Serum CRP and ESR Values do not Correlate with Clinical and Radiographic Severity of Knee Osteoarthritis

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Purpose: *Low levels of inflammatory markers in osteoarthritis can now be detected with modern laboratory tests. We questioned whether inflammatory markers are higher in patients with more severe knee osteoarthritis, such as those with significant radiographic joint attrition or who require total knee arthroplasty.*
Methods: *A cross-sectional study of serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values in knee osteoarthritis patients with various clinical and radiographic severities was performed. The diagnosis of knee osteoarthritis was made according to the criteria of the American College of Rheumatology. For clinical severity, comparison was made between patients who were satisfied with conservative treatment and those who were scheduled for total knee arthroplasty (TKA) due to inadequate improvement. Radiographic severity was graded by the Ahlbäck classification and whether the involved compartments were joint-sparing or bone-on-bone.*
Results: *One-hundred and ten patients were included in our study. There were 54 patients with a mean age of 69.4 years in the conservative group and 56 patients with a mean age of 68.2 years in the pre-TKA group. Serum CRP was higher in patients who were scheduled for TKA than out patient department (OPD) patients, but this difference was not statistically significant (6.4±7.4 mg/L vs 3.6±1.0 mg/L; P=0.80). Serum ESR of the two groups were also not significantly different (26.8±16.9 mm/hr vs 23.0±16.4mm/hr; P=0.17). Neither serum levels of CRP nor ESR were significantly different when patients were categorized by the Ahlbäck classification (P=0.20 and 0.83, respectively) or divided into joint-sparing and bone-on-bone groups (P=0.65 and 0.37 for CRP and ESR, respectively)*
Conclusion: *Elevation of serum CRP and ESR represent the body's response to an inflammatory condition and should correspond well to the level of joint inflammation. However, the current study did not find significant relationships between CRP and ESR and clinical or radiographic severity of knee osteoarthritis. A possible explanation is that there are several factors other than inflammation that contribute to the severity of knee osteoarthritis such as pain, deformity, and instability.*

Keywords: *Osteoarthritis, Knee, Severity, C-reactive protein, CRP, Erythrocyte sediment rate, ESR, Total knee arthroplasty, TKA*

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Introduction

Osteoarthritis was previously considered a non-inflammatory joint disease. This was due to more subtle signs of inflammation when compared to inflammatory joint diseases such as rheumatoid arthritis as well as an inability to detect the lower amounts of inflammatory markers with older laboratory methods. However, with modern laboratory tests, elevation of serum inflammatory markers, particularly C-reactive protein (CRP), can now be detected and thus have been studied in many aspects[1-4]. Erythrocyte sedimentation rate (ESR) is another commonly used inflammatory marker in orthopaedic surgery. Correlations between these markers and the severity of osteoarthritis have been studied but were inconclusive[2-4]. This study examined whether levels of CRP and ESR are more elevated in knee osteoarthritis patients with a higher degree of clinical and radiographic severities.

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Materials and Methods

Demographic and laboratory data and knee radiographs of patients who were participating in previous clinical research studies of knee osteoarthritis at a University-affiliated tertiary hospital were reviewed and analyzed. Exclusion criteria were secondary osteoarthritis of the knee (either post-traumatic or inflammatory joint

disease), other connective tissue diseases, active infection of the knee and other sites, previous major knee surgery, concurrent steroid therapy, and patients with hepatic and renal impairments. Two groups of patients were included in the study, the first group composed of patients with mild and moderate symptoms who were receiving conservative treatment at the out-patient clinic. The second group composed of patients who were scheduled for total knee arthroplasty (TKA) due to dissatisfaction of conservative methods. These 2 groups were labeled "OPD" and "Pre-TKA" groups, respectively. Standardized weight-bearing radiographs of the affected knee were obtained and graded according to the Ahlbäck classification[5] (Table 1). They were also divided by whether the affected joint space was still present (joint-sparing) or has been obliterated (bone-on-bone) (Fig. 1). Blood samples were usually taken on the same day that knee radiographs were done and not more than 1 week apart. Serum values for CRP and ESR were consider elevated when CRP > 5 mg/L and ESR > 28 mm/hr. OPD patients went through a "wash-out" period of two weeks without NSAIDs or SYSADOAs before their blood samples were obtained. For Pre-op TKA patients, their blood samples were taken a day before surgery. In surgical cases, NSAIDs and/or SYSADOAs were discontinued at least 7-10 days before surgery. Only acetaminophen was allowed for pain control during the wash-out and pre-operative periods.

Table 1 Ahlbäck radiographic classification for knee osteoarthritis[5]

Ahlback Classification	Definitions
Stage I	Joint space narrowing (joint space < 3 mm)
Stage II	Joint space obliteration
Stage III	Bone defect/loss < 5 mm
Stage IV	Bone defect/loss between 5-10 mm
Stage V	Bone defect/loss > 10 mm

Fig. 1 Standing knee radiograph of osteoarthritis patient with remaining medial joint space "joint-sparing" (left) and obliterated medial joint space "bone-on-bone" (right)

The Kruskal-Wallis one-way analysis of variance test was used for comparing multiple groups. Mann-Whitney U-test was used for comparison between 2 groups. *P*-values < 0.05 were considered statistically significant.

Results

There were a total of 110 patients matching our criteria. There were 97 female and 13 male patients with an average age of 68.8 years (range 53-82). The mean value of CRP in all patients was 5.0±5.5 mg/L and was elevated (>5mg/L) in 14.5% (16/110) of patients. The mean ESR was 24.9±16.7 mm/hr and was elevated (>28mm/hr) in 30.9% (34/110) of patients.

Patients were then separated into the OPD group and pre-TKA group. There were 54 patients in the OPD group and 56 patients in the pre-TKA group. The mean ESR value for the OPD group and the pre-TKA group were 26.8±16.9 mm/hr and 23.1±16.4 mm/hr, respectively with no statistical difference (*P*=0.17). The mean CRP values were 3.6±1.0 mg/L for OPD cases and 6.4±7.4 mg/L for pre-TKA cases. Again, the difference was not statistically significant (*P*=0.80). (Table 2)

Table 2 Mean value of ESR and CRP with standard deviations when patients were categorized as OPD cases or pre-op TKA

	OPD (n=54)	Pre-op TKA (n=56)	*P*-value
CRP (mg/L)	3.6±1.0	6.4±7.4	0.80
ESR (mm/hr)	26.8±16.9	23.1±16.4	0.17

When the Ahlbäck classification was use for categorization, 26 knees were grade I, 23 knees were grade II, 39 knees were grade III, 14 knees were grade IV, and 8 knees were grade V. The means and standard deviations of CRP of each grade were, grade I = 3.6±0.9, grade II = 4.0±2.0, grade III = 4.6±2.9, grade IV = 5.9±9.4, and grade V = 12.8±12.7 mg/L. These values were not statistically different (*P*=0.20). The means and standard deviations of ESR of each grade were, grade I = 28.5±20.5, grade II = 21.4±13.5, grade III = 24.0±13.7, grade IV = 24.4±12.4, and grade V = 30.1±28.9 mm/hr. There were no statistical differences (*P*=0.93). (Table 3)

Lastly, patients were categorized by the presence or obliteration of joint space on radiographs; 26 patients were in the joint-sparing group and 84 patients in the bone-on-bone group. CRP values were 3.6±0.9 mg/L and 5.5±6.2 mg/L for the joint-sparing and bone-on-bone groups, respectively. ESR values for the joint sparing group was 28.5±20.5 mm/hr and for the bone-on-bone group was 23.8±15.3 mm/hr. The difference of both markers between the two groups were not statistically significant (CRP; *P*=0.65, ESR; *P*=0.37). (Table 4)

Table 3 Mean values and standard deviations of CRP and ESR when severities of knee osteoarthritis were graded by the Ahlbäck classification

	Ahlbäck I (n =26)	**Ahlbäck II (n=23)**	**Ahlbäck III (n=39)**	**Ahlbäck IV (n=14)**	**Ahlbäck V (n=8)**	***P*-value**
CRP (mg/L)	3.6±0.9	4.0±2.0	4.6±2.9	5.9±9.4	12.8±12.7	0.20
ESR (mm/hr)	28.5±20.5	21.4±13.5	24.0±13.7	24.4±12.4	30.1±28.9	0.93

Table 4 Mean values of ESR and CRP with standard deviations when severities of knee osteoarthritis were categorized by joint-sparing or bone-on-bone radiographs.

	Joint-sparing (n=26)	**Bone-on-bone (n=84)**	***P*-value**
CRP (mg/L)	3.6±0.9	5.5±6.2	0.65
ESR (mm/hr)	28.5±20.5	23.8±15.3	0.37

Discussion

There have always been attempts to quantify the severity of osteoarthritis by other means than radiography. Acute-phase proteins which are surrogate markers of inflammatory processes have been extensively studied for such a purpose. Historically, osteoarthritis was classified as a non-inflammatory joint disease, but this was later proved wrong with improved laboratory techniques that could detect the lower levels of inflammatory markers in both serum and synovial fluid[1,6]. CRP and ESR have many clinical applications in orthopaedic surgery, ranging from making diagnosis to monitoring response to treatment[7]. Elevation of serum CRP and ESP should correspond well to the level of joint inflammation in osteoarthritis. However, outcomes of studies regarding these two markers and severity of osteoarthritis have been, at best, equivocal[2-4,8].

Wolfe investigated the association between CRP, ESR and the clinical severity of hip and knee osteoarthritis patients[8]. The study concluded that CRP was elevated in OA patients and correlated with functional disability and pain. A similar association was not found with ESR. This study, however, did not involve radiographic categorization.

The current study includes two extremes of knee osteoarthritis patients, those with mild-moderate pain and stiffness who are satisfied with conservative treatment at OPD and those who suffered intolerable pain and disability requiring knee replacement. We believe that this categorization truly represents the success and failure of conservative treatment.

The Ahlbäck classification was used to classify our patients by radiographic findings. Even though its variability and reliability have been questioned, it is still the most widely used classification[9,10]. In order to simplify the matter, we also categorized our patients into a joint-sparing group and a bone-on-bone group. Such differences are more obvious, especially on weight-bearing radiographs. We are unable to demonstrate any significant difference of CRP and ESR values despite widely different clinical and radiographic severities. A plausible explanation is that there are several factors other than inflammation that contribute to the severity of knee osteoarthritis and failure of conservative treatment such as pain, deformity and instability. Vice versa, levels of CRP and ESR are not solely elevated by osteoarthritis and can be affected by any inflammatory processes in the body as well.

One notable finding in this study is that levels of CRP seem to elevate to more than the normal value (>5mg/L) only in the most severe cases (e.g. Ahlbäck V). These values are comparable to those reported by Loose et al. and Wolfe[1,8].

A weakness of this study maybe the unequal distribution of patients in each severity. A prospective study with a larger number of cases may be able to clarify the topic once and for all.

Conclusion

The current study cannot demonstrate a correlation between serum levels of CRP and ESR with clinical and radiographic severity of knee osteoarthritis. Inflammation is not the sole predictor of severity and failure of conservative treatment. Several other factors can contribute to the severity of knee osteoarthritis including pain, deformity, and instability.

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การศึกษาความสัมพันธ์ระหว่างระดับ C-reactive protein ในเลือดและอัตราการตกตะกอนของเม็ดเลือดแดงกับความรุนแรงของโรคข้อเข่าเสื่อมในทางคลินิกและภาพถ่ายรังสี

สีหธัช งามอุโฆษ, พบ, กลยุทธ ตัณนิติศุภวงษ์, พบ, อารี ตนาวลี,พบ

วัตถุประสงค์: *เพื่อศึกษาถึงความสัมพันธ์ระหว่างระดับ C-reactive protein (CRP) ในเลือดและอัตราการตกตะกอนของเม็ดเลือดแดง (erythrocyte sedimentation rate, ESR) ในผู้ป่วยข้อเข่าเสื่อมระยะต่างๆ โดยใช้เกณฑ์ของผลการรักษาแบบอนุรักษ์นิยมและภาพถ่ายรังสีเอกซเรย์*

วิธีการศึกษา: *เปรียบเทียบระดับ CRP และ ESR ระหว่างกลุ่มผู้ป่วยข้อเข่าเสื่อมที่พึงพอใจกับการรักษาโดยวิธีอนุรักษ์นิยมกับกลุ่มผู้ป่วยที่รอรับการผ่าตัดข้อเข่าเทียม และเปรียบเทียบระดับ CRP และ ESR ในผู้ป่วยทั้งสองกลุ่ม โดยจำแนกกลุ่มผู้ป่วยตามภาพถ่ายรังสีเอกซเรย์โดย Ahlbäck classification และสภาพการคงอยู่ของช่องข้อ (joint space)*

ผลการศึกษา: *จำนวนผู้ป่วยในการศึกษา 110 ราย โดยแบ่งเป็นผู้ป่วยที่รักษาโดยวิธีอนุรักษ์นิยมจำนวน 54 ราย โดยมีอายุเฉลี่ย 69.4 ปี และกลุ่มผู้ป่วยที่รอรับการผ่าตัดข้อเข่าเทียมจำนวน 56 ราย โดยมีอายุเฉลี่ย 68.2 ปี ผลตรวจระดับ CRP เฉลี่ยในผู้ป่วยที่รอรับการผ่าตัดข้อเข่าเทียมมีค่า 6.4±7.4 มก./ล. ส่วนกลุ่มอนุรักษ์นิยมมีค่า 3.6±1.0 มก./ล. โดยความแตกต่างไม่มีนัยสำคัญทางสถิติ (P=0.80) ค่า ESR เฉลี่ยในผู้ป่วยที่รอรับการผ่าตัดข้อเข่าเทียมเท่ากับ 26.8±16.9 มม./ชม. ส่วนกลุ่มอนุรักษ์นิยมมีค่า 23.1±16.4 มม./ชม. โดยความแตกต่างไม่มีนัยสำคัญทางสถิติ (P=0.17) เมื่อแบ่งกลุ่มผู้ป่วยตามภาพถ่ายรังสีเอกซเรย์โดย Ahlbäck classification พบว่าความแตกต่างไม่มีนัยสำคัญทางสถิติของทั้งค่า CRP และ ESR (P=0.20 และ 0.83 ตามลำดับ) และเมื่อแบ่งผู้ป่วยตามภาพถ่ายรังสีเอกซเรย์ว่ายังมีช่องว่างในข้อเหลืออยู่หรือไม่ ก็ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของ CRP และ ESR เช่นเดียวกัน (P=0.65 และ 0.37 ตามลำดับ)*

สรุป: *ระดับ CRP และ ESR สามารถใช้เพื่อประเมินระดับการอักเสบในร่างกายรวมถึงการอักเสบของข้อด้วย อย่างไรก็ตาม การศึกษานี้ไม่พบความสัมพันธ์ระหว่างระดับของ CRP และ ESR กับความรุนแรงของข้อเข่าเสื่อมทั้งในด้านผลของการรักษาและภาพถ่ายรังสีเอกซเรย์ ทั้งนี้อาจเป็นเพราะมีปัจจัยอื่นๆที่มีผลต่อความรุนแรงของโรคข้อเข่าเสื่อมนอกเหนือจากการอักเสบ เช่น อาการปวด การผิดรูปและความไม่มั่นคงของข้อเข่า เป็นต้น*