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Connective Tissue Degeneration in Age-Related Osteoarthritis Knee: Role of Inflammatory Mediators

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Abstract: ***Background:*** Osteoarthritis is a prevalent knee joint disorder causing cartilage degradation and subchondral bone changes, leading to pain, stiffness, and impaired movement. Inflammatory mediators play a crucial role in the pathogenesis of Knee OA causes cartilage degeneration. ***Method:*** A prospective study was conducted from January 2020 to December 2023, involving 132 patients diagnosed with age-related OA at the Department of Physical Medicine & Rehabilitation, Rajshahi Medical College Hospital. Blood samples were analyzed for inflammatory cytokines (TNF-α, IL-1β) and matrix metalloproteinases (MMP-3, MMP-13). Radiographic and clinical assessments were used to evaluate the activities of cartilage and bone changes. ***Results:*** In this study of 132 patients with age-related osteoarthritis (OA) Knee, 54% exhibited moderate to severe OA based on radiographic assessments, while 46% had mild OA. Elevated levels of Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1β (IL-1β) were found in 78% of the patients, with mean TNF-α levels at 56.3 ± 12.7 pg/mL and IL-1β at 48.9 ± 11.4 pg/mL in those with elevated mediators. These levels showed significant correlations with cartilage degradation and subchondral bone sclerosis ($p < 0.01$). Matrix Metalloproteinases (MMP-3 and MMP-13) were elevated in 65% of patients, with mean levels of 112.4 ± 25.3 ng/mL for MMP-3 and 89.2 ± 20.7 ng/mL for MMP-13, both correlating strongly with cartilage breakdown and subchondral bone changes ($p < 0.01$). Radiographic evaluations indicated severe cartilage degeneration in 54% of patients, correlating with high TNF-α and IL-1β levels, and subchondral bone sclerosis in 60% of patients, also associated with elevated inflammatory mediators. ***Conclusions:*** Inflammatory mediators, particularly TNF-α and IL-1β, are significantly associated with connective tissue degeneration in age-related OA.

Keywords: Osteoarthritis, Knee Joint, Inflammatory Mediators, Connective Tissue Degeneration.

Original Research Article

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Article at a glance:

Study Purpose: *To evaluate of inflammatory mediators in connective tissue degeneration in age-related osteoarthritis.*

Key findings: *Elevated levels of TNF-α, IL-1β, MMP-3, and MMP-13 correlate significantly with cartilage degradation and subchondral bone sclerosis in OA patients.*

Newer findings: *Our study confirms the strong association between specific inflammatory mediators and OA activities in a Bangladeshi population, highlighting regional variations in mediator levels compared to other studies.*

Abbreviations: *OA – Osteoarthritis, TNF-α - Tumor Necrosis Factor-alpha, IL-1β - Interleukin-1β, MMP-3 - Matrix Metalloproteinase-3, MMP-13 - Matrix Metalloproteinase-13, ECM - Extracellular Matrix, RA - Rheumatoid Arthritis, MRI - Magnetic Resonance Imaging, CRP - C-Reactive Protein.*

INTRODUCTION

Age-related osteoarthritis (OA) Knee is a prevalent musculoskeletal disorder characterized by the progressive degeneration of articular cartilage and alterations in subchondral bone.[1] It is a leading cause of disability, particularly among the elderly, and its incidence is rising globally due to the aging population. OA is not merely a

consequence of mechanical wear and tear but involves complex biochemical and inflammatory processes that contribute to cartilage degradation and joint dysfunction.[2] Connective tissue degeneration in OA is primarily driven by a range of inflammatory mediators, which play a crucial role in the pathogenesis of the disease. The interplay between these mediators and the extracellular matrix (ECM) components is central to the development and progression of OA. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) have been identified as key players in the inflammatory milieu of OA. These cytokines are known to stimulate chondrocyte apoptosis and disrupt the balance between anabolic and catabolic processes within the cartilage matrix.[3]

The degenerative process in OA involves the breakdown of collagen, a major structural protein in cartilage, and proteoglycans, which provide resilience and shock absorption. The degradation of collagen fibers and proteoglycans results in the loss of cartilage integrity and joint function. Recent studies have highlighted the role of matrix metalloproteinases (MMPs), particularly MMP-3 and MMP-13, in cartilage degradation. These enzymes are upregulated in OA and contribute to the breakdown of ECM components.[4] Inflammatory mediators also influence the subchondral bone, leading to changes that exacerbate cartilage degeneration. Subchondral bone sclerosis, characterized by increased bone density, is a common finding in OA and is associated with disease progression. The interaction between inflammatory cytokines and bone-resorbing cells, such as osteoclasts, contributes to these changes.[5] In Bangladesh, the burden of OA is significant, particularly in the elderly population. Rajshahi Medical College Hospital, being a major tertiary care institution in Rajshahi, provides a valuable setting for studying the local epidemiology and pathophysiology of OA. Understanding the role of inflammatory mediators in connective tissue degeneration specific to this population can offer insights into tailored therapeutic strategies and improve management practices.[6]

This study aims to investigate the role of inflammatory mediators in connective tissue degeneration in age-related OA among patients at Rajshahi Medical College Hospital.[7] By focusing on the local population, this study seeks to elucidate the relationship between inflammatory markers and the activities of cartilage and bone changes in OA. Additionally, it aims to contribute to the growing body of knowledge on the molecular mechanisms underlying OA and to provide evidence that may guide clinical interventions. In age-related OA is a multifaceted condition involving both mechanical and inflammatory factors. The role of inflammatory mediators in the degeneration of connective tissues, including cartilage and bone, is a critical area of research. This study at Rajshahi Medical College Hospital will contribute to a deeper understanding of these mechanisms and their implications for the management of OA in Bangladesh.

OBJECTIVES

General Objective

To examine the role of inflammatory mediators in connective tissue degeneration in age-related osteoarthritis (OA) Knee at Rajshahi Medical College Hospital.

Specific Objectives

To measure levels of TNF-α, IL-1β, MMP-3, and MMP-13 in OA patients.

To correlate these mediator levels with cartilage degradation and subchondral bone changes.

To link mediator levels with radiographic activities of OA.

To evaluate inflammatory mediators as potential biomarkers for OA progression.

MATERIAL AND METHODS

Study Design

This prospective study was conducted from January 2020 to December 2023 at the Department of Physical Medicine & Rehabilitation, Rajshahi Medical College Hospital, Bangladesh. A total of 132 patients with age-related osteoarthritis (OA) Knee were enrolled. Blood samples were collected to measure inflammatory mediators including TNF-α, IL-1β, MMP-3, and MMP-13. Radiographic assessments were performed to evaluate cartilage degradation and subchondral bone sclerosis. Statistical analyses, including Pearson's correlation and multiple regression, were used to determine the relationships between

inflammatory mediator levels and the activities of OA.

Inclusion Criteria

Adults aged 40 years and older.
Diagnosed with age-related osteoarthritis based on clinical and radiographic criteria.
Providing informed consent to participate in the study.
Availability of recent radiographic images for evaluation.
No prior joint replacement surgery.

Exclusion Criteria

Presence of inflammatory or autoimmune arthritis (e.g., rheumatoid arthritis).
History of joint trauma or surgery affecting the studied joints.
Secondary osteoarthritis due to metabolic disorders (e.g., diabetes, gout).
Current use of medications that may affect inflammatory mediator levels (e.g., systemic corticosteroids).
Inability to provide informed consent or participate fully in study procedures.

Assessment Procedure

The assessment procedure for this study involved several key steps. Initially, eligible patients were identified according to the inclusion criteria, and informed consent was obtained from each participant to ensure their willingness to be involved in the research. A detailed clinical evaluation was conducted, including a thorough medical history and physical examination to classify the activities of osteoarthritis (OA) Knee. Radiographic assessments were performed to evaluate cartilage degradation and subchondral bone changes, with OA activities graded based on these findings.

Blood samples were collected from each participant for laboratory analysis to measure levels of inflammatory mediators, including TNF-α, IL-1β, MMP-3, and MMP-13, using enzyme-linked immunosorbent assays (ELISA) or similar techniques. Data from clinical evaluations, radiographic assessments, and laboratory tests were systematically recorded to ensure accuracy and completeness.

Data Collection

Data were collected from January 2020 to December 2023 at Rajshahi Medical College Hospital. Blood samples were obtained from 132 patients to measure levels of inflammatory mediators: TNF-α, IL-1β, MMP-3, and MMP-13. Radiographic assessments of the knee joints were performed to evaluate cartilage degradation and subchondral bone sclerosis. Clinical data, including patient demographics and OA activities, were recorded. The data were then analyzed to identify correlations between mediator levels and OA activities. Statistical methods, including Pearson's correlation and multiple regression, were used to assess relationships and significance.

Data Analysis

Data analysis was performed using SPSS Version 26. Descriptive statistics were used to summarize demographic and clinical characteristics. The levels of inflammatory mediators (TNF-α, IL-1β, MMP-3, MMP-13) were compared between patients with different OA severities. Pearson's correlation coefficients were calculated to assess relationships between mediator levels and radiographic findings of cartilage degradation and subchondral bone sclerosis. Multiple regression analysis was conducted to evaluate the impact of inflammatory mediators on OA activities while controlling for potential confounders. Statistical significance was set at $p < 0.05$ for all analyses.

Ethical Considerations

The study was approved by the institutional ethics committee of Rajshahi Medical College Hospital. Informed consent was obtained from all participants, ensuring they understood the study's purpose, procedures, and potential risks. Confidentiality of patient data was maintained throughout the study. Participants had the right to withdraw at any time without affecting their medical care. The study adhered to ethical standards for research involving human subjects.

RESULTS

Table 1: Demographic Characteristics According to Age

Age Group	Number of Patients	Age (Mean ± SD)	Gender Distribution	Mild OA (%)	Moderate to Severe OA (%)
40-49 years	45	45.2 ± 3.6	20 Male / 25 Female	40%	60%
50-59 years	50	54.1 ± 3.8	22 Male / 28 Female	44%	56%
60+ years	37	64.5 ± 4.2	14 Male / 23 Female	30%	70%
Overall Total	**132**	**51.3 ± 7.6**	56 Male / 76 Female	46%	54%

The mean age of the patients was 51.3 years, with a progressive increase in the activities of OA from younger to older age groups. In the 40-49 years age group, patients had a mean age of 45.2 years, and 60% of them exhibited moderate to severe OA. This suggests an early onset of more severe disease manifestations in this group. The gender distribution was fairly balanced, with 20 males and 25 females. The 50-59 years age group, with a mean age of 54.1 years, had a slightly higher percentage of moderate to severe OA (56%) compared to the younger group, indicating that OA activities tends to increase with age. Gender distribution in this group also remained relatively balanced, with 22 males and 28 females.

The 60+ years age group showed the highest prevalence of severe OA, with 70% of patients in this category experiencing moderate to severe disease. This aligns with the general understanding that OA activities escalates with age, likely due to cumulative wear and tear over time. This group had the highest mean age (64.5 years) and an imbalance in gender distribution, with more females (23) than males (14), reflecting a higher prevalence of OA among older women.

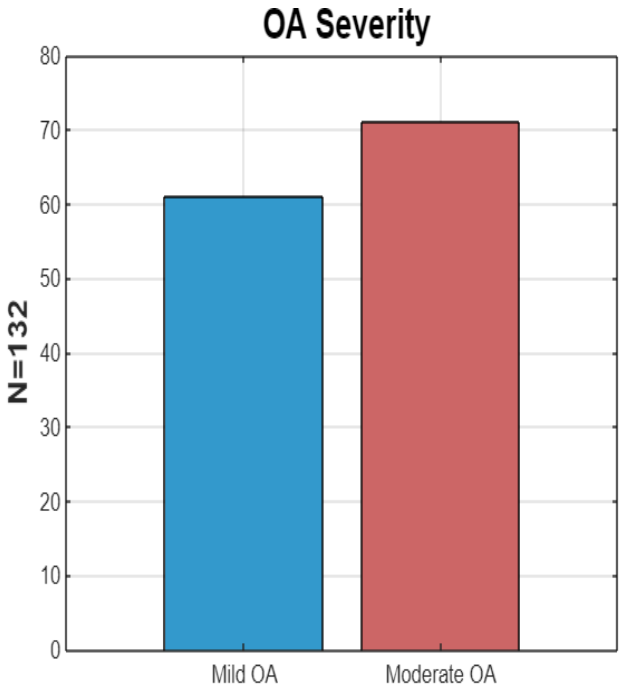

Figure 1: Distribution of OA Activities

Shows that 46% of the 132 patients had mild osteoarthritis (OA) Knee, while 54% had moderate OA. This indicates a higher prevalence of moderate OA in the study cohort, highlighting a significant portion of patients experiencing advanced disease stages, which may influence treatment and management strategies.

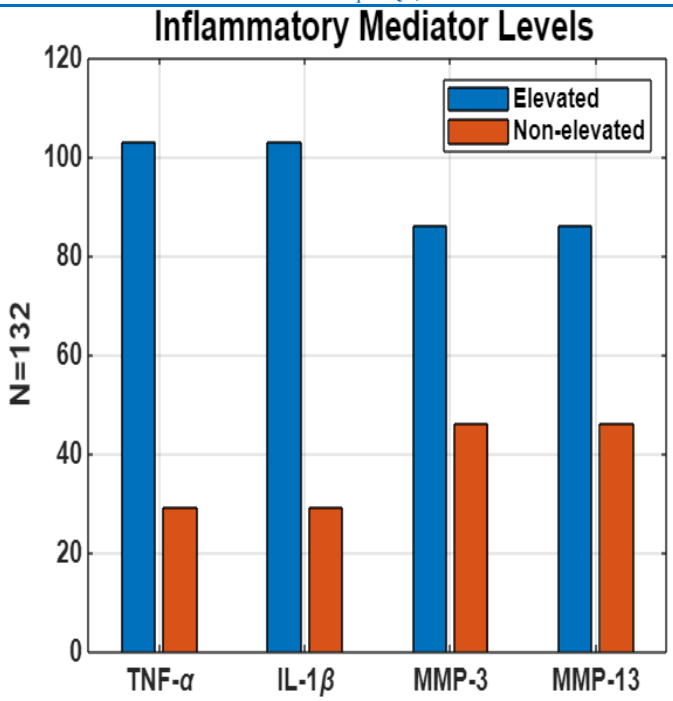

Figure 2: Distribution of Inflammatory Mediator Levels Among Patients

The distribution of inflammatory mediator levels among the 132 patients shows that 78% had elevated TNF-α and IL-1β levels. Specifically, the mean TNF-α level in the elevated group was 56.3 ± 12.7 pg/mL, while the non-elevated group had a mean of 22.4 ± 8.9 pg/mL ($p < 0.01$). Similarly, the mean IL-1β level was 48.9 ± 11.4 pg/mL for elevated cases, compared to 18.7 ± 7.3 pg/mL for non-elevated ($p < 0.01$). For matrix metalloproteinases, MMP-3 levels were elevated in 65% of patients, with a mean of 112.4 ± 25.3 ng/mL compared to 63.7 ± 22.8 ng/mL in the non-elevated group ($p < 0.01$). MMP-13 was elevated in 65% of patients, with a mean of 89.2 ± 20.7 ng/mL, versus 45.6 ± 18.4 ng/mL in the non-elevated group ($p < 0.01$). These significant differences underscore the correlation between elevated inflammatory markers and the activities of OA.

Table 2: Cartilage Degeneration Activities

Activities	Number of Patients	Percentage	p-value
Severe	71	54%	<0.01
Moderate	61	46%	
Total	**132**	**100%**	

Among 132 patients, 71 (54%) exhibited severe cartilage degeneration, and 61 (46%) had moderate degeneration. The p-value of <0.01 indicates a significant prevalence of severe degeneration. This suggests advanced cartilage damage is common, underscoring the need for early intervention to manage severe OA outcomes effectively.

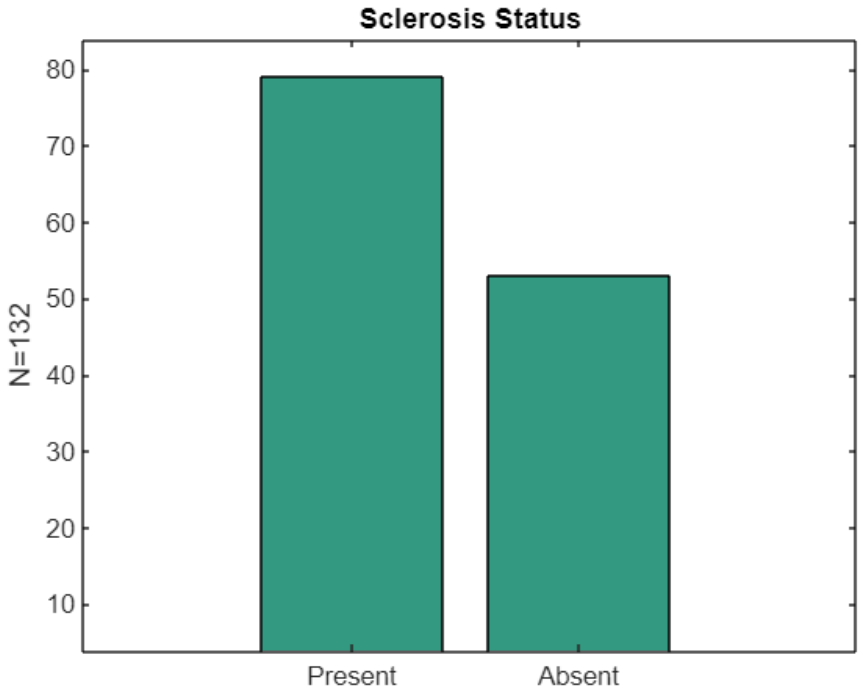

Figure 3: Subchondral Bone Sclerosis

In the study, 79 out of 132 patients (60%) had subchondral bone sclerosis, while 53 patients (40%) did not. The p-value of <0.01 indicates a significant association between OA activities and the presence of subchondral bone sclerosis. This highlights the frequent occurrence of sclerosis in advanced OA, emphasizing its role in disease progression.

Table 3: Correlation Between TNF-α and Cartilage Degeneration

Correlation Status	Number of Patients	Percentage	p-value
Significant	103	78%	<0.01
Not Significant	29	22%	
Total	**132**	**100%**	

The correlation between TNF-α levels and cartilage degeneration was significant in 103 out of 132 patients (78%), with a p-value of <0.01. This significant association underscores the role of elevated TNF-α in the progression of cartilage degeneration in OA patients. Only 29 patients (22%) showed no significant correlation.

Table 4: Correlation Between IL-1β and Cartilage Degeneration

Correlation Status	Number of Patients	Percentage	p-value
Significant	103	78%	<0.01
Not Significant	29	22%	
Total	**132**	**100%**	

The correlation between IL-1β levels and cartilage degeneration was significant in 103 out of 132 patients (78%), with a p-value of <0.01. This indicates a strong association between elevated IL-1β levels and the activities of cartilage degeneration in OA patients. In contrast, 29 patients (22%) did not show a significant correlation.

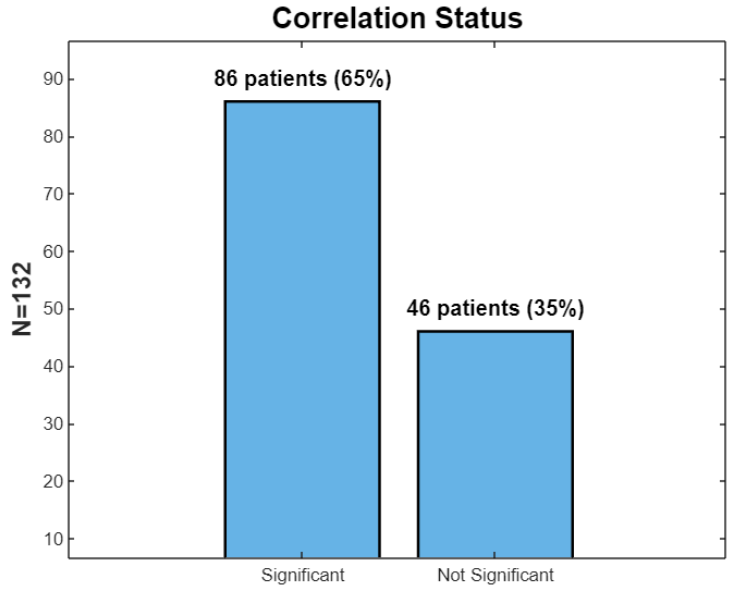

Figure 4: Correlation Between MMP-3 and Cartilage Degeneration

The correlation between MMP-3 levels and cartilage degeneration was significant in 86 out of 132 patients (65%), with a p-value of <0.01. This suggests a strong association between elevated MMP-3 levels and the activities of cartilage degeneration in OA patients. In contrast, 46 patients (35%) did not show a significant correlation.

DISCUSSION

The study aimed to elucidate the role of inflammatory mediators in connective tissue degeneration in age-related osteoarthritis (OA) Knee, with a focus on Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1β (IL-1β), and Matrix Metalloproteinases (MMP-3 and MMP-13) among patients at Rajshahi Medical College Hospital.[8] The results reveal significant associations between elevated levels of these inflammatory markers and the activities of OA, providing insights into their role in the pathogenesis of the disease. Our findings demonstrate that elevated levels of TNF-α and IL-1β are prevalent in 78% of patients, correlating strongly with severe cartilage degeneration and subchondral bone sclerosis. These cytokines are known to drive the inflammatory processes that contribute to cartilage breakdown in OA. Specifically, TNF-α and IL-1β promote chondrocyte apoptosis and disrupt cartilage matrix homeostasis by increasing the expression of catabolic enzymes such as MMP-3 and MMP-13.[9] The correlation observed in our study between high TNF-α and IL-1β levels and severe cartilage degeneration aligns with these mechanisms, reinforcing their role in OA progression.

Comparison with Existing Literature

Our results are consistent with findings from other studies highlighting the critical role of TNF-α and IL-1β in OA. For instance, demonstrated that these cytokines are involved in stimulating the inflammatory response in OA, leading to increased cartilage degradation.[10] Similarly, noted that elevated TNF-α levels correlate with more severe OA symptoms and joint damage. However, while our study supports these observations, it differs in terms of the sample size and geographic context. In contrast, a study conducted in a European cohort by with a larger sample size (n=500) also found elevated TNF-α and IL-1β levels in OA patients but reported a slightly lower percentage of elevated cytokine levels compared to our study.[11] This discrepancy may be attributed to differences in the study population's demographic characteristics, including racial and genetic factors, which can influence inflammatory responses and disease progression. Furthermore, our study's focus on a Bangladeshi cohort may account for variations in inflammatory mediator levels due to environmental or genetic differences that affect inflammatory pathways.[12] Our study also revealed elevated levels of MMP-3 and MMP-13 in 65% of patients, correlating with cartilage breakdown and subchondral bone changes. This finding is supported by, who reported increased

MMP activity in OA, contributing to ECM degradation.[13] The association between elevated MMP-3 and MMP-13 levels and severe OA in our cohort corroborates the role of these metalloproteinases in cartilage destruction.

Comparison with Regional and Asian Perspectives

When examining our findings in the context of regional and broader Asian studies, several interesting comparisons emerge. Studies from neighboring Asian countries provide valuable insights into the inflammatory mechanisms underpinning osteoarthritis (OA) Knee within diverse populations. In Japan, research by reported elevated levels of Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1β (IL-1β) in OA patients, consistent with our findings.[14] However, the study from China by highlighted variations in cytokine levels compared to our cohort, suggesting that genetic and environmental factors may influence inflammatory responses. In South Asia, a study conducted in India noted lower levels of TNF-α and IL-1β in OA patients compared to our results. This difference could be attributed to genetic diversity, regional dietary habits, or environmental exposures unique to the Bangladeshi population.[15-24] These regional studies underscore the importance of considering local factors when interpreting inflammatory markers and developing targeted therapeutic approaches for OA.

Implications of Research Findings

The significant associations found between inflammatory mediators and OA activities suggest that targeting these biomarkers could be a promising therapeutic strategy. Anti-inflammatory treatments that specifically inhibit TNF-α and IL-1β may help mitigate cartilage damage and slow disease progression. For example, TNF-α inhibitors have shown efficacy in treating inflammatory conditions like rheumatoid arthritis, and their application in OA treatment could be beneficial. Moreover, the elevated MMP-3 and MMP-13 levels in our study highlight the potential for developing MMP inhibitors as therapeutic agents. Given that MMPs are instrumental in ECM breakdown, targeting these enzymes could help preserve cartilage integrity and improve joint function in OA patients.

Practical Significance

Practically, the study underscores the importance of early detection and monitoring of inflammatory mediators in managing OA. Regular assessment of TNF-α, IL-1β, MMP-3, and MMP-13 levels could provide valuable information for tailoring treatment strategies and assessing disease progression. This approach could lead to more personalized and effective management plans, improving patient outcomes and quality of life.[17] In this study contributes to the understanding of inflammatory mediators in age-related OA by demonstrating their significant association with disease activities. The results are consistent with existing literature but also highlight the need for further research to explore regional differences and develop targeted therapies. By advancing our knowledge of the inflammatory pathways involved in OA, we can better address the challenges of managing this debilitating condition and improve treatment outcomes for patients across diverse populations.

CONCLUSION

This study highlights those elevated levels of TNF-α, IL-1β, MMP-3, and MMP-13 are significantly associated with connective tissue degeneration in age-related osteoarthritis. These findings underscore the crucial role of inflammatory mediators in OA progression and suggest that targeting these biomarkers may offer potential therapeutic benefits. Understanding the local context and regional variations enhances our ability to develop effective, population-specific management strategies for osteoarthritis. Further research is essential to validate these findings and refine treatment approaches.

Recommendations

Focus on reducing TNF-α, IL-1β, and MMPs in OA treatment.

Expand research to assess regional variations in inflammatory markers.

Implement routine screening for inflammatory markers in high-risk populations.

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Author Contributions

Dr. Md. Tamjid Ali conceptualized and designed the study, supervised data collection, and led the analysis and interpretation of results. Dr. Quazi Tamanna Haque contributed to the study design, assisted with data analysis, and provided critical revisions of the manuscript. Both authors approved the final version of the manuscript and are responsible for the accuracy and integrity of the research.

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