Journal of Medical Research and Health Sciences
Received 25 May 2024| Revised 25 June 2024 | Accepted 20 July 2024 | Published Online 20 August 2024

DOI: https://doi.org/10.52845/JMRHS/2024-7-8-1

JMRHS 7 (8), 3178–3187 (2024)

ISSN (O) 2589-9031 | (P) 2589-9023

Original Article **Open Access Journal**

Interleukin-6 Role in Systemic Inflammation in Rheumatoid Arthritis Iraqi Patients with T2DM

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Abstract

Background: Rheumatoid arthritis (RA) and diabetes mellitus (DM) are chronic conditions associated with significant morbidity.

Aim of study: This study amid to investigate the impact of interleukin-6 (IL6) and the relationship between inflammatory markers, glycemic control, and disease characteristics.

Methods: A cross-sectional study was conducted on 100 patients (64 with RA only and 34with RA+DM). The sample was collected between June 2023 and January 2024 from the Rheumatology Clinics at the Out-Patient Department of Imam Al-Hussain Medical City in Karbala, Iraq. Serum levels of IL-6, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Glycated hemoglobin (HbA1c), and fasting blood sugar (FBS) were assessed as indicators of glycemic control. Demographic data and disease duration were also recorded. Statistical analyses were done by using SPSS version 29.

Results: The result of current study revealed that there is a significant difference in IL-6 level between RA (65.53 ± 18.69) and RA+DM (120.36 ± 23.55) groups ($p<0.001$). A strong positive correlation was observed between HbA1c and IL-6 ($r=0.72$, $p<0.001$). There is a significant increased level of IL-6 in female compared to male in RA+DM group (124.84 ± 24.03). The levels of IL-6 correlated positively and significantly with RA duration ($r=0.54$, $p<0.01$).

Conclusion: This study demonstrates a complex interplay between RA, DM, and systemic inflammation. The presence of DM in RA patients is associated with heightened inflammatory responses, while poor glycaemic control correlates with increased inflammation. These findings underscore the importance of managing both conditions concurrently and suggest that inflammatory markers, particularly IL-6, may serve as useful indicators for assessing disease severity and comorbidity risk in RA patients.

Keywords: rheumatoid arthritis, diabetes mellitus, Interleukin-6, glycemic control

How to Cite: Mahdi, Z. A.-A. (2024). Interleukin-6 Role in Systemic Inflammation in Rheumatoid Arthritis Iraqi Patients with T2DM. Jour Med Resh and Health Sci, 7(8), 3178–3187. https://doi.org /10. 52845/JMRHS/2024-7-8-1

Introduction:

Two of the widespread chronic inflammatory diseases that are globally affecting healthcare systems are: rheumatoid arthritis (RA) and type 2 diabetes mellitus (T2DM) (1). While both diseases are individually complex their co-occurrence presents a unique and challenging clinical outcome (2). In understudied populations like Iraq, it is crucial for effective treatment strategies to clarify the relationship between RA and T2DM.

As a chronic autoimmune disease characterised by synovial inflammation, joint destruction, and systemic manifestations RA affect approximately 1% of the worldwide population (3, 4). Its complexity is compounded by frequent association with comorbidities, one of which is T2DM stands out as particularly significant due to its prevalence and potential impact on RA outcomes (5, 6). Patients with both RA and T2DM experience more severe disease progression and poorer treatment outcomes compared to those with RA alone, recent studies have revealed (4, 7, 8). Yet, the association between RA and T2DM remain under investigation (2). Nonetheless, numbers of hypotheses have been put forward. Both conditions have prevalent characteristic that plays a crucial role is the systemic inflammation. Pro-inflammatory cytokines released by immune cells such as Interleukin-6 (IL-6), are implicated in the pathogenesis of both diseases (8, 9). This synergistic effect is hypothesized to be influenced by overlapping pathways of inflammation and the dysregulation of metabolic functions (10).

A cytokine like IL-6, has pleiotropic effects on the: immune system, inflammation, and hematopoiesis (11). IL-6 is produced by various cell types, including T cells, macrophages, and endothelial cells (12). Chronic elevation of IL-6 contributes to the development of various inflammatory diseases and it exhibits beneficial functions in acute inflammation (12). IL-6 in RA stimulates the production of other inflammatory mediators in the synovium causing joint destruction. Likewise, in T2DM, it disrupts insulin signaling and endorses insulin resistance (13-16). Other markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) continue to be important in assessing overall inflammatory burden (17).

Glycaemic control: measured by glycated haemoglobin (HbA1c) and fasting blood sugar (FBS) is fundamental in DM monitoring (18). Yet, its relationship with inflammatory markers in the context of RA with DM comorbidity remains incompletely understood (5). Some articles have suggested that poor glycaemic control may worsen inflammation in RA potentially leading to more aggressive joint destruction and increased cardiovascular risk (19, 20). The extent of RA has been associated with growing joint damage and increased systemic inflammation. Though, the interaction between disease duration, glycaemic control, and inflammatory markers in patients with both RA and T2DM requires further investigation (2, 19).

Existing researches focusing on Western individuals; at the same time limited data available on the specific features of RA and T2DM co-occurrence are available in Iraqi population. Reasons like: genetics, environmental exposures, and access to healthcare may play crucial roles in determining disease presentation and co-morbidity patterns in Iraqi patients compared to others. This study aims to fill the knowledge gap by investigating the role of IL-6 in systemic inflammation in Iraqi patients diagnosed with both RA and T2DM by comparing biomarkers associated with inflammation and disease severity in patients with and without T2DM. The research pursues to understand the impact of T2DM on the inflammatory profile of RA in the Iraqis. This article will hold significant value for improving the management of RA patients with T2DM in Iraq. This study may pave the way for the development of targeted therapies aimed at controlling inflammation and improving patient outcomes by clarifying the role of IL-6 in systemic inflammation.

Material and Methods

Patients

A total of one hundred participants aged 33–70 years were enlisted in this cross-sectional study. All of them diagnosed earlier with RA according to the 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria (21). The sample was collected between Jun 2023 and

January 2024 from the Rheumatology Clinics at the Out-Patient Department of Imam Al-Hussain Medical City in Karbala, Iraq. Participants were divided into two groups, rheumatoid arthritis with type two diabetes mellitus (n=64) and RA without T2DM (n=36). Patients with history of acute or chronic conditions other than T2DM and RA were excluded in order to reduce the possibility of results being confounded, likewise, those receiving drugs other than non-steroidal anti-inflammatory drugs (NSAIDs). The research has been complied with all the relevant national regulations, institutional policies, and in accordance with the tenets of the Helsinki Declaration through the Institutional Ethics Committee.

Sample Collection and Laboratory Assessment

A fasting blood sample of 10 mL was collected from each participant. Subsequently, 5 mL of these blood samples underwent centrifugation to facilitate the separation of serum from the supernatant. The isolated serum was then transferred into Eppendorf tubes and stored at -20°C until the Enzyme-linked Immunosorbent Assay (ELISA) test was conducted to quantify the serum concentration of interleukin-6 (IL-6), following the manufacturer's guidelines provided by Elabscience - China. Additionally, the serum level of fasting blood glucose (FBG) was assessed using a glucose kit sourced from Roche - Switzerland, C reactive protein (CRP) measured by using latex agglutination kit (Chromatest - Spain), rheumatoid factor (RF) using latex (Chromatest - Spain). And the rest (5ml) of whole blood (3ml) used to measured erythrocyte sedimentation rate (ESR) (Westergren - China) and (2ml) used for HbA1c measured by (Roche - Switzerland).

Statistical Analyses

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 29 software package using paired t-test, Pearson correlation, multiple regression and Roc curve. The summary measures were described as mean ± standard deviation (SD). All statistical tests were performed at ($P < 0.05$) significance level.

Results

The main characteristics of patients including the mean age and disease duration of the two groups are demonstrated in Table 1.

Table 1: The main characteristics of RA and RA+DM patients as mean ± SD and p-value

Characteristic	RA/DM+RA	Mean ± SD	p-value
Age (years)	RA	44.75 ± 10.77	0.00
	DM+RA	57.27 ± 11.54	
Period of disease (years)	RA	7.19 ± 4.58	0.02
	DM+RA	4.66+3.19	

A Comparison between mean level and standard deviation (SD) of the biochemical markers in both RA and RA+DM Groups are revealed in table 2. The results designate a significant difference in IL-6 level between the two groups (p value <0.001). While CRP levels are elevated in the RA+DM group compared to the RA group, the difference was not significant (p=0.97). ESR, likewise, showed a similar trend with higher values in the RA+DM group compared to the RA group (p=0.34). On the other hand, the RF acted differently by showing nearly similar means in both groups.

Table 2: The biochemical markers of RA and RA+DM patients as mean ± SD and p-value

Biochemical Marker	RA/DM+RA	Mean ± SD	p-value
Rheumatoid Factor(IU/ml)	RA	49.37 ± 47.85	0.41
	DM+RA	49.64 ± 39.35	
CRP (mg/l)	RA	29.96 ±15.56	0.97
	DM+RA	31.67 ± 15.28	
ESR (mm/hr)	RA	15.14 ± 12.88	0.34
	DM+RA	18.01 ± 15.08	

HbA1c%	RA	4.23 ± 1.07	<0.001
	DM+RA	10.18 ± 2.15	
FBS (mg/dl)	RA	103.77 ± 17.96	<0.001
	DM+RA	239.65 ± 76.02	
IL6 (pg/ml)	RA	65.53 ± 18.69	<0.001
	DM+RA	120.36 ± 23.55	

Increasing in IL-6 level in female DM+RA comparing to male DM+RA groups as presented in Table 3 and Fig 1.

Table 3: Descriptive statistics comparing IL6 level between subjects

Patients' sex	DM+RA/RA	Mean
Male	DM+RA	116.15 ± 22.65
	RA	65.13 ± 16.86
	Total	97.51 ±32.22
Female	DM+RA	124.84 ± 24.03
	RA	65.97 ± 21.07
	Total	103.99 ± 36.46
Total	DM+RA	120.36 ± 23.55
	RA	65.53 ± 18.69
	Total	100.62 ± 34.30

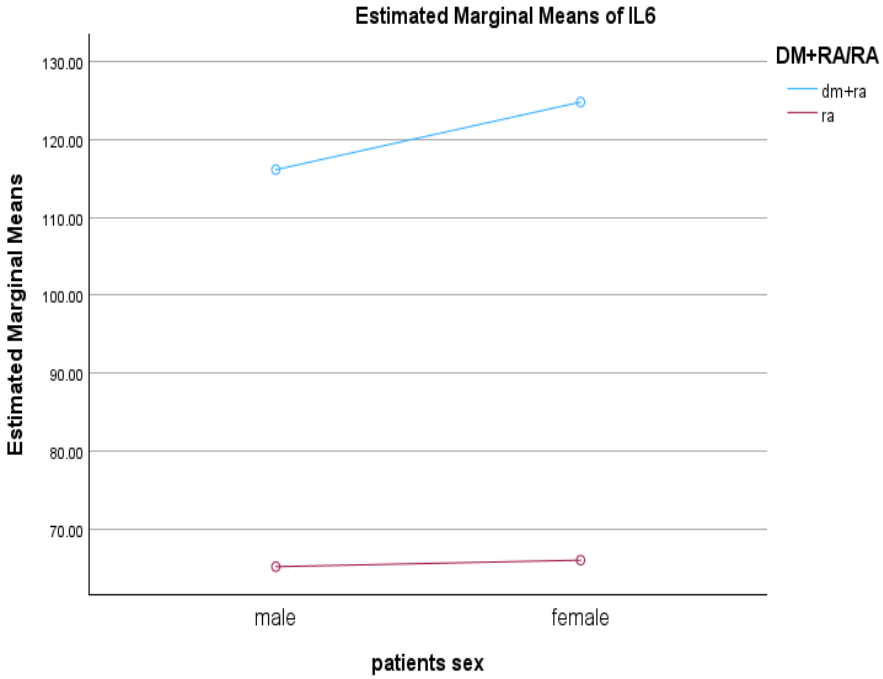

Figure 1: Means of IL-6 level for female in RA+DM comparing to RA group

Moreover, in the RA+DM group, HbA1c levels showed a strong positive correlation with IL-6 (r=0.73, p< 0.001), while there is no correlation between Il-6 and the other inflammatory markers.

Disease duration exhibited positive correlation with IL-6 level in RA group (r=0.54, p< 0.01) as shown in table 4.

Table 4: Pearson correlation of all studied parameters

Correlations										
		IL6	CRP	ESR	HbA1c	FBS	age (years)	Rheumatoid Factor	Period of RA in years	Period of DM in years
IL6	Pearson Correlation	1	.00	.12	.73**	.62**	.36**	-.12	.54**	.10*
	Sig. (2-tailed)		1	.23	<.001	<.001	<.001	.25	.00	.05
CRP	Pearson Correlation	.00	1	.74**	.07	.10	-.11	-.13	-.12	-.02
	Sig. (2-tailed)	1		<.001	.51	.30	.29	.22	.26	.82
ESR	Pearson Correlation	.12	.74**	1	.14	.20*	.07	-.23*	-.07	-.01
	Sig. (2-tailed)	.231	<.001		.160	.04	.49	.02	.52	.91
HbA1c	Pearson Correlation	.73**	.07	.14	1	.72**	.36**	-.08	.54	.35**
	Sig. (2-tailed)	<.001	.51	.16		<.001	<.001	.45	.00	.00
FBS	Pearson Correlation	.62**	.10	.20*	.716**	1	.44**	-.07	.63**	.31
	Sig. (2-tailed)	<.001	.30	.04	<.001		<.001	.51	.00	.002
age (years)	Pearson Correlation	.36**	-.11	.07	.358**	.44**	1	.06	.713**	.56**
	Sig. (2-tailed)	<.001	.29	.49	<.001	<.001		.56	.00	.00
Rheumatoid Factor	Pearson Correlation	-.12	-.13	-.23*	-.077	-.07	.06	1	.04	-.11
	Sig. (2-tailed)	.25	.22	.02	.445	.51	.56		.07	.30
Period of RA in years	Pearson Correlation	.54	-.12	-.07	.54	.63	.713**	.04	1	.37**
	Sig. (2-tailed)	.00	.26	.52	.00	.00	.00	.07		.00
Period of DM in years	Pearson Correlation	.10	-.02	-.01	.35	.31	.56	-.11	.37	1
	Sig. (2-tailed)	.05	.82	.91	.00	.002	.00	.30	.00	
**. Correlation is significant at the 0.01 level (2-tailed).										
*. Correlation is significant at the 0.05 level (2-tailed).										

ROC Curve Analysis

ROC curve analysis for IL-6 as a predictor of RA+DM comorbidity yielded an area under the curve (AUC) of 0.946 (95% CI (0.895-0.997), p<0.001) as presented in Table 5.

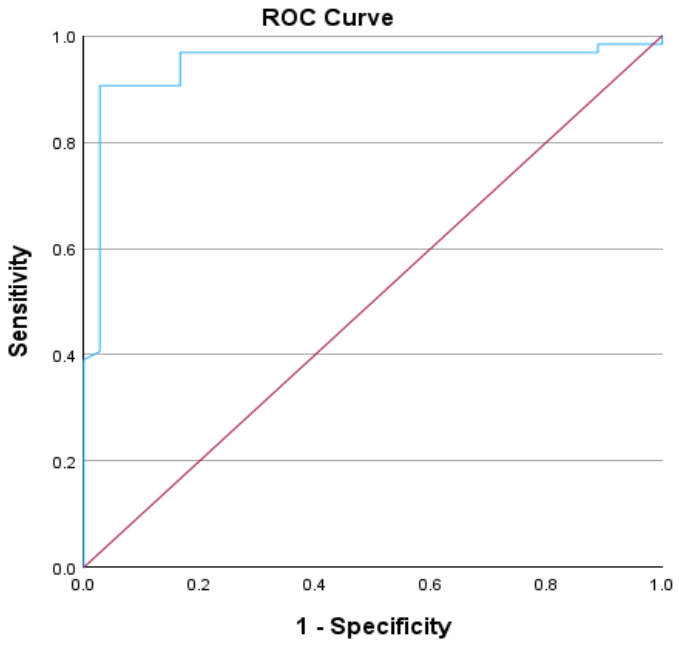

Figure 2: Roc analysis to test IL-6 ability to differentiate between RA and RA+DM patients

Table 5: Validity of the IL-6 as diagnostic marker

AUC	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.946	92%	83%	0.895	0.997
The test result variable(s): IL6 has at least one tie between the positive actual state group and the negative actual state group.				

A regression model was constructed to predict IL-6 levels, with the HbA1c as shown in Fig 3. The model explained 58% of the variance in IL-6 levels ($R^2 = 0.0015$, $p<0.001$).

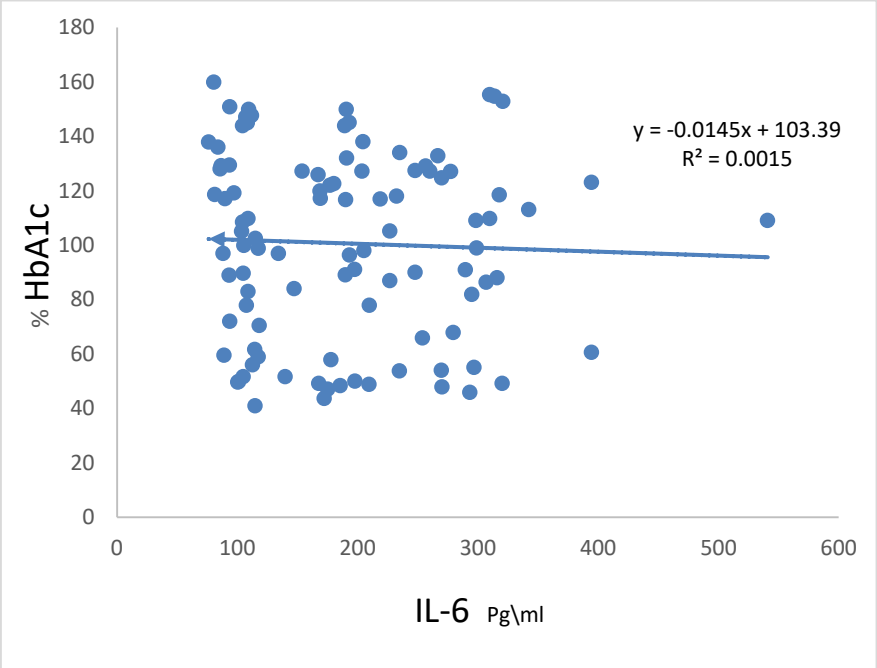

Figure 3: A regression model

Discussion:

The findings of this study indicate that individuals with both RA and DM have substantially IL-6 in comparison to those who have only rheumatoid arthritis ($p<0.001$). Such results are in agreement with previous investigations that suggest a synergistic effect between these two diseases on the enhancement of systemic inflammation (22). The presence of IL-6 in patients exhibiting both: rheumatoid arthritis and diabetes mellitus could be clarified by the simultaneous inflammatory activities. This conclusion raises the possibility that these diseases and via shared mechanisms might mutually reinforce their inflammatory processes (23).

Recent meta-analysis revealed that patients suffering from RA are at 1.5 times greater risk of developing T2D than those without this condition (24). This high risk suggests a critical interaction between autoimmune and metabolic diseases that warranting further investigation to create preventive strategies for affected individuals.

A compelling association between certain pathogenic mediators implicated in RA and the emergence of T2DM has been established in another research (25). This relationship points to a potential mechanism through that chronic inflammation may influence metabolic disease risk among those suffering from RA.

This study, also reviled a significant positive correlation between (HbA1c) levels and inflammatory markers especially IL-6 with correlation coefficient of $r=0.73$ and p-value < 0.001. This relationship could explain the complex relationship between glycaemic management and systemic inflammation in patients with coexisting RA and DM. This finding suggests that glycaemic miscontrol as per elevated HbA1c values is linked with an increased inflammatory state which could hypothetically exacerbate the both RA and DM (19). This correlation, also, suggests that IL-6 may serve as a predictive marker for the development of DM as a comorbidity during the management of patients with RA (25). Furthermore, the results indicate that there may be a related role of inflammatory mediators in the appearance of metabolic diseases like DM (5).

β-cells may exhibit an increased susceptibility to the harmful effects of these cytokines based on observations of interleukin overexpression in RA. This phenomenon is not specific to IL-1β but, also, includes other inflammatory mediators like IL-6 and tumour necrosis factor (TNF) (2, 26). Furthermore, the presence of TNF with IL-6 could negatively trigger insulin signalling pathways through promoting the development of insulin resistance. IL-6 is secreted by adipocytes and macrophages exist in in adipose tissue, skeletal muscle, and liver tissues; and its activity is notably increased in patients with RA (27). Moreover, hyperinsulinemia cause high concentrations of IL-6 in the blood. Subsequently, initiate a further vicious cycle that involves a pro-inflammatory cytokine and glucose metabolism instabilities (28, 29). Over the past years, substantial evidence have demonstrated the effectiveness of IL-6 inhibition in patients diagnosed with RA. This therapeutic approach is primarily facilitated through the use of tocilizumab and sarilumab, both of which function as antagonists of the IL-6 receptor. Several studies have explored the impact of IL-6 inhibition on insulin resistance and type 2 diabetes in patients with RA (30, 31)

This study has acknowledged a significant positive correlation between disease duration and IL-6 level ($r=0.54$, $p<0.01$). This finding suggests that chronic inflammation may have cumulative effects as the disease persists, likely contributing to ongoing joint damage as well as systemic manifestations related to RA (32, 33). The significance of this finding is profound for clinical practice, as it suggests that patients experiencing longer durations of illness particularly those with associated DM may benefit aggressive anti-inflammatory strategies. This also reinforces the importance of initiating treatment early and maintaining strict control to prevent chronic inflammatory problems.

The current study explored differences in IL-6 levels between different sexes within the RA and DM cohort. The findings revealed that IL-6 concentrations were significantly higher in females compared to males. This phenomenon can be elucidated by existing literatures, which have consistently shown that healthy subjects display distinct sex differences in their IL-6 responses

when subjected to acute stressors, whether psychological or physiological in nature (34-36). Research indicates that IL-6 reactivity is markedly elevated in postmenopausal women when subjected to a mental stressor, particularly in comparison to their male counterparts (35). The prevailing body of literature suggests that, relative to men, women exhibit heightened IL-6 reactivity not only in response to acute mental stressors (34, 35) but also in reaction to physical stressors (37) and pharmacological inflammatory stimuli (38, 39). It is essential to approach with caution when considering the various mechanisms that may elucidate the observed differences in IL-6 reactivity between sexes. One primary factor involves the influence of sex chromosomes and gonadal hormones on cytokine-producing cell activity and immune system regulation. Research has shown that even during periods with relatively low oestrogen levels—such as childhood or post-menopause—differences in sex chromosomes can significantly affect immune responses among males and females (40, 41). Additionally, testosterone has been identified as having anti-inflammatory properties by reducing IL-6 levels (42). This suggests that gonadal hormones might further enhance these disparities in immune response (43).

Conclusion: This research highlights a complex interplay between RA, DM, and systemic inflammation. The incidence of DM among RA patients is associated with elevated inflammatory responses, while poor glycaemic control appears to worsen inflammation levels. Such findings underline the importance of managing both diseases simultaneously and indicate that inflammatory markers, notably IL-6, might be effective tools for evaluating disease severity and the potential risk of comorbidities in those affected by RA.

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