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Serum and synovial fluid interleukin-17 concentrations in rheumatoid arthritis patients: Relation to disease activity, radiographic severity and power Doppler ultrasound

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ABSTRACT

Aim of the work: To investigate serum and synovial fluid levels of IL-17 in rheumatoid arthritis (RA) patients, and its correlation with disease activity and severity.
Patients and methods: 20 RA patients together with 20 primary knee osteoarthritis (KOA) patients and 15 healthy individuals matched for age and sex as control groups were enrolled in this study. Both RA and KOA patients presented with knee effusion. Paired samples of serum and synovial fluid (SF) were collected from RA, OA patients and serum samples from the healthy individuals. RA disease activity was assessed using DAS-28 score and power Doppler ultrasound (PDUS) according to the European League against Rheumatism (EULAR). Radiographic damage was evaluated according to Larsen score.
Results: Serum levels of IL-17 were significantly elevated in RA patients compared to controls ($p < 0.001$). Also, SF of IL-17 was significantly higher in RA patients compared to OA patients ($p < 0.001$). In addition, synovial level of IL-17 was significantly higher in RA patient compared to their serum level ($p < 0.001$). Regarding disease activity grading among RA patients, significant differences ($p < 0.05$) in mean serum and synovial IL-17 levels were reported being higher in severe active disease. Positive correlations of serum and SF IL 17 levels with PDUS findings and Larsen score were reported.
Conclusion: Serum and synovial IL-17 levels were significantly elevated in RA patients which clarifies its possible role in RA pathogenesis and correlates positively with disease activity parameters, PDUS findings and Larsen score. Thus targeting IL-17 may provide a promising role in suppressing RA.

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent joint inflammation, causing synovitis and cartilage damage with subsequent joint destruction and significant deformity [1]. The etiology and pathogenesis of RA remain unknown, it is generally considered an autoimmune pathology in which autoreactive T cells of pathogenic potential, such as T-helper1 (Th1) and T-helper 17 (Th17) cells, are thought to play an important role [2]. The prevalence of RA in Northern Europe and North America is estimated at 0.5–1%, and is expected to increase as populations' age and mortality decreases [3].

Osteoarthritis (OA) is a chronic, degenerative joint disease characterized by the progressive destruction of articular cartilage, joint-space narrowing, subchondral bone remodeling, joint marginal osteophyte formation and synovitis. OA shares several characteristics with rheumatoid arthritis, including joint destruction and synovitis [4]. Although the etiology and pathophysiology of OA are both poorly understood, it is believed that secreted inflammatory molecules such as proinflammatory cytokines are among the critical mediators of the disturbed processes implicated in OA pathophysiology [5]. In Egyptian patients with knee OA, cytokine imbalance contributed to the disease risk and manifestations [6].

The Th17 subset of T-helper cells is pro-inflammatory, plays vital roles in host defense and is involved in the pathogenesis of

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RA primarily by secreting IL-17 [7]. Interleukin-17 (IL-17) is a pro-inflammatory cytokine which is comprised of a family of six distinct but homologous units (A-F) [8]. Its family have been recognized for involvement in the pathogenesis of autoimmune diseases, particularly RA [9] and was further found to promote osteoporosis and increase the liability to fracture in Egyptian RA patients [10]. Moreover, another related cytokine, IL-23/Th17 axis was found as a key marker for disease activity in Egyptian RA patients [11]. IL-17 promotes recruitment of both neutrophils and monocytes by means of inducing various chemokines which can in turn mediate inflammation in RA [12].

The aim of this study is to investigate serum and synovial fluid levels of IL-17 in rheumatoid arthritis patients, and its correlation with both activity and severity of the disease.

2. Patients and methods

The study was carried out at Rheumatology, Rehabilitation and Physical Medicine inpatients' Department and outpatients' clinic of Benha University Hospitals between March 2018 and March 2019. 20RA patients fulfilling the 2010 classification criteria of the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) [13] and 20 with primary knee OA fulfilling the ACR criteria [14] were enrolled. Fifteen apparently healthy volunteers were recruited from the hospital personnel and matched for age and sex to RA patients. This study was approved by the ethical committee of our institution. All subjects gave their written informed consent before participation in this study.

All RA patients were subjected to complete history taking, clinical examination and assessment of the disease activity score (DAS-28) [15] which was graded as remission (<2.6), low (2.6–3.2), moderate (>3.2–5.1) and high (>5.1) [16]. Laboratory investigations included complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum rheumatoid factor (RF) and anti-cyclic citrullinated peptide anti-bodies (anti-CCP).

Five milliliters of whole venous blood was drawn from each participant under aseptic conditions and left until coagulation at room temperature for 30 min. The samples were then centrifuged at 1000xg for 15 min. The separated serum was stored at −80 °C until assay of human IL-17. 1 ml synovial fluid was aspirated from the affected knee of RA and OA patients by needle aspiration with the use of sterile technique and was placed in a sterile propylene tubes, centrifuged at 1000xg for 10 min to remove cells and joint debris, then frozen at −80 °C until assay of human IL-17. The serum and synovial human IL-17 were measured by double-antibody sandwich ELISA technique using human IL-17 ELISA kit (Cat. # 201-12-0143; Sunred Bio Technology Company, Shanghai, China) according to the manufacturer's instructions.

Plain x-ray (PA views) both hands, wrists and feet were obtained and scored by Larsen score [17]. For each RA patients power Doppler ultrasound (PDUS) examination was done for 22 joints; both wrists, metacarpophalangeal joints (MCPs) and proximal inter phalangeal joints (PIPs) to assess inflammation using longitudinal and transverse scanning (8–13 MHz) of the dorsal aspects of the selected joints according to the European League against Rheumatism (EULAR) guidelines [18].

2.1. Statistical analysis

It was performed using SPSS (Statistical Package for the Social Sciences program) version 16. The difference between the two groups was analyzed via student's *t*-test. One-way analysis of variance (ANOVA) was used to compare more than two groups. Chi-square test (X2) was used for comparison of frequencies. Spearman's correlation coefficient (r) was used to assess the degree of association between 2 continuous variables. To assess the diagnostic value the sensitivity and specificity were calculated. A value of $P < 0.05$ was considered significant.

3. Results

This study included 20 RA patients; 15 (75%) females and 5 (25%) males with a mean age of 45.8 ± 8.5 years and disease duration 7.67 ± 3.43 years (1–12 years) together with age and sex matched 20 KOA patients; 12 (60%) females and 8 (40%) males with a mean age of 55.7 ± 7.5 years and disease duration 8.4 ± 5.3 years (3–20 years) and 15 healthy adults: 9 (60%) females and 6 (40%) males with 44.8 ± 10.1 years (30–62 years).The characteristics of the RA patients are presented in Table 1.

The mean serum level of IL-17 was significantly higher in RA patients compared to OA and healthy control ($p < 0.001$). SF IL-17 in RA was significantly elevated ($p < 0.001$) compared to OA. The mean SFIL-17 in RA (75.2 ± 10.9 pg/ml) was significantly high compared to serum level (39.3 ± 16.1 pg/ml) ($p < 0.001$) (Fig. 1). PDUS signals in RA patient presented in Fig. 2.

Table 1
The characteristics of rheumatoid arthritis patients.

Variable mean ± SD or n (%)	RA patients (n = 20)
Age (years)	45.8 ± 8.5
Disease duration (years)	7.7 ± 3.4
RF positivity	17 (85)
Anti-CCP positivity	15 (75)
DAS-28	5.1 ± 1
Low	7 (35)
Moderate	11 (55)
Severe	2 (10)
Larsen's grades	
Grade I	6 (30)
Grade II	7 (35)
Grade III	7 (30)
PDUS score	11.2 ± 3.36

RA: rheumatoid arthritis, RF: rheumatoid factor, anti-CCP: anti-cyclic citrullinated peptide, DAS-28: disease activity score, PDUS: power Doppler ultrasound.

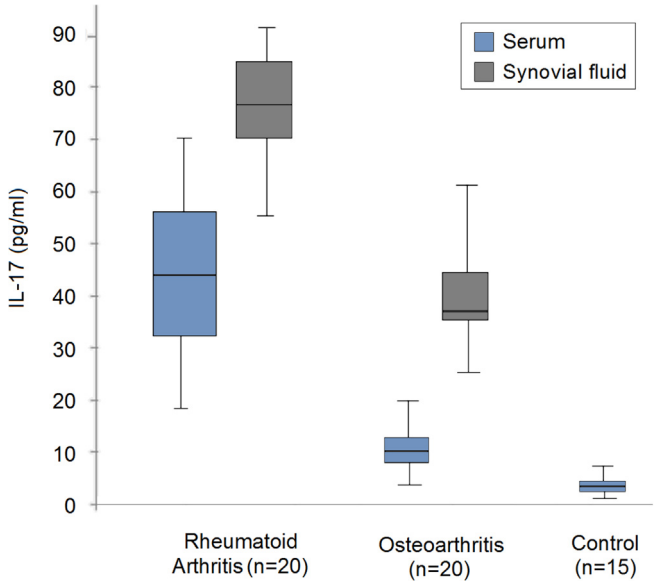

Fig. 1. Serum and synovial fluid interleukin-17 in rheumatoid arthritis, osteoarthritis and healthy control.

No significant differences in serum or SF IL-17 were reported between male and female RA patients as regard mean serum and SF levels of IL-17.

In patients with low, moderate and high activity, the mean serum IL-17 (35.7 ± 2.9 pg/ml, 42.5 ± 2.2 pg/ml and 44.4 ± 6.4 pg/ml respectively)and SF levels (60.5 ± 3.4 pg/ml, 70.6 ± 6.2 pg/ml and 79.2 ± 5.9 pg/ml) were significantly different (p = 0.039 and p = 0.042 respectively).

The correlation of serum and SFIL-17 with the studied variables in RA patients are presented in Table 2. The diagnostic value, sensitivity and specificity of IL-17 in diagnosing RA and OA are presented in Table 3 and Fig. 3.

Table 3
Diagnostic value, sensitivity and specificity of interleukin-17 in discriminating rheumatoid arthritis and osteoarthritis.

	RA vs OA		OA vs control
	serum	SF	serum
AUC	0.99	0.99	0.98
95%CI	0.97–1	0.973–1	0.941–1
Cut off point	23.5	65.5	5.5
Sensitivity	100	100	90
Specificity	85	90	95
PPV	87	90.9	94.7
NPV	100	100	90.5
Accuracy	92.5	95	92.5

RA: rheumatoid arthritis, OA: osteoarthritis, AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value.

4. Discussion

Rheumatoid arthritis (RA) is characterized by the presence of a relative state of imbalance between pro- and anti-inflammatory cytokines [19]. IL-17 is a novel inflammatory factor, that is involved in RA inflammation and joint injury [20]. It is highly expressed in the synovium and synovial fluid of RA patients. T cells and the cytokines, IL-17 and tumor necrosis factor alpha (TNF-α) have been shown to activate RA synovial fluid resulting in the expression of pro-inflammatory cytokines such as IL-6 and IL-8, which are mediators of joint inflammation [9].

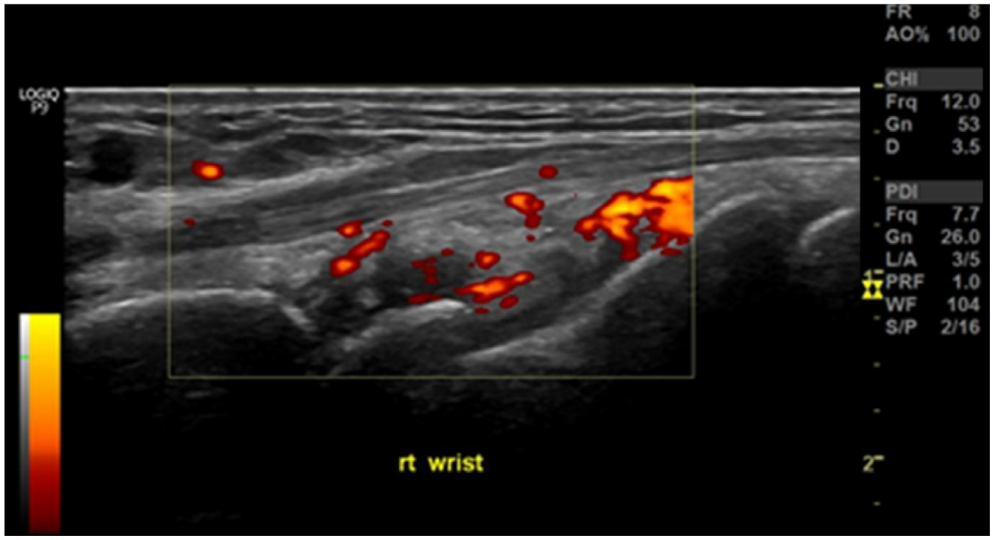

Fig. 2. Power Doppler ultrasound (PDUS) signals of the right wrist of a 47 years female rheumatoid arthritis patient.

Table 2
Correlations of serum and synovial fluid interleukin-17with variables in rheumatoid arthritis patients.

Parameter r (p)	RA patients (n = 20)			
	Serum IL-17		SF IL-17	
Serum IL-17	–	–	0.33 (**0.021**)	
SF IL-17	0.33	(**0.021**)	–	–
Age	0.07	(0.25)	0.9	(0.42)
dis. Duration	0.49	(**0.023**)	0.3	(**0.03**)
TJC	0.32	(**0.03**)	0.35	(**0.042**)
SJC	0.40	(**0.01**)	0.39	(**0.027**)
VAS	0.16	(0.43)	0.003	(0.51)
ESR	0.48	(**0.014**)	0.35	(**0.03**)
CRP	0.55	(**0.016**)	0.76	(**0.0002**)
Hb	−0.5	(**0.0003**)	−0.49	(**0.014**)
WBC	0.23	(0.63)	−0.30	(0.41)
Platelet	0.52	(**0.0004**)	0.62	(**0.0005**)
RF titer	0.4	(**0.048**)	0.5	(**0.034**)
Anti-CCP	0.01	(0.52)	0.02	(0.49)
DAS-28	0.42	(**0.02**)	0.62	(**0.0004**)
PDUS score	0.32	(**0.046**)	0.31	(**0.049**)
Larsen score	0.38	(**0.031**)	0,36	(**0.02**)

RA: rheumatoid arthritis, SF: synovial fluid, IL-17: interleukin-17, TJC: tender joint count, SJC: swollen joint count, VAS: visual analogue scale, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Hb: hemoglobin, WBC: white blood cells, RF: rheumatoid factor, anti-CCP: anti-cyclic citrullinated peptide, DAS-28: disease activity score, PDUS: power Doppler ultrasound. Bold values are significant at p < 0.05.

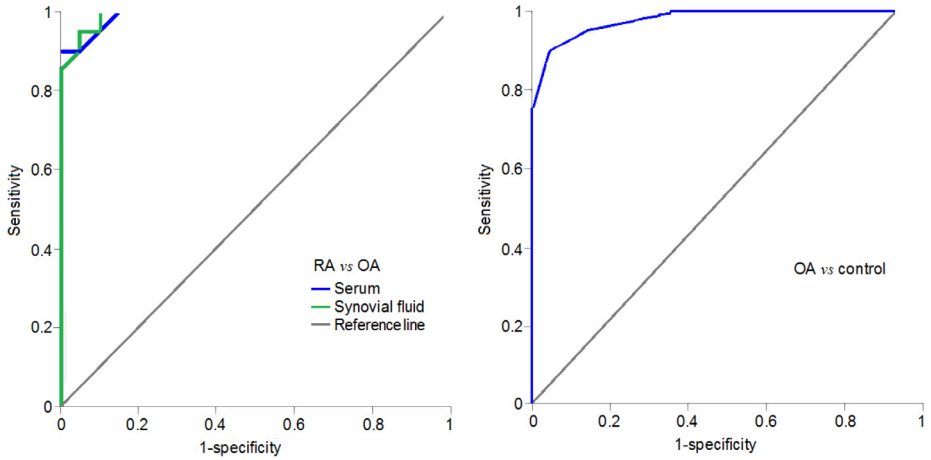

Fig. 3. Receiver operating characteristic (ROC) curve for discriminating rheumatoid arthritis (RA) from osteoarthritis (OA) in serum and synovial fluid (left) and OA from healthy control serum (right).

In the present study, the mean serum IL-17 level was highly significantly increased in RA patients compared with control ($p < 0.001$). This was in agreement with results of previous studies [21–26] who found that the mean serum IL-17 levels were higher in RA patients. Also Kellner [27] and Park et al. [28] reported that the mean serum levels of IL-17 in RA patients were highly significantly increased compared to OA ($p < 0.001$). $CD4^{+}CD45RO^{+}$ memory T cells are a major T cell subset present in the synovium of RA patients. The same subset of T cells produces large amounts of IL-17 on stimulation. Moreover, in synovial tissue of RA patients, these cells are immunoreactive with anti-IL-17 Abs [29].

In the current study, there was highly significant increase in the mean SF levels of IL-17 in RA patients compared to OA patients. These results go hand in hand with Roşu et al. [26], Leipe et al. [30] and Moran et al. [31] who demonstrated that the mean serum and SF IL-17 levels in samples from RA patients were significantly higher than those in OA patients. They concluded that IL-17 in SF may contribute in distinguishing RA from other arthritic diseases.

There was highly significant increase in the mean IL-17 SF levels than serum levels in RA patients. Similarly, Moran et al. [31] reported that levels of IL-17A (previously known as IL-17) in SF were significantly higher than their matched serum levels suggesting that the cytokine is predominantly produced locally in the inflamed joint.

The present study revealed significant correlation between the mean serum and SF levels of IL17 and TJC, SJC, CRP, ESR, RF, DAS and U/S score but not with VAS or ACPA. In support to these results, the studies done by Pavlovic et al. [32] showed a significant correlation between serum concentrations of IL-17 and laboratory measures such as ESR, CRP, but not with RF, while Silo Gi et al. [33] reported significant correlation with CRP only. In addition, serum level of IL-17 correlated significantly with TJC, SJC, DAS 28 but insignificantly with ESR, RF, VAS [34]. Interestingly, Roşu et al. [26] noted a weaker correlation of synovial IL-17 levels with CRP, compared with ESR. It was suggested that IL-17 is a potent inducer of CRP from human smooth muscle cells and hepatocytes [35] and a strong correlation between these parameters, but only in established RA was demonstrated [31].

In this study, there was a significant correlation between serum, synovial IL-17 and platelet and inversely with hemoglobin and no significant correlation with age, VAS, ACPA and WBCs. These results go hand in hand with SiloGi et al. [33] and Pavlovic et al. [32] who found that no significant correlations were found between serum levels of IL-17 and patients' ages.

There were significant differences between patients' activity grades regarding the mean serum and SF levels of IL-17 which go hand in hand with Elhewala et al. [22]. A significant correlation was found between DAS-28 and serum and SF levels of IL-17which coincides with results reported by others [2,21,26,34]. In contrast, these results were not in agreement with Tukaj et al. [36], Ongkowijaya et al. [37] and Yamada et al. [38] who found that there were no significant correlation between the mean serum levels of IL-17 and DAS-28 in RA patients.

Regarding PDUS, we found significant correlations with both serum and SF levels of IL-17. Correspondingly, Elhewala et al. [22] observed significant increase in IL-17A level in the blood with increased erosive changes detected by MSUS of the knee and wrist joints in the RA patients. Thus IL-17A cytokine could be used as a parameter for prediction of erosive and destructive changes and rapid disease progression in RA patients [39].

Larsen Grading Scale is used to determine the extent of radiographic changes due to rheumatoid arthritis. In addition to the mentioned results in this study, there was high significant correlation between serum and SF IL-17 levels with Larsen score, which was in agreement with Elatar et al. [40].

Among the study limitations, the small number of patients and cross sectional design affect the integrity of the reached results. Detailed analysis of the impact of medications is also missing.

In conclusion, from these data we conclude that Serum and synovial IL-17 levels were significantly elevated in RA patients which clarifies its possible role in RA pathogenesis and correlates positively with disease activity parameters, PDUS findings and Larsen score. Targeting IL-17 may provide a promising role in suppressing RA.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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