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Assessment of Relationship between IL-6 Serum Level with Increased Risk for Depression and Anxiety in Patients with Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease (AID), affecting about 1.2% of the adults all over the world. It has been demonstrated that 17% of RA cases showed signs of depression, and inflammation has an essential role in the pathophysiology of depression, including IL-6.

Aim of Study: To assess the relationship between IL-6 serum level with increased risk for depression and anxiety in cases with RA.

Patients and Methods: Forty-three consecutive RA cases and 43 age and sex matched group were invited to participate in the study. All participants were subjected to history taking and general examination. Clinical related RA features and DAS28 were assessed in the RA group. Anxiety and depression in RA group was assessed using HAM-A, HAM-D questionnaires. In addition, the RA patients completed HAQ-DI questionnaire to assess the functional status. The serum level of IL-6 was measured in both groups.

Results: Depression and anxiety were prevalent in RA cases. RA cases were associated with a significant increase in IL-6 compared to the controls. Patient factors accompanied by higher anxiety and depression scores include younger age and female gender. Depression and anxiety scores were significantly correlated with the HAQ-DI score. In terms of RA, a significant correlation was recorded between depression score and anxiety score. Both depression and anxiety scores had a positive correlation with serum IL-6 level in RA patients (p<0.05).

Conclusion: Depression and anxiety are common in RA patients, particularly in younger and female patients. These psychological conditions are significantly correlated with IL-6 serum levels, suggesting that inflammation plays a role in their pathogenesis.

Key Words: *IL-6 Serum – Depression – Anxiety – Rheumatoid Arthritis.*

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Introduction

RHEUMATOID arthritis (RA) is a chronic inflammatory AID, affecting about 1.2% of the adults all over the world **[1]**. The hall mark feature of RA is persistent symmetric polyarthritis (synovitis) that predominantly affects the hands and feet. However, RA demonstrates a significant correlation with several systemic extra-articular manifestations (EAMs) and may predispose to several co-morbidities which include cardiovascular, kidney, and gut diseases, infections, malignant tumours and osteoporosis **[2]**. In addition, psychological disturbances, such as depression and anxiety frequently recorded among caseswith RA **[3]** and may contribute to worsening of RA symptoms and associated with low self-esteem, greater levels of mortality and suicidal tendency **[4]**.

Depression had been detected in 17% **[5]** to 42% **[6]** of RA patients. In addition, cases with RA are at higher possibility for anxiety, with a prevalence rate around 38.5% **[7]**. RA patients with anxiety and depression incline to reveal bad health outcomes, poor medication adherence, mild response to therapy, high economic burden, and decreased life quality **[3]**. Accordingly, the EULAR recommended screening for depression and anxiety in cases suffering from chronic inflammatory rheumatic disorders such as RA **[8]**.

Many factors could participate in depression and anxiety development among RA cases, such as higher disease activity, pain, and easy fatigability; loss of employment owing to disease and disabili-

ties; as well as adverse events related to medications [9]. On the other hand, new advancements in molecular biology have greatly expanded our understanding of the pathophysiology of RA and reinforced the development of an inflammatory theory to clarify the correlation between the systemic inflammatory process of RA and consequent adverse cerebral effects [10].

It has been demonstrated that inflammation has a primary function in terms of the pathogenesis of depression [11] and anxiety [12]. Patients with depression and anxiety tend to have greater levels of proinflammatory cytokines, which comprise IL-1β, IL-6, and TNF-alpha [13]. All these proinflammatory cytokines are comprised in RA pathogenesis. Supporting to the previous data, it has been demonstrated that the use of particular antidepressant agents seems to decrease peripheral values of proinflammatory cytokines [14].

Despite the high risk of development of mood disorders among RA cases, a few published studies assessed the correlation between serum IL-6 level and the greater risk of depressive and anxiety manifestations in RA cases. Understanding the shared inflammatory pathways that may mediate the relationship of depression and anxiety with RA could be accompanied by a detailed model for targeting intervention to prevent depression and anxiety in RA.

Aim of work:

To assess the relationship between IL-6 serum level with increased risk for depression and anxiety in RA cases.

Patients and Methods

This was a cross-sectional study conducted on a total of 43 consecutive RA cases, diagnosed based on the 2010 ACR/EULAR criteria [15], were invited to participate in the study. Patients were recruited from attendants to Rheumatology Outpatient Clinic, Mansoura University Hospitals in the period from March 2023 to January 2024. The study also invited 43 age and sex matched healthy volunteers to participate in the study as a control group.

All participants received comprehensive information about the study's purpose and methods prior to their involvement. The Mansoura University Faculty of Medicine's Institutional Research Board (IRB) gave its approval to the study's design and methods (MS. 21.09.1687). Every participant signed written, informed consent.

Sample size calculation:

Based on Li et al. [16] study (significance level of 5%, and power of study of 80%), the sample size could be calculated depending on the next formula:$n = [(Z_{\alpha/2}+Z_{\beta})^2 \times 2(SD)^2] / (\text{mean difference between the two groups})^2$, in which SD = SD; $Z_{\alpha/2}$:. Accordingly, $n = [(1.96+0.84)^2 \times 2(0.29)^2] / (0.175)^2 = 43$. The measured sample size is 43 in each group.

All cases who met the 2010 ACR/EULAR classification criteria and whose ages were between 18 and 85 years and who were willing to contribute and provided informed written consent were included. Exclusion criteria include other inflammatory or autoimmune diseases, impaired cognition, or neurologicdiseases that couldaffect preciserecording of depression and anxiety manifestations. History of psychiatric disorders prior to developing RA, Medication that may induce or worsen depression or anxiety symptoms, such as high doses of corticosteroids, malignant diseases, pregnant or lactating females (secondary to hormonal affection), and coexisting chronic conditions.

Methods:

All participants were subjected to full history taking which include personal history, complaint: taken in patient's own words and history of present Illness (Duration of RA, Onset and course of disease, Joint involvement: joint pain distribution, releasing and precipitating factors and existence of joint redness, warmth or deformities, Presence of morning stiffness and its duration, Current RA medications, Non-specific manifestations: Fever, easy fatigability, weight loss and muscle pain, History of involvement of other systems and Functional disability.

In addition, a complete history of present or past use of medications was conducted including dose, duration of use, and adverse events were obtained from all cases. In addition, medications for any other diseases were recorded. Family history of similar condition was also asked. General examination was conducted which included Complexion, Measurement of vital signs, Measurement of anthropometric measures with calculation of BMI and oedema of lower limbs. Systemic Examination was conducted and included Skin, Ocular, Oral, Neurological, Cardiac, Abdominal and Chest examination.

Every case was subjected also to complete musculoskeletal evaluation by assessing the existence of swelling, redness, and deformities, palpation for warmth, tenderness and range of motion (ROM) (goniometer).

Evaluation of RA:

1- *Visual Analog Scale (VAS):*

This scale is used to assess the degree of pain, in which zero indicates no pain, while 10 is the worst pain. A mark representing the RA patient's perceived level of pain severity was placed on the horizontal line. It was determined that the distance between the patient's mark and the left end represented the degree of pain [17].

2- Tender and swollen joint counts:

Twenty eight joints involving bilateral gleno-humeral, elbow, wrist, MCP joints, PIP joints, knee and ankle joints were evaluated for all patients to detect TJC and SJC.

3- Assessment of disease activity:

We used the DAS28 **[18]**, which is a combined score that depends on the next 4 items: Detecting SJC, detecting TJC, measuring the ESR or CRP levels, and detecting the patient global assessment. The records of the four parameters are after that fed into the formula of DAS28 score [Appendix 4]. The cut-off points of DAS28 are also shown in Appendix 4.

Assessment of physical function:

The physical function of the RA patients was evaluated using the HAQ-DI [Appendix 5]. The score of HAQ-DI is based on self-report questionnaires that are conducted for classifying and grading functional capacity according to the ability of the patient to practice activities every day. There are 8 domains: Dressing, arising, eating, walking, hygiene, reach, grip, and activities. The patient was asked two or three questions in each section to get a score ranging from zero (no difficulty) to three (cannot do it). The sum of the eight section scores is divided by eight to get the net result **[19]**.

Assessment of depression and anxiety:

We used HAM-D which is a 17-item tool that measures the severity of depression pertaining to manifestations of depression acquired over the last-seven days **[20]**. The response for each symptom was represented in a 4-point scale for items 1 to 8 and represented in a 3-point scale for items 9 to 17. The severity of the depression increases with the total score. Depression level on the HAM-D scale: mild (ten–thirteen); moderate (fourteen–seventeen); and severe (more than seventeen) **[20].**

High validity was shown by the HAM-D with a diagnosis of depression. It has been translated into Arabic **[21].** The Arabic HAM-D was validated, and the psychometric items of the Arabic HAM-D scale were sufficient, warranting its use clinically and in research [Appendix 6] **[22].**

We also use HAM-A, which consists of 14 parameters; each parameter was scored according to a five-point Likert scale ranging from absent (zero) to very severe (4) **[23]**. The total score I ranging from zero to fifty six and was divided into four levels: No anxiety (zero – seven), mild anxiety (eight – seventeen), moderate anxiety (eighteen – twenty four) and severe anxiety (twenty five – fifty six) **[24].** HAM-A was translated into Arabic **[25]** [Appendix 7]. The Arabic version of this scale also revealed-good validity **[26].**

Laboratory investigation:

A morning venous sample was withdrawn from each participant after overnight fastingon the same day of assessment. Laboratory investigations included measurement of ESR, CRP, RF level, Anti-CCP antibodies. In addition assessment of serum level of IL-6 was conducted using Enzyme linked immunoassay (ELISA) (Gen-Probe, Diaclone France) as per the user manufacturer.

Statistical analysis:

We used SPSS, version 20.0 to analyse the current data. Continuous data were normally distributed and were expressed in Mean ± SD. The anti-CCP titer displayed abnormality in distribution and was expressed as median and IQR. Numbers and percentages were used to represent categorical data. Concerning two variables with continuous data, the independent sample Student's *t*-test was used to determine the comparisons. Variables with categorical data were compared using the Chi-square test. Using continuous data, the correlation between 2 variables was investigated using the Pearson correlation coefficient (PCC). Statistical significance was set at $p<0.05$.

Results

Forty-three RA cases (33 females and 10 males) were enrolled in our study. In addition, 43 healthy volunteer subjects (32 females and 11 males) contributed to the study as healthy controls. The mean age of the RA group was 57.7±9.3 years and the mean age in the control group was 58.4±9.8 years. Both groups demonstrated insignificant difference regarding both age and sex (Table 1).

The clinical data in the RA patients were demonstrated in Table (2). The mean disease duration was 16.5±7.8 years (ranged between 3 and 30 years). The morning stiffness duration ranged from 30 and 120min with a mean of 73.3±32.3min. The mean TJC was 12.2±5.1 joints with a range between 5 and 22 joints. The SJC ranged between 4 and 24 joints with a mean of 14.9±6.4 joints. The mean VAS-pain score ranged from 15 and 78mm with a mean of 48.5±18.6mm.

The mean DAS28-ESR in the RA group was 4.6±1.2 (range, 2 to 5.9). The mean DAS28-CRP in the RA group was 4.1±1.4 (range, 1.21 to 5.35). The mean HAQ-DI in the RA group was 1.3±0.6 (range 0 to 2.63) (Table 3).

Table (4) compares the ESR ^{1st} hour, CRP and IL-6 serum levels between the RA patients and the controls. The mean ESR ^{1st} hour was significantly elevated the RA group (62.3±26.2mm) compared to the controls (28.1±8.3mm) ($p<0.001$). Likewise, the mean CRP level was significantly elevated the RA group (43.7±19.6mg/dl) compared to the controls (17.5±8.5mg/dl) ($p<0.001$).

Moreover, the mean serum level of IL-6 of the RA cases was 31.6±14.9ng/L while in the control group IL-6 serum level was 8.4±1.8ng/L. This difference regarding the IL-6 between both group was significant (95% confidence interval of this difference: From 18.6 to 27.8, $p<0.001$).

The median [IQR] of RF titer in RA patients was 32.0 [53.0] and the median [IQR] of anti-CCP titer was 99.8 [156.0]. Of the RA patients, 83.7% and 60.5% were positive for RF and Anti-CCP antibodies respectively (Table 5).

The HAM-A score of the RA patients ranged from 3 to 33 with a mean of 18.1±8.2. According to our findings, only 16.3% of RA patients reported having no anxiety, where as 83.7% reported having it, with 18.6% reporting mild anxiety, 44.2% reporting moderate anxiety, and 20.9% reporting severe anxiety (Table 6).

On the other hand, the Hamilton depression score of the RA patients ranged from 8 to 38 with a mean of 17.1±6.3). HAM-D score revealed that only 10 (23.3%) of the RA patients had no depression while 76.7% of the patients had depression with the proportion of patients with mild, moderate and severe depression were 32.6%, 18.6% and 25.6% respectively (Table 6).

HAM-A and HAM-D scores have anegative correlation with the age of the patients ($p=0.025$ and $p=0.011$ respectively) (Table 7).

Female patient with RA showed significantly higher HAM-A score than male RA patients (19.6±6.9 and 13.0±8.7 respectively, $p=0.016$). Similarly, female patient with RA had significantly higher HAM-D score than male RA patients (18.4±6.6 and 13.2±4.8 respectively, $p=0.025$) (Table 8).

HAM-A score was significantly accompanied bydisease duration ($p=0.011$), morning stiffness duration ($p=0.004$). TJC (p=0.039), SJC ($p=0.024$) and VAS score (0.043) (Table 9).

HAM-D score was significantly accompanied by disease duration ($p=0.040$), morning stiffness duration ($p=0.029$). TJC ($p=0.010$), SJC ($p=0.015$) and VAS score (0.008) (Table 9).

HAM-A score and HAM-D score didn'tvary significantly between RA patients taking and patients not taking MTX, HCQ, Leflunomide, glucocorticoids or biologicals (Table 10).

HAM-A score was significantly associated with ESR ^{1st} hour ($p=0.046$) and CRP serum level ($p<0.001$) in RA cases (Table 13). Similarly, HAM-D score was significantly associated with ESR ^{1st} hour ($p=0.025$) and CRP serum level ($p=0.017$) in RA cases (Table 11).

In contrast, no significant relationship was detected between the HAM-A score or HAM-D score and RF or anti-CCP titer in RA cases (Table 11).

There was insignificant difference in the HAM-A score and the HAM-D score between RF-ve and RF+ve RA patients. In the same line, there was in significant difference in the HAM-A score and the HAM-D score between Anti-CCP-ve and Anti-CCP+ve RA cases (Table 12).

Serum IL-6 level was significantly correlated with HAM-A score ($p=0.030$) and HAM-D score ($p=0.013$) (Table 13).

HAM-A score showed significant correlation with DAS28-ESR ($p=0.033$), DAS28-CRP ($p<0.001$) and HAQ-DI score ($p=0.016$) (Table 14). Similarly, HAM-D score was significantly correlated with DAS28-ESR ($p=0.027$), DAS28-CRP ($p=0.013$) and HAQ-DI score ($p=0.037$) (Table 14). HAM-A score was significantly correlated with HAM-D score in RA patients (Table 15).

Table (1): Comparison of the demographic data between the RA group and control group.

	RA Group	Control Group	Significance	
Age (years) (mean ± SD)	57.7±9.3	58.4±9.8	$t=0.384$	$p=0.702$
Sex (n, %):				
Females	33, 76.7%	32, 74.4%	$X^2=0.063$	$p=0.802$
Males	10, 23.3%	11, 25.6%		

Table (2): Descriptive analysis of the clinical data of the RA patients.

	Range	Mean ± SD
Disease duration (years)	3 – 30	16.5±7.8
Morning stiffness duration (minutes (min)	30 – 120	73.3±32.3
TJC	5 – 22	12.2±5.1
SJC	4 – 24	14.9±6.4
VAS-pain score (mm)	15 – 78	48.5±18.6

Table (3): Descriptive analysis of the DAS28, HAQ-DI score of the RA patients.

	Range	Mean ± SD
DAS28-ESR	2.00 – 5.90	4.6±1.2
DAS28-CRP	1.21 – 5.35	4.1±1.4
HAQ-DI	0.00 – 2.63	1.3±0.6

Table (4): Laboratory findings of the studied groups.

	RA	Control	Student's *t*-test	
	Mean ± SD	Mean ± SD	*t*	*p*
Acute Phase Reactants:				
ESR (mm 1st hour)	62.3±26.2	28.1±8.3	8.174	<0.001
CRP (mg/ml)	43.7±19.6	17.5±8.5	5.569	<0.001
Marker of inflammation:				
IL-6 (ng/L)	31.6±14.9	8.4±1.8	*t*=10.162	*p*<0.001

Table (5) Descriptive analysis of the autoantibodies of the RA patients.

	Range	Median [IQR]	+ve cases (n, %)	
			n	%
RF Titer (IU/ml)	10.0 – 256.0	32.0 [53.0]	36	83.7
Anti-CCP Titer (U/ml)	3.4 – 830.0	99.8 [156.0]	26	60.5

Table (6): Descriptive analysis of the Hamilton depression and anxiety scores of the RA patients.

	Range	Mean ± SD
HAM-A score	3 – 33	18.1±8.2
HAM-D score	8 – 38	17.1±6.3

Table (7): Correlation of the HAM-A and HAM-D with the age of the RA patients.

	Correlation of the HAM-A		Correlation of the HAM-D	
	r	*p*	*r*	*p*
Age	–0.341	0.025	–0.382	0.011

Table (8): Comparison of the HAM-A score and HAM-D score between female and male RA patients.

	Female RA patients	Male RA patients	*t*	*p*
HAM-A score (mean ± SD)	19.6±6.9	13.0±8.7	2.510	0.016
HAM-D score (mean ± SD)	18.4±6.6	13.2±4.8	2.320	0.025

Table (9): Correlation of the HAM-A and HAM-D with the age and clinical findings of RA patients.

	Correlation of the HAM-A		Correlation of the HAM-D	
	r	*p*	*r*	*p*
Disease duration	0.385	0.011	0.314	0.040
Morning stiffness duration	0.430	0.004	0.333	0.029
TJC	0.315	0.039	0.390	0.010
SJC	0.344	0.024	0.368	0.015
VAS-pain score	0.310	0.043	0.399	0.008

Table (10): Comparison of the HAM-A and HAM-D between RA patients taking and not taking medications.

	HAM-A score Mean ± SD	HAM-D score Mean ± SD
MTX:		
No	19.6±6.9	17.6±6.2
Yes	15.3±8.5	16.1±6.6
Student's *t*-test	*t*=1.783, *p*=0.182	*t*=0.757, *p*=0.454
HCQ:		
No	20.7±6.8	16.7±5.1
Yes	16.3±7.9	17.3±7.1
Student's *t*-test	*t*=1.858, *p*=0.170	*t*=0.302, *p*=0.765
Leflunomide:		
No	19.4±9.5	15.6±6.4
Yes	17.4±6.8	17.8±6.3
Student's *t*-test	*t*=0.754, *p*=0.455	*t*=1.081, *p*=0.286
Biologics:		
No	17.9±7.8	17.2±6.4
Yes	21.2±3.9	13.9±3.1
Student's *t*-test	*t*=1.390, *p*=0.172	*t*=1.801, *p*=0.079
Glucocorticoids:		
No	17.6±8.7	17.1±6.0
Yes	20.3±4.5	17.8±8.9
Student's *t*-test	*t*=0.829, *p*=0.412	*t*=0.256, *p*=0.799

Table (11): Correlation of the HAM-A and HAM-D with the laboratory findings of RA patients.

	Correlation of the HAM-A		Correlation of the HAM-D	
	r	*p*	*r*	*p*
Acute phase reactants:				
ESR	0.306	0.046	0.341	0.025
CRP	0.486	<0.001	0.362	0.017
Autoantibodies:				
RF Titer	0.126	0.420	0.201	0.195
Anti-CCP Titer	0.054	0.732	0.105	0.501

Table (12): Comparison of the HAM-A and HAM-D between RA patients with +ve and -ve RF and anti-CCP RA cases.

	RF -ve RA patients	RF +ve RA patients	*t*	*p*
HAM-A score	19.1±7.8	17.9±7.8	0.397	0.693
HAM-D score	20.1±4.6	16.5±6.5	1.421	0.163
	Anti-CCP -ve RA patients	Anti-CCP +ve RA patients	*t*	*p*
HAM-A score	16.8±9.3	18.9±7.3	0.864	0.393
HAM-D score	18.5±8.0	16.1±4.9	1.230	0.226

Table (13): Correlation of the HAM-A and HAM-D with the IL-6 level of RA patients.

	Correlation of the HAM-A		Correlation of the HAM-D	
	r	*p*	*r*	*p*
IL-6	0.331	0.030	0.375	0.013

Table (14): Correlation of the HAM-A with HAQ-DI &DAS28 score of RA patients.

	Correlation of the HAM-A		Correlation of the HAM-D	
	r	*p*	*r*	*p*
DAS28-ESR	0.325	0.033	0.338	0.027
DAS28-CRP	0.428	<0.001	0.376	0.013
HAQ-DI	0.364	0.016	0.319	0.037

Table (15): Correlation of the Hamilton depression and anxiety scores of the RA patients.

	r	*p*
HAM-D/HAM-A	0.337	0.027

Discussion

We demonstrated that anxiety and depression were predominant in RA patients with 83.7% and 76.7% of the patients had anxiety and depression respectively. Our results showed that among the RA patients, 18.6% had mild anxiety, 44.2% had moderate anxiety while 20.9% had severe anxiety. Additionally, we displayed that the ratio of patients with mild, moderate and severe depression were 32.6%, 18.6% and 25.6% respectively. These findings indicated that RA affects patients both physically and psychologically.

A previous meta-analysis study recorded that depression frequently co-occurs with RA, in the range of 13% to 20% *[27]*. Another study found that 34.9% of people had any depressive disorder, while 22.9% of people had any anxiety disorder *[28]*. A meta-analysis study of 7 studies, included 1078 cases with RA revealed that depression has been revealed to affect 9.5 to 41.5% of RA cases *[29]*. In addition, Kekow et al., conducted their study the 389 RA patients and displayed that 158 (40.6%) suffered from depression symptoms *[30]*. Moreover, Covic et al., conducted their study on 169 RA patients and reported that 13.5% had anxiety alone, 6.4% had depression alone, and 21.8% had combined disorders *[31]*. Matcham et al., *[5]* demonstrated in their systematic review (72 studies including 13,189 RA cases) that the prevalence of depression was 38.8% among RA patients *[30]*.

In addition, many studies were performed to estimate prevalence of depression and anxiety among the RA patients in Egypt. A recent study estimated the prevalence of anxiety and depression in 100 Egyptian RA patients and found that all patients had anxiety with most of the patients had mild anxiety (83%) and moderate to severe anxiety was reported in 17% of the patients. The same study found that while 65% of the patients had no depression, 22% had mild depression, 11% had moderate depression and 2% had severe depression *[32]*. Another study in Egypt, that estimated depression in hospitalized RA patients found that 15% of the patients had no depression while 32%, 48.5% and 4.5% of the patients had mild, moderate and severe depression respectively *[33]*. The wide range of prevalence of depression and anxiety among the studies may have occurred because of the various ways in which the depressive and anxiety manifestations were assessed and evaluated *[34]*. However, gathering these findings together indicate that RA could have a unfavorable effect on mood and mental well being as patients are worried about their condition, prognosis and disability that may occur later and warrant considering the management of these mood disorders along with the management of RA.

We compared the serum levels of IL-6 between the RA patients and controls and demonstrated that the mean serum IL-6 level was significantly increased in RA cases than controls, confirming that IL-6 is crucial in terms of RA pathogenesis.

Likewise, Helal et al., *[35]* revealed in their study that the levels of serum IL-6 in the RA cases were significantly elevated in RA patients in comparison to the controls. In addition, Wei et al., conducted a meta-analysis that included 14 studies in which 890 cases with RA were compared with 441 normal subjects (acting as controls). They illustrated that there was a significant elevation in the level of serum IL-6 among RA cases compared to the controls; as a result, they concluded that it shares in RA pathogenesis *[36]*.

It is of great significance to identify patient predisposing factors related to anxiety and depression. Our study illustrated that female gender and younger age were correlated with higher HAM-A and HAM-D scores.Such outcomes were in the same line with findings of previous studies *[37,38]*. Fragoulis et al., examined the risk factors accompanied by depression and anxiety in 848 patients with early RA and found that depression and anxiety scores at baseline were accompanied by younger age and female sex; however, depression scores at six months and one year were accompanied by male sex *[37]*. On the other hand, in the study of Rabei and El Sonbaty, there is no significant correlation between sex and depression, yet the *p*-value approached but did not exceed the threshold of significance (p=0.084). Females are generally more prone to developing anxiety and depression, nearly by 2-fold *[39]*. This gender gap could be clarified by biological factors (e.g., hormonal changes) and personal life circumstances, experiences, and culture (e.g., females are overwhelmed with household work and have more responsibilities) *[40]*.

Several RA-related features were found to be significantly accompanied by depression and anxiety. Our study showed that depression and anxiety scores had a significant correlation with disease duration as well as clinic-laboratory parameters of RA activity, such as morning stiffness duration, TJC, SJC, VAS-pain score, ESR, and CRP serum level. In addition, depression and anxiety scores were significantly linkedto DAS28-ESR and DAS28-CRP. Our results also revealed that depression and anxiety scores had a significant correlation with HAQ-DI scores. The significant correlations of anxiety and depression and indices of RA activity and HAQ observed in our study are in agreement with the findings of Rabei and El Sonbaty *[39]*, who displayed a significant relationship between depression and duration of RA. Moreover, a disease duration of 10 years or more was significantly accompanied by a higher incidence of anxiety and depression development in RA cases *[41]*.

Also, in the same linetothe present study findings, Margaretten et al. *[6]* found that comorbid depression is significantly elevated in a lot of consequences among cases with RA, such as pain, inflammation severity, and disability. Kwiatkowska et al., *[42]* reported that DAS28, as well as the components of DAS28, were significantly correlated to depression in RA cases. Our outcomes were also in agreement with Sadawy Salim et al., who showed that HAQ-DI was significantly correlated with the anxiety and depression scores in Egyptian cases with RA *[32]*. On the contrary, few studies did not support the positive relationship between RA activity and depression. For example, Moudi et al., couldn't determinea correlation between anxiety and depressive manifestations and disease activities assessed by DAS 28-CRP. However, the same study reported that patient global assessment of disease activity, the DAS28 component, was potently accompanied by anxiety and depression *[43]*.

Evidence from studies recommends an essential inflammatory role in the pathogenesis of depression and anxiety *[6]*. In this context, Li et al., carried out a study aimed to recognize the effects of proinflammatory cytokines on the depression and anxiety among cases with RA. The study found that patients with elevated IL-6 or IL-17 had a greater possibility for depression and anxiety. Interestingly, that study found that there was no association between mood symptoms and cytokine levels in healthy controls *[16]*. The current results came also in accordance with Figueiredo-Braga et al., *[44]* who showed that serum IL-6 level was positively linked to anxiety and depressive symptoms.

However, opposite to our findings, the relationship between IL-6 and both depressive and anxiety manifestations was not supported by Parlindungan et al., IL-6 is a main cytokine in RA pathophysiology and is found to be involved in mood changes in RA, possibly via modulation of the HPA axis, which is the main neuroendocrine system that controls mood and *[45]*. Comorbid depression and anxiety in RA are in particular worrying as they often gounnoticed and/or unmanaged *[46]*. Along the lines of this, EULAR recently recommended screening for depression among cases with chronic inflammatory rheumatic diseases *[8]*.

Our results also showed that HAM-A score was significantly linked to HAM-D score in RA patients. In agreement with our finding, symptoms of anxiety were demonstrated to bevery common in RA cases with major depression compared tocases with RA (in general) or healthy controls *[47]*.Considering the relation between anxiety and depression in clinical and empirical research, this pattern of findings isn't surprising *[31]*. As with depression, anxiety manifestations also correlate with functional disability in cases with RA *[30]*.

The study's limitations comprise a small sample size, being a single-center study, and not examining other proinflammatory cytokines. It may be a combination of cytokines that may induce the development of mood disorders in RA patients. An area of future study is to explore whether administration of anti-IL-6 drugs may be an efficient therapy for depression and anxiety in RA patients, perhaps reducing the need for antidepressants. More studies with larger samples sizes and collecting patients from various localities are required to prove our results. A future study is recommended to explore whether administration of anti-IL-6 agents may be an efficient-therapy for depression and anxiety in RA patients, perhaps reducing the need for antidepressants.

Conclusion: Depression and anxiety are common in RA patients, particularly in younger and

female patients. These psychological conditions are significantly correlated with IL-6 serum levels, suggesting that inflammation plays a role in their pathogenesis.

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تقييم العلاقة بين مستوى انترلوكين ٦ فى المصل وزيادة خطر الاصابة بالإكتئاب والقلق فى مرضى إلتهاب الروماتويد المفصلى

نظرة عامة: يعد مرض إلتهاب المفاصل الروماتويدى من أمراض المناعة الذاتية المزمنة، ويصيب هذا المرض حوالى ١,٢٪ من الأشخاص البالغين في جميع أنحاء العالم. بينت الدراسات أن ١٧٪ من مرضى إلتهاب المفاصل الروماتويدى يعانون من الإكتئاب حيث أن الإلتهاب له دور أساسى فى الفيزيولوجيا المرضيه بما فى ذلك إنترلوكين ٦ .

الهدف من الدراسة: تقييم العلاقة بين مستوى إنترلوكين ٦ فى المصل وزيادة خطر الإصابة بالإكتئاب والقلق فى مرضى إلتهاب المفاصل الروماتويدى.

المواد والطرق: تم دعوة ٤٣ مريضا متتالياً من مرضى إلتهاب المفاصل الروماتويدي ، كما شملت أيضا ٤٣ من المتطوعين الأصحاء متطابقين فى العمر والجنس مع المرضى كمجموعة ضابطة للمرضى. تم جمع البيانات من جميع المشاركين عن طريق أخذ التاريخ المرضى الكامل والفحص العام، كما تم تقييم سمات مرض إلتهاب المفاصل الروماتويدى السريرية، كما تم قياس درجة نشاط مرض المجموعة المصابة بالمرض، بالإضافة إلى ذلك قام مرضى إلتهاب المفاصل الروماتويدى باستكمال إستبيان هاميلتون للقلق والإكتئاب وإستكمال التقييم الصحى لتقييم الحالة الوظيفية، وتم قياس مستوى إنترلوكين ٦ فى كلا المجموعتين.