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Potential Role of IL-6 in Inflammatory Arthritis: A Comparative Study

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ABSTRACT

Background: A pro-inflammatory cytokine called interleukin 6 (IL-6) is important for both autoimmune and chronic inflammation. **Objective:** This study aimed to evaluate the ability to use serum level of IL-6 in differentiating between inflammatory and non-inflammatory arthritis and to correlate its level with clinical manifestations, disease activity, laboratory parameters, radiological grading and disease severity.

Methods: This comparative cross-sectional study was carried out on 60 patients diagnosed as rheumatoid arthritis (RA) (Group I), osteoarthritis (Group II) and psoriatic arthritis (PsA) (Group III) together with 20 apparently healthy volunteers selected as control (Group IV), all were age- and sex-matched. The disease activity score 28 (DAS-28) and disease activity index in PsA were developed to quantify disease activity among RA and PsA patients, respectively. Radiographic changes were evaluated by Larsen score among RA patients and by modified Steinbrocker score among PsA patients. Routine lab work was done and serum IL-6 was measured by ELIZA.

Results: Highly statistically significant differences were reported between the studied groups regarding serum IL-6 level ($P < 0.05$) being higher among patients with inflammatory arthritis than others. Significant positive correlations were found between IL-6 with disease activity and severity parameters among RA and PsA patients. Regarding univariate analysis, among RA patients, it was found that DAS-28 score, disease severity, morning stiffness, number of tender and swollen joints, ESR and radiographic changes (Larsen score) were significantly associated with IL-6.

Conclusions: IL-6 is a strong predictor of disease activity and severity in RA and PsA patients but not in OA patients because it plays an important role in mediating inflammation and joint degradation, therefore monitoring the blood level of this cytokine may be beneficial in determining clinical status.

Keywords: IL-6, Inflammatory arthritis, RA, PsA.

INTRODUCTION

RA is a long-term inflammatory condition marked by systemic inflammation, loss of cartilage and bone, and synovial inflammation that causes swelling in the joints [1]. Although the precise cause of the disease is still unknown, genetics account for 50% of the risk. Because people with RA present with a wide range of symptoms and often delay seeking medical attention, it has been challenging to quantify the incidence of RA. But according to reports, the incidence of RA is just 1% worldwide, with lower prevalence in some nations [3]. Overall, it has been observed that the condition is more common in women and that its prevalence rises with age, with women over 65 having the greatest rates [2].

Individuals suffering from RA experience decreased quality of life, increased disability, and increased rates of death and morbidity [4]. The main signs of osteoarthritis (OA), a chronic condition, are stiffness in the joints and decreased joint function [5].

PsA is a musculoskeletal inflammatory condition linked to cutaneous psoriasis. Between 40 to 50 years old, it affects men and women about equally [6]. A wide range of organ systems are impacted, including the entheses, skin, nails, and axial and peripheral joints. PsA has been linked to comorbid conditions such cardiovascular disease, subclinical intestinal inflammation, uveitis, and osteoporosis [7].

Pro-inflammatory cytokines like IL-6 are important players in autoimmune and chronic inflammation. It is regarded as a multifunctional cytokine that controls immunological responses, acute phase reactions, hematopoiesis, and bone metabolism in a variety of target cells. It also possesses a broad spectrum of biological functions [8].

By inducing neutrophil migration, osteoclast maturation, and VEGF-stimulated pannus proliferation, IL-6 can worsen synovitis and joint degradation. Numerous other systemic signs of RA, such as the induction of the acute-phase response (including CRP), anaemia due to hecipidin synthesis, exhaustion through the HPA axis, and osteoporosis due to its influence on osteoclasts, may also be mediated by IL-6 [9]. Additionally, through TH-17 differentiation and B-cell maturation, IL-6 may aid in the initiation and maintenance of the autoimmune process [10]. This work's objective was to evaluate the ability to use serum level of IL-6 in differentiating between inflammatory and non-inflammatory arthritis and to correlate its level with clinical manifestations, disease activity, laboratory parameters, radiological grading and disease severity.

PATIENTS AND METHODS

This comparative cross-sectional study was carried out on 60 patients diagnosed as rheumatoid arthritis (RA diagnosed according to the ACR/EULAR 2010 criteria for the diagnosis of RA [11]) (Group I), osteoarthritis diagnosed according to the ACR [12] (Group II) and psoriatic arthritis (PsA diagnosed

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according to the CASPAR classification criteria for diagnosis of PsA [13]) (Group III) together with 20 apparently healthy volunteers selected as control (Group IV). All were age- and sex-matched. The study was conducted from August 2022 to July 2023.

Exclusion criteria: Patients aged <16 years old, patients with other autoimmune diseases, infection, fibromyalgia, cancer, diabetes mellitus, hypertension, CV, respiratory, gastrointestinal, renal, endocrine or neuropsychiatric disorders and infectious arthritis.

All patients had a history-taking, clinical examination, locomotor system evaluation, and assessment of disease activity and RA disease activity using the DAS28 score [14], laboratory investigations [CBC, ESR by the Westergren's method, CRP by quantitative nephelometry, liver function tests [SGPT, SGOT], kidney function tests [BUN and serum creatinine], rheumatoid factor (RF) by latex agglutination test, Anti-CCP by ELISA and IL-6 using a validated ELIZA according to manufacturer's instructions]. Also, radiological investigation.

RA patients were evaluated by DAS-28: A DAS-28 of more than 5.1 indicates high disease activity, a DAS-28 of more than 3.2 and less than or equal to 5.1 indicates moderate disease activity, a DAS-28 less or equal to 3.2 and greater than 2.6 indicates low disease activity and a DAS-28 of less than 2.6 indicates remission.

The RA Severity Scale (RASS) was used to evaluate the severity of the illness in RA patients [15]: Three visual analogue scales with 10 cm lines each to depict disease activity, functional impairment, and physical damage make up the RASS. The following were the scale's end points: 100 represented the worst RA disease activity (functional impairment or physical damage), 0 represented no disease activity (physical damage or functional impairment). The subscales were added together to create the RASS total, an indication of general health status.

The Western Ontario and McMaster Universities Arthritis Index was used to assess OA disease activity and severity: this measure evaluates joint pain, stiffness, and physical functionality [16].

PsA disease activity was assessed using the DAPSA score [17]: Disease Activity: 0-4 remission, 5-14 mild, 15-28 moderate, and >28 high disease activity.

Serum level of IL-6 was measured by ELISA: Human IL-6 was measured by Human IL-6 SunRedBio, Shanghai, China ELISA kit, Catalogue Number:201-12-0091. The detection limits ranged from 3-4000 pg/ml. The ELISA protocols were carried out in compliance with the manufacturers' guidelines. Immediately after, the optical density of every well was measured using a microplate reader that was calibrated to 450 nm. The Bio Rad ELISA data analysis programme transformed the obtained optical density values into pg/mL. Every experiment was carried out twice, and the data showed average values. The mean absorbance value of the negative controls plus three standard deviations was used to compute the cut-off value.

Sample size calculation: The Epi-Info statistical programme Version 2002, developed by the WHO and the Centres for Disease Control and Prevention in Atlanta, Georgia, USA, was used to compute the sample size and power analysis. The following criteria were applied for calculating the sample size: [The sensitivity of IL-6 in distinguishing between inflammatory and non-inflammatory arthritis is 70% with a margin of error of 10% (60-80%) and the study design is comparative cross sectional with a 95% confidence limit. The sample size based on the previously mentioned criteria was determined at N=80].

Ethical approval: approval by the Benha University Hospitals' Ethics Committee was taken. Before the trial began, the patients gave their signed informed consents. Throughout the course of the investigation, the Helsinki Declaration was adhered to.

Statistical analysis

SPSS v27 was used for the statistical analysis. The normality of the data distribution was assessed using the Shapiro-Wilks test and histograms. ANOVA (F) test with post-hoc test (Tukey) was used to analyse quantitative parametric data, which were given as mean ± SD. Quantitative non-parametric data were analysed using the Mann Whitney test and the Kruskall-Wallis test to compare each group. The results were given as the median and IQR. The X^2-test was used to analyse the qualitative variables, which were given as frequency and percentage. For a linear relationship with normally distributed variables, Pearson moment correlation equation was used. To determine the association between one independent variable and one dependent variable, univariate regression was utilised. Multivariate regression was used for estimating the connection between a dependent variable and several independent variables. For statistical significance, a two-tailed P value ≤ 0.05 was used.

RESULTS

In terms of demographic data, there were no statistically significant differences ($p > 0.05$) between the analysed groups, with the majority of our patients being females. Inflammatory markers were found to be significantly greater in RA patients than in OA patients ($p < 0.001$). There were statistically significant differences ($p < 0.05$) between PsA patients and OA patients, with PsA patients having greater levels. There were no statistically significant differences ($p > 0.05$) between the study groups in terms of laboratory measures. There were highly statistically significant variations in serum IL-6 between RA patients and the study groups, with RA patients having greater levels (Table 1).

Table (1): Demographic data, laboratory parameters among the studied groups

		RA (n = 20)	OA (n = 20)	PsA (n = 20)	Control (n = 20)	p
Age (years)		45.45±6.72	49.80±7.08	47.30±7.73	45.25±9.14	0.222
		0.231	0.211	0.762	--	
Sex	**Male**	1(5.0%)	4(20.0%)	3(15.0%)	2(10.0%)	^{MC}p= 0.673
	Female	19(95.0%)	16(80.0%)	17(85.0%)	18(90.0%)	
Duration of disease		4.50(1.50-8.0)	5.0(3.0-10.0)	4.0(2.50-5.0)	--	**0.130**
Inflammatory markers						
ESR 1st hr.		30.0(20.0 – 48.50)	6.0(6.0–9.0)	22.0(14.0–35.0)	6.0(4.0–9.0)	< **0.001***
P0		**<0.001***	<0.415	**<0.001***		
Sig. between grps.		**p_1<0.001***, p_2=0.332, **p_3<0.001***				
ESR 2nd hr.		58.50(35.0–86.50)	11.0(10.0–15.0)	43.50 (28.0–62.0)	12.0(10.0–18.0)	< **0.001***
P0		**<0.001***	0.978	**<0.001***		
Sig. between grps.		**p_1<0.001***, p_2=0.303, **p_3<0.001***				
CRP		11.0(4.50–12.0)	3.50(2.0–4.0)	5.0(3.0–11.0)	3.0(2.0–4.0)	**<0.001***
Negative		1(5.0%)	**20(100.0%)**	2(10.0%)	**20(100.0%)**	
Positive		19(95.0%)	0(0.0%)	18(90.0%)	0 (0.0%)	
p_0		**<0.001***	0.977	**0.017***		
Sig. between grps.		**p_1<0.001***, p_2=0.245, **p_3=0.018***				
		Laboratory Parameters				
SGPT (U/L)		23.70±5.90	24.60±3.23	23.46±4.39	24.35±4.30	0.842
SGOT (U/L)		24.58±5.98	23.20±3.56	23.55±5.75	27.30±4.94	0.099
Blood urea (mg/dL)		27.01±6.61	28.10±4.47	27.09±5.02	28.10±3.84	0.884
S. Creatinine (mg/dl)		0.91±0.20	0.93±0.19	0.89±0.19	0.92±0.15	0.898
Hb (g/dL)		11.64±1.03	12.15±0.69	12.44±1.37	12.13±0.95	0.111
WBC (mcL)		7.45±1.75	6.47±1.21	6.44±1.60	6.29±1.54	0.090
Platelet (mcL)		256.2±37.19	247.6±33.05	267.6±44.23	245.6±41.15	0.709
Serum level of IL-6 (pg/mL)		18.9(9.92-57.40)	7.75(5.70-9.10)	9.0(6.51-11.62)	7.50(5.0-9.0)	< **0.001***
		32.09 ± 7.72	7.97 ± 1.88	9.61 ± 2.39	7.20 ± 2.42	
		p_1<0.001*, **p_2=0.004***, p_3=0.277, **p_4<0.001***, p_5=0.767, p_6=0.167				

Data are presented as mean ± SD or frequency (%) or median (IQR). * Significant p value <0.05. p0: p value for comparing between Control and each other, p1: p value for comparing between RA and OA, p2: p value for comparing between RA and PsA, p3: p value for comparing between OA and PsA, P4: p value for comparing between group RA and control, p5: p value for comparing between group OA and control, p6: p value for comparing between group PsA and control. RA: rheumatoid arthritis, OA: Osteoarthritis, PsA: psoriatic arthritis, ESR: estimated sedimentation rate, CRP: C- reactive protein, SGPT: Serum Glutamic Pyruvic Transaminase, SGOT: Serum Glutamic-Oxaloacetic Transaminase, Hb: Haemoglobin, WBC: White blood cells, IL-6: Interleukin 6.

Regarding DAS-28 score, 50% of RA patients had high DAS-28 score, 25% with low disease activity, 20% with moderate disease activity and 5% with remission. All cases had RF and Anti-CCP positive except one case had Anti-CCP negative. The mean of WOMAC score was 51.88 ± 19.57. Regarding PsA disease activity, 55% of PsA patients had moderate DAPSA score, 30% with high disease activity and 15% with low disease activity. All cases had bilateral knee OA. 82.5% of OA patients had no knee effusion. 70% of patients had tenderness of joint line. The higher percentage (55% & 22.5%) of OA patients were KL grade III and II respectively (Table 2).

Table (2): Disease activity, severity parameters, anti-CCP and RF among the studied RA patients, WOMAC score among the studied OA patients, DAPSA score in group III PsA patients and its clinical and radiological data

RA group (N=20)		
DAS 28 score		4.64 ± 1.84
Low		5(25.0%)
Moderate		4(20.0%)
High		10(50.0%)
Remission		1(5.0%)
Disease severity		40.0(40.0-60.0)
Anti- CCP		185.0(69.05-458.0)
Negative		1(5.0%)
Positive		19(95.0%)
RF		128.0(64.0-192.0)
Clinical and radiological data		
Disease duration (years)		4.50 (1.50 – 8.0)
Morning stiffness (min)		77.50(60.0 – 90.0)
No of tender joints		7.0(2.0 – 12.0)
No of swollen joints		4.0(1.0 – 8.0)
OA group (N=20)		
WOMAC score		51.88 ± 19.57
Clinical and radiological data		
Knee effusion (n=40)	**No effusion**	33(82.5%)
	Left knee effusion	1(2.5%)
	Right knee effusion	2(5.0%)
	Right, Left knee effusion	4(10.0%)
Radiographic changes (KL grading (n=40)	**I**	1(2.5%)
	II	9(22.5%)
	III	22(55.0%)
	IV	8(20.0%)
Tenderness of joint line (n=40)		5.0 (3.0 – 10.0)
Morning stiffness (min)		10.0 (5.0 – 12.50)
PsA (N=20)		
PsA disease activity (DAPSA score)		26.50(18.50 – 33.0)
Low		3(15.0%)
Moderate		11(55.0%)
High		6(30.0%)
Clinical and radiological data		
Disease duration (years)		4.0 (2.50 – 5.0)
No of tender joints		10.0(6.50 – 12.0)
No of swollen joints		1.0(1.0 – 2.0)
Modified Steinbrocker score (Radiographic)		41.50(37.0 – 64.50)

Data are presented as mean ± SD or frequency (%) or median (IQR). Group I: RA patients, Group II: OA group, DAS28 score: disease Activity Score-28, Anti-CCP: Anti-cyclic citrullinated peptide anti-bodies, RF: Rheumatoid factor, WOMAC score: Western Ontario and McMaster Universities Arthritis Index, DAPSA score: Disease Activity index in Psoriatic Arthritis, RA: rheumatoid arthritis, OA: Osteoarthritis, PsA: psoriatic arthritis.

Regarding to medications, 18 (90%) of RA patients received combined therapy, methotrexate was the most common DMARD used by the RA patients. All PsA patients received monotherapy, methotrexate was the most common DMARD used by the PsA patients 16 (80 %) **(Table 3).**

Table (3): Distribution of the studied cases according to Medications in RA and PsA patients

		Medications in RA (n=20)
Monotherapy	**MTX**	1(5.0%)
	Anti TNF(Enbrel)	1(5.0%)
Combined therapy	**Leflunamide, HCQ, GCs**	1(5.0%)
	MTX, GCs	1(5.0%)
	MTX, HCQ	4(20.0%)
	MTX, HCQ, GCs	7(35.0%)
	MTX, Leflunamide, GCs	2(10.0%)
	MTX, Leflunamide, HCQ, GCs	3(15.0%)
		Medications in PsA (n=20)
Anti TNF (Enbrel)		2(10.0%)
Anti TNF (simponi)		1(5.0%)
Colosalazine		1(5.0%)
MTX		16(80.0%)

Data are presented as frequency (%). MTX: Methotrexate, Anti TNF: Anti-tumor necrosis factor alpha, HCQ: Hydroxychloroquine, GCs: Glucocorticoids, MTX: Methotrexate, Anti TNF: Anti-tumor necrosis factor alpha, RA: rheumatoid arthritis, PsA: psoriatic arthritis.

There was significant positive correlation between IL-6 with DAS-28 score, disease severity, morning stiffness, no of tender and swollen joints, ESR (1st and 2nd hours) and radiographic changes (Larsen score) in RA patients. In PsA patients, IL-6 was significantly positively correlated with disease activity (DAPSA score) and radiographic changes (modified Steinbrocker score) (Table 4).

Table (4): Correlation between serum IL-6 and different parameters in each group

	IL-6					
	RA patients		**OA patients**		**PsA patients.**	
	r_s	**P**	**r_s**	**P**	**r_s**	**P**
Age	-0.140	0.555	0.051	0.833	-0.102	0.668
Disease duration	-0.126	0.596	0.152	0.522	-0.159	0.504
DAS28 score	0.728*	<0.001*	–	–	–	–
Disease severity	0.762*	<0.001*	–	–	–	–
Womac score	–	–	0.215	0.363	–	–
PsA disease activity	–	–	–	–	0.470	0.036*
Morning stiffness (min)	0.644	0.002*	0.193	0.415	–	–
No of tender joints	0.476	0.034*	–	–	0.207	0.381
No of swollen joints	0.490	0.028*	–	–	0.213	0.367
ESR 1st	0.452*	0.045*	0.086	0.720	0.313	0.179
ESR 2nd	0.493*	0.027*	-0.033	0.889	0.345	0.136
CRP	0.442	0.058	-0.273	0.245	0.075	0.768
RF	0.203	0.390	–	–	–	–
Anticcp	-0.048	0.846	–	–	–	–
Hb	-0.209	0.376	0.319	0.171	0.239	0.309
Radiographic changes	0.689	0.001*	0.283	0.227	0.565*	0.009*

r_s: Spearman coefficient, *: Statistically significant at $p \leq 0.05$

There was a strong relationship between IL-6 level and DAS-28 score in RA patients, IL-6 levels were greater in patients with high disease activity. There was a strong relationship between IL-6 level and disease activity (DAPSA score) in PsA patients where IL6 level was greater in patients with high disease activity (Table 5).

Table (5): Relation between DAS28 score and serum IL-6 in RA group and between PsA disease activity (DAPSA score) and serum IL-6 in PsA patients' group

	DAS28 score			**P**
	Low + Remission (n= 6)	**Moderate (n= 4)**	**High (n= 10)**	
IL-6	9.22(5.80 – 13.40)	18.90(15.60–46.10)	57.40(6.12–78.20)	**0.014***
	PsA disease activity			
	Low (n= 3)	**Low (n= 3)**	**Low (n= 3)**	
IL-6	8.09(5.80 – 8.49)	7.65(3.72 – 19.60)	13.14(9.47 – 18.90)	**0.015***

*: Statistically significant at $p \leq 0.05$

Regarding univariate analysis, it was found that DAS-28 score, disease severity, morning stiffness, number of tender and swollen joints, ESR (1st and 2nd hours) and radiographic changes (Larsen score) were significantly associated with IL-6. Regarding multivariate analysis, it was found that disease severity was significantly independently affecting IL-6 in RA patients. Regarding univariate analysis, there was insignificantly correlation between IL-6 and different parameters in OA patients. Regarding univariate analysis, it was found that PsA disease activity and radiographic changes (modified Steinbrocker score) were significantly associated with IL-6. Regarding multivariate analysis, it was found that none of the different parameters were significantly independently associated with IL-6 in PsA patients (Table 6).

Table (6): Univariate and multivariate linear regression analysis for the parameters affecting IL-6 in RA, OA and PsA patients

	Univariate		**#Multivariate**	
	P	**B (LL – UL 95%C.I)**	**P**	**B (LL – UL 95%C.I)**
RA patients				
Age	0.552	-0.555(-2.477 – 1.368)		
Disease duration	0.819	0.363(-2.913 – 3.639)		
DAS28 score	**<0.001***	10.177(5.163 – 15.191)	0.270	3.482(-3.123–10.086)
Disease severity	**<0.001***	1.410(0.873 – 1.947)	**0.032***	1.015(0.105–1.924)
Morning stiffness (min)	**0.004***	0.783(0.278 – 1.287)	0.082	0.418(-0.062–0.899)
No of tender joints	**0.023***	2.164(0.337 – 3.992)	0.703	-0.951(-6.293–4.392)
No of swollen joints	**0.011***	2.803(0.718 – 4.889)	0.922	0.282(-5.916–6.479)
ESR 1st	**0.039***	0.584(0.034 – 1.133)	0.662	-0.269(-1.585–1.047)
ESR 2nd	**0.030***	0.377(0.042 – 0.712)	0.958	0.019(-0.782–0.820)
CRP	0.052	1.016(-0.009 – 2.042)		
RF	0.260	0.050(-0.040 – 0.139)		
Anticcp	0.640	0.016(-0.056 – 0.088)		
Hb	0.484	-4.235(-16.691 – 8.221)		
Radiographic changes	**0.001***	0.746(0.371 – 1.121)	0.135	0.290(-0.106–0.686)
OA patients				
Age	0.189	-0.132(-0.335 – 0.071)		
Disease duration	0.918	-0.021(-0.443 – 0.401)		
Womac score	0.882	0.005(-0.066 – 0.076)		
Morning stiffness (min)	0.526	0.085(-0.192 – 0.363)		
ESR 1th	0.475	0.264(-0.496 – 1.023)		
ESR 2nd	0.481	0.131(-0.252 – 0.514)		
CRP	0.075	-1.138(-2.404 – 0.128)		
Hb	0.254	0.990(-0.775 – 2.755)		
Radiographic changes	0.586	0.521(-1.451 – 2.493)		
PsA patients				
Age	0.840	-0.028(-0.315 – 0.259)		
Disease duration	0.892	-0.077(-1.240 – 1.087)		
PsA disease activity	**0.037***	0.210(0.014 – 0.405)	0.405	0.095(-0.140 – 0.330)
No of tender joints	0.453	0.186(-0.323 – 0.695)		
No of swollen joints	0.230	0.510(-0.351 – 1.371)		
ESR 1st	0.254	0.100(-0.078 – 0.277)		
ESR 2nd	0.097	0.090(-0.018 – 0.197)		
CRP	0.835	-0.056(-0.619 – 0.506)		
Hb	0.389	0.670(-0.924 – 2.263)		
Radiographic changes	**0.012***	0.118(0.029 – 0.206)	0.109	0.090(-0.022 – 0.202)

B: Unstandardized Coefficients, #: All variables with $p<0.05$ was included in the multivariate, *: Statistically significant at $p \leq 0.05$. ESR: estimated sedimentation rate, CRP: C- reactive protein, RF: Rheumatoid factor, Anti-CCP: Anti-cyclic citrullinated peptide anti-bodies, Hb: Haemoglobin.

DISCUSSION

Inflammatory arthritis is a type of arthritis caused by an overactive immune system. It is less common than other types of arthritis. In addition to immunological responses, IL-6 is also implicated in inflammation, hematopoiesis, bone metabolism, and the development of the embryo. IL-6 has a function in cancer, autoimmune disorders, and chronic inflammation, all of which are strongly linked to one another [18].

In the present study, there were highly statistically significant differences regarding serum IL-6 between RA patients and the studied groups being higher among RA patients. Consistent with our findings, **Ali *et al.*** [19] demonstrated that between RA patients and a healthy control group, there was a highly statistically significant difference in blood IL-6 levels. However, another investigation discovered that there was no difference in the distribution of IL-6 genotypes between RA patients and control patients [20]. The synthesis of IL-6 and its receptor (IL6R), which is expressed on effector cells that initiate and sustain inflammation, is a consequence of chronic joint inflammation in RA. Patients with RA have higher quantities of IL -6 in both synovial fluid and serum, indicating overexpression of the protein in this tissue [21].

Regarding the relation between IL6 and PsA, **Pietrzak *et al.*** [22] showed that PsA was linked to increased IL-6 serum concentrations. Furthermore, a significant predictor of serum IL-6 levels was PASI.

Among OA patients, **Abdel Monem *et al.*** [23] investigated IL-6 serum level associated to control groups and revealed higher levels of serum IL-6 of OA patients, which was significantly correlated with WOMAC, K-L scores, ESR and CRP. That is against our results, as the current study did not document any significant difference between OA and healthy controls regarding serum IL-6 levels. **Ahmed *et al.*** [24] showed that serum IL-6 levels were substantially higher in OA patients than in controls. Serum IL-6 was substantially linked with the WOMAC and KL scores.

In the current study, RA patients had a disease duration of 5.05 ± 3.98 years, morning stiffness was 80.75 ± 20.54 min, number of tender joints was 7.90 ± 6.16, number of swollen joints was 5.30 ± 5.21 and Larsen score (radiographic) was 76.30 ± 24.81. Regarding laboratory parameters, ESR and CRP were significantly higher in RA and PsA patients than healthy controls and OA patients being higher in RA (34.95 ± 21.02) than PsA patients (24.50 ± 12.05), than OA (7.45 ± 1.96) than healthy controls (7.05 ± 2.93).

Currently, there was significant positive correlation between IL-6 with ESR (1st and 2nd hour) among RA patients. Supporting our results, **Ali *et al.*** [19], **Abdel Meguid *et al.*** [25] reported that IL-6 had a significant positive correlation with ESR in RA patients. Also, they suggested that IL-6 is highly correlated with the severity of the disease.

In current investigation, the length of morning stiffness and IL-6 showed a strong positive connection. It's possible that RA patients with MS don't produce enough endogenous cortisol throughout the night to balance out high IL-6 levels [26]. Prolonged MS is still a significant indicator of active illness and should be followed up on in RA patients who are in remission [27].

Regarding our results, 50% of RA patients had a high DAS-28 score, 25% with low disease activity, 20% with moderate disease activity and 5% in remission. All cases had RF and anti-CCP positive except one case had anti-CCP negative.

Increased activity of IL-6 has been connected to the elevated blood levels of IL-6 observed with RA. Currently, there was significant positive correlation between IL-6 with DAS-28 score, disease severity, number of swollen and painful joints, ESR (1st and 2nd hours) and radiographic changes (Larsen score) in RA patients. In PsA patients, IL-6 was significantly positively correlated with disease activity (DAPSA score) and radiographic changes (modified Steinbrocker score).

Conversely, in OA patients, no significant relationship was seen between IL-6 and any of the measures. In RA patients, **Chung *et al.*** [28] did not find a significant correlation between DAS-28 and IL-6 cytokine levels. Both abatacept and tocilizumab medication produced a comparable apparent fall in DAS-28 in RA patients. However, the patients receiving tocilizumab showed a faster rate of decreasing disease activity, which can be directly attributed to IL-6 inhibition [29].

According to our results, patients with high disease activity had higher levels of IL-6, and there was a significant correlation between their DAS-28 score and IL-6 level in RA patients. **Koper-Lenkiewicz *et al.*** [30] observed a favourable correlation between the DAS-28 score and IL-6 in their case-control research assessing sP-selectin, IFN-γ, IL-1β, and RA patient concentrations. These findings are consistent with our findings. No correlation between DAS-28 and IL-6 cytokine levels was observed by **Chung *et al.*** [28].

In the current study, regarding univariate analysis, it was found that DAS-28 score, disease severity, stiffness in the morning, a lot of sore and swollen joints, ESR (1st and 2nd hours) and radiographic changes (Larsen score) were significantly associated with IL-6. While, in multivariate analysis, it was found that disease severity was significantly independent affecting IL-6 in RA patients.

Our results revealed that 55% of PsA patients had moderate DAPSA score, 30% with high disease activity and 15% with low disease activity with mean of 25.65 ± 10.04. Additionally, IL-6 level and disease activity (measured by the DAPSA score) in PsA

patients were significantly correlated. Patients with higher disease activity also had higher IL-6 levels.

Regarding univariate analysis, it was found that PsA disease activity and radiographic changes (modified Steinbrocker score) were significantly associated with IL-6. But in multivariate analysis, it was found that none of the different parameters was significantly independently associated with IL-6 in PsA patients. Increased production of IL-6 is well known in psoriasis and PsA [31, 32].

In our investigation, regarding univariate analysis, there was no significant correlation between IL-6 and different parameters in OA patients. Studies examining the function of IL-6 in OA models have yielded mixed results, despite the protein's potential involvement in OA. Using IL-6 to stimulate chondrocytes in vitro has been shown to have both catabolic and anabolic effects, including down-regulating cartilage matrix genes and up-regulating tissue inhibitor of metalloproteinases-1 (TIMP-1) [33] and type II collagen[34].

Since the activity of IL-6 may depend on other components in the joint, namely the synovial fluid, one explanation for this lack of impact might be found in the many studies that have reduced the setup to add IL-6 [35].

One of the study's limitations was the very small sample size. It was a research with just one centre. It was a cross-sectional study as it could not find causality due to their observational nature.

CONCLUSIONS

Monitoring the serum level of this cytokine may be helpful in assessing the clinical status because IL-6 is a significant predictor in patients with RA and PsA but not in patients with OA. It was significantly associated with DAS-28 score, disease severity, morning stiffness duration, number of tender and swollen joints, ESR, and radiographic changes in RA patients, and with disease activity and radiographic changes in PsA patients. An essential function of IL-6 is to mediate joint degradation, auto-antibody synthesis, and inflammation.

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