Arch Rheumatol 2022;37(2):187-194
doi: 10.5606/ArchRheumatol.2022.7931

ORIGINAL ARTICLE

Serum and synovial fluid levels of interleukin-17a in primary knee osteoarthritis patients: Correlations with functional status, pain, and disease severity

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ABSTRACT

Objectives: This study aims to assess the serum and synovial fluid (SF) levels of interleukin (IL)-17A in primary knee osteoarthritis (KOA) patients and to study their correlations with functional status, pain, and disease severity.

Patients and methods: This cross-sectional study was conducted between December 2017 and March 2018 and it included 70 patients (46 males, 24 females; mean age 57.3±10.0 years; range 34 to 76 years) with primary KOA and 30 age-, sex-, and body mass index-matched healthy individuals (20 males, 10 females; mean age 53.3±10.3 years; range, 35 to 70 years). Western Ontario and McMaster Universities osteoarthritis index (WOMAC), visual analog scale (VAS), Lequesne index, and Kellgren and Lawrence (KL) grading scale were used for assessment of the disease. IL-17A levels were measured in the serum for patients and healthy controls, and in SF for patients only using an enzyme-linked immunosorbent assay.

Results: Serum levels of IL-17A were significantly higher in KOA patients than controls (p=0.04). A positive correlation was found between serum and SF IL-17A levels. Serum and SF IL-17A levels had positive correlations with VAS, WOMAC pain score, Lequesne pain score, WOMAC function score, and Lequesne index. SF IL-17A levels had strong positive correlations with radiographic severity (KL grade) and duration of OA.

Conclusion: Higher IL-17A levels in primary KOA patients were significantly associated with longer disease duration, higher pain scores, worse quality of life, extreme disability, and advanced structural damage. Therapeutics that target IL-17A warrant further investigation.

Keywords: Interleukin-17, knee, osteoarthritis, serum, synovial fluid.

Osteoarthritis (OA) is the most common form of arthritis causing pain and disability. It is characterized by loss of articular cartilage and formation of osteophytes with synovial inflammation present in a significant proportion of patients.[1] Primary OA most frequently affects the hips and the knees.[2]

Proinflammatory cytokines (interleukin-1 beta [IL-1β], tumor necrosis factor-alpha [TNF-α], IL-6, IL-15, IL-18 and IL-17) have been shown to play important roles in the destruction of cartilage, synovitis, and pain.[3] IL-17 is the original member of a new group of cytokines (IL-17 A-F), produced mainly by IL-17-secreting $CD4^+$ cells (also known as T helper 17 [Th17] cells).[4] The most frequently investigated members of IL-17 family were two proteins: IL-17A and IL-17F.[5] In rheumatoid arthritis (RA), IL-17A and IL-17F affected the synoviocytes by stimulating similar yet different signaling pathways. Also, IL-17A regulated a larger number of genes associated with inflammatory processes than IL-17F.[6] Increased expression of

Received: November 16, 2019 ***Accepted:*** March 10, 2020 ***Published online:*** March 03, 2022

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Citation:
Kamel S, Khalaf R, Moness H, Ahmed S. Serum and synovial fluid levels of interleukin-17a in primary knee osteoarthritis patients: correlations with functional status, pain, and disease severity. Arch Rheumatol 2022;37(2):187-194.

IL-17A was not restricted to synovial tissues of RA patients, as it was also observed in other forms of arthritis, including primary OA.[7]

Interleukin-17 can promote cartilage, synovial cells, macrophages, and osteocytes to produce the inflammatory cytokines such as TNF-α, IL-1β, and IL-6. IL-17 cells can promote receptor activator of nuclear factor-kappa B ligand (RANKL) differentiation in osteoblasts, and stimulate the degradation of matrix metallopeptidases and extracellular matrix, and the activity of bone resorption. In addition, IL-17 can also stimulate many chemokines; these chemokines can cause aggregation of neutrophils, macrophages, and lymphocytes in the synovial membrane, which creates a cascade amplification effect, resulting in more severe joint damage.[8]

Multiple studies have confirmed that IL-17 is the main factor leading to OA bone injury.[7,9,10] Clinical data also indicate that the levels of IL-17 and IL-17R are higher in the synovial fluid (SF) of patients with arthritis.[10] However, the impact of elevated IL-17 levels on OA severity and/or disability is still poorly investigated. Thus, in this study, we aimed to assess the serum and SF levels of IL-17A in primary knee OA (KOA) patients and to study their correlations with functional status, pain, and disease severity.

PATIENTS AND METHODS

The present cross-sectional study was conducted at Department of Rheumatology and Rehabilitation, Minia University Hospital between December 2017 and March 2018. EPi Info software version 2000 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA) was used to determine the sample size considering the target population as 85 patients per month, the prevalence of OA as 40%[11] with the confidence level at 95%, a power of 80%, alpha=0.05, and beta=0.10. Accordingly, 70 primary KOA patients with knee effusion (46 males, 24 females; mean age 57.3±10.0 years; range 34 to 76 years) who fulfilled the American College of Rheumatology clinical and radiographic diagnostic criteria for KOA[12] were included. Thirty healthy age-, sex-, and body mass index (BMI)-matched individuals (20 males, 10 females; mean age 53.3±10.3 years; range, 35 to 70 years) without any sign or symptom suggestive of OA, gout, RA, trauma, diabetes or other orthopedic disease served as the control group.

Patients with secondary OA due to trauma (known history of fracture or previous surgery) or known inflammatory arthritis or autoimmune diseases, patients with history of steroid injections over the past three months or those with neurological conditions or medical comorbidity (e.g., terminal conditions such as end-stage renal disease, associated severe liver dysfunction heart failure or malignancy) were excluded.

For anthropometry, height was measured to the nearest 0.1 cm, weight was measured in the upright position to the nearest 0.1 kg, and BMI was calculated as weight in kilograms divided by the square of height in meters.

For disease assessment, visual analog scale (VAS) was utilized which is a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient marks on the line the point that represents their perception of their current state. A higher score indicates greater pain intensity.[13] Moreover, Western Ontario and McMaster Universities osteoarthritis index (WOMAC) was used which is a valid and reliable instrument for the assessment of OA of the lower extremities.[14] It consists of 24 items divided into three subscales. The pain scale includes five items asking about pain at activity or rest. The stiffness scale includes two questions. The function dimension explores the degree of difficulty in daily activities. The scores are summed for items in each subscale, with possible ranges as follows: pain=0-20, stiffness=0-8, physical function=0-68, and total WOMAC score is created by summing the items for all three subscales (0-96).

Lequesne index was used to evaluate the severity for knee disease. It is a 10-question survey, five questions pertaining to pain or discomfort, one question dealing with maximum distance walked, and four questions about activities of daily living. The total questionnaire is scored on a 0 to 24 scale. Lower scores indicate less functional impairment.[15]

Table 1. Demographic and clinical characteristics of studied population

	Healthy controls (n=30)			Knee osteoarthritis patients											
				Total (n=70)			KL Grade 2 (n=26)			KL Grade 3 (n=30)			KL Grade 4 (n=14)		
	n	Mean±SD	Range	n	Mean±SD	Range	n	Mean±SD	Range	n	Mean±SD	Range	n	Mean±SD	Range
Age (year)		53.3±10.3	35-70		57.3±10.0	34-76		56.5±10.8	34-70		56.3±9.9	35-72		62.7±8.2	50-76
Sex															
Male	20			46			16			20			10		
Female	10			24			10			10			4		
BMI (kg/m^2)		27.1±3.1	21.6-32.6		27.8±3.3	21.8-32.9		25.2±2.7	21.8-29.5		28.6±2.3	22.1-32.4		31.3±1.4	29.3-32.9
Disease duration (year)		NA	NA			1-15			1-5			3-8			5-15

KL: Kellgren and Lawrence grading scale; SD: Standard deviation; BMI: Body mass index; NA: Not applicable; No statistically significant differences between groups (p>0.05; analysis of variance test).

Table 2. Assessment of pain and functional status in knee osteoarthritis patients

	Knee osteoarthritis patients									
	Total (n=70)		KL Grade 2 (n=26)		KL Grade 3 (n=30)		KL Grade 4 (n=14)			
	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	F	p^*
VAS pain	48.6±21.3	20-80	26.2±9.6	20-40	55.3±7.4	40-60	78.6±3.8	70-80	24.87	<0.001
WOMAC pain score	11.6±3.4	6-19	9.2±1.7	6-12	13.5±1.5	11-16	16.7±1.5	14-19	15.63	<0.001
WOMAC stiffness score	3.9±2.3	0-7	1.7±1.8	0-5	4.5±1.1	3-7	6.6±0.8	5-7	21.47	<0.001
WOMAC functional score	41.1±11.2	20-58	28.7±6.1	20-42	45.6±3.4	41-51	54.6±3.9	47-58	19.88	<0.001
WOMAC overall score	57.3±16.5	26-82	38.8±8.4	26-56	63.7±3.8	59-70	77.9±5.1	67-82	23.67	<0.001
Lequesne pain score	4.3±1.5	2-8	2.8±0.6	2-4	4.6±0.6	4-6	6.7±1.0	5-8	86.14	<0.001
Lequesne maximum distance walked score	2.3±1.1	1-6	1.3±0.5	1-2	2.5±0.5	2-3	3.9±1.1	3-6	65.19	<0.001
Lequesne activities of daily living score	3.8±1.3	2-7	2.7±0.6	2-4	3.9±0.6	3-5	5.7±0.8	5-7	47.9	<0.001
Lequesne overall score	10.4±3.6	5-21	6.8±1.1	5-9	11±1.3	9-13.5	15.9±2.3	14-21	121.6	<0.001

KL: Kellgren and Lawrence grading scale; SD: Standard deviation; VAS: Visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; * Significant p value <0.05 (analysis of variance test for comparison between three groups of patients).

Grading of KOA severity was performed using the Kellgren and Lawrence (KL) grading scale. The radiological severity was categorized into four grades as follows: very mild (Grade 1), mild (Grade 2), moderate (Grade 3), and severe (Grade 4).[16]

The IL-17A levels were measured in the serum of patients and controls and in the SF of patients only using human IL-17 PicoKine enzyme-linked immunosorbent assay (ELISA) Kit (Boster Biological Technology, Pleasanton CA, USA). SF specimens were collected through knee arthrocentesis. The symptomatic knee was pointed as the index joint. If patients had bilateral KOA, the most symptomatic one was selected for aspiration.

Statistical analysis

Statistical analysis was performed using the SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) software. Descriptive statistics were presented by number and percentage as well as mean and standard deviation. Statistical differences between groups were tested using Chi-square test for qualitative variables, independent sample t-test, and analysis of variance (ANOVA) for quantitative normally distributed variables. When there was a statistically significant difference, post hoc test by Tukey's honest significant difference (HSD) method was used to confirm where the differences occurred between groups. Assessment of normality was analyzed using the Shapiro-Wilk test. Correlations were calculated using Pearson's correlation coefficient. The level of statistical significance was set at $p<0.05$.

RESULTS

The demographic and clinical characteristics of the studied population are displayed in Table 1. According to KL grading scale, 26 (37.1%) patients had Grade 2, 30 (42.8%) had Grade 3, and 14 (20%) had Grade 4. Sixty-eight patients (97.1%) were using non-steroidal anti-inflammatory drugs and six patients (8.6%) were using chondroprotective drugs. Assessment of pain and functional status in KOA patients are shown in Table 2.

Levels of IL-17A in serum and SF are shown in Table 3. In OA patients, serum and SF IL-17A levels were analyzed according to the KL classification. ANOVA analysis demonstrated that serum and SF IL-17A levels tended to be higher with the increment of KL grade with statistically significant differences ($p<0.001$ for each one). Serum IL-17A levels were significantly higher in patients with KL Grade 4 OA than in controls ($p<0.001$). There were no significant differences between patients with KL Grade 2 ($p=0.054$) or KL Grade 3 OA ($p=0.93$) and controls. SF IL-17A levels were significantly higher in patients with KL Grade 4 OA than in those with KL Grade 3 or KL Grade 2 and significantly higher in patients with KL Grade 3 than those with KL Grade 2 OA ($p<0.001$ for each comparison). Post hoc comparisons using Tukey's HSD test were performed. There were statistically significant differences in serum and SF IL-17A levels between the group of patients with KL Grade 2 and those with KL Grade 3, between group of patients with KL Grade 2 and those with KL Grade 4, and between group of

Table 3. Serum and synovial fluid interleukin-17A levels in knee osteoarthritis patients and controls

		Osteoarthritis patients			
	Healthy controls (n=30)	Total (n=70)	KL Grade 2 (n=26)	KL Grade 3 (n=30)	KL Grade 4 (n=14)
Parameter	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Serum IL-17A (pg/mL)	10.5±1.9	11.6±1.6*	10.2±0.7	11.8±0.7	14.1±1.2*
Synovial fluid IL-17A (pg/mL)	NA	39.2±9.5	29.4±3.7	41.3±3.1†	53.1±4.7†‡

KL: Kellgren and Lawrence grading scale; SD: Standard deviation; IL-17: Interleukin-17; NA: Not applicable.
Serum IL-17 concentrations: * $P<0.05$ vs. controls;
Synovial fluid IL-17 concentrations: † $P<0.05$ vs. KL Grade 2, ‡ $P<0.05$ vs. KL Grade 3;
Student's t-test or analysis of variance test.

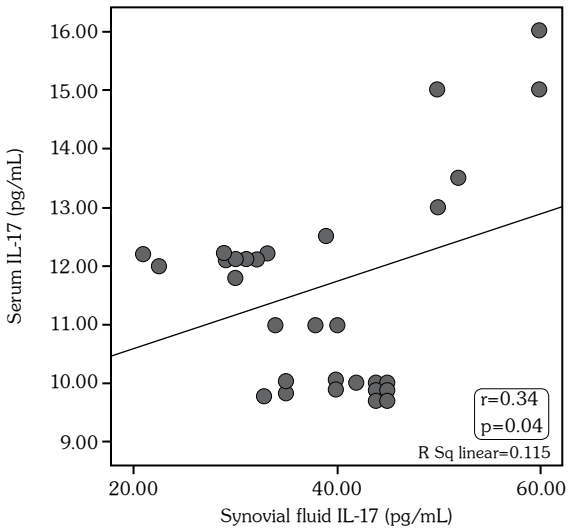

Figure 1. Correlation between serum and SF IL-17A levels in primary knee osteoarthritis patients.
SF: Synovial fluid; IL-17: Interleukin-17.

patients with KL Grade 3 and those with KL Grade 4 ($p<0.001$ for each).

There was a significant weak positive correlation between serum and SF IL-17A levels in OA patients ($r=0.34$, $p=0.04$) as shown in Figure 1. The correlations between IL-17A profile and analyzed parameters in OA patients are shown in Table 4.

DISCUSSION

In the present study, the serum levels of interleukin-17A were significantly higher in KOA patients than controls, as reported by previous studies.[4,17-21] Wang and Mu[22] reported increased serum IL-17A levels in KOA patients while they were not statistically different from those in the controls (1.6±0.0 *vs.* 1.1±0.0), which may be referred to patients' selection as they included patients who underwent arthroscopic surgery for advanced KOA. However, they observed that SF and synovial membrane IL-17 levels were significantly higher in patients with KOA compared with controls.

Our results revealed that serum and SF IL-17A levels tended to be higher with the increment of KL grade with statistically significant differences. Serum IL-17A levels were significantly higher in patients with KL Grade 4 than in controls. SF IL-17A levels were significantly higher in patients with KL Grade 4 than in those with KL Grade 3 or KL Grade 2, and significantly higher in patients with KL Grade 3 than those with KL Grade 2. These findings were in agreement with the studies of Chen et al.[4] and Wan et al.[20]

The current study showed a significant positive correlation between serum and SF IL-17A levels in primary KOA patients. A similar correlation

Table 4. Correlations between IL-17A profile and analyzed parameters

	Serum IL-17A		Synovial fluid IL-17A	
	r	*p*	r	*p*
Age of the patients	0.15	0.38	0.12	0.48
Disease duration	0.29	0.09	0.66	<0.001*
Body mass index	0.24	0.15	0.51	0.002*
Visual analog scale	0.42	0.01*	0.91	<0.001*
WOMAC pain score	0.37	0.02*	0.87	<0.001*
WOMAC stiffness score	0.37	0.02*	0.82	<0.001*
WOMAC functional score	0.35	0.03*	0.90	<0.001*
WOMAC overall score	0.39	0.02*	0.92	<0.001*
Lequesne pain score	0.37	0.02*	0.81	<0.001*
Lequesne maximum distance walked score	0.40	0.01*	0.78	<0.001*
Lequesne activities of daily living score	0.37	0.02*	0.85	<0.001*
Lequesne index	0.40	0.01*	0.87	<0.001*
KL grading scale	0.33	0.052	0.93	<0.001*

IL-17: Interleukin-17; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; KL: Kellgren and Lawrence grading scale; * Significant p value <0.05.

was reported by Lubbeke et al.[23] and Snelling et al.[24] and this correlation proposed capability of IL-17 as a non-invasive biomarker for disease stratification.

To our knowledge, our study is the first reporting a strong positive correlation between SF IL-17A levels and the duration of KOA.

Miller and Malfait[25] suggested that IL-17 may have a significant role in mechanical pain. Our results support this suggestion, as we found that serum and SF IL-17A levels had significant positive correlations with VAS, WOMAC pain score, and Lequesne pain score, with notable very strong positive correlations of SF IL-17A levels with pain scores. In agreement with our results, Mohamed et al.[19] and Askari et al.[18] observed a significant positive correlation between serum IL-17 and WOMAC pain score; and results of Liu et al.[17] revealed a significant positive correlation between SF IL-17 levels and WOMAC pain score in primary KOA patients. On the contrary, Torres et al.[26] found that pain had indirect relation to IL-17 as it might be related to other factors occurring in the pathology of OA such as bone attrition.

Our results also revealed that serum IL-17A levels had significantly weak positive correlations with total WOMAC score, WOMAC stiffness score, and WOMAC function score, while SF IL-17A levels had significantly very strong positive correlations with the previous scores. In agreement with our results, several authors.[14,27-30] have described the association of disability, measured by the WOMAC scores, with higher levels of proinflammatory cytokines.

In the current study, serum and SF IL-17A levels had positive correlations with Lequesne index (an objective assessment of OA severity), Lequesne maximum distance walked score, and Lequesne activities of daily living score.

In agreement with our results, Chen et al.[4] reported positive correlation between SF IL-17 level and Lequesne index among 98 primary KOA patients; however, they observed no correlation between serum IL-17 concentrations and Lequesne index and suggested that local and systemic production of IL-17 by synovial cells and chondrocytes in local and extra-articular tissues might be leading to increased level of SF IL-17 only. Mohamed et al.[19] support our results as they reported positive correlation between serum IL-17 and Lequesne index.

In the present study, SF IL-17A level not serum had a very strong positive correlation with severity of KOA (KL grade) which reflects the bone destructive role of IL-17 in OA. In concordance with our results, Wang and Mu[22] showed that IL-17 levels in the SF and synovial membrane are positively correlated with KOA severity, while they evaluated the severity of knee articular cartilage damage and synovitis-related pathological changes by arthroscopy using the Outerbridge and Ayral scores. In contrast to our results, Liu et al.[17] reported no correlation between SF IL-17 level and KL grade, which may be referred to the method of patients' selection as they included KOA patients with KL grade ≥1.

In agreement with our study, researchers in a cross-sectional study[31] reported that serum IL-17 was not associated with KL grade. On the contrary, Mathiessen and Conaghan[32] and Mohamed et al.[19] found a positive link between serum IL-17 levels and the severity of KOA using KL grade. The low number of patients in our study with absence of patients with KL Grade 1 may explain the difference with the previous studies.

The present study had some limitations. Firstly, there were statistical limitations mainly in terms of power due to the relatively low number of patients. Secondly, we measured IL-17A levels in serum and SF of KOA patients; however, the detection of IL-17A expression in synovial membrane of KOA patients could have revealed more valuable information on the potential pathophysiological role of IL-17A. Lastly, we could not measure other inflammatory biomarkers (e.g., IL-1, IL-6, and TNF-α) which may provide further valuable information on the role of the IL-17 signaling pathway in OA related-pain and in radiographic progression.

In conclusion, higher IL-17A levels in primary KOA patients were significantly associated with longer disease duration, higher pain scores, worse quality of life, extreme disability, and advanced structural damage. These findings are important because they open a window of possibility for the early use of IL-17 antagonists for the prevention of joint destruction. Further studies with higher

numbers of KOA patients are recommended to classify patients according to IL-17 levels and to verify our results.

Ethics Committee Approval: The study protocol was approved by the Faculty of Medicine Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each participant.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Wrote manuscript: S.K.; Contributes to preparation: R.K.; Measured IL-17 in all patients: H.M.; Performed analytic calculation: S.A.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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