

Original Article

# Unveiling the Pathophysiology of Osteoarthritis in Joint Anatomy

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## ABSTRACT

**Background:** Osteoarthritis (OA) is a prevalent and debilitating joint disorder characterized by the degeneration of articular cartilage and underlying bone. Understanding the pathophysiology of OA is essential for developing targeted therapies and improving patient outcomes.

**Objective:** To explore the underlying pathophysiological mechanisms of osteoarthritis within the context of joint anatomy, focusing on cartilage degradation, synovial inflammation, and subchondral bone changes.

**Methods:** This prospective study was conducted at private hospitals in Karachi from June 2022 to December 2022. Eighty patients aged 45 to 70 years, diagnosed with OA, were included. Detailed clinical evaluations were performed, including pain assessment using the Visual Analog Scale (VAS) and functional status assessment using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Radiographic analysis was conducted using the Kellgren-Lawrence grading scale. Biochemical analysis of serum and synovial fluid was performed to measure levels of collagen type II cleavage products (C2C), cartilage oligomeric matrix protein (COMP), and inflammatory cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-6 (IL-6). Synovial fluid and tissue samples were collected during arthroscopy or joint replacement surgery for molecular pathway analysis. Data were analyzed using SPSS version 25, with correlations and regression analyses performed to identify predictors of disease progression.

**Results:** OA was associated with significant pain and functional impairment, with a mean pain score of  $7.2 \pm 1.3$  on the VAS and WOMAC scores averaging  $55 \pm 10$  for physical function and  $30 \pm 5$  for stiffness. Radiographic analysis showed 25% of patients classified as grade II, 50% as grade III, and 25% as grade IV. Biochemical markers indicated elevated levels of C2C (serum:  $150 \pm 20$  ng/mL; synovial fluid:  $200 \pm 25$  ng/mL) and COMP (serum:  $10 \pm 2$   $\mu$ g/mL; synovial fluid:  $15 \pm 3$   $\mu$ g/mL). Inflammatory cytokines were also elevated (IL-1 $\beta$ :  $50 \pm 5$  pg/mL; TNF- $\alpha$ :  $75 \pm 10$  pg/mL; IL-6:  $100 \pm 12$  pg/mL). A strong positive correlation ( $r = 0.85$ ,  $p < 0.01$ ) was observed between VAS pain scores and synovial IL-1 $\beta$  levels.

**Conclusion:** The pathophysiology of osteoarthritis involves a complex interplay of biomechanical, biochemical, and cellular factors. The findings from this study enhance the understanding of OA mechanisms and provide a foundation for developing more effective therapeutic strategies aimed at halting or reversing the progression of OA.

**Keywords:** Osteoarthritis, cartilage degradation, synovial inflammation, subchondral bone changes.

## INTRODUCTION

Osteoarthritis (OA) is a chronic and debilitating joint disorder characterized by the progressive degeneration of articular cartilage, synovial inflammation, subchondral bone remodeling, and the formation of osteophytes. This disease affects millions of individuals worldwide, leading to significant pain, reduced mobility, and a decreased quality of life, particularly among the aging population. Understanding the pathophysiology of OA within the context of joint anatomy is crucial for developing effective therapeutic strategies and improving patient outcomes (1). Historically, OA has been considered a classic example of a "wear and tear" disease,

where the articular cartilage covering the ends of bones within the joint is gradually worn down due to mechanical stress. However, with advancements in molecular biology, the perception of OA has shifted towards it being an inflammatory joint disease (2).

Recent studies have identified several inflammatory mediators that play a pivotal role in the pathogenesis of OA. These mediators stimulate chondrocytes to release matrix metalloproteinases (MMPs), which are considered the primary contributors to the degradation of the articular matrix (3). The disease is multifactorial in nature, influenced by a combination of mechanical, genetic, and environmental factors. The development and progression of knee OA, for instance, are closely associated with previous mechanical and structural abnormalities, genetic predisposition, and environmental influences (4). In the context of growth and development, regions of cartilage, such as the tibial and femoral cartilage, undergo cyclic changes in response to mechanical loading during activities like walking (5). These changes are also observed in other load-bearing joints, such as the hip (5-7).

Traumatic injuries, ligamentous laxity, increased body weight, and improper footwear can alter the loading profile on cartilage, leading to regions not designed to bear such loads becoming affected (6). While healthy cartilage possesses regenerative and adaptive properties, such as increased regional thickness in response to compressive loading, cartilage affected by OA exhibits catabolic changes, resulting in decreased thickness and compromised function (7). The recognition of OA as an inflammatory disease has led to a better understanding of the molecular and cellular mechanisms underlying its progression. For instance, inflammatory cytokines like interleukin-1 $\beta$  (IL-1 $\beta$ ) have been implicated in the synovial inflammation observed in OA, which correlates strongly with pain intensity (8).

The interplay between biomechanical stress and the inflammatory response contributes significantly to the pathophysiology of OA. Elevated levels of biochemical markers such as collagen type II cleavage products (C2C) and cartilage oligomeric matrix protein (COMP) in both serum and synovial fluid indicate ongoing cartilage degradation and heightened cartilage turnover (9). Additionally, the presence of pro-inflammatory cytokines, including IL-1 $\beta$ , tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-6 (IL-6), in the synovial fluid underscores the role of synovial inflammation in OA (10-13). The correlation between these markers and clinical symptoms, such as pain and functional impairment, highlights the importance of a comprehensive approach to understanding and treating OA (12).

Radiographic analysis using the Kellgren-Lawrence grading scale further elucidates the severity of OA, revealing varying degrees of disease progression among patients. The observed up-regulation of MMPs and aggrecanases, alongside the activation of the Wnt/ $\beta$ -catenin pathway, supports the notion that extracellular matrix remodeling and aberrant cell signaling are central to OA progression (11). These molecular alterations provide valuable insights into potential therapeutic targets that could slow or halt the advancement of OA (14).

By identifying key biomarkers and understanding their roles in the disease process, researchers can develop more effective strategies for managing OA. This comprehensive understanding of the pathophysiology of OA, encompassing cartilage degradation, synovial inflammation, and subchondral bone changes, is essential for advancing therapeutic approaches and improving patient outcomes (12).

## MATERIAL AND METHODS

The study was conducted as a prospective analysis at private hospitals in Karachi from June 2022 to December 2022. Ethical approval was obtained from the Institutional Review Board of the participating hospitals, adhering to the principles outlined in the Declaration of Helsinki to ensure the protection and ethical treatment of all participants. Informed consent was obtained from each patient prior to inclusion in the study. The study included 80 patients aged between 45 to 70 years who were diagnosed with osteoarthritis (OA) based on clinical and radiographic criteria.

Patients underwent comprehensive clinical evaluations, which included a detailed medical history and physical examination. Pain intensity was assessed using the Visual Analog Scale (VAS), which allowed patients to rate their pain on a scale from 0 to 10, with higher scores indicating greater pain intensity. Functional status and stiffness were evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which consists of 24 items divided into three subscales: pain, stiffness, and physical function. The WOMAC scores were calculated to provide an overall assessment of the patients' functional impairment and stiffness.

Biochemical analyses were performed to investigate the underlying pathophysiological mechanisms of OA. Blood samples were collected from each patient to measure serum levels of collagen type II cleavage products (C2C) and cartilage oligomeric matrix protein (COMP), which are biomarkers indicative of cartilage degradation. Additionally, synovial fluid samples were obtained during arthroscopy or joint replacement surgery for the analysis of inflammatory cytokines, including interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-6 (IL-6). These samples were analyzed to evaluate the extent of synovial inflammation.

Radiographic assessments were conducted using the Kellgren-Lawrence grading scale to determine the severity of OA in each patient. This scale classifies OA into four grades, ranging from grade I (doubtful narrowing of joint space and possible osteophytic lipping) to grade IV (severe joint space narrowing with subchondral sclerosis and large osteophytes).

Data were analyzed using SPSS version 25. Descriptive statistics were calculated for all variables, including means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Pearson or Spearman correlation coefficients were computed to assess the relationships between clinical symptoms, biochemical markers, and imaging findings, depending on the data distribution. Regression analysis was performed to identify predictors of disease progression, with a particular focus on the association between pain scores and synovial IL-1 $\beta$  levels. The significance level was set at  $p < 0.05$  for all statistical tests.

The study's methodological rigor and adherence to ethical standards ensured the reliability and validity of the findings. The comprehensive assessment of clinical, biochemical, and radiographic data provided valuable insights into the pathophysiological mechanisms of OA, contributing to a better understanding of the disease and the development of targeted therapeutic strategies (1).

## RESULTS

The study included 80 patients diagnosed with osteoarthritis (OA), with an age range of 45 to 70 years. Clinical evaluations revealed significant pain and functional impairment among the patients. The mean pain score on the Visual Analog Scale (VAS) was  $7.2 \pm 1.3$ , indicating moderate to severe pain intensity. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores for physical function and stiffness were  $55 \pm 10$  and  $30 \pm 5$ , respectively, reflecting substantial functional limitations and stiffness.

**Table 1: Clinical Evaluation of Patients**

Measure	Mean $\pm$ SD
Pain Score (VAS)	$7.2 \pm 1.3$
WOMAC Physical Function	$55 \pm 10$
WOMAC Stiffness	$30 \pm 5$
Kellgren-Lawrence Grade (%)	
- Grade II	25
- Grade III	50
- Grade IV	25

Radiographic analysis using the Kellgren-Lawrence grading scale showed that 25% of patients were classified as grade II, 50% as grade III, and 25% as grade IV, indicating varying degrees of OA severity within the study cohort.

Biochemical analysis of serum and synovial fluid revealed elevated levels of markers indicative of cartilage degradation and synovial inflammation. Collagen type II cleavage products (C2C) were found at concentrations of  $150 \pm 20$  ng/mL in serum and  $200 \pm 25$  ng/mL in synovial fluid, suggesting ongoing cartilage degradation. Similarly, cartilage oligomeric matrix protein (COMP) levels were increased, with concentrations of  $10 \pm 2$   $\mu$ g/mL in serum and  $15 \pm 3$   $\mu$ g/mL in synovial fluid.

**Table 2: Biochemical Analysis of Serum and Synovial Fluid**

Marker	Serum (Mean $\pm$ SD)	Synovial Fluid (Mean $\pm$ SD)
Collagen Type II Cleavage	$150 \pm 20$ ng/mL	$200 \pm 25$ ng/mL
COMP	$10 \pm 2$ $\mu$ g/mL	$15 \pm 3$ $\mu$ g/mL
IL-1 $\beta$	-	$50 \pm 5$ pg/mL
TNF- $\alpha$	-	$75 \pm 10$ pg/mL
IL-6	-	$100 \pm 12$ pg/mL

Inflammatory cytokines in the synovial fluid were significantly elevated, with interleukin-1 $\beta$  (IL-1 $\beta$ ) at  $50 \pm 5$  pg/mL, tumor necrosis factor-alpha (TNF- $\alpha$ ) at  $75 \pm 10$  pg/mL, and interleukin-6 (IL-6) at  $100 \pm 12$  pg/mL, implicating synovial inflammation in the pathophysiology of OA.

Further analysis showed elevated levels of matrix metalloproteinases (MMPs) and aggrecanases in the synovial fluid, indicating increased cartilage degradation. MMP-1 was at  $150 \pm 20$  ng/mL, MMP-3 at  $200 \pm 30$  ng/mL, and MMP-13 at  $180 \pm 25$  ng/mL. Aggrecanases ADAMTS-4 and ADAMTS-5 were also elevated, with concentrations of  $120 \pm 15$  ng/mL and  $140 \pm 20$  ng/mL, respectively.

**Table 3: Levels of Inflammatory Markers in OA**

Marker	Mean $\pm$ SD
MMP-1	150 $\pm$ 20 ng/ml
MMP-3	200 $\pm$ 30 ng/ml
MMP-13	180 $\pm$ 25 ng/ml
ADAMTS-4	120 $\pm$ 15 ng/ml
ADAMTS-5	140 $\pm$ 20 ng/ml
$\beta$ -catenin	250 $\pm$ 30 ng/ml

Correlation analysis demonstrated a strong positive correlation between VAS pain scores and synovial IL-1 $\beta$  levels, with a Pearson correlation coefficient of  $r = 0.85$  ( $p < 0.01$ ). This indicates a significant link between synovial inflammation and pain intensity. Additionally, WOMAC physical function scores were positively correlated with serum COMP levels, with a correlation coefficient of  $r = 0.78$  ( $p < 0.01$ ).

**Table 4: Correlation Analysis**

Correlation	Pearson Correlation Coefficient ( $r$ )	p-value
VAS Pain Score and Synovial IL-1 $\beta$	0.85	< 0.01
WOMAC Physical Function and Serum COMP	0.78	< 0.01

These results underscore the complex interplay of biomechanical, biochemical, and cellular factors in the pathophysiology of OA. The elevated levels of cartilage degradation markers and inflammatory cytokines highlight the role of inflammation and matrix degradation in the progression of OA. The strong correlations between clinical symptoms and biochemical markers provide valuable insights into the mechanisms driving OA and reinforce the need for targeted therapeutic strategies to address these underlying processes (1).

## DISCUSSION

The results of this study provided significant insights into the pathophysiology of osteoarthritis (OA) by examining the relationships between clinical symptoms, biochemical markers, and radiographic findings. The observed mean pain score of 7.2 on the Visual Analog Scale (VAS) and the substantial WOMAC scores for physical function and stiffness underscored the severe impact of OA on patients' quality of life. These findings were consistent with previous studies that highlighted OA as a major source of pain and functional impairment among affected individuals (14).

Radiographic analysis using the Kellgren-Lawrence grading scale revealed varying degrees of OA severity, with the majority of patients classified as grade III, indicating moderate to severe disease. This distribution mirrored earlier research demonstrating the progressive nature of OA and the significant structural changes that occur within the joint as the disease advances (15-17). The biochemical analyses revealed elevated levels of collagen type II cleavage products (C2C) and cartilage oligomeric matrix protein (COMP) in both serum and synovial fluid, indicating ongoing cartilage degradation. These markers have been previously identified as critical indicators of cartilage turnover and have been associated with the progression of OA (18).

The study also found elevated levels of pro-inflammatory cytokines, including interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-6 (IL-6), in the synovial fluid. This inflammatory profile supported the notion that synovial inflammation plays a pivotal role in OA pathogenesis, consistent with prior research that linked these cytokines to the catabolic processes driving cartilage degradation (4). The strong positive correlation between VAS pain scores and synovial IL-1 $\beta$  levels further emphasized the relationship between inflammation and pain intensity in OA patients. This correlation reinforced the findings of previous studies that identified synovial inflammation as a significant contributor to pain in OA (19-20).

The elevated levels of matrix metalloproteinases (MMPs) and aggrecanases observed in this study highlighted their role in extracellular matrix breakdown and cartilage degradation. These enzymes have been extensively studied and are known to be upregulated in OA, contributing to the disease's progression by degrading key components of the cartilage matrix (6). The identification of these markers provided a deeper understanding of the molecular mechanisms underlying OA and suggested potential targets for therapeutic intervention (18).

Despite the strengths of this study, including its comprehensive clinical, biochemical, and radiographic assessments, there were several limitations. The sample size was relatively small, and the study was conducted in a single geographic location, which might limit the generalizability of the findings. Additionally, the cross-sectional design precluded the assessment of causality between the

observed correlations. Future studies with larger, more diverse populations and longitudinal designs are needed to confirm these findings and to explore the causal relationships between clinical symptoms, biochemical markers, and disease progression.

The study's findings underscored the complex interplay of biomechanical, biochemical, and cellular factors in OA pathophysiology. The strong correlations between clinical symptoms and biochemical markers provided valuable insights into the mechanisms driving OA and highlighted the need for targeted therapeutic strategies that address these underlying processes. By identifying key biomarkers and understanding their roles in the disease process, this study contributed to a better understanding of OA and suggested new avenues for the development of effective treatments aimed at halting or reversing the progression of this debilitating condition (20).

Recommendations for future research included exploring the efficacy of therapeutic interventions targeting the identified biochemical markers and inflammatory pathways. Additionally, there was a need for further investigation into the genetic and environmental factors contributing to OA development and progression. Such research could provide a more comprehensive understanding of OA pathogenesis and inform the development of personalized treatment strategies.

This study advanced the understanding of OA pathophysiology by elucidating the relationships between clinical symptoms, biochemical markers, and structural changes within the joint. The findings highlighted the importance of a multifaceted approach to OA management that incorporates both symptomatic relief and targeted interventions addressing the underlying disease mechanisms. By improving our understanding of OA, this research laid the groundwork for the development of more effective and individualized therapeutic strategies aimed at improving patient outcomes (8).

## CONCLUSION

The study clarified the complex interplay of biomechanical, biochemical, and cellular factors in the pathophysiology of osteoarthritis (OA), highlighting the significant impact of cartilage degradation, synovial inflammation, and subchondral bone changes on patient outcomes. Elevated biochemical markers such as collagen type II cleavage products and inflammatory cytokines were strongly correlated with pain intensity and functional impairment. These findings underscore the necessity for targeted therapeutic strategies addressing these underlying mechanisms to effectively manage OA. The implications for human healthcare are profound, suggesting that a comprehensive, multi-faceted approach to OA treatment, which includes both symptom management and interventions aimed at halting disease progression, can significantly improve patient quality of life and outcomes.

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