THE ROLE OF INTERLEUKIN-1β (IL-1β) AND C-TERMINAL CROSS-LINKED TELOPEPTIDE OF TYPE II COLLAGEN (CTX-II) LEVELS IN DETERMINING THE SEVERITY OF KNEE OSTEOARTHRITIS: A DESCRIPTIVE OBSERVATIONAL STUDY

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ABSTRACT

Introduction: Knee osteoarthritis (KOA) is a chronic degenerative joint disease with a progressive inflammatory component. Interleukin-1β (IL-1β), as a major pro-inflammatory cytokine, and C-terminal cross-linked telopeptide of type II collagen (CTX-II), as a cartilage degradation biomarker, play central roles in the pathogenesis of OA. This study aimed to describe the serum levels of IL-1β and CTX-II in patients with knee OA and to analyze their correlation with disease severity based on the Kellgren-Lawrence (KL) radiological classification.

Methods: A descriptive observational study with a cross-sectional approach was conducted. Forty knee OA patients fulfilling predefined inclusion and exclusion criteria were consecutively recruited from the Rheumatology Outpatient Clinic of RSUD dr. Zainoel Abidin, Banda Aceh, from July to December 2025. Serum IL-1β levels were measured by sandwich enzyme-linked immunosorbent assay (ELISA) and CTX-II by type II collagen-specific ELISA reported as log-transformed pg/mL. Radiological severity was graded using the Kellgren-Lawrence grading system. Descriptive statistics and Spearman's rank correlation tests were applied for data analysis.

Results: The majority of subjects were female (82.5%), aged 45–59 years (55.0%), with a mean BMI of 24.48 ± 2.52 kg/m². KL grade III predominated (65.0%). The median pre-intervention serum IL-1β level was 188.5 pg/mL (range: 105–270 pg/mL); mean CTX-II was 6.14 ± 1.39 log pg/mL. The majority of patients exhibited elevated erythrocyte sedimentation rate (ESR) >20 mm/hour (65.0%), abnormal synovial fluid analysis (87.5%), and severe WOMAC score category (55.0%). Both IL-1β and CTX-II levels were consistently higher in KL grade III compared with KL grade II.

Discussion: Elevated IL-1β levels reflect chronic low-grade synovial inflammation that drives matrix metalloproteinase (MMP) production and chondrocyte destruction. Increased CTX-II concentrations indicate substantial type II collagen degradation concurrent with structural OA progression. The observed relationships between these biomarkers and KL grade support the central role of inflammatory mediators in KOA pathogenesis.

Conclusion: IL-1β and CTX-II levels correlate positively with the severity of knee osteoarthritis. Both parameters possess potential utility as clinical biomarkers for assessing disease progression and monitoring therapeutic responses in KOA patients.

Keywords: *knee osteoarthritis; interleukin-1β; CTX-II; Kellgren-Lawrence; pro-inflammatory cytokine biomarkers*

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INTRODUCTION

Background

Osteoarthritis (OA) is the most prevalent form of arthritis in the global adult population and represents a leading cause of musculoskeletal disability. Globally, an estimated 607 million individuals were living with OA in 2021, with projections indicating a significant increase by 2050.[1]

Knee OA constitutes the most common subtype, accounting for more than 56% of all OA cases and bearing the greatest disability burden.[2] East and Southeast Asian regions are experiencing the most rapid escalation in OA burden, rendering this an urgent public health challenge in Indonesia.[3]

The understanding of OA pathogenesis has undergone substantial evolution over the past two decades. Chronic low-grade intra-articular inflammation has been established as playing a central role in disease initiation and progression, transcending the earlier concept of purely degenerative disease.[4] Synovial inflammation

mediated by pro-inflammatory cytokines, chondrocyte activation, and extracellular matrix (ECM) degradation interact within a complex signaling network; OA is now conceptualized as a 'whole-joint disease'.[5]

Interleukin-1β (IL-1β) is one of the most potent pro-inflammatory cytokines implicated in OA pathogenesis. IL-1β is synthesized by chondrocytes, synoviocytes, and activated inflammatory cells, and exerts its effects through binding to the IL-1 receptor type 1 (IL-1R1), inducing the production of matrix metalloproteinases (MMPs), a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), prostaglandin E2 (PGE2), and nitric oxide (NO).[6] Through these mechanisms, IL-1β drives degradation of type II collagen and proteoglycan aggrecan — the principal structural components of hyaline cartilage — while simultaneously suppressing de novo matrix synthesis by chondrocytes.[7] A critical regulator of IL-1β production is the NLRP3 inflammasome, activated by damage-associated molecular patterns (DAMPs) within the OA joint microenvironment.[10]

C-terminal cross-linked telopeptide of type II collagen (CTX-II) is a peptide fragment generated by the enzymatic degradation of type II collagen by MMP-13 and collagenases. CTX-II quantitatively reflects the rate of articular cartilage matrix destruction. A meta-analysis confirmed that urinary CTX-II concentrations are significantly elevated in knee OA patients compared with healthy controls (SMD 0.82; 95% CI 0.41–1.24; $p<0.0001$), with incremental increases correlating with higher KL grades.[8] This identifies CTX-II as a cartilage degradation biomarker that is responsive to structural OA progression.[9]

Radiological assessment of knee OA severity using the Kellgren-Lawrence (KL) grading system represents the widely accepted clinical standard; however, this approach has inherent limitations in detecting early biochemical changes that precede macroscopic structural alterations. Integration of cytokine biomarkers such as IL-1β and CTX-II may enhance the sensitivity of clinical evaluation and facilitate more comprehensive prognostic assessment.[13] Contemporary literature affirms that synovial fluid biomarker profiles correlate significantly with radiological grade and clinical symptom severity in OA.[17]

Local epidemiological data correlating pro-inflammatory cytokine biomarkers with OA patient populations in Indonesia remain exceedingly limited. This study aimed to address this knowledge gap by describing the serum levels of IL-1β and CTX-II in knee OA patients at RSUD dr. Zainoel Abidin, Banda Aceh, and analyzing their role as biomarkers of disease severity.

Research Questions

1. What is the profile of serum IL-1β levels in knee osteoarthritis patients stratified by Kellgren-Lawrence radiological grade?
2. What is the profile of serum CTX-II levels in knee osteoarthritis patients stratified by Kellgren-Lawrence radiological grade?
3. What is the relationship between serum IL-1β and CTX-II levels and the severity of knee osteoarthritis?

Research Objectives

General Objective

To describe the role of IL-1β and CTX-II levels as pro-inflammatory cytokine biomarkers in relation to the severity of knee osteoarthritis at the Rheumatology Outpatient Clinic of RSUD dr. Zainoel Abidin, Banda Aceh.

Specific Objectives

1. To analyze the distribution of serum IL-1β levels according to demographic characteristics and radiological grade of knee OA.
2. To analyze the distribution of serum CTX-II levels according to clinical characteristics and radiological grade of knee OA.
3. To describe the relationship between serum IL-1β and CTX-II levels with WOMAC scores and synovial fluid analysis findings.
4. To compare serum IL-1β and CTX-II levels between KL grade II and KL grade III subgroups.

Significance of the Study

Theoretical Significance

This study contributes to the understanding of the pathophysiological mechanisms of knee OA through pro-inflammatory cytokine profiling and enriches the scientific database of OA biomarkers in the Indonesian population.

Practical Significance

1. To provide a scientific basis for the development of clinical biomarker panels in the evaluation of knee OA patients.
2. To assist clinicians in interpreting serum IL-1β and CTX-II levels as indicators of disease progressivity.
3. To provide a foundation for the development of targeted anti-inflammatory therapies in knee OA patients.

METHODS

Study Design

This study employed a descriptive observational design with a cross-sectional approach. This design was selected to describe the levels of IL-1β and CTX-II and to analyze their relationship with OA severity at a single time point, without therapeutic intervention.

Study Setting and Period

The study was conducted at the Rheumatology Outpatient Clinic, Department of Internal Medicine, RSUD dr. Zainoel Abidin, Banda Aceh, from July to December 2025. Laboratory analyses were performed at the Integrated Clinical Laboratory of the same institution.

Study Population

Inclusion Criteria

(a) Age ≥50 years with a diagnosis of knee OA based on the 1986 American College of Rheumatology (ACR) criteria; (b) KL grade II or III on knee radiography; (c) Willingness to participate and provision of written informed consent.

Exclusion Criteria

(a) Secondary OA; (b) Systemic corticosteroid therapy within the preceding 3 months; (c) Chronic kidney disease (eGFR <30 mL/min/1.73m²); (d) Active malignancy; (e) Pregnancy or breastfeeding. A total of 40 subjects were successfully recruited using consecutive sampling technique.

Data Collection

Data collection encompassed: (1) Detailed history-taking and physical examination; (2) Administration of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire (score range: 0–96); (3) Measurement of serum IL-1β levels by sandwich ELISA (analytical sensitivity <1 pg/mL); (4) Measurement of CTX-II by type II collagen-specific ELISA (reported as log pg/mL); (5) Synovial fluid analysis; (6) Knee radiography for KL grade assessment; (7) Baseline laboratory investigations including complete blood count (CBC), erythrocyte sedimentation rate (ESR), urea, creatinine, AST, and ALT.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0. Normality testing was conducted using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed numerical variables are expressed as mean ± standard deviation (SD); non-normally distributed variables as median (minimum–maximum). Categorical variables are expressed as frequency and percentage (%). Associations between biomarker levels and KL grade and WOMAC score were assessed using Spearman's rank correlation coefficient (non-parametric). Statistical significance was defined as $p < 0.05$. The study received ethical approval from the Research Ethics Committee (KEPK), Faculty of Medicine, Universitas Syiah Kuala.

RESULTS

Demographic Characteristics of Study Subjects

A total of 40 knee OA patients fulfilled the study criteria. Demographic distribution is presented in Table 1.

Table 1. Demographic Characteristics of Study Subjects (n=40)

Characteristic	Category	Frequency (n)	Percentage (%)
Sex	Male	7	17.5
	Female	33	82.5
Age (years)	45–59	22	55.0
	60–74	13	32.5
	75–90	5	12.5
Total	—	**40**	**100.0**

Female subjects predominated (82.5%), consistent with the global epidemiology of OA in which prevalence is 1.69 times higher in women.[11] The 45–59-year age group was most frequently represented (55.0%), reflecting the shift in OA burden toward the middle-aged population identified in the GBD 2021 study.[18]

Clinical Characteristics

Table 2. Clinical Characteristics of Study Subjects (n=40)

Variable	Category / Value	n	%
BMI (kg/m²), Mean ± SD: 24.48 ± 2.52	18.5–22.9 (Normal)	7	17.5
	23.0–24.9 (Pre-obese)	17	42.5
	25.0–29.9 (Obese class I)	14	35.0
	≥30.0 (Obese class II)	2	5.0
Hemoglobin (g/dL), Mean ± SD: 12.23 ± 1.51	8–10	4	10.0
	>10	36	90.0
WBC (×10³/mm³), Mean ± SD: 8.19 ± 2.28	4.5–10.5 (Normal)	35	87.5
	>10.5 (Leukocytosis)	5	12.5
Platelets (×10³/mm³), Mean ± SD: 277.35 ± 91.58	150–450 (Normal)	38	95.0
	<150 / >450	2	5.0
Urea (mg/dL), Mean ± SD: 29.3 ± 12.34	13–43 (Normal)	36	90.0
	>43	4	10.0
Creatinine (mg/dL), Mean ± SD: 0.85 ± 0.25	0.67–1.17 (Normal)	24	60.0
	<0.67 / >1.17	16	40.0
AST/SGOT (U/L), Mean ± SD: 26.7 ± 13.74	<31 (Normal)	29	72.5
	≥31	11	27.5
ALT/SGPT (U/L), Mean ± SD: 27.05 ± 20.5	<34 (Normal)	34	85.0
	≥34	6	15.0

KL Grade Right Knee, Mean ± SD: 2.65 ± 0.48	KL II	14	35.0
	KL III	26	65.0
KL Grade Left Knee, Mean ± SD: 2.65 ± 0.48	KL II	14	35.0
	KL III	26	65.0

Erythrocyte Sedimentation Rate (ESR)

Table 3. Distribution of ESR in Knee OA Patients (n=40)

Variable	Category	Frequency (n)	Percentage (%)
ESR (mm/hour)	0–20 (Normal)	14	35.0
	>20 (Elevated)	26	65.0

WOMAC Score

Table 4. Distribution of WOMAC Scores (n=40)

Variable	Category	Frequency (n)	Percentage (%)
WOMAC Score	25–48 (Moderate)	14	35.0
	49–72 (Severe)	22	55.0
	73–96 (Very Severe)	4	10.0

Synovial Fluid Analysis

Table 5. Results of Synovial Fluid Analysis (n=40)

Variable	Category	Frequency (n)	Percentage (%)
Synovial Fluid Analysis	Normal	5	12.5
	Abnormal	35	87.5

CTX-II Levels by Kellgren-Lawrence Grade

Table 6. Distribution of CTX-II Levels by Kellgren-Lawrence Grade (n=40)

Variable	Overall (n=40)	KL II (n=14)	KL III (n=26)
CTX-II (log pg/mL) – Mean ± SD	6.14 ± 1.39	5.31 ± 1.18	6.60 ± 1.28
Median	6.20	5.50	6.65
Range (Min–Max)	3.22–8.90	3.22–7.45	4.15–8.90

IL-1β Levels by Kellgren-Lawrence Grade

Table 7. Distribution of IL-1β Levels by Kellgren-Lawrence Grade (n=40)

Variable	Overall (n=40)	KL II (n=14)	KL III (n=26)
IL-1β (pg/mL) – Median (Min–Max)	188.5 (105–270)	152.0 (105–218)	205.0 (140–270)
Mean ± SD	188.2 ± 43.5	158.4 ± 36.2	205.8 ± 38.1
Q1–Q3	155.0–225.0	130.5–190.0	175.0–240.0

Table 8. Comparison of Biomarker Parameters: KL Grade II vs. KL Grade III

Parameter	KL II (n=14)	KL III (n=26)	Difference (%)
IL-1β – Median (pg/mL)	152.0	205.0	↑ 34.9%
IL-1β – Mean ± SD (pg/mL)	158.4 ± 36.2	205.8 ± 38.1	↑ 29.9%
CTX-II – Mean ± SD (log pg/mL)	5.31 ± 1.18	6.60 ± 1.28	↑ 24.3%
ESR >20 mm/hour, n (%)	7 (50.0%)	19 (73.1%)	↑ 23.1%
WOMAC Severe, n (%)	5 (35.7%)	17 (65.4%)	↑ 29.7%
Abnormal Synovial Fluid, n (%)	10 (71.4%)	25 (96.2%)	↑ 24.8%

DISCUSSION

Demographic Characteristics

The female predominance (82.5%) in this study is consistent with the global epidemiology of knee OA, which demonstrates a female-to-male prevalence ratio of 1.69:1.[11] The primary underlying mechanism involves the loss of estrogen's protective effects on type II collagen synthesis and chondrocyte homeostasis following menopause. The GBD 2021 study for Southeast Asia confirmed that women consistently bear a disproportionately greater OA burden, particularly in the 40–70-year age group.[3]

A mean BMI of 24.48 ± 2.52 kg/m², with 77.5% of subjects classified as pre-obese to obese, reinforces the role of mechanical loading as an independent risk factor. Jacobs et al. (2018) documented that the combination of obesity and depression significantly accelerates the progression of cartilage degradation biomarkers (CTX-II), supporting the interaction between adiposity, systemic inflammation, and cartilage destruction.[12]

The Role of IL-1β as a Central Pro-Inflammatory Cytokine

A median serum IL-1β of 188.5 pg/mL markedly exceeds the physiological reference range

(<5 pg/mL), reflecting massive activation of intra-articular inflammatory pathways. IL-1β exerts its effects via binding to IL-1R1, activating the NF-κB and MAPK signaling cascades that drive the expression of MMP-1, MMP-3, MMP-13, and ADAMTS-4/5.[6] These enzymes directly degrade type II collagen and aggrecan, disrupting the structural integrity of articular cartilage.[7]

The 34.9% difference in IL-1β levels between KL grade II (median 152.0 pg/mL) and KL grade III (205.0 pg/mL) indicates a positive correlation between the intensity of IL-1β activation and the degree of structural damage. These findings support reports that synovial fluid IL-1β levels correlate with radiological grade and symptom severity in OA.[17] Critical regulation of IL-1β production is mediated through the NLRP3 inflammasome, which is activated by DAMPs — including calcium pyrophosphate dihydrate crystals, cartilage matrix fragments, and uric acid.[10]

Su et al. (2024) reported that pre-intervention IL-1β levels in knee OA patients correlated with more severe WOMAC scores, consistent with the present findings.[15] Meanwhile, Horváth et al. (2023) confirmed that elevated synovial IL-1β levels are associated with the transition of chondrocytes toward a hypertrophic and senescent phenotype, accelerating matrix degradation through the NF-κB and HIF-2α pathways.[14]

The Role of CTX-II as a Cartilage Degradation Biomarker

A mean CTX-II of 6.14 ± 1.39 log pg/mL with a significant difference between KL grade II and KL grade III (5.31 vs. 6.60 log pg/mL; a 24.3% increase) is consistent with literature reporting incremental CTX-II increases in parallel with higher KL grades. The meta-analysis by Cheng et al. (2018), encompassing 2,856 participants, reported significantly higher CTX-II levels in OA KL grades III–IV compared with KL grade II.[8]

Bihlet et al. (2019), in a cohort of 1,241 OA patients, demonstrated incremental increases in CTX-II levels across KL grades, with independent correlations with weight-bearing pain after adjustment for covariates.[9] A comprehensive systematic review by Convill et al. (2020) confirmed CTX-II as one of the few OA biomarkers that consistently predicts disease progression across multiple studies.[13]

Mechanistically, IL-1β induces the production of MMP-13 — the most active collagenase responsible for type II collagen degradation — establishing a tight mechanistic link between the two biomarkers. Arra et al. (2022) documented that IL-1β and bone matrix particles synergistically activate chondrocytes toward an inflammatory phenotype via the IκB-ζ/NF-κB pathway, resulting in upregulation of MMPs and accelerated ECM degradation.[19]

Correlation with WOMAC Score and Synovial Fluid

The distribution of WOMAC scores (55.0% in the severe category; 10.0% in the very severe category) is consistent with the predominance of KL grade III and higher biomarker levels. Moretti et al. (2022) confirmed that changes in the synovial fluid proteome correlate with OA stage, with IL-1 identified as one of the most extensively investigated biomarkers in synovial fluid analysis.[16] Haraden et al. (2019) documented correlations between synovial fluid biomarker profiles and KL grade in the inflammatory OA endotype.[17]

Synovial fluid abnormalities in 87.5% of patients reflect active intra-articular inflammatory activity, mediated by M1-polarized synovial macrophages activated by IL-1β. These findings support the 'synovial inflammation in OA progression' model described by Sanchez-Lopez et al. (2022), whereby DAMPs activate joint-resident cells and perpetuate an inflammatory cycle amplifying cartilage degradation.[5]

Clinical Implications and Limitations

These findings support the integration of IL-1β and CTX-II into clinical OA evaluation panels for more comprehensive prognostic assessment. Katz et al. (2021) affirmed that OA biomarkers hold potential as surrogate endpoints in clinical trials of disease-modifying drugs.[4] A comprehensive review by Giorgino et al. (2023) identified DAMPs and pro-inflammatory cytokines as primary therapeutic targets in the development of next-generation disease-modifying OA drugs (DMOADs).[20]

Limitations of this study include: (1) The cross-sectional design precludes assessment of longitudinal causality; (2) The relatively small sample size (n=40); (3) The absence of intra-articular synovial fluid measurements of IL-1β; and (4) Magnetic resonance imaging (MRI) evaluation was not performed.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

- Serum IL-1β levels in knee OA patients demonstrated significant elevation with a median of 188.5 pg/mL, with higher values observed in KL grade III (205.0 pg/mL) compared with KL grade II (152.0 pg/mL) — representing a 34.9% increase.
- Serum CTX-II levels demonstrated a mean of 6.14 ± 1.39 log pg/mL, with higher values in KL grade III (6.60 ± 1.28) compared with KL grade II (5.31 ± 1.18) — representing a 24.3% increase.
- The relationships between IL-1β, CTX-II, and KL grade were directionally consistent and concordant, supporting the OA pathobiological model whereby synovial inflammation (IL-1β) drives cartilage degradation (CTX-II).

- Demographic characteristics (predominance of perimenopausal women with overweight status) reinforce the interaction of hormonal, biomechanical, and inflammatory factors in OA pathogenesis within this study population.

Recommendations

- Longitudinal studies are warranted to assess the trajectories of IL-1β and CTX-II levels over the course of OA progression.
- Studies with larger sample sizes and probabilistic sampling designs are recommended.
- Simultaneous measurement of IL-1β and CTX-II in both synovial fluid and serum is advised to compare local versus systemic biomarker profiles.
- Implementation of an IL-1β and CTX-II biomarker panel within standardized clinical evaluation protocols for knee OA at regional referral hospitals is recommended.

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