Hidden aspects of inflammation in radiographic knee osteoarthritis

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Abstract. Primary osteoarthritis (OA) is known historically to be a non inflammatory condition but recent observations indicate that a low grade inflammation is encountered in pathophysiology of OA's symptoms and progression. We enrolled 150 female patients aged between 50-70 years old diagnosed as OA. Exclusion criteria were any recent infection, trauma, and proved rheumatologic disease. Bilateral standing knee joint radiography was taken and all were categorized according to Kellgren and Lawrence scale. Markers of inflammation consisting of ESR (1st hour), CRP, Anti-CCP and IgM RF were measured in harvested blood samples. Laboratory results from the patients with low radiographic knee OA (grade I and II) were compared to those in high grade patients (grade III and IV). The mean serum level of ESR in low and high grade groups was 12.85±18.65 and 13.65±15.25 respectively (p = 0.77). As for the anti-CCP, the values of 13.87±43.75 and 23.42±58.87 were obtained for low and high grades respectively (p = 0.26). The differences between the positivity of RF (p = 0.51) and CRP (p = 0.56) in both groups was also not statistically significant. But inflammation score was significantly higher in high grade group than low grade group (p = 0.03). We conclude that although the differences weren't remarkable but severity of inflammation in higher radiographic grades should be taken into consideration of OA's progression.

Keywords: Radiographic knee osteoarthritis, Kellgren and Lawrence scale, inflammatory markers, ESR, CRP, RF, anti-CCP

Introduction

Primary knee osteoarthritis (OA) is a common chronic degenerative disease characterized by the loss of articular cartilage components due to an imbalance between extracellular matrix destruction and repair [1]. OA is the main cause of arthralgia and also the most important rheumatologic underlying cause of disability [2] which lead to premature retirement [3]. Pathological mechanism in OA consists of destruction of articular cartilage, increased activity of sub-chondral bone and creating osteophytes. In progressive OA, synovitis and thickening of articular capsule also exist. By the progression of pathology, the radiologic signs appear [4].

The principal risk factors for OA are age, gender and weight [5]. Age has the strongest relation with OA among others. About 80% of patients over the age of 70 years old have radiologic changes compatible with OA [6]. In some countries because of some specific activities in their life style, their knees are under pressure to a greater extent and OA represent in very early ages [7]. Other less important risk factors for OA are biomechanical stress on articular cartilage, genetic factors, alignment disorders, repeated trauma to the ligaments and meniscus [8]. Another risk factor which can be added to this list is systemic inflammation. Most known rheumatologic conditions can cause secondary osteoarthritis but hidden spectrum of systemic inflammation is the case. Inflammation influences the synovium. It then synthesizes biological stimulators such as cytokines and growth factors that lead to destruction of articular cartilage. Inflammation not only destructs the matrix of cartilage but also prevent any reconstruction [9]. One of the mechanisms that can lead to OA is systemic low grade inflammation. OA in non-weight bearing joints of obese patients is a good example to explain the role of inflammation. Adipose tissue secretes Leptin and growth factors. Leptin proliferates T-cells, monocytes and neutrophils which secret interleukin 6 (IL-6), tumor necrosing factor (TNF), C4 inhibitor, C3 and etc and finally destruct the joint [10-14].

Recent studies on molecular pathogenesis of OA revealed new pathways that contribute to inflammation. By activating these pathways, phenotypic shift occurs in chondrocytes and normal homeostasis deregulates which finally all these pathways lead to upregulation of metalloproteinase 13 that causes the damage in joint. Along with this the antagonist of IL-1 cannot be produced due to increase in nitric oxide concentration which exacerbates the destruction process of joint [15, 16].

 Destruction process in OA is usually known to be a non-inflammatory event to be discriminated from rheumatoid arthritis. However, the results of recent studies and the considerable amount of patients showing clinical

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and laboratory signs and symptoms related to inflammation such as morning stiffness and therapeutic effect of NSAIDs, bring this idea to the forefront to search for any possible trace of inflammation in OA.

In this study we evaluated the markers of inflammation including ESR (1st hour), CRP, anti-CCP and IgM RF in different grades of radiographic knee OA and compared the high grade and low grade groups to each other.

Materials and Methods

In this comparative diagnostic study, 150 female patients between the ages of 50 to 70 years old, diagnosed as OA and were under treatment at least for 6 months who admitted to Shahid Sadoughi rheumatology clinic were selected. Exclusion criteria were the history of any recent infection, anemia, any trauma to knees, any kind of proved rheumatologic disease such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, septic arthritis, CPPD. After getting the inform consents, bilateral standing knee radiography was taken in an antero-posterior view in patients. All radiographs were categorized according to Kellgren and Lawrence scale [17] into 4 grades by an expert radiologist as follows: grade 0: normal, grade 1: doubtful narrowing of joint space and possible osteophytic lipping, grade 2: definite osteophytes, possible narrowing of joint, grade 3: moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour, and grade 4: large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour.

In the sequence order, markers of inflammation consisting of ESR (1st hour), CRP, anti-CCP and IgM RF were measured in harvested blood samples. At least one month before doing the lab tests patients should not use any non-steroidal inflammatory drugs (NSAIDs). Westergren tube was used to measure ESR (1st hour) and less than 30mm/h was assumed to be normal. Augglutination method was used to measure both CRP and IgM RF. The results were reported as positive or negative. Anti-CCP was measured by ELISA and less than 15mg/dl was assumed to be normal. Laboratory results from the patients with low radiographic knee OA (grade I and II) were compared to those with high radiographic knee OA (grade III and IV). In addition patients of both groups were matched according to their age and also presence of diabetes mellitus to reduce any possible bias in the results of measuring inflammatory markers.

For each patient in both groups inflammation score was also calculated in such a way that normal serum level of anti-CCP and ESR (1st hour) and negative result of RF and CRP receives the score of zero for each of the lab tests, so patients with all normal lab tests receive a 0 scores for inflammation. Having higher serum level of anti-CCP, ESR and positive RF and CRP, receives 1 score for each abnormal laboratory test. Inflammation scores of patients ranged from 0 to 4.

All patients’ data were analyzed using SPSS software version 18 (SPSS, Chicago, IL) and t-test and chi-square test were used. A P value <0.05 was considered significant.

Results

This study was carried out on 150 female patients who were diagnosed as OA at least for 6 months and were under treatment. Of these 75 patients who had knee radiography compatible with grade I and II by Kellgren and Lawrence scale were allocated to low radiographic knee osteoarthritis grade group and 75 patients with Grade III and IV were allocated to high grade group.

The mean age of patients in low grade group was 54.45±9.05 years old and this was 56.24±10.45 years old in high grade group. The difference between the ages of both groups was not statistically significant (p= 0.73).

The mean serum level of anti-CCP in low and high grade OA was 14.70±9.05 mg/l and 18.70±10.95 mg/l respectively with a P value of 0.51 which was not statistically significant.

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TABLE 1

<table>
<thead>
<tr>
<th>Radiologic grade</th>
<th>Inflammation score</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>High (%)</td>
<td>53.3</td>
</tr>
<tr>
<td>Low (%)</td>
<td>29.3</td>
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* Mean inflammation score: high grade vs. low grade, p = 0.03.

Grade radiographic knee OA was 13.87±43.75 and 23.42±58.87 mg/dl respectively. Although a difference of 10 mg/dl was seen between the groups but this difference was not statistically significant (p=0.26) (Fig. 1). 12 patients (16%) in low grade radiographic knee OA and 25 patients (33.3%) in high grade radiographic knee OA had higher serum level of anti-CCP than normal range. This difference was significant statistically (p=0.01). The mean serum level of ESR (1st hour) was 12.85±18.65 in low grade radiographic knee OA group and 13.65±15.25 in high grade group.

The value of ESR (1st hour) was also higher in high radiographic knee OA group but was not statistically significant (P=0.77) (Fig. 2). The number of patients showing higher serum level of ESR (1st hour) than normal range in low and high radiographic knee OA was 11 (14.7%) and 14 (18.7%) respectively which was not statistically significant (p=0.33).

The frequency of IgM RF positivity in low grade radiographic knee OA group was 14.7% and in high grade group was 18.7%. The difference between both groups was not statistically significant (p=0.51) (Fig. 3).

The frequency of CRP positivity in low and high grade radiographic knee OA group was 21.3% and 25.3% respectively, showing a 4% increase in high grade group but this difference was not statistically significant (p=0.56) (Fig. 3).

The mean inflammation score in low and high grade radiographic knee OA was 0.67±0.87 and 0.96±0.79 respectively. Statistical analysis showed that the difference between two groups was significant (p=0.03) (see Table 1).

Therefore, considering four markers of inflammation for each patient showed a higher trace of inflammation in higher radiologic OA grades.

Discussion

In recent studies systemic inflammation has been introduced to have a role in pathogenesis and progression of OA, thus in this study we evaluated the inflammatory markers consisting of anti-CCP, ESR (1st hour), CRP and IgM RF among female patients between the ages of 50 to 70 years old who were diagnosed as OA and were under treatment. The results of this study showed higher serum level of inflammatory markers in high grade radiologic knee OA (grade III and IV) than low grade group (grade I and II) but this difference was not statistically significant. But the number of patients showing abnormal lab test for anti-CCP and also the inflammation score which was based on the frequency of abnormality of four lab tests together showed significant difference.

The result of early studies showed elevated inflammatory markers in OA compared to normal serum and synovial samples but not exclusive to rheumatoid arthritis [18]. In recent studies at least in some cases the trace of inflammation in OA has been proved. The theory of "wear and tear" was questioned and this disease is no longer assumed to be completely non-inflammatory [19].

In a review by Berenbaum, OA is introduced not to be osteoarthrosis and low grade systemic inflammation caused by metabolic syndrome, innate immunity and inflamming are not in favor of assuming OA as a non-inflammatory disease anymore [20]. In another review by Liu-Bryan, inflammatory complement of innate immune system has a key role in progression of OA [21].

The results of a study done by Pearl et al. showed that patients with OA who had cartilage inflammatory infiltration in pathology had a higher CRP that can be representative for synovial inflammation. Our results also indicated a higher rate of CRP positivity in higher grade radiographic knee OA group. Of all patients, 23.3% had positive CRP. If CRP in our study would be quantitatively measured, a better comparison could be defined. In addition in our study high sensitivity CRP was measured [13].

Stannus et al. showed that CRP is positively associated with total knee pain adjusted for radiographic OA or MRI detected structural abnormalities [22]. They concluded that systemic inflammation can predict worsening of knee pain independently. It should be mentioned that CRP measured in this study also was high sensitivity CRP. The study by Smith et al. showed that patients with higher CRP had more destruction in their knees and this can be a good marker to predict the severity of OA [23]. The results of a study by Dolzani et al. underlines the lack of inflammatory markers consisting of anti-CCP and highly sensitive CRP in different radiologic grades of hand OA that corresponds to our results. In this study only one patient in erosive hand OA had positive anti-CCP but in our study a total of 37 patients had positive anti-CCP [24]. Although reaching the same results but they just investigated the patients who had only hand OA without hip or knee involvement. Selecting patients just to have hand OA is somehow against systemic inflammation. Because systemic inflammation cannot have local effects only restricted to hand, other factors might be involved in the pathogenesis and progression of hand OA alone.

In another study done by Sumithsa Orita, the relation of inflammatory markers consisting of TNFα, IL-6, NGF (Nerve Growth Factor) were evaluated in different radiologic grades of OA and the results showed higher inflammatory markers in lower radiologic grades. It has been vindicated that in higher radiologic grades of OA, due to destruction of cartilage there is no more active cartilage to secrete any inflammatory agents. The results of this study are somehow against our results but considering the differences it can be explained. First, they have measured different inflammatory markers than ours and second these inflammatory markers have been measured in synovial
fluid that is local but our inflammatory markers represented systemic inflammation [25].

In the study of Dan Caspi et al., inflammatory markers in OA, rheumatoid arthritis and psoriatic arthritis were compared. Although inflammatory markers were significantly higher in rheumatoid arthritis than OA but the mean serum level of IgA RF in patients with OA has been reported more than the normal upper limit which corresponds to our results. Of our patients, 16.6% showed higher level of IgM RF [26].

Vangness’s study investigated 21 inflammatory markers in patients who underwent knee arthroscopy and their results indicated no significant difference in synovial fluid of Kellgren and Lawrence grades of knee OA but it was significant by the International Cartilage Repair Society (ICRS) classification [27].

In Vlad’s study, 17 different markers of inflammation has been measured but none of them were significant in various grades of OA. Their results were consistent with our findings but the difference was that the blood samples were harvested 5 years before taking the radiographs, so almost all of the patients may not have OA or were developing it at the time of measuring markers of inflammation [28].

In Haywood’s study, 31% of synovial tissue samples of patients with OA showed severe inflammation and it was not confined to end stage patients [29].

Glucosamine is a drug introduced as a remedy for OA in different studies. This drug accelerates the reconstruction of synovial fluid and may increase the synthesis of articular cartilage. Another mechanism is the inhibitory effect on neutrophils which in result prohibits the inflammation. The effectiveness of this drug on OA can explain the inflammatory basis of OA [30-36].

The markers of ESR, anti-CCP, CRP and RF are the inflammation markers which can be used in clinical practice readily and according to the result of this study can represent the systemic inflammation in OA for evaluating the progression of this disease.

Conclusion

Although inflammatory markers were higher in high grade radiologic OA than the low grade ones but it was not statistically significant. On the other hand, the number of patients with abnormal lab tests which is representative for inflammation is remarkable in apparently primary OAs and should be taken into consideration in future discussion and studies.

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Conflict of Interest

The authors declare no conflicts of interest.

References


