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Signature of IL-33 and Leptin as Early Progression Markers in Rheumatoid Arthritis

Ahmed Jawad[1], Rana M. Hameed[2*], Jasem Hanoon Hashim AL-AWADI [3]

[1]Postgraduate student (Msc.) College of Science University of Kerbala

[2]Ph.D. Biochemistry/ Kerbala University, Faculty of Medicine, Department of Biochemistry, Kerbala, Iraq

[3]Ph.D./ Kerbala University, College of Science, Department of Biology, Kerbala, Iraq

***Corresponded Author**

Rana M. Hameed: rana.m@uokerbala.edu.iq

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disorder characterized by progressive and irreversible joint damage as a consequence of sustained synovitis. Adipokine levels and interleukin have been reported to be significantly increased in serum and synovial fluid (SF) of RA patients.

The study aimed to investigate the association between the levels of Leptin in the circulation of individuals with rheumatoid arthritis (RA).

Methods and Patients: The present work included a case-control study for a group of (90) samples: (60) patient samples and (30) healthy control samples. Patients with Rheumatoid arthritis were selected from Imam Hassan al-Mujtaba Hospital in Kerbala. The sociodemographic aspects of the patients were collected through the self-reported technique (student questionnaire). All patients underwent clinical history, clinical examination, and relevant laboratory investigations. The degree of rheumatoid was identified based on the evaluation of laboratory measurements for the clinical assessment of rheumatoid arthritis. An enzyme-linked immunosorbent assay system (ELISA) was performed using the sandwich-ELISA method to measure the concentrations of serum IL-33. At the same time, a competitive enzyme immunoassay kit was used to detect human Leptin in serum samples quantitatively. Statistical analysis was performed, and the efficiency of the predicting value was assessed using the receiver operating characteristic (ROC) curve.

Results: Results indicated a significant difference in IL-33 and Leptin hormone levels among the study groups, which increased with increasing age, BMI, and duration of the disease. Both biomarkers showed highly significant differences in such disease and represented a risk factor. Leptin was illustrated to be a three-time risk factor for Rheumatoid arthritis disease compared to IL33. AUC analysis for IL-33 as a diagnostic parameter showed that IL-33 performs well in predicting such cases.

Conclusion: This study confirms a significant association between elevated leptin and IL-33 levels in RA patients, with leptin showing a three-fold higher risk than IL-33. Both biomarkers increase with age, BMI, and disease duration, highlighting their potential role in RA progression and diagnosis.

بصمة IL-33 واللبتين كعلامات مبكرة لتطور التهاب المفاصل الروماتويدي

أحمد جواد، رنا حميد، جاسم حنون هاشم العوضي

الخلاصة

المقدمة: **التهاب المفاصل الروماتويدي (RA) هو اضطراب مزمن التهابي ذاتي المناعة يتميز بتلف المفاصل التدريجي وغير القابل للعكس نتيجة التهاب الغشاء الزليلي المستمر. تم الإبلاغ عن زيادة ملحوظة في مستويات الأديبوكين والإنترلوكين في مصل الدم والسائل الزليلي لمرضى التهاب المفاصل الروماتويدي.**

الهدف: **هدفت الدراسة إلى التحقيق في العلاقة بين مستويات هرمون اللبتين في الدورة الدموية للأفراد المصابين بالتهاب المفاصل الروماتويدي(RA).**

المرضى وطرق العمل: **شملت الدراسة الحالية دراسة حالة-شاهد لمجموعة من (90) عينة: (60) عينة من المرضى و(30) عينة ضابطة صحية. تم اختيار المرضى المصابين بالتهاب المفاصل الروماتويدي من مستشفى الإمام حسن المجتبى في كربلاء. تم جمع الجوانب الاجتماعية والديموغرافية للمرضى من خلال تقنية التقرير الذاتي (استبيان الطلاب). خضع جميع المرضى لتاريخ سريري وفحص سريري والتحقيقات المخبرية ذات الصلة. تم تحديد درجة التهاب المفاصل الروماتويدي بناءً على تقييم القياسات المخبرية للتقييم السريري لالتهاب المفاصل الروماتويدي. تم إجراء نظام مقايسة الممتز المناعي المرتبط بالإنزيم (ELISA) باستخدام طريقة الساندويتش ELISA-لقياس تركيزات IL-33 في المصل، وفي نفس الوقت، تم استخدام مجموعة مقايسة مناعية إنزيمية تنافسية للكشف عن هرمون اللبتين البشري في عينات المصل بشكل كمي. تم إجراء التحليل الإحصائي وتقييم كفاءة القيمة التنبؤية باستخدام منحنى خاصية التشغيل.(ROC)**

النتائج :أظهرت **النتائج وجود فرق كبير في مستويات هرمون IL-33 واللبتين بين مجموعات الدراسة، والتي زادت مع زيادة العمر، مؤشر كتلة الجسم (BMI)، ومدة المرض. كلا العلامتين البيولوجيتين أظهرتا فروقات ذات دلالة كبيرة في مثل هذا المرض ومثلت عوامل خطر. تبين أن اللبتين يمثل عامل خطر ثلاثي للإصابة بمرض التهاب المفاصل الروماتويدي مقارنة بـ .IL-33 أظهر تحليل AUC لـ IL-33 كمعامل تشخيصي أن IL-33 يعمل بشكل جيد في التنبؤ بهذه الحالات.**

الاستنتاج: **تؤكد هذه الدراسة وجود ارتباط كبير بين ارتفاع مستويات اللبتين والـ IL-33 لدى مرضى التهاب المفاصل الروماتويدي، حيث يظهر اللبتين خطرًا أعلى بثلاثة أضعاف مقارنةً بالـ .IL-33 وتزداد مستويات كلا العلامتين الحيويتين مع تقدم العمر وزيادة مؤشر كتلة الجسم ومدة المرض، مما يبرز دورهما المحتمل في تقدم المرض وتشخيصه.**

1. Introduction

RA is a systemic disease characterized by a complex pathogenesis involving interactions between various cell types located in synovial compartments and peripheral blood rather than resulting from a single pathogenic factor (Alivernini et al., 2022). These cell populations, comprising fibroblast-like synoviocytes (FLSs), innate and adaptive immune cells, and bone-related cells, change in number, status, and behavior in response to the dynamic microenvironment, which perturbs cytokine secretion, intracellular signaling networks, and homeostasis and consequently leads to corresponding pathology. Multiple dysfunctional cell types and the crosstalk between these pathogenic cells collectively contribute to the onset, progression, and perpetuation of RA (Petrelli et al., 2022)

Under normal physiological conditions, FLSs express components of the extracellular matrix (ECM) and synovial fluid to lubricate and nourish cartilage surfaces, thereby maintaining the homeostasis of joints. However, accumulating studies have identified FLSs as critical players in many pathogenic events in the RA synovium. In pathological conditions, such as RA, FLSs increase rapidly. They are redistributed in the synovium and joints, exhibiting heterogeneity across different locations within the synovium and across other joints (Dakin et al., 2018). FLSs in RA display unique aggressive behavior that arises from their reduced apoptosis rate, deregulated proliferation, migration, and invasion, and improved ability to secrete inflammatory mediators and matrix metalloproteinases (MMPs) into the synovial fluid (Mousavi et al., 2021).

IL-33 was recently described as a new member of the IL-1 family, whose common characteristic is pro-inflammatory activity (Pisetsky, 2023). IL-33 plays an important immune role associated with Th2 response, significantly stimulating the secretion of IL-5 and IL-13 by Th2-polarized cells.

Basophils activated by immunoglobulin E (IgE) produce IL-33 and release histamine. Additionally, basophil migration appears to be regulated by IL-33. These findings aid in the understanding of independent immune responses to antigens present in tissues that express the mRNA of IL-33, such as smooth muscle cells in bronchial tissue and epithelial cells of the airways (Wright et al., 2017).

Mast cells are very responsive to IL-33, which results in increased production of IL-6, IL-13, IL-1beta, TNF, prostaglandin D2, and MCP-1 (Xu et al., 2008). In addition, IL-33 promotes survival, adhesion, and cytokine production in human mast cells and mast cell progenitors (Ali et al., 2007).

Several studies using experimental models of arthritis have evaluated the participation of IL-33 in pictures of joint inflammation. Proposed mechanisms for joint inflammation induction by IL-33 were activation of mast cells, and therefore, the production of inflammatory cytokines; increased secretion of IL-6 and IL-1beta by activated mast cells; or CD4+ cell stimulation that would lead to production of IL-5 and IL-13. This latter mechanism would increase the activation of B cells and immunoglobulin production, worsening the joint inflammation process and stimulating mast cell degranulation and the formation of immune complexes with collagen. These authors also demonstrated that mast cells are important in this experimental model, albeit not essential, for developing arthritis (Trimarchi et al., 2022; Xu et al., 2008).

Adipokine levels have been reported to be significantly increased in serum and synovial fluid (SF) of RA patients (Chihara et al., 2020). Furthermore, several studies outlined the implication of adipokines in the progression and severity of OA and the chronic inflammation in articular joints (Hu et al., 2011).

Leptin is a 16 kDa protein discovered in 1994 by Friedman and collaborators. It belongs to the class I helical cytokine family, which includes growth hormone (GH), leukemia-inhibiting factor (LIF), granulocyte colony-stimulating factor (G-CSF), interleukins (IL) (Zhang et al., 2005). Leptin is the main adipokine secreted by adipose cells. It exerts its role by binding to the long isoform receptor Ob-Rb and transducing the signal through the Janus kinase/signal transducer and activator of the transcription (JAK/STAT) signaling pathway (Boroń et al., 2021). In addition to its evident role in regulating energy homeostasis and food intake, it also has pleiotropic functions (Kelesidis et al., 2010). Leptin is implicated in adaptive and innate immunity. Increasing evidence suggests that Leptin exerts potent modulatory actions in the network of factors involved in the pathophysiology of rheumatic diseases such as OA and RA (Conde et al., 2010). This review recapitulates the most relevant data regarding the involvement of Leptin in these two diseases.

Leptin and its receptor are associated with the stage of OA disease and related pain. Notably, high leptin concentrations in RA patients are correlated with joint pain (Lübbeke et al., 2013). mRNA expression of Leptin and its receptor was more elevated in RA cartilage (Simopoulou et al., 2007) . Leptin has been described as implicating in RA pathogenesis. However, the results of clinical studies comparing serum or SF leptin concentrations in healthy individuals and RA patients still need to be clarified. Many authors have reported significant elevation of serum and SF leptin levels in RA patients compared to healthy controls (18); Popa and Collaborates said, in addition, that plasma leptin concentrations were inversely correlated to inflammatory markers in RA patients, suggesting that chronic inflammation in RA decreases leptin production (Rusu et al., 2012).

The role of Leptin in RA is not only associated with articular tissues; it might also have a potent effect on cell-mediated immune function (Fraser et al., 2000; Popa et al., 2005).

2. Material, Patients and Method

The present work included a case-control study for a group of (90) samples: (60) patient samples and (30) healthy control samples. Patients with Rheumatoid arthritis were selected from Imam Hassan al-Mujtaba Hospital in Kerbala. The sociodemographic aspects of the patients were collected through the self-reported technique (student questionnaire). All patients underwent clinical history, clinical examination, and relevant laboratory investigations. The degree of rheumatoid was identified based on the evaluation of laboratory measurements for the clinical assessment of rheumatoid arthritis.

The leptin-Ab ELISA kit applies the competitive enzyme immunoassay technique, which was used to measure the Leptin level, while the Sandwich-ELISA principle was used to measure the IL-33

Before their inclusion in the study, the hospital administration obtained valid written, signed consent, and each patient and control subject provided valid verbal consent.

Statistical analysis was performed, and the efficiency of the predicting value was assessed using the receiver operating characteristic (ROC) curve.

3. Results

Difference between the level of biological parameters (IL33 and Leptin) in the rheumatic arthritis cases and control group. Generally, patients with rheumatic arthritis disease showed an increasing range of IL-33 and Leptin Hormone levels compared to the healthy control groups.

Results indicated a significant difference in IL-33 and Leptin Hormone levels among groups; the means and standard deviations were presented in Table 1 & Fig.1. The mean level of IL-33 in patients was (950.80±463.07) which was significantly higher than for the Control group (297.10±44.81) ($p \leq 0.001$) and the mean level of Leptin. The hormone was (7.21±1.54) for the patient and (2.78±0.37) for the control,

Table 1: Results of The Analysis of Essential Rheumatic Arthritis Characteristics for Disease with Control Groups.

Biomarkers	Groups	Mean±SD	P value
IL-33	Patient	950.80±463.07	<0.001
	Control	297.10±44.81	
Leptin. Hormone	Patient	7.21±1.54	0.010
	Control	2.78±0.37	

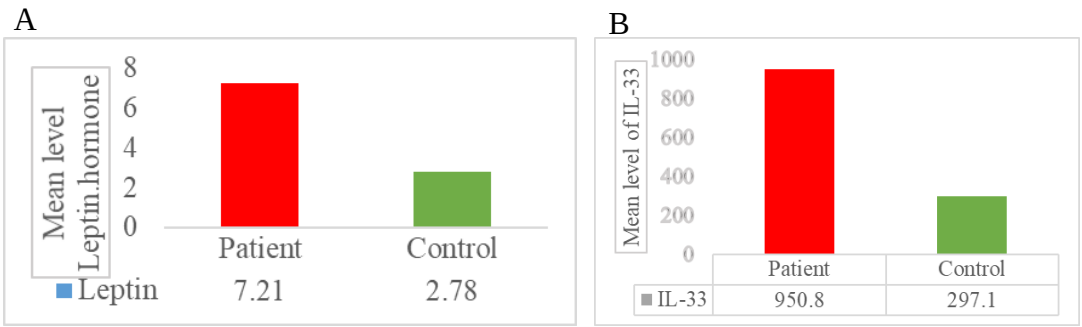

Figure 1: Results of the Analysis of Basic Rheumatic Arthritis for Patients with Control Groups (T-Test Was S= Significant at $P \leq 0.05$, NS= Non-Significant). **A)** Describes Medical Levels of Leptin Hormone. **B)** Refers to The Medical Levels Of IL-33.

Mean Difference of the biological parameters (IL33 and Leptin) based on the duration of disease. Biomarker levels were examined based on the duration of rheumatic arthritis disease. Generally, there were insignificant differences in the mean IL-33 and Leptin Hormone levels. The mean level of IL-33 was increased slightly with increasing the duration of rheumatic arthritis disease through (7-12 Years) compared to the group whose duration was less than one year and the group having a duration of rheumatic arthritis disease (1-6 Years), the differences were insignificant p-value > 0.05, as shown in Table 2 & Fig.2.

Table 2: Mean Difference of Biochemical Parameters for the Duration of Rheumatic Arthritis Disease.

Biomarkers	Groups	Mean±SD	P-value
IL-33	Less than 1 years	953.09±240.58	0.967
	1-6 Years	881.78±612.96	
	7-12 Years	992.01±153.06	
Leptin. Hormone	Less than 1 years	7.08±0.94	0.460
	1-6 Years	7.37±1.80	
	7-12 Years	6.61±0.79	

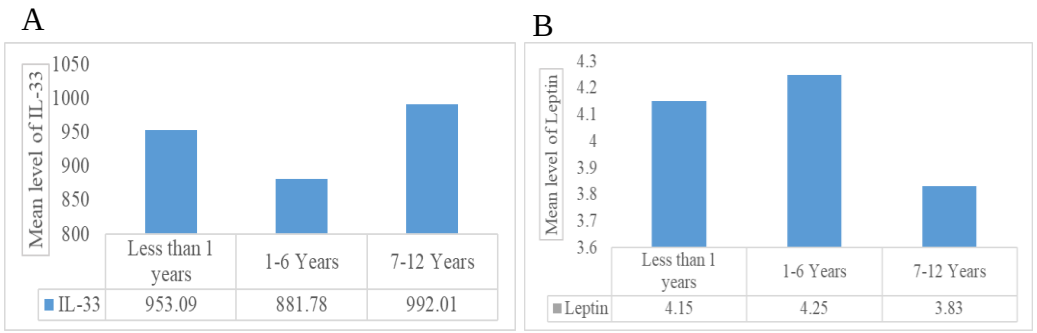

Figure 2: Difference Between Mean Levels of Biomarkers in Rheumatic Arthritis Disease According to Duration of Treatment (T Test Was *: Significant P ≤ 0.05; SD: Standard Deviation; S: Significant; NS= Non-Significant). **A)** Describes Medical Levels of Leptin Hormone. **B)** Refers to The Medical Levels of IL-33.

Table 3: Illustrates the Mean Level of IL-33 and Leptin in the Patients and Control Groups According to Gender

Biomarker	Male			Female		
	Patients Mean±SD N=30	**Control Mean±SD N=15**	**P value**	**Patients Mean±SD N=16**	**Control Mean±SD N=8**	**P value**
IL-33	994.1±458.5	401.3±53.5	<0.001[S]	830.8±540	352.94±93	**<0.001[S]**
Leptin	6.01±0.43	3.80±0.61	<0.001[S]	5.95±0.3	4.54±2.59	**0.003[S]**
T test was *: significant at p ≤ 0.05, N: number of cases; SD: standard deviation; S: significant; NS= Non significant						

Results showed that the levels of IL-33 and Leptin hormone were increased markedly in the patient's group in both males and females compared to the control; p values were <0.001.

In Fig.3. and Fig.4. a comparison of serum levels of IL-33 and Leptin (pg/ml) in different age groups was performed. The levels of IL-33 and Leptin increased significantly within all the age ranges and were highly statistically significant ($p<0.05$).

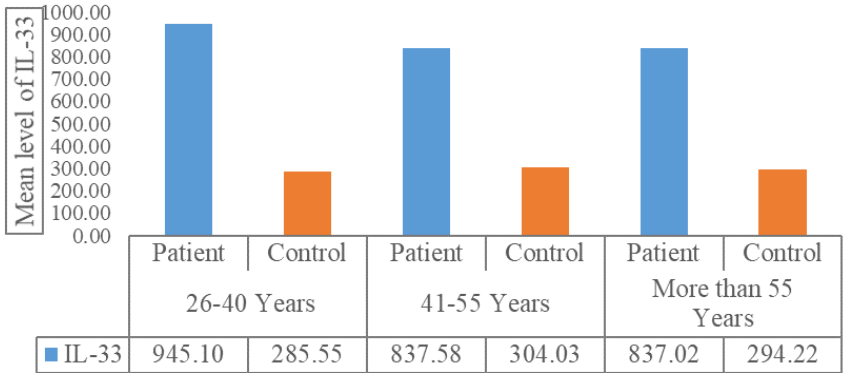

Figure 3: The Effect of Age Groups on the IL-33 According to The Patient and Control Groups

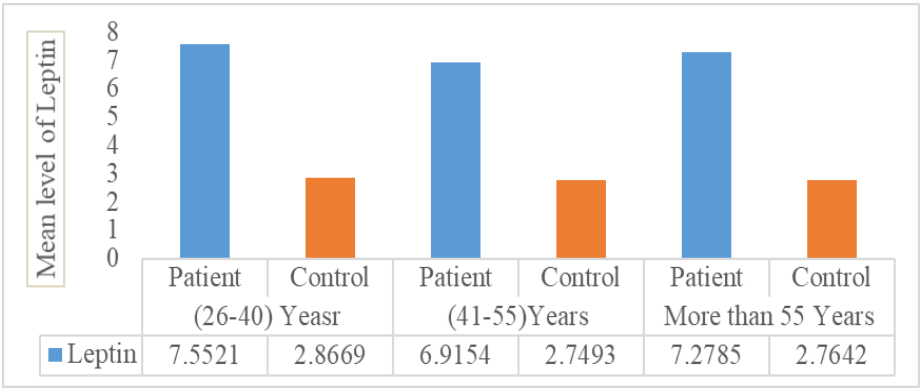

Figure 4: The Effect of Age Groups on Leptin According to the Patient and Control Groups.

In Fig.5. and Fig.6. A Comparison of Serum Levels of Il-33 And Leptin (Pg/Ml) In Different Age Groups Was Performed. Both Levels of Il-33 And Leptin Were Increased Within All the Bmi Ranges And Were Highly Statistically Significant ($P<0.05$).

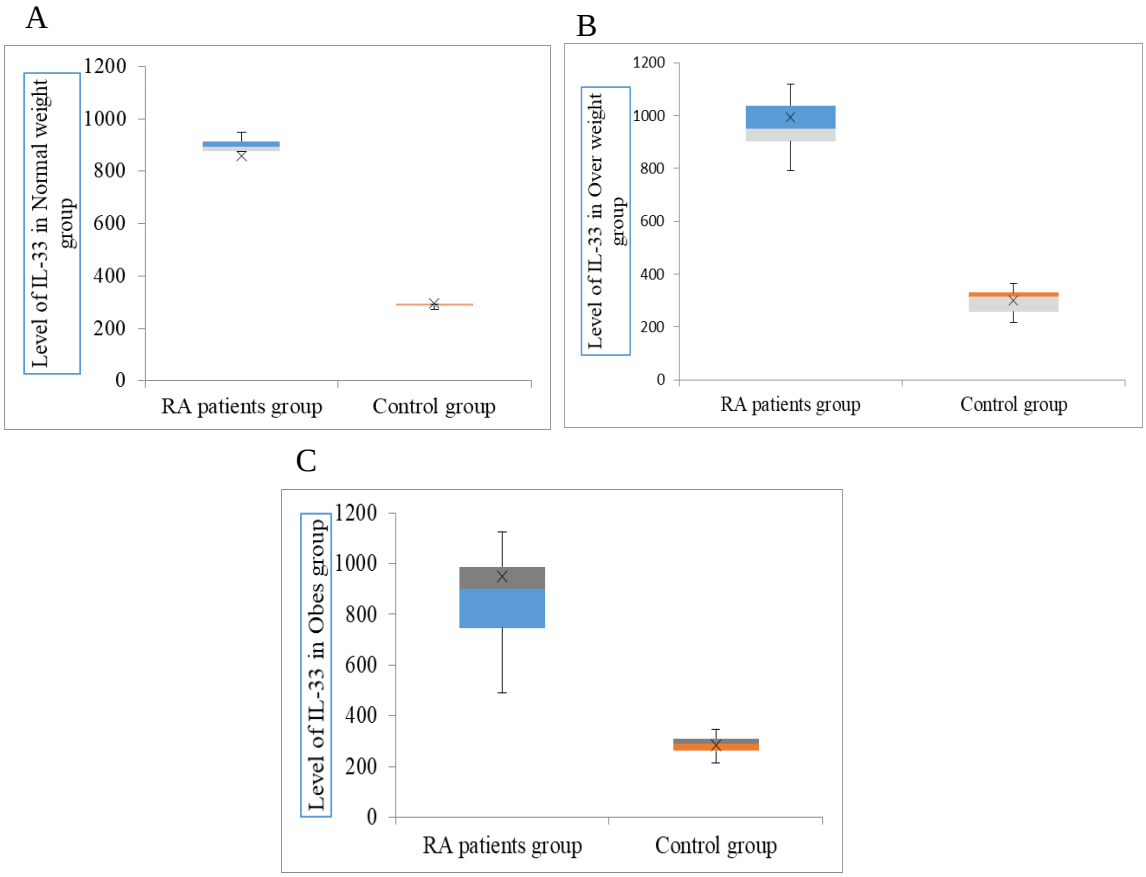

Figure 5: The Effect of BMI Groups on the IL-33 According to The Patient and Control Groups. **A)** According to Normal Weight, **B)** According to Overweight And **C)** According to Obesity.

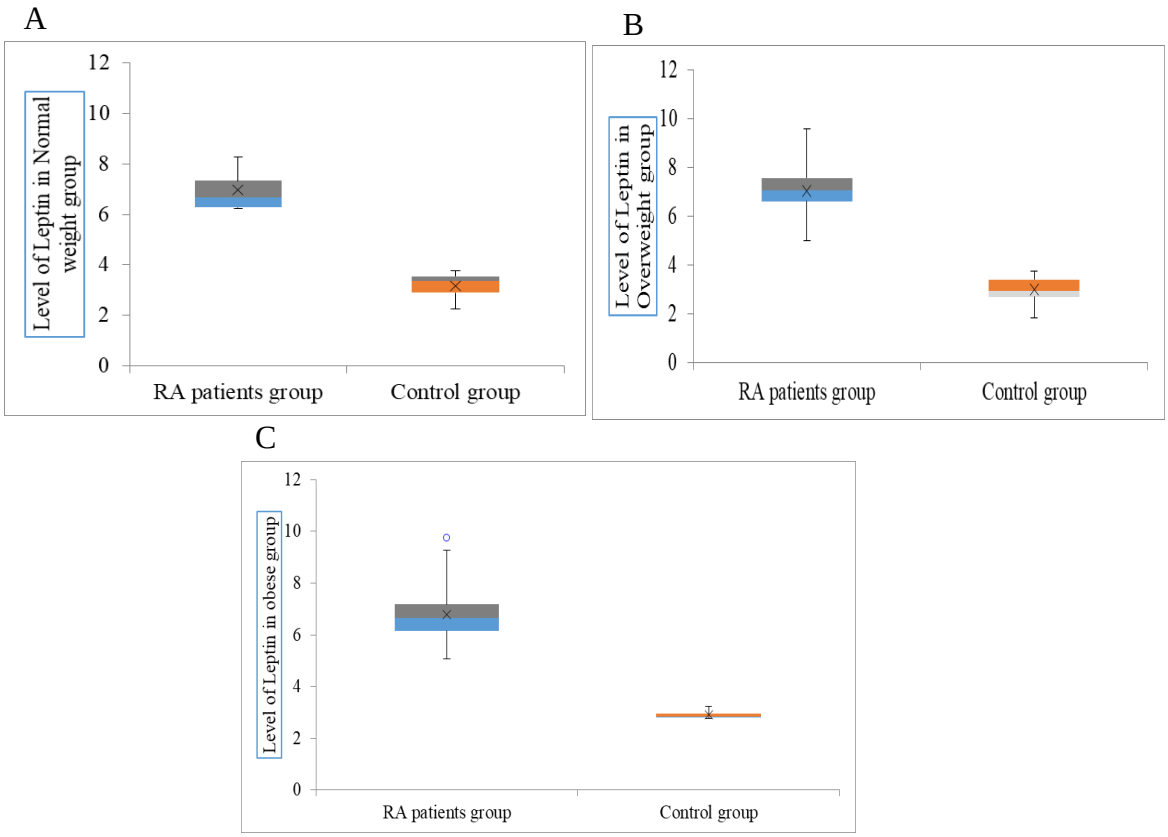

Figure 6: The Effect of BMI Groups on Leptin According to the Patient and Control Groups. **A)** According to Normal Weight, **B)** According to Overweight and **C)** According to Obesity.

Multinominal Logistic Regression Was Performed to Analyze the Association Between Il-33 And Leptin Hormone with Rheumatoid Arthritis Disease. It Was Found That Both Biomarkers Were Shown Highly Significant Differences in Such Disease and Represented A Risk Factor. Leptin Was Illustrated to Be A Three-Time Risk Factor for Rheumatoid Arthritis Disease Compared to Il33. The Odd Ratio of Il33 Was (Or 1.487; 95% Ci: (0.778-2.841), And for Leptin Hormone Was (Or: 3.796; 95% Ci: 1.21-5.632), As Shown in Table 4.

Table 4: The Binary Logistic Regression of Rheumatic Arthritis Disease (RA) with Levels of Biomarkers

Biomarkers	OR (Lower-Upper)	P value
Leptin Hormone	3.796(1.21-5.632)	0.004
IL-33	1.487 (0.778-2.841)	0.001

ROC curve and AUC analysis for the Leptin for rheumatic arthritis disease ROC curve and AUC analysis were performed for the IL-33 patients compared to the control group. Results of the receiver operating curve (ROC) curve and AUC analysis for the IL-33 as a diagnostic parameter showed that IL-33 has a good performance for predicting such cases; data are presented in Table 5 & Fig.7. For IL-33 levels: (sensitivity 83.3 %, specificity 97%) at a level = 593. The p-values of the AUC were <0.001 and highly statistically significant. Results sensitivity & Specificity results were confirmed using Youden's J statistics to find parameters.

Table 5: Receiver Operating Characteristic Curve Showing Sensitivity and Specificity Of IL-33 In Patients Compared to Control

Test Result Variable(s)	IL-33
AUP	88.5%
Sensitivity %	83.3%
Specificity %	97%
Youden index	0.803
Cut-off points	593.464
CI (95%)	0.811-0.959
PPV	99%
NPV	75%
Accuracy	88.8%
P value	<0.001

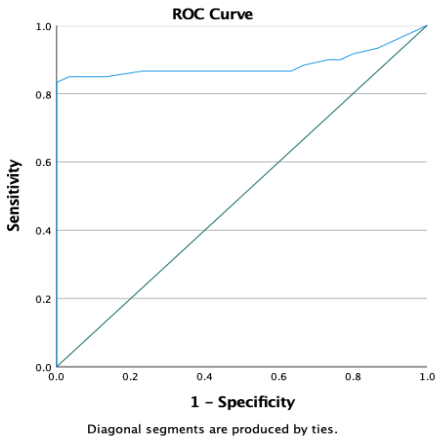

Figure 7: Receiver Operating Characteristics (ROC) Curve Analysis of Il33 Levels in Rheumatoid Arthritis Cases

Roc Curve and Auc Analysis for The Leptin for Rheumatic Arthritis Disease. ROC curve and AUC analysis for the IL-33 patients compared to the control group were performed. Results of the receiver operating curve (ROC) curve and AUC analysis for Leptin as a diagnostic parameter showed that Leptin performs well in predicting such cases; data are presented in Table 6 and Fig.8. For Leptin levels: (sensitivity 98.3%, specificity 99%) at a level = 5.0387. The p-values of the AUC were <0.001 and highly statistically significant. The Sensitivity & Specificity results were confirmed using Youden's J statistics to the parameters.

Table 6: Receiver Operating Characteristic Curve Showing Sensitivity and Specificity of Leptin In Patients Compared To Control.

Test Result Variable(s)	Leptin
AUP	98.3%
Sensitivity %	98.3%
Specificity %	99%
Youden index	0.883
Cut-off points	5.0387
CI (95%)	0.962-1.000
PPV	99%
NPV	75%
Accuracy	88.8%
P value	<0.001[S]

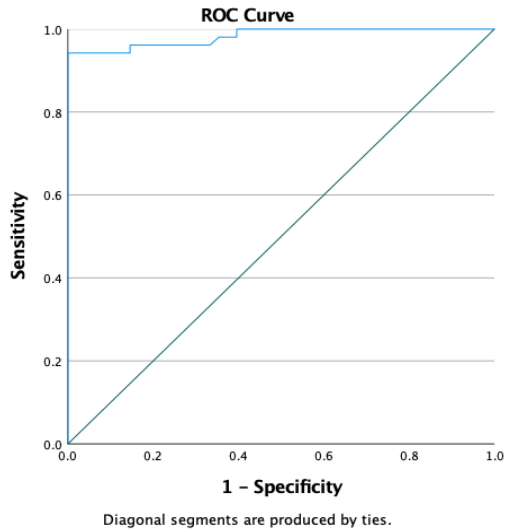

Figure 8: Receiver Operating Characteristics (ROC) Curve Analysis of Leptin Levels in Rheumatoid Arthritis Cases

4. Discussion

Rheumatoid arthritis is a severe chronic and progressive autoimmune disorder characterized by synovium inflammation (Lai et al., 2017). Although the pathological mechanisms involved in RA are different, the onset and progression of both diseases are associated with inflammation, immune mechanisms, and metabolic factors (Francisco et al., 2018a; Lai et al., 2017). Mechanical loading and inflammatory mediators such as adipose-tissue-derived cytokines (adipokines) have been reported as a link between obesity and RA(Smekal and Vaclavik, 2017) . Adipokines, including Leptin, are secreted principally by white adipose tissue (WAT) (Carrión et al., 2019). Through their endocrine, autocrine, or paracrine actions, they are implicated in several physiological and pathological processes

and lead to a low-grade inflammatory state (Lago et al., 2007). Indeed, they are demonstrated to be involved in the pathogenesis of rheumatic diseases by the modulation of the inflammatory process in the joint, the imbalance between catabolic and anabolic factors, and the remodelling of bone and cartilage (La Cava, 2017).

In this study, Leptin levels have significantly increased in the serum of RA patients. Leptin is implicated in both innate and adaptive immune responses. It promotes the synthesis and secretion of pro-inflammatory cytokines. It enhances T-cell proliferation and memory-T-cells differentiation to T-helper (Th1), inhibits regulatory-T-cell (Treg) proliferation, (Carrión et al., 2019; La Cava, 2017; Lago et al., 2007)

In RA, Autoantibodies and rheumatoid factor (RF) are the first immune abnormalities detected, followed by joint damage starting in the synovial membrane. Synovium inflammation appears in the early stages of the disease after activation of endothelial cells that express adhesion molecules and chemokines following the infiltration of leukocytes through the synovium; leptin has been described as implicated in RA pathogenesis(Alam et al., 2017; Radu and Bungau, 2021) .

Leptin has been described as modulating bone homeostasis through locally and centrally mediated mechanisms. It inhibits osteoclast differentiation in peripheral blood mononuclear cells (PBMCs) and murine spleen cells in bone culture via the RANKL/RANK/OPG system, thus contributing to the inhibition of bone resorption (Holloway et al., 2002).

Increasing levels of Leptin were confirmed due to their role in activated macrophage inducing the release of IL-6 and TNF-α. In vitro macrophage chemotactic activity is associated with Leptin induction. In autoimmune diseases, the deregulated immune response of cells is affected by the alteration of metabolic processes within these cells (Francisco et al., 2018b; La Cava et al., 2004) because Leptin binds to its long isoform receptor (Ob-RB) to induce its biological and physiological effect through the JAK/STAT signalling pathway. JAK/STAT signal transduction is caused by the involvement of Janus kinase 2 (JAK2), activators of transcription (STAT), and transducers found on more extended receptor isoform (Ob-Rb) (Stofkova, 2009).

In addition to Leptin, this signalling pathway requires the interaction between complex molecules, including node-like receptor pyrin domain-containing protein 3 (NLRP3) and IL-33(Giles et al., 2011) .

Throughout the roc analysis, leptin level was found to be a reliable surrogate biomarker of RA disease progression. Our results were consistent with those of others (Francisco et al., 2018b; Giles et al., 2011; Holloway et al., 2002; La Cava et al., 2004; Stofkova, 2009) who reported that the predictive value of Leptin showed an excellent diagnostic value for RA.

Since Leptin is a pro-inflammatory factor that stimulates the innate and acquired immune response, and its concentration increases during infection and inflammation, this study analyzed the cut-off point of Leptin in patients with RA. Given that this value has been defined in the Kerbala population compared to controls, it is worth highlighting the values to identify a more sensitive value for the other disease and population.

Conclusion

This study confirms the significant role of leptin as a pro-inflammatory factor in rheumatoid arthritis (RA). Elevated leptin levels were strongly associated with RA progression, as demonstrated through ROC analysis, highlighting its diagnostic value. Leptin's involvement in both innate and adaptive immune responses, particularly its influence on cytokine production and T-cell differentiation, underscores its contribution to RA pathogenesis. Furthermore, the identification of a leptin cut-off point specific to the Kerbala population suggests the potential for more sensitive diagnostic markers tailored to different populations.

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