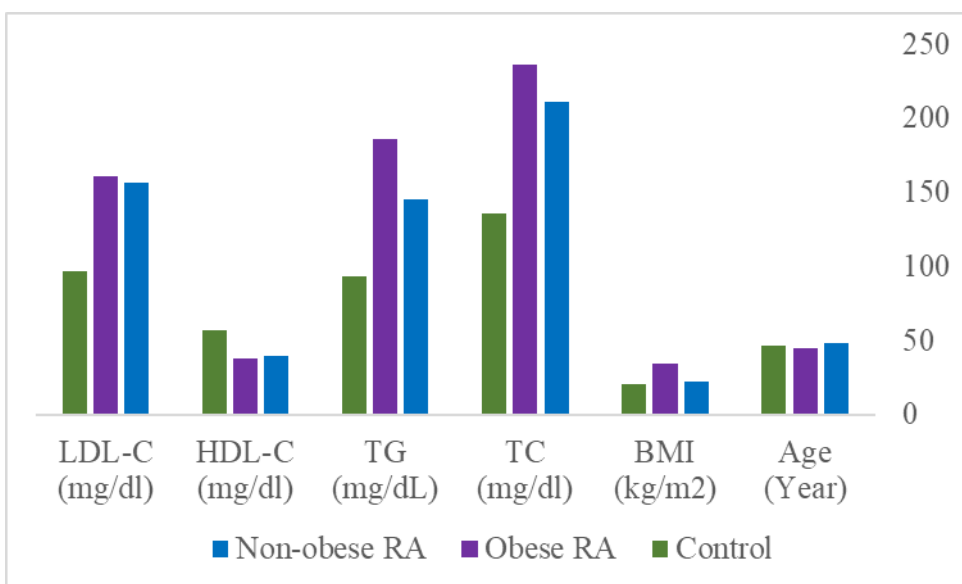


Figure 2: Displays the Variance in The Mean of Age, BMI, And Lipid Profile Between the Two Groups Of (Obese and Non-Obese) RA Patients and Controls.

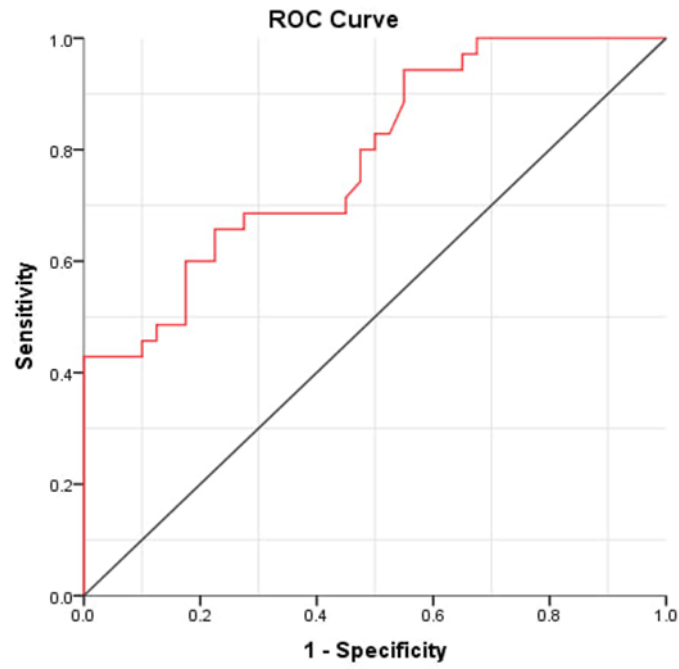


Figure 3: Receiver Operating Characteristic (ROC) Curve of Serum IL-6 Level as Discriminators of Patients with Non-Obese RA.

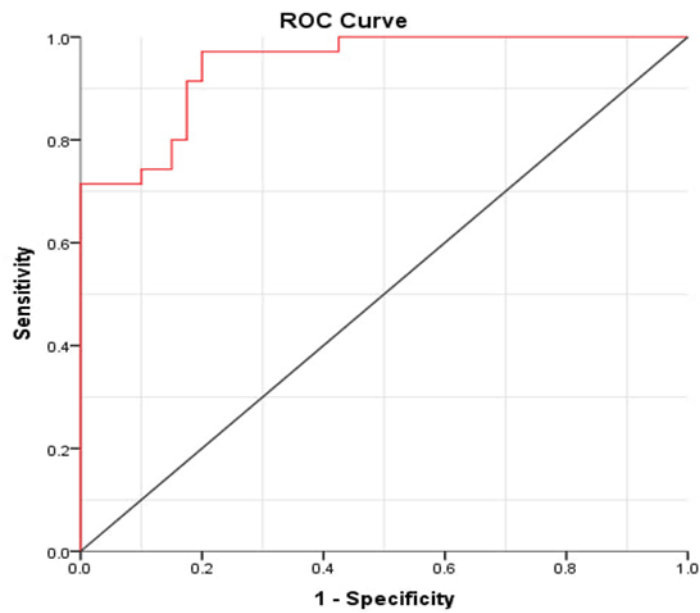


Figure 4: Receiver Operating Characteristic (ROC) Curve of Serum IL-6 Level as Discriminators of Patients with Obese RA.

4. Discussion

According to this study, Table-1 and Figure-2 found that age has a non-significant with RA and control. It agrees with the studies (Mititelu *et al.*, 2020) (Ahmad and Zgair, 2021). Gao *et al.* suggest aging is associated with an increased incidence of autoimmune diseases such as RA, immunosenescence may have special importance on the development of all immune-mediated conditions (Gao *et al.*, 2022). RA is associated with premature immunosenescence, which is characterized by many changes including reduced thymic functioning, expansion of late-differentiated effector T cells, increased telomeric attrition, and heightened production of pro-inflammatory cytokines (Bauer, 2020), while others show aging is characterized by an accumulation of genetic alterations (Qiang, Lipscombe and Lega, 2020). According to this study, Table-1 and Figure 2 found that BMI has a significant association between RA and control. Multiple research have examined the correlation between obesity and the development of RA yet, the connection between the two is still not well understood (Qin *et al.*, 2015). Prior research has indicated that approximately 60% of individuals with RA are classified as obese or overweight, with a body mass index ($BMI \geq 25 \text{ kg/m}^2$). Moreover, obesity is a notable and progressively prevalent coexisting medical condition, especially during the initial phases of rheumatoid arthritis manifestation (Feng *et al.*, 2019). BMI is regarded as a risk factor for predicting chronic inflammation, which tends to accumulate during the overweight phase (Liqiang *et al.*, 2023). Induce enhanced oxidative stress in the endoplasmic reticulum, leading to the release of proinflammatory substances into the bloodstream (Hotamisligil, 2010), while others suggested an increased in serum proinflammatory, then causes RA (Bedeković *et al.*, 2023). The observed results showed that the group of patients had higher levels of IL-6, as illustrated in Table 1 and Figure-1. The levels of IL-6 were considerably higher in individuals with obesity RA compared to non-obese patients and the control group, with a mean \pm standard deviation of ($71.02 \pm 11.39 \text{ pg/ml}$) in obese RA, ($59.85 \pm 14.50 \text{ pg/ml}$) in non-obese RA patients and ($5.87 \pm 1.91 \text{ pg/ml}$) in the control group. The study is similar to other study performed by (Mohammed *et al.*, 2023). Interleukin 6 (IL-6) has been discovered by researchers to have a critical regulatory role in the development and course of a variety of inflammatory diseases (Mohammed *et al.*, 2023). A previous study suggests that IL-6 is a crucial mediator of inflammation in RA and has a central function in the advancement and progression of RA. The physiological effects of IL-6 are significant in inflammatory conditions like RA, where persistent immune activation and repeated acute phase reactions are typical (Shrivastava *et al.*, 2015). Multiple studies have demonstrated that in RA, persistent inflammation in the joints results in the generation of IL-6 and its receptor (IL-6R), which are found in cells responsible for initiating and sustaining inflammation (Jarlborg and Gabay, 2022). This study assessed IL-6 as a predictive biomarker for several disease groups, comparing them to a group of healthy individuals. Interleukin 6, which was discovered many years ago, has been found to have multiple functions and is involved in various inflammatory processes that contribute to the development of autoimmune diseases when its regulation is impaired (Grebenciucova and VanHaerents, 2023). . Interleukin 6, which was discovered many years ago, has been found to have multiple functions and is involved in various inflammatory processes that contribute to the development of autoimmune diseases when its regulation is impaired (Korn *et al.*, 2009). Interlukin-6, a cytokine is known for its involvement in both chronic inflammatory responses and acute (Uciechowski and Dempke, 2020); (Jawad *et al.*, 2024) (Aljabawi and Farhan, 2023). The source of the proinflammatory cytokines is the active macrophagocytes, which mainly have the functions of inflammatory reactions up-regulation. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) are the main members of the proinflammatory cytokines and frequently play a role in the mediation of fever, tissue damage, and, in some cases, shock and even death during the inflammation process. Endothelial adhesion molecules like IL-1 and TNF are essential for leukocyte attachment to endothelial cell surfaces prior to tissue

emigration (Farhan, Zghair and Hadi, 2022). Our study found that obese individuals with rheumatoid arthritis (RA) had elevated levels of IL-6, which is a key proinflammatory cytokine that plays a crucial role in activating the immune response. Furthermore, the obese population exhibits elevated levels of proinflammatory cytokines (Popko *et al.*, 2010). Adipose tissue plays a significant role in producing and releasing IL-6 into the bloodstream. The increase in adipose tissue associated with obesity can lead to elevated levels of IL-6 in the bloodstream (Wueest and Konrad, 2020). Many studies that show excess macronutrients in adipose tissues induce the release of inflammatory adipokines such as interleukin-6 (IL-6), resulting in a condition of chronic inflammation in obese patients (El-Mikkawy *et al.*, 2020).

5. Conclusion

An increase in serum pro-inflammatory cytokines interleukin-6 (IL-6) in patients suffering from obese RA more than non-obese RA is considered a predictor and biomarker for the inflammation in RA and obesity diseases.

6. Ethical Approval

The study's ethical approval had been verified by the Kerbala Health Directorate (Ethics Board, 3544 on 24/10/2023), Obtained from the joint consolation clinic, Al-Hassan Teaching Hospital, Kerbala Health Directorates / Kerbala – Iraq and College of Medicine, University of Kerbala. Consent was acquired from the patients themselves as well as the Kerbala Center organization for the combined consolation clinic following an explanation of the study's purpose and nature.

7. Acknowledgments

The authors acknowledge the contribution of the College of Medicine, University of Kerbala / Kerbala - Iraq (www.uokerbala.edu.iq) to this work. The authors acknowledge the control group and the sick research participants.

References

- Abdellatif, E.A. *et al.* (2024) 'Obesity among Rheumatoid Arthritis Patients and its Relation to Disease Activity: Cross-sectional Study among the Egyptian Population', *Suez Canal University Medical Journal*, 27(1), p. 0.
- Ahmad, R. and Zgair, A. (2021) 'Immunological and Biological Manifestation of Rheumatoid Arthritis Patient in Iraq', *Indian Journal of Forensic Medicine & Toxicology*, 15(4), pp. 1344–1350.
- Aljabawi, R.A.A. and Farhan, N.H. (2023) 'Tocilizumab for severe COVID-19: Review and meta-analysis', *kerbala journal of pharmaceutical sciences*, 1(21).
- Bauer, M.E. (2020) 'Accelerated immunosenescence in rheumatoid arthritis: impact on clinical progression', *Immunity & Ageing*, 17(1), p. 6.
- Bautista-Molano, W. *et al.* (2024) 'Burden of disease in psoriatic arthritis in Latin America: a systematic literature review', *Clinical Rheumatology*, 43(2), pp. 677–693.
- Bedeković, D. *et al.* (2023) 'Role of Inflammatory cytokines in rheumatoid arthritis and development of atherosclerosis: A review', *Medicina*, 59(9), p. 1550.
- El-Mikkawy, D.M.E. *et al.* (2020) 'Circulating level of interleukin-6 in relation to body mass indices and lipid profile in Egyptian adults with overweight and obesity', *Egyptian Rheumatology and Rehabilitation*, 47, pp. 1–7.
- Farhan, N.H., Zghair, M.A. and Hadi, H.N. (2022) 'Cytokine storm in covid-19.', *Karbala Journal of Pharmaceutical Sciences*, 1(20).
- Fendler, A. *et al.* (2021) 'Adaptive immunity and neutralizing antibodies against SARS-CoV-2 variants of concern following vaccination in patients with cancer: the CAPTURE study', *Nature cancer*, 2(12), pp. 1305–1320.
- Feng, X. *et al.* (2019) 'Body mass index and the risk of rheumatoid arthritis: an updated dose-response meta-analysis', *BioMed research international*, 2019(1), p. 3579081.
- Gao, Y. *et al.* (2022) 'Immunosenescence of T cells: a key player in rheumatoid arthritis', *Inflammation Research*, 71(12), pp. 1449–1462.
- Grebenciucova, E. and VanHaerents, S. (2023) 'Interleukin 6: at the interface of human health and disease', *Frontiers in immunology*, 14, p. 1255533.
- Hasanzad, M. *et al.* (2021) 'A systematic review of miRNAs as biomarkers in osteoporosis disease', *Journal of Diabetes & Metabolic Disorders*, 20(2), pp. 1391–1406.
- Hotamisligil, G.S. (2010) 'Endoplasmic reticulum stress and the inflammatory basis of metabolic disease', *Cell*, 140(6), pp. 900–917.
- Jarlborg, M. and Gabay, C. (2022) 'Systemic effects of IL-6 blockade in rheumatoid arthritis beyond the joints', *Cytokine*, 149, p. 155742.
- Jawad, A. *et al.* (2024) 'Signature of IL-33 and Leptin as early progression markers in Rheumatoid Arthritis', *kerbala journal of pharmaceutical sciences*, 1(23).
- Kondo, N., Kuroda, T. and Kobayashi, D. (2021) 'Cytokine networks in the pathogenesis of rheumatoid arthritis', *International journal of molecular sciences*, 22(20), p. 10922.

Korn, T. *et al.* (2009) 'IL-17 and Th17 Cells', *Annual review of immunology*, 27(1), pp. 485–517.

Liqiang, S. *et al.* (2023) 'Threshold effect and sex characteristics of the relationship between chronic inflammation and BMI', *BMC Endocrine Disorders*, 23(1), p. 175.

Mititelu, R.R. *et al.* (2020) 'Inflammatory and oxidative stress markers—mirror tools in rheumatoid arthritis', *Biomedicines*, 8(5), p. 125.

Mohammed, A.M. *et al.* (2023) 'Diagnostic and predictive values of IL-6 in a group of Iraqi patients with rheumatoid arthritis', *Journal of the Faculty of Medicine Baghdad*, 65(2).

Mushtaq, I. *et al.* (2024) 'Association of serum IL12 with clinical and biochemical parameters in a cohort of diagnosed rheumatoid arthritis patients on oral conventional synthetic disease modifying anti-rheumatic drugs.', *Journal of Pakistan Medical Association*, 74(2), p. 310.

Pawłowska-Kamieniak, A., Krawiec, P. and Pac-Kożuchowska, E. (2021) 'Interleukin 6: biological significance and role in inflammatory bowel diseases', *Advances in Clinical and Experimental Medicine*, 30(4), pp. 465–469.

Popko, K. *et al.* (2010) 'Proinflammatory cytokines IL-6 and TNF- α and the development of inflammation in obese subjects', *European journal of medical research*, 15, pp. 1–3.

Qiang, J.K., Lipscombe, L.L. and Lega, I.C. (2020) 'Association between diabetes, obesity, aging, and cancer: review of recent literature', *Translational Cancer Research*, 9(9), p. 5743.

Qin, B. *et al.* (2015) 'Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis', *Arthritis research & therapy*, 17, pp. 1–12.

Rufino, A.T. *et al.* (2024) 'Rufino, A. T., Freitas, M., Proença, C., Ferreira de Oliveira, J. M. P., Fernandes, E., & Ribeiro, D. (2024). Rheumatoid arthritis molecular targets and their importance to flavonoid-based therapy. Medicinal Research Reviews, 44(2), 497–538.', *Medicinal Research Reviews*, 44(2), pp. 497–538.

Sandhu, R. *et al.* (2020) 'Older adults living with food insecurity: the impact on psychological health', *Innovation in Aging*, 4(Suppl 1), p. 378.

Shi, G. *et al.* (2023) 'Estimation of the global prevalence, incidence, years lived with disability of rheumatoid arthritis in 2019 and forecasted incidence in 2040: results from the Global Burden of Disease Study 2019', *Clinical Rheumatology*, 42(9), pp. 2297–2309.

Shrivastava, A.K. *et al.* (2015) 'Inflammatory markers in patients with rheumatoid arthritis', *Allergologia et immunopathologia*, 43(1), pp. 81–87.

Soliman, S.A. *et al.* (2022) 'Serum irisin level in rheumatoid arthritis patients: Relationship to disease activity, subclinical atherosclerosis, and cardiovascular risk factors', *The Egyptian Rheumatologist*, 44(2), pp. 109–114.

Tanaka, T., Narazaki, M. and Kishimoto, T. (2018) 'Interleukin (IL-6) immunotherapy', *Cold Spring Harbor perspectives in biology*, 10(8), p. a028456.

Uciechowski, P. and Dempke, W. (2020) 'Interleukin-6: a masterplayer in the cytokine network', *Oncology*, 98(3), pp. 131–137.

Wang, T. and He, C. (2020) 'TNF- α and IL-6: the link between immune and bone system', *Current drug targets*, 21(3), pp. 213–227.

- Werner, L.E. and Wagner, U. (2023) 'Calcium-sensing receptor-mediated NLRP3 inflammasome activation in rheumatoid arthritis and autoinflammation', *Frontiers in Physiology*, 13, p. 1078569.
- Wu, F. *et al.* (2021) 'B cells in rheumatoid arthritis : pathogenic mechanisms and treatment prospects', *Frontiers in immunology*, 12, p. 750753.
- Wu, G. *et al.* (2021) 'Umbelliferone ameliorates complete freund adjuvant–induced arthritis via reduction of NF- κ B signaling pathway in osteoclast differentiation', *Inflammation*, 44, pp. 1315–1329.
- Wueest, S. and Konrad, D. (2020) 'The controversial role of IL-6 in adipose tissue on obesity-induced dysregulation of glucose metabolism', *American Journal of Physiology-Endocrinology and Metabolism*, 319(3), pp. E607–E613.
- Xiang, Y.-J. and Dai, S.-M. (2009) 'Prevalence of rheumatic diseases and disability in China', *Rheumatology international*, 29, pp. 481–490.
- Zhou, P. *et al.* (2024) 'PTEN: an emerging target in rheumatoid arthritis?', *Cell Communication and Signaling*, 22(1), p. 246.