

Relation of interleukin-15 with the severity of primary knee osteoarthritis

Ibrahim K. Ibrahim^a, Emmanuel K. Aziz Saba^a, Neveen L. Mikhael Saad^b,
Doaa Y.A. Mohammed^c

Departments of ^aPhysical Medicine, Rheumatology and Rehabilitation, ^bClinical and Chemical Pathology, Faculty of Medicine, Alexandria University, ^cPhysical Medicine, Rheumatology and Rehabilitation Department, Ministry of Health Hospitals, Ministry of Health, Alexandria, Egypt

Correspondence to Emmanuel K. Aziz Saba, MD, Physical Medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Alexandria University, Alexandria, 21131, Egypt.
Tel: +20 122 471 8376;
e-mail: emadaziz55@yahoo.com

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Background

Interleukin-15 (IL-15) is a proinflammatory cytokine. IL-15 could be considered a potential biomarker for primary knee osteoarthritis (OA).

Aim

This study aimed to assess the serum level of IL-15 in primary knee OA patients and assess its relation to clinical severity, functional disabilities, and radiological grading of knee OA.

Patients and methods

This study included 40 patients with primary knee OA and 40 apparently healthy individuals. Assessment of knee OA was performed using clinical examination, the Western Ontario and McMaster Universities Osteoarthritis Index score, and Health Assessment Questionnaire-Disability Index. Radiological assessment was performed using the Kellgren–Laurence grading scale. Serum level of IL-15 was measured in both patients and control participants.

Results

There were no statistically significant differences between patients and the control group in sex ($P=1.000$) and age ($P=0.247$). The patient group had a statistically significantly higher serum IL-15 level than its level in the control group ($P\leq 0.0001$). Serum IL-15 level was significantly higher among patients with knee joint line tenderness and effusion ($P\leq 0.0001$). There were statistically significant positive correlations between serum IL-15 level with the Western Ontario and McMaster Universities Osteoarthritis Index total score ($P\leq 0.0001$), the Health Assessment Questionnaire-Disability Index score ($P\leq 0.0001$), and the Kellgren–Laurence grading scale ($P\leq 0.0001$).

Conclusion

Serum IL-15 is elevated and correlated positively with pain, stiffness, functional disabilities, as well as radiological damage in primary knee OA. This suggests that IL-15 plays an important critical role in the pathogenesis of primary knee OA-related pain, stiffness, and joint damage. IL-15 might be a potential biomarker for assessing the severity of primary knee OA.

Keywords:

interleukin-15, Kellgren–Laurence grading, osteoarthritis, primary knee osteoarthritis, Western Ontario and McMaster universities osteoarthritis index

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Introduction

Osteoarthritis (OA) is a common articular degenerative disorder that affects mainly the knee joints. The most common form is primary OA [1]. It is a common cause of musculoskeletal disability worldwide [2,3]. The pathogenesis of primary OA is complex and involves several cytokines such as interleukins and adipocytokines [4,5]. It is known that the proinflammatory cytokines are essential mediators implicated in the pathophysiology of knee OA [6,7].

It is important for detection of biochemical markers that could assess the OA progression and determine its severity early enough before radiological joint damage takes place. Inflammation is believed to play a critical

role in the pathogenesis of OA. Subsequently, the inflammatory mediators that are released in OA could be considered as important mediators in the pathogenesis of OA. They could be candidates for biochemical markers for OA severity and progression [8].

Interleukin-15 (IL-15) is a proinflammatory cytokine. It plays a role in the regulation of T-cells and the activation and proliferation of natural killer cells [6,9]. IL-15 could be considered a potential biomarker for

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primary knee OA. Very few studies have assessed the role of IL-15 in primary knee OA and its relation to OA severity and progression [10,11].

The aim of this study was to assess the serum level of IL-15 in primary knee OA patients and assess its relation to clinical severity, functional disabilities, and radiological grading of knee OA.

Patients and methods

This cross-sectional study included 40 patients with primary knee OA diagnosed according to the clinical and radiographic criteria of the American College of Rheumatology criteria for the classification of primary knee OA (1986) [12]. Patients were recruited from among those attending the outpatient clinic of Physical Medicine, Rheumatology and Rehabilitation Department, Alexandria Main University Hospital. Exclusion criteria included patients with diabetes mellitus, endocrine disorders, overlap with other rheumatologic diseases, traumatic arthritis, secondary OA, and patients with diseases in which IL-15 increased such as inflammatory bowel diseases. The study included 40 apparently healthy volunteers as a control group. The study was explained to the participants. Each participant provided an informed consent. This study was approved by the Ethics Committee of the Faculty of Medicine, Alexandria University, Egypt.

All the patients studied were subjected to demographic data collection, anthropometric measurements, which included height, body weight, and body mass index (BMI), and musculoskeletal examination focusing on both knees. Assessment of primary knee OA severity was performed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The WOMAC has three different subscales for the assessment of pain, stiffness, and function. The scores are summed for items in each subscale. The total WOMAC score of the three subscales was graded as follows: mild (from 0 to 24), moderate (from 25 to 48), severe (from 49 to 72), and extreme (from 73 to 96) [13]. Functional assessment was performed using the Health Assessment Questionnaire-Disability Index (HAQ-DI). The HAQ-DI score of 0–1 is considered to represent mild to moderate functional disability, more than 1–2 to represent moderate to severe functional disability, and more than 2–3 to represent severe to very severe functional disability [14]. Radiological grading of knee OA severity was performed using the Kellgren–Laurence (K/L) 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) [15]. Laboratory investigation in the form of measurement of IL-15 serum level was performed using the enzyme-linked immunosorbent assay (ELISA) technique for the quantitative detection of IL-15. This was performed using human IL-15 ELISA kit (81275C, EIAab; WUHAN EIAAB Science, Wuhan, China) read on ELISA reader (Stat-Fax 2100; Awareness Technology Inc., Palm City, Florida, USA).

Statistical analysis of data was carried out using the statistical package of the social sciences (SPSS version 17) software (University of Cambridge computing service, London, United Kingdom) [16]. This included descriptive measures and analytic measures. The descriptive measures included the count, frequency, minimum, maximum, median, mean, and standard deviation (SD). The analytic measures included the Mann–Whitney test, the Kruskal–Wallis test, the Chi-square test, and the Spearman correlation test. Statistical significance was assigned to any *P* value at less than 0.05. The reference cut-off value of serum IL-15 was calculated by rounding the mean plus two SD to measure the upper limit of normal.

Results

This study included 40 patients with primary knee OA [30 (75%) females]. Their mean age was 54.15±5.18 years (ranged from 45 to 65 years). The study included 40 apparently healthy volunteers [30 (75%) females] as a control group. Their mean age was 52.95±4.13 years (ranged from 48 to 65 years). There were no statistically significant differences between patients and controls in sex ($\chi^2=0.000$, $P=1.000$) and age ($Z=-1.158$, $P=0.247$). Different demographic data and anthropometric measures of the patients and control groups are summarized in Table 1. Different clinical characteristics and radiological assessment of the patients are summarized in Table 2.

The patient group had a statistically significantly higher serum IL-15 level than its level in the control group ($P\leq 0.0001$; Table 3 and Fig. 1). The reference cut-off value for the serum IL-15 level obtained from the apparently healthy individuals was up to 43.1 pg/ml. An elevated serum level of IL-15 was considered if it was above its cut-off value. In 37 (92.5%) patients, the serum IL-15 level exceeded its reference cut-off value.

The patient group with knee joint line tenderness had a statistically significantly higher serum IL-15 level than

Table 1 Different demographic data and anthropometric measures of the patient and the control groups

Different demographic data and anthropometric measures	Patient group (n=40) (mean ±SD)	Control group (n=40) (mean ±SD)	Test of significance	P
Age (years)	54.15±5.18	52.95±4.13	Z=-1.158	0.247
Women [n (%)]	30 (75)	30 (75)	$\chi^2=0.000$	1.000
Anthropometric measures				
Height (cm)	165.67±7.56	165.07±5.98	Z=-0.217	0.828
Weight (kg)	84.65±7.78	81.70±5.88	Z=-1.860	0.063
BMI (kg/m ²)	31.19±2.21	30.20±1.88	Z=-1.742	0.081
BMI categories [n (%)]				
Overweight	13 (32.5)	14 (35.0)	$\chi^2=0.056$	0.813
Obesity	27 (67.5)	26 (65.0)		

BMI, body mass index; n, number of subjects; SD, standard deviation; Z, value of Mann-Whitney test, χ^2 , value of Chi-square test.

* $P<0.05$, statistically significant.

Table 2 Different clinical characteristics and radiological assessment of the patient group

Different clinical characteristics and radiological assessment	Patient group (n=40) (mean±SD)
Duration of the complaints (years)	4.05±1.94
Affected side (right/left) [n (%)]	
Unilateral	3 (7.5)
Right side only	2 (5.0)
Left side only	1 (2.5)
Bilateral	37 (92.5)
Clinical examination [n (%)]	
Presence of knee joint line tenderness	32 (80.0)
Presence of knee effusion	18 (45.0)
WOMAC	
Pain subscale	10.27±4.84
Stiffness subscale	3.95±1.67
Function subscale	24.95±8.563
WOMAC total score	39.07±14.11
WOMAC total score interpretation [n (%)]	
Mild	8 (20.0)
Moderate	21 (52.5)
Severe	9 (22.5)
Extreme	2 (5.0)
HAQ-DI	
HAQ-DI score	0.07±0.11
HAQ-DI score interpretation [n (%)]	
Mild to moderate disability	40 (100)
Radiological assessment	
K/L scale of the right knees (39 knees) [n (%)]	
Grade 1	6 (15.4)
Grade 2	19 (48.7)
Grade 3	12 (30.8)
Grade 4	2 (5.1)
K/L scale of the left knees (38 knees) [n (%)]	
Grade 1	5 (13.2)
Grade 2	20 (52.6)
Grade 3	11 (28.9)
Grade 4	2 (5.3)

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; HAQ-DI, Health Assessment Questionnaire-Disability Index; K/L, Kellgren-Laurence grading scale; n, number of subjects; SD, standard deviation.

its level in patients without knee joint line tenderness and the control group ($P\leq 0.0001$; Table 4). This was

also found for the patient group with knee effusion ($P\leq 0.0001$; Table 5).

Correlations between serum IL-15 level and different demographic data, anthropometric measures, clinical characteristics, and radiological assessment of the patients are summarized in Table 6.

Figures 2–4 show graphical illustrations for the correlation between serum IL-15 level with the total WOMAC score, the HAQ-DI score, and the K/L scale of the right knee.

Discussion

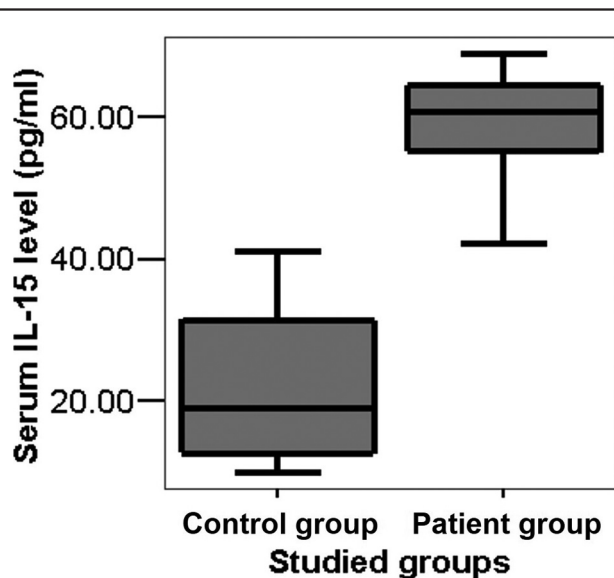
Primary knee OA is a debilitating disease. Its cause is not yet well known. However, it appears to be a response to a complex set of various environmental, genetic, and biomechanical factors. It results in pain, with subsequent functional disabilities limiting the quality of life of the patients. OA is a major cause of disability worldwide with a great economic consequence on the society [1–4,17]. OA is considered to be an inflammatory condition and it is related to a group of inflammatory cytokines [4,5,18]. These cytokines could be good biochemical markers for primary OA. Subsequently, it is essential to detect a reliable chemical biomarker in primary knee OA to facilitate early assessment of OA progression and determine its severity. This also helps to determine effective therapeutic management directed toward the underlying pathophysiological mechanism of OA [10,19,20]. There are several inflammatory markers in OA [6,7,21]. Also, several studies have been carried out on Egyptian patients with primary knee OA that aimed to assess novel biomarkers related to the pathogenesis and/or severity of OA [22–25].

In this study, serum IL-15 level was significantly higher in the patient group in comparison with the

Table 3 Comparison between the two studied groups regarding serum interleukin-15 level

Serum IL-15 level (pg/ml)	Patient group (n=40)	Control group (n=40)	Test of significance	P
Median	60.67	18.99	Z=-7.698	≤0.0001*
Mean±SD	59.29±7.41	21.86±10.61		
Minimum-maximum	42.07-68.87	9.84-40.98		

IL-15, Interleukin-15; SD, standard deviation; n. number of subjects; Z, value of Mann-Whitney test for comparing between the two groups. *P<0.05, statistically significant.

Figure 1

This graph illustrates the comparison between the patient group and the control group in terms of the serum interleukin-15 level ($Z=7.698$, $P\leq 0.0001$). The data are presented as boxplots. The boxes represent the 25th to 75th percentiles; the minimal and maximal values are represented as the below boxes and above boxes lines outside the boxes, respectively. IL-15, interleukin-15; Z, value of Mann-Whitney test for comparing between the two groups.

control group. This was in agreement with previous studies [10,11,26]. IL-15 is a proinflammatory cytokine. Subsequently, it plays a role in the pathogenesis of primary knee OA. It also plays a role in the pathogenesis of other arthritic disorders such as rheumatoid arthritis [27].

In the current study, knee joint line tenderness was present in 80% of the patients. Knee joint effusion was present in 45% of the patients studied. These were in partial agreement with Mohamed *et al.* [25]. They reported that knee joint line tenderness and joint effusion were present in 57.5 and 15% of their studied patients, respectively. The differences between the current study and the Mohamed *et al.* [25] study could be because of the inclusion of relatively more female patients than in this study and the inclusion of patients who were relatively younger than those included in this study. IL-15 serum level was significantly higher among patients with knee joint line tenderness in comparison with patients without

knee joint line tenderness and the control group. Also, patients without knee joint line tenderness had a statistically significantly higher serum level of IL-15 than the control group. These were also found for knee effusion. Although IL-15 serum level was elevated in the majority of the knee OA patients (92.5%), it was higher in patients with evidence of OA active synovitis than those OA patients with less evidence of active inflammation. These were indicators that IL-15 played a role in the inflammatory reaction in knee OA [19]. The low-grade synovitis in knee OA is associated with cartilage degeneration [28,29]. This inflammation is associated with inflammatory cellular infiltration of macrophages and lymphocytes with the contribution of a large group of inflammatory mediators such as tumor necrosis factor- α (TNF- α), IL-1 β , and IL-6 [30].

In the present study, there was a statistically significant negative correlation between serum IL-15 level and the duration of knee OA complaints. This was in agreement with Scanzello *et al.* [11]. This indicated that IL-15 is mainly elevated early in the course of OA. This could be because of the potential contribution of innate immune system activation in the early stages of knee OA pathogenesis [11].

In this study, there was a statistically significant positive correlation between serum IL-15 level and the WOMAC total score as well as WOMAC pain, stiffness, and function subscales. It was reported that inflammatory reaction increases pain sensitivity by increasing the responses of the peripheral nociceptive fibers [31]. This indicates that IL-15 plays a critical role in the pathogenesis of knee OA pain as well as stiffness. Consequently, serum IL-15 was correlated positively with the WOMAC function subscale and the WOMAC total score in addition to the statistically significant positive correlation between serum IL-15 level and the HAQ-DI score. This was in agreement with Sun *et al.* [10] in terms of the WOMAC pain subscale. However, no previous studies have assessed the relation between serum IL-15 level and the WOMAC total score and other WOMAC subscales as well as the HAQ-DI score.

Table 4 Comparison between patients with knee joint line tenderness versus those without tenderness and the control group regarding serum interleukin-15 level

Serum IL-15 level (pg/ml)	Patient group with joint line tenderness (n=32)	Patient group without joint line tenderness (n=8)	Control group (n=40)	Test of significance	P
Median	62.25	55.63	18.99	K=60.700	≤0.0001*
Mean±SD	60.64±6.74 ^{†,‡}	53.91±7.96 ^{†,§}	21.86±10.61 ^{‡,§}		
Minimum–maximum	42.53–68.87	42.07–63.17	9.84–40.98		

IL-15, Interleukin-15; SD, standard deviation; n, number of subjects; K, value of Kruskal–Wallis test for comparing between the three groups. * $P < 0.05$, statistically significant. [†]Significant difference between the patient group with joint line tenderness versus the patient group without joint line tenderness ($Z = -2.384$, $P = 0.017$). Z, value of the Mann–Whitney test for comparison between the two groups. [‡]Significant difference between patients group with joint line tenderness versus the control group ($Z = -6.051$, $P \leq 0.0001$). Z, value of the Mann–Whitney test for comparison between the two groups. [§]Significant difference between the patient group without joint line tenderness versus the control group ($Z = -7.253$, $P \leq 0.0001$). Z, value of the Mann–Whitney test for comparison between the two groups.

Table 5 Comparison between patients with knee effusion versus those without effusion and the control group regarding serum interleukin-15 level

Serum IL-15 level (pg/ml)	Patient group with knee effusion (n=18)	Patient group without knee effusion (n=22)	Control group (n=40)	Test of significance	P
Median	64.49	55.63	18.99	K=63.698	≤0.0001*
Mean±SD	64.20±3.69 ^{†,‡}	55.27±7.30 ^{†,§}	21.86±10.61 ^{‡,§}		
Minimum–maximum	56.31–68.87	42.07–67.32	9.84–40.98		

IL-15, Interleukin-15; SD, standard deviation; n, number of subjects; K, value of Kruskal–Wallis test for comparing between the three groups. * $P < 0.05$, statistically significant. [†]Significant difference between the patient group with knee effusion versus the patient group without knee effusion ($Z = -4.187$, $P \leq 0.0001$). Z, value of the Mann–Whitney test for comparison between the two groups. [‡]Significant difference between the patient group with knee effusion versus the control group ($Z = -6.051$, $P \leq 0.0001$). Z, value of the Mann–Whitney test for comparison between the two groups. [§]Significant difference between the patient group without knee effusion versus the control group ($Z = -6.473$, $P \leq 0.0001$). Z, value of the Mann–Whitney test for comparison between the two groups.

Table 6 Correlation between serum interleukin-15 level and different demographic, anthropometric, clinical, and radiological parameters of the patient group (n=40 patients)

Different demographic, anthropometric, clinical, and radiological parameters	Serum IL-15 level (pg/ml)	
	r_s	P
Age (years)	0.217	0.179
Duration of complaints (years)	-0.796	≤0.0001*
Anthropometric measures		
Height (cm)	-0.076	0.641
Weight (kg)	0.118	0.467
BMI (kg/m ²)	0.281	0.079
WOMAC		
Pain subscale	0.775	≤0.0001*
Stiffness subscale	0.726	≤0.0001*
Function subscale	0.837	≤0.0001*
WOMAC total score	0.877	≤0.0001*
WOMAC total score interpretation	0.776	≤0.0001*
HAQ-DI score	0.720	≤0.0001*
Radiological assessment		
K/L scale of the right knee	0.815	≤0.0001*
K/L scale of the left knee	0.830	≤0.0001*

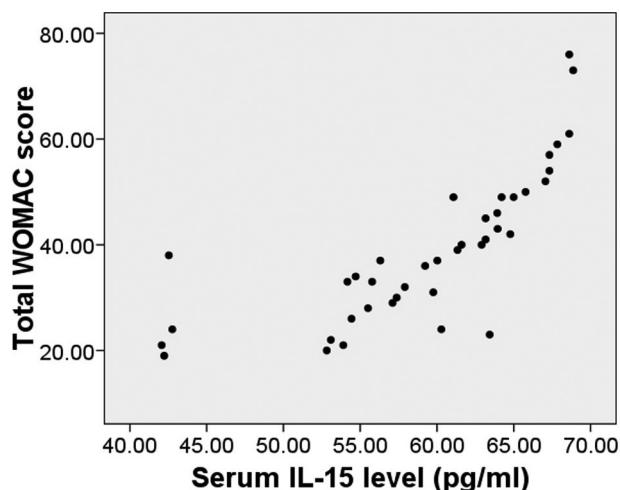
BMI, body mass index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; HAQ-DI, Health Assessment Questionnaire–Disability Index; K/L, Kellgren–Laurence grading scale; IL-15, Interleukin-15; r_s , Spearman correlation coefficient. * $P < 0.05$, statistically significant.

There was a statistically significant positive correlation between the serum IL-15 level and the K/L scale. This indicated that IL-15 could be a marker of knee joint damage by OA. This was not in agreement with Sun *et al.* [10] and Scanzello *et al.* [11]. This could be because of differences in the age and anthropometric measures of the patients included in their studies and the current study. Also, Scanzello *et al.* [11] assessed

the synovial fluid level of IL-15 and not the serum level.

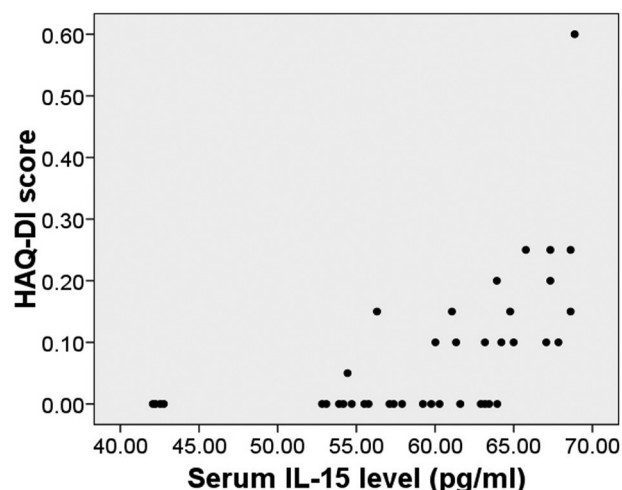
The statistically significant positive correlations between serum IL-15 level with different aspects of primary knee OA indicated that the higher the serum level of IL-15, the more the patient perceived pain, the worse the stiffness and functional disabilities, and the

Figure 2



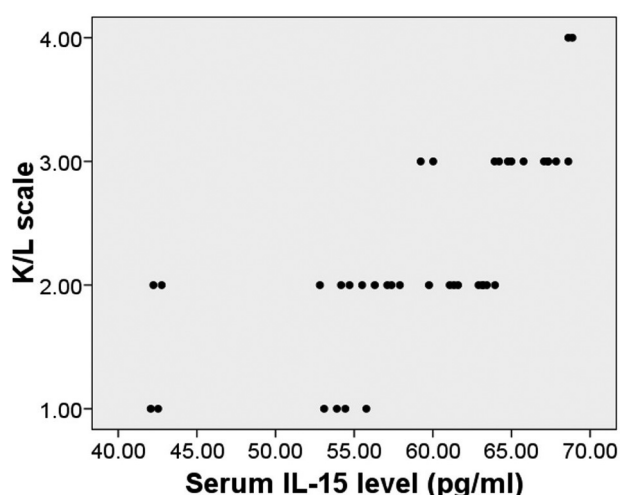
This graph shows the correlation between serum interleukin-15 level and the total Western Ontario and McMaster Universities Osteoarthritis Index score ($r_s=0.877$, $P\leq 0.0001$). IL-15, interleukin-15; r_s , Spearman correlation coefficient; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 3



This graph shows the correlation between serum interleukin-15 level and the Health Assessment Questionnaire-Disability Index score ($r_s=0.720$, $P\leq 0.0001$). HAQ-DI, Health Assessment Questionnaire-Disability Index; IL-15, interleukin-15; r_s , Spearman correlation coefficient.

Figure 4



This graph shows the correlation between serum interleukin-15 level and the Kellgren–Laurence grading scale of the right knee ($r_s=0.815$, $P\leq 0.0001$). IL-15, interleukin-15; K/L, Kellgren–Laurence grading scale; r_s , Spearman correlation coefficient.

more the joint radiological damage. Therefore, IL-15 could be a potential serum biomarker for the detection of the severity of primary knee OA [6]. Also, IL-15 could be a potential target for a therapeutic intervention in primary knee OA [6].

IL-15 affects all aspects of primary knee OA in terms of pain, stiffness, functional disability, and radiological deterioration. IL-15 could be considered an OA biomarker that provides important information on disease severity and radiological damage with

prediction of disease progression. This was in agreement with the concept that systemic inflammatory markers are associated with a severe course of OA [6].

The results of this study showed that IL-15 played a role in the inflammatory reaction in knee OA. IL-15 is a cytokine produced in the innate immune response as IL-1 β , TNF- α , and IL-6 [11]. IL-15 is a proinflammatory cytokine. It has many physiological functions. It is produced by many cell types. It is produced by activated lymphocytes and dendritic cells, in addition to synovial fibroblasts and macrophages [32]. It acts by modulating immune cells of the innate and adaptive immune systems [33]. IL-15 has the ability to recruit and activate the natural killer cells and CD8 T lymphocytes within the OA joint [9,34–36]. It was described as a T-cell growth factor [9]. It promotes the production of other proinflammatory cytokines such as TNF- α and IL-6 by the synovial T-cells within the synovial membrane [30]. These cytokines have been found to contribute in the pathogenesis of OA by increasing articular cartilage degeneration [37]. IL-15 has the ability to induce matrix metalloproteinase production and mainly matrix metalloproteinase-1 production by fibroblasts. All these promote articular cartilage and subchondral bone damage [38].

Therefore, the proinflammatory effects of IL-15 explain the statistically significant correlations found in this study [27]. Subsequently, studies on targeting

IL-15 in treatment of primary knee OA could be expected to result in adequate therapeutic improvement in OA.

This study had some limitations. First, this cross-sectional study included a relatively small number of patients. Further studies with more patients are needed to verify the results of the current study. Second, the current study only assessed the serum IL-15 level. It did not assess the level of IL-15 in the synovial fluid aspirated from knee OA joints, which could provide new information on its role in the pathogenesis of knee OA. Third, this study only assessed the serum IL-15 level and did not investigate other inflammatory mediators such as IL-1 β to assess the relationship between serum IL-15 and other cytokines in patients with primary knee OA.

Conclusion

Serum IL-15 is elevated and correlated positively with pain, stiffness, functional disabilities, as well as radiological damage in primary knee OA. This suggests that IL-15 plays an important critical role in the pathogenesis of primary knee OA-related pain, stiffness, and joint damage. IL-15 might be a potential biomarker for assessing the severity of primary knee OA. Further studies on the efficacy of blocking IL-15 signaling pathways to control and delay primary knee OA degenerative processes are recommended.

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Conflicts of interest

There are no conflicts of interest.

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