ORIGINAL ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

Level of Inflammation and its Association with Pain, Physical Functioning and KL-Grade in Patients With Knee Osteoarthritis

Ayesha Kherani[1]*, Geeta Ibrahim[1], Zubair Sorathia[2]

Abstract

Background: Knee osteoarthritis (OA), also known as degenerative arthritis, causes a progressive loss of articular cartilage. In recent years, there has been a shift in the understanding of OA from a "wear and tear" disease to an "inflammatory" condition. **Aims and Objectives:** The objective of this study was to assess the level of inflammation and to evaluate the relationship between inflammation, pain, physical functioning, and Kellgren Lawrence (KL)-grade in patients with knee OA. **Materials and Methods:** Sixty patients with radiographic evidence of knee OA (KL Grade I/II/III) were cross-sectionally analyzed. Data about their anthropometry, inflammatory markers high-sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate-(ESR), pain, and physical functioning were collected. **Results:** The mean hsCRP among the patient population was 4.6 ± 4.0 mg/L and the mean ESR was 40.4 ± 21.8 mm/h. There was a strong significant association of visual analog scale (VAS) pain score with hsCRP (r = 0.353; *P* = 0.005) and ESR (r = 0.269; *P* = 0.036). There was a strong significant association of Western Ontario and McMaster Universities OA Index score with hsCRP (r = 0.415; *P* = 0.001) and ESR (r = 0.413, *P* = 0.001). However, there was no significant difference in hsCRP or ESR when classified according to KL-grade (*P* > 0.05). **Conclusion:** The level of inflammation is high in knee OA patients. Inflammation is significantly associated with pain intensity and physical functioning in knee OA patients. However, there is no significant difference in hsCRP, ESR, and VAS when classified according to KL-grade. This emphasizes the need to study inflammatory markers in addition to radiographic evidence for informed clinical decision-making.

Keywords: Inflammation, Kellgren Lawrence-grade, Knee osteoarthritis, Visual analog scale, Western Ontario and Mcmaster Universities osteoarthritis index

Asian Pac. J. Health Sci., (2023); DOI: 10.21276/apjhs.2023.10.3.02

Introduction

The global burden of disease study suggests that musculoskeletal diseases are the second most common cause of disability throughout the world, as measured by years lived with disability.[1] The prevalence is increasing at an alarming rate in India too. In a study conducted in 2020, the prevalence of knee Osteoarthritis (OA) in India was found to be 28.7%.[2]

OA is one of the most common joint disorders characterized by degradation of the articular cartilage, abnormal bone formation (osteophytes), and inflammation of the synovial membrane (synovitis). Synovial and systemic inflammation has been identified to play a major role in the pathogenesis of knee OA. In recent years, there has been a shift in the understanding of OA from a "wear and tear" disease to an "inflammatory" disease characterized by chronic systemic inflammation. Pro-inflammatory cytokines, including interleukin (IL)-1β, tumor necrosis factor-α, IL-6, and others, are produced by the synovium and chondrocytes and contribute to the progression of cartilage degradation.[3] Recent studies suggest that this inflammation may be observed systemically.[4] High sensitivity C-reactive protein (hsCRP) is a quantitative marker of the acute phase response and is identified to be a potential biomarker of incident OA of the knee.[5] hsCRP is one of the most widely studied markers of systemic inflammation and is associated with the presence and progression of knee OA.[6] Erythrocyte sedimentation rate (ESR) was also found to be higher in patients with knee OA and was related to clinical features.[7] The hallmark of knee OA that typically drives clinical decision-making is the patient's complaint of pain and reduced physical functioning. However, the heterogeneity between clinical symptoms and radiographic evidence of knee OA makes it difficult to make a clear diagnosis and treatment course. OA is now recognized as an inflammatory disease. Hence, there is a need for the identification of inflammatory markers that would correlate with worsening of symptoms in patients with knee OA. Hence, this study aimed at assessment of inflammation in knee OA patients and its association with pain and physical functioning. This study highlights the role of inflammation in the pathogenesis and severity of symptoms, in early knee OA.

[1]Department of Foods, Nutrition and Dietetics, College of Home Science Nirmala Niketan, Affiliated to be University of Mumbai, Maharashtra, India

[2]Department of Orthpaedics, Medicare Hospital, Mumbai, Maharashtra, India

Corresponding Author: Dr. Ayesha Kherani, M.Sc. (Home Science), PhD Research Scholar (Senior Research Fellow), Department of Foods, Nutrition and Dietetics, College of Home Science Nirmala Niketan, Affiliated to be University of Mumbai, Maharashtra, India. E-mail: ayeshakherani2595@gmail.com

How to cite this article: Kherani A, Ibrahim G, Sorathia Z. Level of Inflammation and its Association with Pain, Physical Functioning and KL-Grade in Patients With Knee Osteoarthritis. Asian Pac. J. Health Sci., 2023;10(3):4-7.

Source of support: Nil.

Conflicts of interest: None.

Received: 19/07/2023 **Revised:** 18/08/2023 **Accepted:** 16/09/2023

Materials and Methods

This study was a secondary, cross-sectional analysis of baseline data from a randomized controlled trial (Clinical Trials Registry of India

trial registration number is CTRI/2022/07/043621). Sixty patients with unilateral or bilateral knee OA were selected using a purposive sampling technique. An anteroposterior and lateral view X-ray of the affected knee joint was performed at the initial examination. Patients diagnosed to have knee OA by the Kellgren Lawrence (KL) classification system (Grade I/II/III) were included in the study. Pain intensity was assessed by the visual analogue scale (VAS) score. VAS score is a validated subjective measure of pain and is self-assessed by the patients. Physical functioning was assessed by the Western Ontario and McMaster Universities OA Index (WOMAC) score. The WOMAC score is composed of 27 parameters that include pain (maximum score: 20), stiffness (maximum score: 8), and difficulty (maximum score: 80) while doing certain activities of daily living (ADL). Inflammation was assessed using hs-CRP and ESR values. The blood samples were obtained by venipuncture. ESR was assessed using the Westergren method. The reference ESR values are 0–20 mm/h. hs-CRP was assessed using Immunoturbidimetry method. Reference hsCRP values are ≤3 mg/L.

The inclusion criteria were as follows: Male and female subjects with primary, unilateral/bilateral knee OA, aged 30–70 years, with radiographic evidence (KL grade I/II/III), and those willing to comply with the study procedures. Patients were excluded if any of the following was present: Chronic illnesses (severe renal or cardiac impairment, cancer, lupus, rheumatoid arthritis, etc.) that could interfere with the study outcomes, patients consuming anti-inflammatory supplements 30 days before the screening visit, and female subjects who are pregnant, lactating, or planning to become pregnant. Written informed consent was obtained from all the participants before inclusion in the study. The study protocol was approved by the Bay View Clinic Ethics Committee (ISO 9001:2000 Certified) (Number 887302745).

Statistical Analysis

Data were analyzed using IBM-Statistical Package for the Social Sciences (software for Windows version 25, 2007, IBM Corporation, Armonk, New York, United State). Data are presented as Mean ± SD or Frequency (percentage). The normality of data was assessed using Shapiro–Wilk Test. Differences in normally distributed parameters were assessed using independent sample *t*-test/ANOVA. The difference in non-normally distributed parameters was assessed using the Kruskal–Wallis-H test. Correlations were assessed using Pearson's Correlation test or Spearman Correlation test. $P < 0.05$ was considered to be statistically significant.

Results

The mean age of the participants was 52.5 ± 8.0 years. Approximately 70% of the population (n = 43) were females and approximately 30% (n = 18) were males. Figure 1 illustrates the grade of knee OA among the study participants.

Table 1 indicates the baseline anthropometric, biochemical, and functional characteristics of the study population.

The mean BMI was 29.1 kg/m^2. About 82% of the patient population (n = 49) were in the overweight and obese category according to the Asian Indian BMI classification. Waist circumference (WC) is used as an indicator of upper-body adiposity. Waist-to-hip ratio (WHR) is a direct measure of abdominal and visceral fat that predisposes to health problems like OA. The mean waist circumference and WHR of the study population were higher than the reference values. Inflammation was also high among the study population as indicated by mean ESR and mean hsCRP values which were higher than the reference ranges. The mean VAS which is the self-reported pain by the patients was 7.2 on a scale of 10. The mean total WOMAC reports pain, stiffness, and difficulty while doing various ADL was 62.2 on a scale of 108.

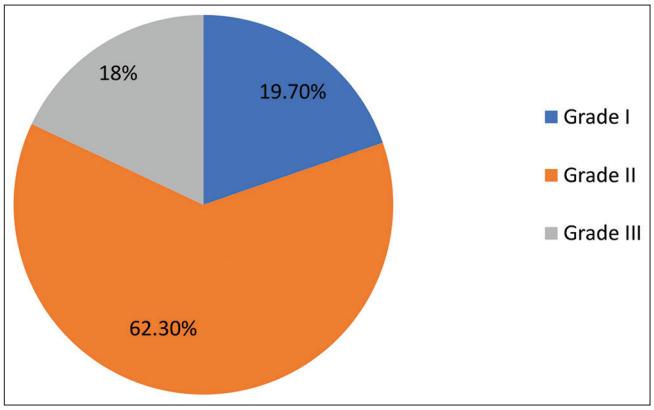

Figure 1: Grade of knee osteoarthritis (KL grade) among study participants (n = 60). Data presented as n (%)

Table 1: Baseline anthropometric, biochemical, and functional characteristics of the study population

Variable	*Study population (n=60), (mean±SD)*
Anthropometric parameters	
Height (cm)	155.6±7.6
Weight (kg)	70.3±15.7
BMI (kg/m^2)	29.1±6.4
Waist circumference (cm)	100.7±13.4
Hip circumference (cm)	108.6±12.0
WHR	0.92±0.05
Inflammatory markers	
hs-CRP (mg/L)	4.6±4.0
ESR (mm/h)	40.4±21.8
Pain and physical functioning	
VAS	7.2±1.7
Total WOMAC	62.2±24.1

BMI: Body mass index, hs-CRP: High-sensitivity C-reactive protein, ESR: Erythrocyte sedimentation rate, VAS: Visual analogue scale, WOMAC: Western Ontario and McMaster Universities osteoarthritis, WHR: Waist-to-hip ratio, SD: Standard deviation

Table 2: Association of anthropometric parameters with VAS, inflammatory markers, and WOMAC

Anthropometric parameter	*VAS*	*hsCRP*	*ESR*	*WOMAC*
Weight	0.296[a]	0.001	0.200	0.159
BMI	0.408[a]	0.200	0.325[a]	0.300[a]
Waist circumference	0.420[a]	0.100	0.200	0.319[a]
Hip circumference	0.430[a]	0.100	0.263[a]	0.332[a]
WHR	0.167	0.001	0.100	0.12

[a]P<0.05. Data presented as Pearson's correlation coefficient (r). BMI: Body mass index, hs-CRP: high-sensitivity C-reactive protein, ESR: Erythrocyte sedimentation rate, VAS: Visual analogue scale, WOMAC: Western Ontario and McMaster Universities osteoarthritis, WHR: Waist-to-hip ratio

Association of Anthropometric Parameters with VAS, Inflammatory Markers, and WOMAC

Table 2 indicates the association of anthropometric parameters with VAS, inflammatory markers, and WOMAC.

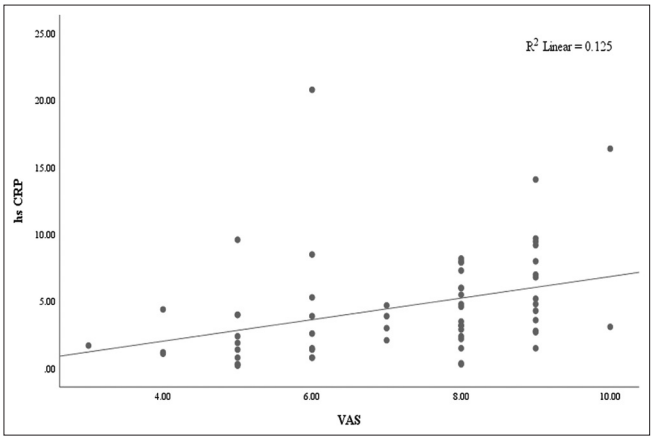

Figure 2: Association of visual analog scale score with high-sensitivity C-reactive protein

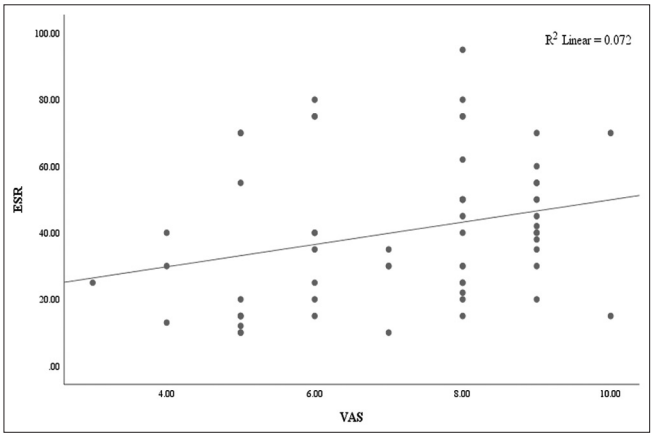

Figure 3: Association of visual analog scale score with erythrocyte sedimentation rate

There was a significant association between the weight and VAS score (r = 0.296, *P* < 0.05), BMI and VAS score (r = 0.408, *P* < 0.05), waist circumference and VAS score (r = 0.420, *P* < 0.05), and hip circumference and VAS score (r = 0.430, *P* < 0.05). VAS pain score reported by the participants was higher in patients with a higher weight, BMI, waist circumference, and hip circumference. There was a significant association between ESR and BMI (r = 0.325, *P* < 0.05) and between ESR and hip circumference (r = 0.263, *P* < 0.05). Inflammation was higher in participants with a higher BMI and hip circumference. There was a significant association between BMI and WOMAC score (r = 0.300, *P* < 0.05), waist circumference and WOMAC score (r = 0.319, *P* < 0.05), and hip circumference and WOMAC score (r = 0.332, *P* < 0.05). WOMAC score was higher in participants with a higher BMI, waist circumference, and hip circumference.

Association of VAS Score with Inflammatory Markers

There was a significant positive association of VAS score with hsCRP (r = 0.353, *P* = 0.005*). Participants with high levels of hsCRP reported a higher level of pain [Figure 2].

Similarly, there was a significant positive association of VAS score with ESR (r = 0.269, *P* = 0.036*). Participants with high levels of ESR reported a higher level of pain [Figure 3]. This indicates that higher systemic inflammation is associated with increased pain in knee OA patients.

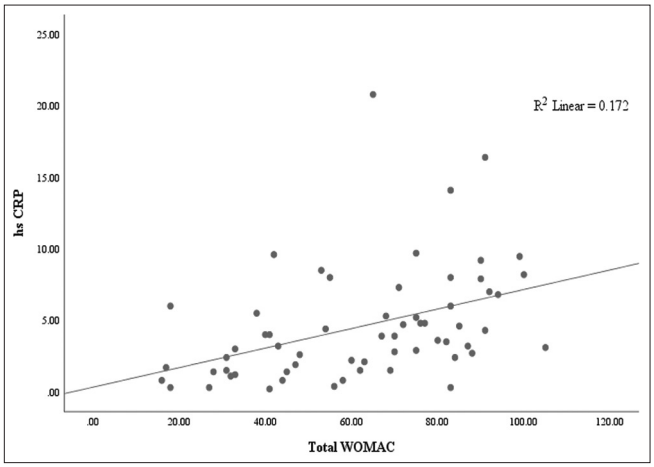

Figure 4: Association of total WOMAC score with high-sensitivity C-reactive protein

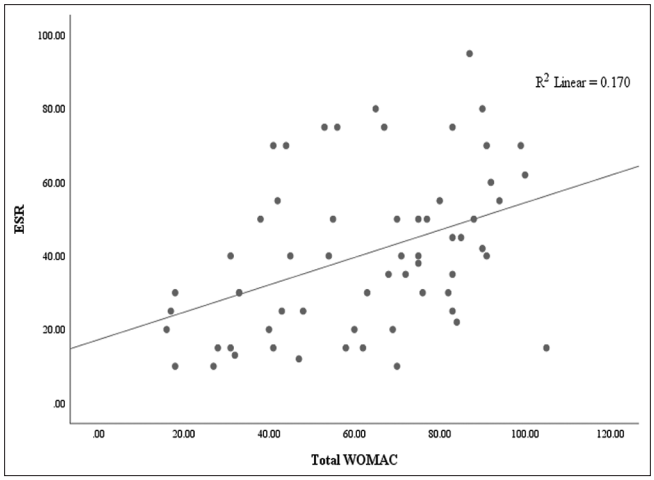

Figure 5: Association of total WOMAC score with erythrocyte sedimentation rate

Table 3: Association of inflammatory markers and pain with KL-grade

Parameter	*KL grade I*	*KL grade II*	*KL grade III*	*P*
hsCRP (mg/L)	2.4(0.3–14.1)	4.0(0.3–20.8)	4.3 (0.2–9.7)	0.536
ESR (mm/h)	30.2±18.1	43.1±22.7	42.1±20.4	0.192
VAS	6.8±1.9	7.3±1.7	7.1±1.9	0.619

Data presented as mean±SD. hs-CRP: High-sensitivity C-reactive protein, ESR: Erythrocyte sedimentation rate, VAS: Visual analogue scale, KL: Kellgren-Lawrence, SD: Standard deviation

Association of WOMAC Score with Inflammatory Markers

There was a significant association of WOMAC score with hsCRP (r = 0.415, *P* = 0.001*). Participants with high levels of hsCRP had a higher WOMAC score. In other words, they had a lower level of physical functioning [Figure 4].

Similarly, there was a significant association of WOMAC score with ESR (r = 0.413, *P* = 0.001*). Participants with high levels of ESR had a higher WOMAC score. In other words, they reported a lower level of physical functioning [Figure 5]. This indicates that higher systemic inflammation is associated with poor physical functioning in knee OA patients.

Association of Inflammatory Markers and Pain with KL-Grade

Table 3 indicates the association of inflammatory markers and VAS with KL-grade. There was no significant difference in hsCRP, ESR, and VAS when classified according to KL-grade (*P* > 0.05).

This suggests that inflammation and pain are not different between KL-grade I, II, and III. Patients with a lower KL-grade also have appreciably high levels of inflammation and thus, may present with a high level of pain and poor physical functioning.

Discussion and Conclusion

As per the results of this study, serum hsCRP and ESR levels are elevated in patients with knee OA. Inflammation is significantly associated with pain intensity and physical functioning in knee OA patients. However, there is no significant difference in hsCRP, ESR, and VAS when classified according to KL-grade. These findings suggest that systemic inflammation may play a greater role in symptoms of knee OA rather than radiographic changes. In clinical practice, a large number of patients with less severe knee OA (KL-Grade I/II) complain of extreme pain and compromised physical functioning as compared to those with more severe knee OA (KL-grade III). Thus, if inflammatory markers are elevated despite a lower KL grade, it may still lead to poor pain and physical function outcomes, and thus, compromised quality of life (QOL). This emphasizes the need to study inflammatory markers in addition to radiographic evidence as these markers correlate with worsening of symptoms in patients. When studied together, radiographic evidence and inflammatory markers can result in a more informed clinical decision-making in terms of severity of knee OA and symptoms of knee pain and reduced physical functioning. Furthermore, a higher systemic inflammation may be amenable to therapeutic intervention by anti-inflammatory substances – even in the early stages of the disease to provide symptomatic relief, prevent progression of disease, and improve QOL of patients. The results add to the growing pool of evidence that the clinical progression of OA may be associated with systemic inflammation. From a clinical perspective, the study findings may guide the development of new therapeutic strategies that target low-grade inflammation for knee OA.

Acknowledgments

I would like to acknowledge my mentor and comentor for being my constant source of strength and guidance. I would also like to thank all the participants for being a part of the study.

Copyright and Permission Statement

We confirm that the materials included in this chapter do not violate copyright laws. Where relevant, appropriate permissions have been obtained from the original copyright holder(s). All original sources have been appropriately acknowledged and/or referenced.

References

1. Sebbag E, Felten R, Sagez F, Sibilia J, Devilliers H, Arnaud L. The world-wide burden of musculoskeletal diseases: A systematic analysis of the world health organization burden of diseases database. Ann Rheum Dis 2019;78:844-8.
2. Kumar H, Pal CP, Sharma YK, Kumar S, Uppal A. Epidemiology of knee osteoarthritis using Kellgren and Lawrence scale in Indian population. J Clin Orthop Trauma 2020;11:S125-9.
3. Scanzello CR, Loeser RF. Editorial: Inflammatory activity in symptomatic knee osteoarthritis: Not all inflammation is local. Arthritis Rheumatol 2015;67:2797-800.
4. Alexander LC Jr, McHorse G, Huebner JL, Bay-Jensen AC, Karsdal MA, Kraus VB. A matrix metalloproteinase-generated neoepitope of CRP can identify knee and multi-joint inflammation in osteoarthritis. Arthritis Res Ther 2021;23:226.
5. Sowers M, Jannausch M, Stein E, Jamadar D, Hochberg M, Lachance L. C-reactive protein as a biomarker of emergent osteoarthritis. Osteoarthritis Cartilage 2002;10:595-601.
6. Engström G, de Verdier MG, Rollof J, Nilsson PM, Lohmander LS. C-reactive protein, metabolic syndrome and incidence of severe hip and knee osteoarthritis. A population-based cohort study. Osteoarthritis Cartilage 2009;17:168-73.
7. Hanada M, Takahashi M, Furuhashi H, Koyama H, Matsuyama Y. Elevated erythrocyte sedimentation rate and high-sensitivity C-reactive protein in osteoarthritis of the knee: Relationship with clinical findings and radiographic severity. Ann Clin Biochem 2016;53:548-53.