Abdel-Naby *et al.*
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Is interleukin-17 implicated in early knee osteoarthritis pathogenesis as in rheumatoid arthritis?

Hoda M. Abdel-Naby[1], Sarah S. El-Tawab[1*], Mohamed M. Rizk[2] and Nesrin A. Aboeladl[3]

Abstract

Background: Interleukin-17 (IL-17) is a cytokine that promotes activation of multiple catabolic pathways resulting in cartilage and tissue damage. It has features making it increasingly attractive as a biological marker, especially in rheumatoid arthritis (RA) and osteoarthritis (OA). However, its expression is heterogeneous; not all patients' exhibit high IL-17 levels, and its level along the disease course is still challenging to predict.

Aim of the work: The objectives of this study were to compare serum IL-17 levels in patients with early knee OA and in RA patients, to determine its correlation with disease activity in RA and to determine if it is correlated with functional scores in both RA and OA.

Subjects and methods: Twenty early knee OA patients (32.7 ± 3.7) years were included. Diagnosis of early OA was based on Luyten et al. 2012 early knee OA classification (early OA 2012). This study also included 25 RA patients aged 32.8 ± 5.1 years, and the diagnosis was according to 2010 ACR-EULAR classification criteria for RA. The current work also included a control group of 20 healthy volunteers aged 31.9 ± 3.2 years. The serum IL-17 level was assessed by using the ELISA technique.

Results: Serum IL-17 level was significantly high in early knee OA patients (5.2 pg/ml) and was significantly higher in RA patients (5.9 pg/ml) compared to the control group (4.9 pg/ml) ($P < 0.001$).

Conclusions: The increased serum IL-17 level in patients with early knee OA suggests its pathogenic role in the disease. Serum IL-17 positive correlation with the severity of knee OA-related pain proposes that it may be a potential marker to target for early treatment of knee OA-related pain.

Keywords: Interleukin 17, IL 17, Knee osteoarthritis, Rheumatoid arthritis

Background

Knee osteoarthritis (OA) is the most common joint disorder causing functional disability and impaired quality of life. Thus, early intervention and secondary prevention of early knee OA allow a window of opportunity to slow down or reverse the disease process, as has been lightened in other chronic arthritic diseases such as RA [1]. However, there is still a lack of understanding of the underlying pathophysiologic mechanisms [2]. Moreover, available treatments are often used at a late disease stage when structural deterioration is already advanced [3].

Interleukin-17 is known to play an essential role in the pathogenesis of many chronic inflammatory and autoimmune diseases such as RA, systemic lupus erythematosus [4], inflammatory bowel disease [5], ankylosing spondylitis, psoriasis, and psoriatic arthritis [6, 7] as well as multiple sclerosis [8–10]. Scientists found that accurate and effective regulation of IL-17 signaling can control most of these disorders [8–10].

*Correspondence: sarah.tawab@alexmed.edu.eg; Sarah.tawab@gmail.com

[1] Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Alexandria University, Alexandria, Egypt
Full list of author information is available at the end of the article

IL-17 is a pro-inflammatory cytokine secreted by many cells like T-helper-17 (Th17), mast, and myeloid cells. It further promotes the production and release of other pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 from chondrocytes, osteocytes, synovial fibroblasts, and macrophages [11]. IL-17 can also drive synovial fibroblast and inflammatory cell survival and increases expression of the monocyte chemo-attractants C-C Motif Chemokine Ligand 2 and 7 (CCL2 and CCL7) [4]. IL-17 cells can stimulate differentiation of receptor activator of nuclear factor-Kβ ligand (RANK) in osteoblasts, and promote the production of matrix metalloproteinases (MMPS) that disrupt the extracellular matrix homeostasis, thereby bone resorption. In addition, IL-17 can also stimulate other chemokines and adipocytokines [12], causing aggregation of neutrophils, macrophages, and lymphocytes in the synovial membrane that enhances the inflammatory cascade resulting in more severe joint damage [13].

Many studies have demonstrated that IL-17 is overexpressed heterogeneously in RA patients [14, 15]. In knee OA, low-grade synovitis often contributes to increased joint pain and dysfunction and, importantly, a more rapid progression of structural joint deterioration by altering the remodeling capacity of the chondrocytes [16].

Several studies showed that factors like biomechanical stresses predispose to OA and trigger synovitis that contributes to the pathophysiology of OA [3].

IL-17 may be a new potential biochemical marker designating OA. It has been widely used for RA investigation and treatment [17]; however, the importance of its expression in patients with early knee OA is still unknown. This study aimed to compare the serum IL-17 levels in Egyptian patients with RA and another group with early knee OA and a healthy control group. Our aim also was to determine if it is correlated with functional scores in both RA and OA.

Subjects

Twenty-five RA patients (3 were males; 12%) aged 32.8 ± 5.1 years and mean BMI of 29.3 kg/m^2 were included in this study. The diagnosis was made according to the 2010 ACR-EULAR classification criteria for RA [18].

This work also included another group of 20 early knee OA patients aged 32.7 ± 3.7 with a mean BMI of 28.5 kg/m^2 comprised of 17 men and 3 women. Diagnosis of early OA was based on Luyten et al. 2012 early knee OA classification (early OA 2012) [19]. Accordingly, early knee OA was defined by the clinical and imaging findings, and should fulfill three criteria: (I) knee pain, (II) Kellgren-Lawrence (KL) grade 0, I, or II (only osteophytes, no joint space narrowing) on plain X-ray, and (III) cartilage lesion diagnosed by arthroscopy and/or MRI findings of OA.

MRI criteria for OA

Changes of the cartilage, bone marrow lesions, and/or meniscus are detected by the Boston Leeds Osteoarthritis Knee Score (BLOKS), Whole Organ Magnetic Resonance Imaging Score (WORMS), and their comparisons.

The group of early OA patients was selected after exclusion of the following:

- Age older than 50 years at the time of evaluation (to exclude primary idiopathic OA according to the ACR criteria [20].
- Any systemic diseases or inflammatory arthritis.
- Pervious knee or any other joint surgery or arthroscopy (other than arthroscopic partial meniscectomy done for isolated meniscal tears).
- Neurological or muscular disease (because these comorbid conditions will affect the patient's relevant outcome).
- Varicose veins of the lower limbs.
- KL grade > 2 on plain knee radiography.
- Any contraindication to MRI examination.
- Any specific knee disorder like osteochondritis dissecans, osteochondromatosis, osteonecrosis, chondromalacia patellae, patellar subluxation, or fracture in or adjacent to the knee.

Twenty healthy volunteers (3 were males; 15%) with a mean BMI of 29.4 kg/m^2 of matching age 31.9 ± 3.2 years to RA and OA groups represented the control group.

Methods

Patients in the RA group were subjected to (1) full history taking. (2) Systematic clinical examination. (3) Disease activity assessment using the disease activity score 28 (DAS-28) [21]. (4) Disability assessment using Health Assessment Questionnaire–Disability Index (HAQ-DI) [22].

The early knee OA group of patients were subjected to (1) comprehensive general and knee-related history taking. (2) The researchers used the knee injury and osteoarthritis outcome score (KOOS) questionnaire, Swedish version LK 1.0 [23] to quantify knee-related symptoms. It consists of five subscales: pain, joint symptoms, activities of daily living, sports and recreation function, and knee-related quality of life. A score from 0 to 100 is deliberated for each subscale, with 100 signifying the best result. (3) Knee joint examination.

Serum IL-17 levels were assessed using the enzyme-linked immunosorbent assay (ELISA) technique [Human IL-17 RayBiotech ELISA kits, USA].

Statistical analysis

Statistical analysis was conducted using the IBM-SPSS software package version 20.0. Qualitative data were described by numbers and percentages. Categorical variables comparison was done by the chi-square test or Monte Carlo test. The means and standard deviations were used to describe quantitative data. Kolmogorov–Smirnov test was used to test quantitative variables for normality. For normally distributed data, comparison was done by independent *t* test, correlations were assessed by the Pearson coefficient. Abnormally distributed data were assessed using Mann–Whitney test. Spearman correlation analysis evaluated the relationship between IL-17 levels and different functional scores. The significance of the obtained results was at the 5% level.

Table 1 Comparison between the studied groups according to different parameters

	RA ($n = 25$)	KOA ($n = 20$)	Control ($n = 20$)	*P*
• Sex				
Male	3 (12%)	17 (85%)	3 (15%)	< 0.001*
Female	22 (88%)	3 (15%)	17 (85%)	
• Age (years)	32.8 ± 5.1	32.7 ± 3.7	31.9 ± 3.2	0.016
• BMI (kg/m^2)	29.3 ± 1.2	28.5 ± 3.3	29.4 ± 2.0	0.127
Underweight	1 (4%)	0 (0%)	0 (0%)	≥ 0.239
Optimal BW	5 (20%)	1 (5%)	3 (15%)	
Overweight	7 (28%)	10 (50%)	12 (60%)	
Obese	12 (48%)	9 (45%)	5 (25%)	

*Statistically significant at $p \leq 0.05$

Results

Table 1 demonstrates the characteristics of the 3 studied groups. No significant difference exists between the groups regarding age and Body mass index. There was a considerable difference in the sex between KOA and the other 2 groups ($p < 0.001^*$).

The mean serum IL-17 level concentration in RA patients was 5.9 (5.3–9.9) pg/ml, in early knee OA patients was 5.2 (2.6–6.6) pg/ml while in control was 4.9 (0.4–5.1) pg/ml. This difference was statistically significant between the three studied groups ($p < 0.05$) (Fig. 1).

In RA patients, the mean disease duration was 5.23 ± 4 years, ranging from 1 to 9 years. DAS-28 showed severe activity in 13 patients (52%), moderate activity in 9 patients (36%), and three patients (12%) showed mild disease activity score. By HAQ-DI, 15 (60%) patients experienced a mild to moderate disability, 5 (20%) showed moderate to severe disability, and 5 (20%) showed severe to very severe disability in their activity of daily living. Serum IL-17 levels showed an insignificant correlation with DAS-28 interpretation and HAQ-DI in RA patients ($p = 0.571$ and 0.286, respectively) (Table 2).

In the early knee OA group, 7 patients (35%) out of the 20 gave a history of an old twisting injury, 3 patients (15%) had a history of falling to the ground, and the remaining 10 patients reported no or minor knee trauma. None of them had effusion, ligamentous laxity nor

Fig. 1 Box plot graph comparing serum IL-17 level (in pg/ml) in the three studied groups

Table 2 Correlation between serum IL-17 and DAS-28 and HAQ-DI in RA patients, and KOOS pain score in early knee OA patients

	Serum IL-17	
	r	*P*
DAS 28 (RA)		
ESR	0.103	0.624
CRP	0.070	0.741
Interpretation	0.119	0.571
HAQ-DI (RA)	0.222	0.286
BLOCKs grading (KOA)	0.159	0.324
WORMs grading (KOA)	0.148	0.252
KOOS (KOA)	0.277	0.009*

r Spearman coefficient

*Statistically significant at $p \leq 0.05$

bursitis either clinically or by MRI. By plain radiography, all patients were KL grade 0 or 1.

Positive MRI OA-related findings of torn degenerated medial meniscus were present in all patients. Torn posterior horn BLOCKs grade 3 and 4 were 55% and 35%, respectively. Torn anterior horn BLOCKs grade 3 was present in 2 patients (10%). Cartilage morphology score was WORMs grade 3 and 5 in 60% and 40% of patients. However, no correlations between IL-17 levels and any of BLOCKs or WORMs grading in those group of patients ($r < 0.2$, $p > 0.05$) (Table 2).

Patients were instructed to complete the KOOS form by considering their painful knee; the mean KOOS score was 62 ± 9.65. Serum IL-17 was positively correlated with KOOS pain score in early knee OA patients ($r = 0.277$, $P < 0.05$) (Table 2).

Discussion

Knee osteoarthritis (OA) is a disease with a high prevalence in our community. It is often associated with low-grade synovitis that contributes to increased joint pain and dysfunction and, significantly, a more rapid progression of structural joint deterioration [16]. Much of what is known about the inflammatory response in the synovial membrane of patients with OA comes from studies of inflammatory serum markers from patients at end-stage disease [24].

In this study, serum IL-17 was compared in early KOA patients with RA patients and with healthy control group. Among the RA group, only 3 males were included (12% of total patients). Similarly, Oliver et al. (2006) [25] previously published data reported a higher prevalence of RA in women, especially during childbearing years. In selecting the KOA patients, the early disease was the target. Indeed, most of the recruited cases were adult males as they participate in more aggressive sports and manual activities. No significant difference existed between healthy men and women in the published studies regarding the circulating IL-17 level [26]. We assumed that the control group was applicable for comparison with the 2 patient groups. RA patients had significantly higher IL-17 serum levels, by a mean of 5.9 pg/ml, compared to a mean level of 4.9 pg/ml in healthy subjects. Similarly, many researchers reported that serum IL-17 was high in RA patients, and this further supports the hypothesis that IL-17 family cytokines are implicated in the pathogenesis of RA [17].

The mean disease duration was 5.23 ± 4 years, the current study showed no significant correlation between serum level of IL-17 and the duration of the RA disease. Similarly, Rosu et al. (2012) [14] have reported the same results.

Regarding DAS-28 in the studied RA patients, it ranged from 3.63 to 7.7 with a mean of 5.81 ± 1.21 representing all grades of disease activity. Actually, no significant relationship could be detected between serum IL-17 and ESR, CRP, or DAS-28 score. These results did not ignore the importance of IL-17 in RA, but this may be due to different times of sampling concerning disease activity. Also, the synovial fluid IL-17 level was found to be higher than its serum level, as mentioned by Rosu et al. (2012) [14]. In agreement with other studies on Egyptian RA patients, IL-17 was significantly increased but did not correlate with clinical, laboratory, or radiographic scores [27, 28].

Also, Kay et al. (2014) [29] had reported that acute phase reactant levels often do not correlate with RA activity as measured by joint counts and global assessments. This finding might explain that there is no relation between disease activity caused by inflammatory cytokines like IL-17 and acute phase reactants.

In contrast to the previous results, Rosu et al. (2012) [14] and Yue et al. (2010) [30] have reported a good correlation between acute phase reactant, DAS-28 score, and serum level of IL-17.

Moreover, Leeb BF et al. (2005) [31] stated that DAS-28 values for expressing disease activity in RA patients might be flawed by coexisting fibromyalgia. And should therefore be regarded cautiously as high pain levels more than impaired mood may lead to higher total scores.

The HAQ-DI ranged from 0.2 to 2.7 with a mean of 1.2 ± 0.81, including all grades of functional disability among the studied RA patients. These results match the results of the study carried out by Abu Al-Fadl et al. (2014) [32], who reported that RA has a significant impact on many areas of an individual's life and tends to have a profound effect on the health-related quality of life. Wickrematilake et al. (2013) [33] reported that the HAQ-DI assesses a

patient's functional ability and has been verified and used in many clinical trials. However, no significant correlation could be detected between the serum level of IL-17 and HAQ-DI. In agreement with Korayem et al. [28] and Yue et al. (2010) [30], no correlation between serum level of IL-17 and HAQ was found. This finding may be due to the small sample size and also could be explained by the HAQ-DI is a subjective questionnaire differing from one patient to another regarding their dependency, socioeconomic class, or grade of disease activity.

Indeed, IL-17 is a cytokine that has a role in RA pathogenesis. So far, there is no agreement between researchers regarding its role in disease activity and functional disability scores among RA patients. This could be explained by the different functional heterogeneity of TH17 cells. It may be necessary during the early stages of the disease. In contrast, Th1 cells differentiate into cytotoxic CD4+ T cells in later stages that drive direct tissue damage and pro-inflammatory cytokine production [34].

Back to its role in OA, this study was also conducted on 20 patients with early knee OA based on Luyten et al. 2012 early knee OA classification criteria [19]. Those patients were healthy other than their agonizing unilateral knee joint pain [even a long time (ranged 2–7 years) following previous arthroscopic partial meniscectomy done in those with isolated partial meniscal tear]. But they did not fulfill ACR criteria for OA as early KOA was targeted. On plain radiography, they were KL grade 0 or 1. Although positive MRI OA-related findings of torn degenerated medial meniscus were present in all patients (their BLOCKs grade ranged between 3 and 4, and the cartilage morphology score using WORMs ranged between grade 3 and 5); however, no correlations between serum IL-17 levels and any of BLOCKs or WORMs grading in those group of patients ($r < 0.2$, $p > 0.05$) (Table 2). This could be attributed to the diversity of physical activity that may play a role in the risk of associated chondral micro-injuries, as all the early knee OA group was of middle aged active adults. Also, β error could be ascribed due to small sample size.

In agreement, Favero M, et al. (2015) [35] emphasized the role of IL-17, in a group of symptomatic early OA patients, in the initiation and further progression of the osteoarthritic disease process and distinguishing it from the course of aging of knee joint structures.

Contrariwise definitely, in patients with advanced OA, elevated serum and synovial fluid levels of IL-17 were positively correlated with radiographic and MRI osteoarthritic features [36–40]. IL-17 levels in these studies range from 1 to 10 pg/ml in both serum and synovial fluid. Additionally, in specific populations, polymorphisms in the IL-17A gene was correlated with increased risk of OA [41].

Also, Wang K et al. (2017) [39] demonstrated that serum IL-17 was highly related to cartilage destruction. They suggested that metabolic and inflammatory factors may play roles in chondral and bone marrow lesions in patients with knee OA.

In this study, the mean serum IL-17 level concentration in early KOA group was 5.2 (2.6–6.6) pg/ml, significantly higher than in the controls 4.9 (0.4–5.1) pg/ml—but not reaching those levels in studied RA patients 5.9 (5.3–9.9) pg/ml (Fig. 1). Serum IL-17 level in those patients was correlated with KOOS functional score. It was found that it was positively correlated with KOOS pain subscale score ($r = 0.277$, $p < 0.05$) (Table 2).

Similarly, Liu Y et al. (2015) [37] explored that the IL-17 level is correlated with the severity of osteoarthritis knee pain and that blocking the IL-17 signaling pathway can delay osteoarthritis-related pain. Those results may provide new ideas and methods for preventing and treating osteoarthritic pain.

In agreement, many researches emphasized the role of inflammation in OA initiation following meniscal tears [42]. In a group of patients with traumatic meniscal injury but no radiographic evidence of OA, the retrieved synovial tissue lining during arthroscopic meniscectomy is inflamed with increased pain and dysfunction scores as well as altered chemokine profile [43].

Since abnormal biomechanical forces exerted upon the articular cartilage following mechanical traumas are responsible for altered chondrocyte matrix synthesis and repair capacity. Hence, triggering the release of inflammatory mediators such as cytokines, proteolytic enzymes, and reactive oxygen species that adversely affect chondrocyte survival and its turnover capacity with further cartilage degeneration, which is challenging, especially in young adult athletes [44, 45].

Several proofs suggest that IL-17A has a role in OA pathophysiology and IL-17-treated chondrocytes from OA patients showed enhanced expression of catabolic factors that are involved in the destruction of cartilage in OA [46]. Furthermore, IL-17F gene rs763780 C allele confers an increased risk of inflammatory arthritis in Caucasians [47–49].

Therefore, understanding how Th17 cells and their downstream cytokines act at a fundamental level is likely to reveal new strategies for treating RA and other autoimmune conditions [50, 51]. Classifying those patients with early structural changes and increased inflammatory biomarkers [52].

According to the results of this study and other studies mentioned, better identifying IL-17-mediated processes in cartilage would benefit both clinical studies and the management of early OA patients [53–55].

This study has certain limitations. Firstly, the sample size is relatively small. Secondly, we measured IL-17 level only in the serum of those patients with early knee OA; still, its expression in the synovium needs further study. Lastly, this study only explored serum IL-17; other inflammatory biomarkers like IL-1, IL-22, and IL-23 may provide more valuable information on the role of the IL-17 signaling pathway in osteoarthritic pain.

Conclusions

This study further confirms the role of IL-17 in RA pathogenesis and the lack of IL-17 correlation with RA disease activity. In knee OA, IL-17 seems to have a pathogenic role. A rheumatologist may use serum IL-17 level to select patients with early knee OA better, and thus appropriate secondary prevention be the target. In doing so, this will substantially decrease the OA disease burden and disability.

Abbreviations

KOA: Knee osteoarthritis; RA: Rheumatoid arthritis; IL-17: Interleukin-17; KL: Kellgren-Lawrence; BLOKS: Boston Leeds Osteoarthritis Knee Score; WORMS: Whole Organ Magnetic Resonance Imaging Score; DAS-28: Disease activity score 28; HAQ-DI: Disability assessment using Health Assessment Questionnaire–Disability Index.

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Authors' contributions

Hoda M Abdel-Naby and Sarah S El-Tawab contributed to the collection of data and writing of the paper. Mohamed M Rizk performed the ELISA technique to measure IL-17. Nesrin A Aboeladl contributed to the idea of the research, collection of data, and analysis of data. All authors read and approved the final manuscript.

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Availability of data and materials

All data and materials are presented in the main paper.

Declarations

Ethics approval and consent to participate

The ethics committee formally approved this study of the Faculty of Medicine, Alexandria University.

Consent for publication

Informed consents from all participants were signed.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Alexandria University, Alexandria, Egypt. [2]Clinical and Chemical pathology, Faculty of Medicine, Alexandria University, Alexandria, Egypt. [3]Rheumatology and Rehabilitation, Faculty of Medicine, Helwan University, Cairo, Egypt.

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