IRONICALLY, SERUM AND SYNOVIAL INTERLEUKIN-17 LEVELS IN PATIENTS WITH KNEE OSTEOARTHRITIS ARE NOT RELATED TO PAIN AND DISEASE SEVERITY

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ABSTRACT

Introduction: Biomarkers measured in blood may provide information on disease inflammatory burden. Although osteoarthritis (OA) is a degenerative disorder, inflammatory episodes may occur on top causing effusion and pain increasing the burden of the disease.

Aim: This study aimed to evaluate serum and synovial interleukin-17 (IL-17) levels in OA patients and their relation to pain and disease severity.

Methods: This is a case control study that was carried out in Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University Hospitals on thirty osteoarthritic patients. Patients were subjected to full history taking, thorough clinical examination, laboratory investigations and radiological examination. Pain was assessed using Visual Analogue Scale (VAS “0-10cm”) and Western Ontario & McMasters Universities (WOMAC) index. Disease severity was evaluated by Kellgren and Lawrence grading scale. Laboratory parameters included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and IL-17. Serum IL-17 level using ELISA was measured for all patients and controls and synovial IL-17 was measured in patients.

Results: The study showed no statistically significant difference between serum and synovial IL-17 level among osteoarthritis patients compared to controls. There was no correlation between serum or synovial IL-17 level and different clinical manifestations of osteoarthritis, patients’ age, disease severity, disease duration, laboratory findings of osteoarthritis patients and different treatment modalities (P>0.05).

Conclusion: Ironically, serum and synovial IL-17 levels were not correlated with pain nor disease severity in Knee OA patients.

Key words: Osteoarthritis, serum IL-17, synovial IL-17, disease severity

Advances in Knowledge

1. The article describes osteoarthritis, a chronic debilitating condition, with incompletely understood pathogenesis till nowadays

2. It emphasizes the fact that osteoarthritis still requires an effective treatment that is still undiscovered

3. Interleukin 17 has been proposed to have a key role in osteoarthritis, is it true?
Application to Patient Care

1. The article discusses whether Interleukin-17 can be used for monitoring disease severity in osteoarthritis.

2. The article discusses the relation of Interleukin 17 to the perpetuation of osteoarthritis, can it become a possible therapeutic target.

I. INTRODUCTION

Knee osteoarthritis (OA) is a progressive intra-articular disease involving tibia-femoral and patello-femoral cartilage, in addition to all related intra-articular and periarticular structures. It is one of the most common causes of walking-related disabilities causing knee pain and deformity.

Osteoarthritis (OA) is the most common type of joint disease in the world. The prevalence of knee OA increases considerably with age, peaking at about 50 years. Knee OA has a lifetime risk of about 46 percent, and symptomatic disease is estimated to affect 10 percent of men and 13 percent of women aged 60 and up. The disease's main negative effects are pain, physical impairment, and loss of function, which are all linked to a lower quality of life.

IL-17 has been shown to have an important role in rheumatoid arthritis patients with elevated serum levels, synovial fluid and synovium concentrations. It has been associated with chronic inflammation, cartilage damage and bone loss. Despite the great difference in pathogenesis, osteoarthritis shares some features of rheumatoid arthritis including joint damage and attacks of synovitis.

The interaction of IL-6 and IL-17 has been proposed to be important in the pathogenesis of chronic inflammatory diseases, with IL-6 inducing Th17 cell differentiation and thus IL-17 formation independent of TNF and IL-1. IL-6 has been identified as a biomarker in OA that can contribute to cartilage degradation in a number of tests, but no relationship between IL-17 and IL-6 in OA has been investigated.

IL-17A primarily regulates the immune system by stimulating the development of pro-inflammatory cytokines and chemokines, which recruit neutrophils and macrophages to the site of inflammation. Non-hematopoietic cells, such as fibroblasts and epithelial cells, and innate immune cells, such as macrophages and neutrophils, all express the IL-17A receptor.

IL-17F can facilitate granulopoiesis and neutrophil recruitment by inducing the development of proinflammatory cytokines (IL-6, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor) and chemokines (CXCL1, CXCL2, and CXCL5), though less potently than IL-17A. Cytokines are an important focus in OA treatment and prevention research. IL-17 has been proven to have a role in many rheumatologic diseases but studies for its role in OA are still limited. Many new therapies targeting IL-17 have been recently developed, despite their use in some rheumatologic conditions their role in osteoarthritis is still not highlighted. The aim of this research was to evaluate the levels of serum and synovial IL-17 in an Egyptian group of OA patients compared to controls and to study their relation to pain and severity.

II. MATERIALS AND METHODS

2.1 Study design and subjects:

This is case-control research carried out in Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University Hospitals. The study included 30 patients who met American College of Rheumatology (ACR) clinical and radiological classification criteria for osteoarthritis of the knee. They were 6 males and 24 females. Also, 30 apparently healthy age and sex matched controls were included in the study. Patients with secondary OA; infection, and those who have cerebrovascular disease, liver or renal insufficiency, malignant tumor, or other diseases were excluded from the study.

2.2 Clinical and laboratory parameters of pain and inflammation

Pain and inflammation were assessed clinically using Visual Analogue Scale (VAS “0-10cm”), morning stiffness, inactivity stiffness, tenderness, hotness, muscle wasting, effusion, synovial thickening and limitation of movements. Laboratory parameters were recorded including erythrocyte sedimentation rate (ESR), C-reactive
proteins and IL-17 levels. Serum IL-17 levels were measured for all patients and controls while synovial IL-17 levels for patients. Also, Western Ontario and McTavish Universities (WOMAC) index was assessed for all patients.

2.3. Radiologic Grading

Kellgren and Lawrence OA grading scale was used to assess the severity of the disease. The Kellgren-Lawrence (KL) grading system is still considered the mainstay for grading OA in clinical research. KL grades start from grade 0 (absence of osteophytes or joint space narrowing) up to grade 4 (severe joint space narrowing in addition to subchondral sclerosis).

2.4. Statistical Methods:

All data were collected, tabulated and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA). Mann Whitney U test was used to compare between two groups of non-normally distributed variables. Percentage of categorical variables were compared using Chi-square test and Fisher Exact test. Spearman's rank correlation coefficient was calculated to assess relationship between various study variables.

III. RESULTS

3.1. Demographic and Disease characteristics

Table (1) shows the demographic data of osteoarthritis patients and controls. The mean age of OA patients was 50.5 ± 7.06. The table shows that there was insignificant difference between patients and controls as regards demographic data and BMI (p>0.05). Table (2) shows disease characteristics, pain, and severity assessments of osteoarthritis patients (n=30).

The most frequent manifestation was painful limitation of movement (96.7%), and the least manifestation was deformity (3.3%) among osteoarthritis patients. No significant association was found between different serum levels of IL-17 and different clinical and radiographic parameters of the patients as shown in Table (3). The median osteoarthritis duration was 2.5 years ranging from one to ten years. Table (5) shows that about 83.3% of osteoarthritis patients used NSAIDs, 26.7% received local corticosteroid injections and 13.3% of them underwent knee surgery. Comparing levels of serum interleukin-17 among OA patients and controls revealed no significant difference (P >0.05) as shown in figure 1.

3.2. Relation between serum and synovial IL-17 level and characteristics of osteoarthritis patients

Table (4) shows the correlation between serum and synovial IL-17 and age, disease severity, disease duration, laboratory findings of osteoarthritis patients. This table shows insignificant difference in serum and synovial IL-17 among osteoarthritis patients with age, disease severity, and disease duration and laboratory findings. Table (5) shows serum and synovial IL-17 level and treatment modalities used by osteoarthritis patients. The table shows insignificant difference in serum and synovial IL-17 level among osteoarthritis patients with different treatment modalities. Synovial IL-17 (median: 39.9 (8.2-425.9) pg/ml) in knee effusion showed insignificant correlation with serum values in osteoarthritis patients (r: 0.039, P value: 0.89).

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<thead>
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<th>Studied groups</th>
<th>( \chi^2 )</th>
<th>p-value</th>
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<td><strong>Control n=30</strong></td>
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<td><strong>Age in years (Mean ±SD)</strong></td>
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<td>7 23.3</td>
<td>3.77 0.052</td>
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<td>1.9 0.17</td>
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<td>7 23.3</td>
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Table (2): Disease characteristics, pain and severity of knee OA patients

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<td>Disease duration (years)</td>
<td>2.5(1-10)</td>
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<td>Duration of MS (minutes)</td>
<td>15(0-30)</td>
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<td>Duration of inactivity stiffness (minutes)</td>
<td>5(0-10)</td>
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<tr>
<td>Mean ±SD</td>
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</tr>
<tr>
<td>VAS score (0-10)</td>
<td>8.56±1.5</td>
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<td>WOMAC score (0-96)</td>
<td>69.8±16</td>
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</table>

Table (3): Relation between serum and synovial IL-17 level and different clinical manifestations of osteoarthritis patients and radiological grading (n=30)

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<tr>
<th>Items</th>
<th>Serum IL-17 Median(range)</th>
<th>No</th>
<th>MW</th>
<th>P</th>
<th>Synovial IL-17 Median(range)</th>
<th>No</th>
<th>M</th>
<th>P</th>
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<td>18</td>
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<td>0.42</td>
<td>44.5(20.5-425.9)</td>
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<td>0.98</td>
<td>0.32</td>
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<tr>
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<td>1.12</td>
<td>0.26</td>
<td>28.95(20.5-37.4)</td>
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<tr>
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<tr>
<td>No</td>
<td>57.1(31-796.5)</td>
<td>15</td>
<td>0.64</td>
<td>0.52</td>
<td>20.5(20.5-20.5)</td>
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<td>1.27</td>
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<td>62.2(12-405.2)</td>
<td>15</td>
<td>40.1(8.2-425.9)</td>
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<tr>
<td>Bony prominence</td>
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<tr>
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<td>57.1(12-544.5)</td>
<td>25</td>
<td>1.47</td>
<td>0.14</td>
<td>38.95(8.2-425.9)</td>
<td>12</td>
<td>0.87</td>
<td>0.38</td>
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<td>207.8(31-796.5)</td>
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<td>50.4(38.3-53.8)</td>
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<td>57.05(12-544.5)</td>
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<td>0.19</td>
<td>39.9(8.2-425.9)</td>
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<td>0.51</td>
<td>0.61</td>
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Figure 1: Comparison between serum IL-17 among OA patients and controls
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MW: Mann Whitney U test, P: P value

Table (4): Correlation between serum and synovial IL-17 and age, disease severity, disease duration, laboratory findings of osteoarthritis patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Serum IL-17 (n=30)</th>
<th>Synovial IL-17 (n=15)</th>
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<tr>
<td></td>
<td>r</td>
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<tr>
<td>Age</td>
<td>0.282</td>
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<td>BMI</td>
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<td>Disease Duration</td>
<td>0.109</td>
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<td>Duration of MS</td>
<td>0.174</td>
<td>0.357</td>
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<tr>
<td>Duration of Inactivity stiffness</td>
<td>0.022</td>
<td>0.907</td>
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<td>VAS score</td>
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<td>WOMAC score</td>
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<td>Hb</td>
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<td>ESR</td>
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<td>CRP</td>
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</table>

r Correlation coefficient, insignificant p>0.05, Hb: Hemoglobin, ESR: Erythrocyte sedimentation rate, CRP: C reactive protein, VAS: Visual analogue scale, WOMAC: Western Ontario and McMaster Universities Arthritis index, MS: morning stiffness, BMI: Body mass index.

Table (5): Serum and synovial IL-17 level and treatment modalities used by osteoarthritis patients (n=30):

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<th>Serum IL-17 Median(range)</th>
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<th>P</th>
<th>No.</th>
<th>Synovial IL-17 Median(range)</th>
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<td>38(38-38)</td>
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<td>Physical therapy</td>
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<td>No</td>
<td>12</td>
<td>57.05(12-544.5)</td>
<td>0.89</td>
<td>0.37</td>
<td>13</td>
<td>38.3(8.2-425.9)</td>
<td>1.19</td>
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IV. DISCUSSION:

Osteoarthritis (OA) is a degenerative joint disease affecting the cartilage, as well as other tissues that cover it. Loss of articular cartilage, subarticular bone remodeling, and formation of osteophytes, ligamentous laxity, and periarticular muscle weakness and in some cases, synovial inflammation may occur.  

Female ethnicity, ageing, and obesity are both risk factors for this multifactorial disorder. Medical characteristics of OA patients vary, including pain, disease development level, bony changes (osteophyte shape, subchondral bone sclerosis), synovitis strike, and functional ratings. Prognostic, surgical, and clinical advancements are all hampered as a result of this. Treatments are restricted to analgesia, intra-articular injection and arthroplasty. 

Interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF) are pro-inflammatory mediators, and adipocytokines including leptin and resistin are found in OA SF and serum, and have been linked to disease progression. The proinflammatory cytokine interleukin (IL) -17 has been linked to the activation of local inflammation as well as joint destruction in rheumatoid arthritis synovial tissue. From chondrocytes and synovial fibroblasts, IL-17 has been shown to facilitate the synthesis and release of pro-inflammatory cytokines such as IL-6. It is thought to promote the synthesis of C-C Chemokine Chemokine Ligand2 (CCL2) and C-C Motif Chemokine and drive synovial fibroblast and inflammatory cell survival.

The findings of this study revealed that the serum and synovial levels of IL-17 in OA patients and controls were not significantly different. Yingsong et al. observed that the amount of IL-17 in OA patients' serum increased dramatically as compared to stable controls, contrary to our findings. Mohamed et al. also found that serum IL-17 concentrations in OA patients were slightly higher than in controls, with a p value of 0.001. Askari et al. discovered that serum levels of IL-17A and IL-23 were statistically higher in OA patients than in healthy controls, implying that IL-17A levels can represent OA progression and may be used as a new biomarker.

Snelling et al. discovered a moderately important association between osteoarthritis patients' serum and synovial fluid IL-17, while IL-17 levels in serum and synovial fluid of patients with knee osteoarthritis had little association with KL grading, according to Yingsong et al. Chen et al. discovered that overall OA patients (n = 98) had slightly higher serum IL-17 concentrations than in controls (n = 50). They stated that “When patients were stratified according to Kellgren–Lawrence (KL) grade, IL-17 serum concentrations were significantly higher in patients with grade 4 osteoarthritis than in controls. There were no significant differences between patients with grade 2 or grade 3 osteoarthritis and controls.” Snelling et al. found no major differences in baseline and clinical characteristics, as well as functional scores, among OA patients with and without detectable synovial fluid IL-17.

There was no substantial association between serum or synovial IL-17 and functional status as measured by the WOMAC score in the current analysis. Mohamed et al. discovered a strong positive association between serum IL-17 levels and the severity of the WOMAC score, pain scale, Lequesne index, and KL scoring. Also, Askari et al. discovered a connection between IL-17A levels in the blood and the WOMAC pain scale. IL-17 level in synovial fluid was positively associated with WOMAC pain score in osteoarthritis patients, according to Yingsong et al.

In synovial fibroblasts, IL-17 concentrations were associated with arthritis disease activity and matrix metalloproteinase production, indicating a role for this cytokine in cartilage degradation, according to Chen et al. According to Mohamed et al. he found a clear link between IL-17 levels in the blood and primary knee osteoarthritis, and this may indicate the seriousness of the condition to some extent.

This study has certain limitations. The sample size in this study was relatively small. A second limitation is that it is a single center study and further research is needed with larger multicenter studies.
In conclusion, there was insignificant association between serum and synovial fluid IL-17 with age, clinical manifestations, disease severity, disease duration, and laboratory findings among this group of Egyptian knee osteoarthritis patients. According to our results there was also no association between levels of serum and synovial fluid IL-17 and severity of knee osteoarthritis. Searching for other biomarkers playing a pivotal role in OA is still needed for optimizing treatment.

Declarations

Ethical approval and consent to participate:

Patients and controls were enrolled in the study after taking an informed consent. The study followed the principles of the Helsinki Declaration and ethical approval was received from the Institutional Review Board (IRB) of Zagazig University Hospitals.

Consent for publication

All authors have approved all parts of the manuscript and a consent for publication has been taken from all authors.

Data Availability

All data material is available upon request.

Competing interests

We all authors confirm that we have no competing interests. There is no conflict of interest to declare.

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REFERENCES