The relationship of IL-1β/IL-10 ratio, pain degree and CTX-II levels with histopathological features of facet joint osteoarthritis in patients with lumbal spinal canal stenosis

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ABSTRACT

Introduction: Osteoarthritis of the facet joint is the final stage of spinal degeneration. Cytokines are believed to play a crucial role in degenerative joint diseases. This study was conducted to prove the relationship between the IL-1β/IL-10 ratio, the degree of pain, and the levels of CTX-II with the histopathological features of facet joint osteoarthritis in patients with lumbal spinal canal stenosis.

Methods: The research design is a Cross-Sectional design with consecutive sampling. This study involves patients diagnosed with lumbar spinal canal stenosis according to the hospital’s standard operating procedure from January 2023 to September 2023. CTX-II and Plasma IL-10 cytokine levels were examined using the Enzyme-Linked Immunosorbent Assay (ELISA) method. Histopathology is obtained through staining under a microscope. The data obtained in the study were analyzed, and significant result was p<0.05.

Results: A total of 38 samples were obtained. There were more males than females, with 52.6% and 47.4%, respectively. The demographic data showed an average age of 58 years. A statistically significant relationship was found between CTX-II and the histological degree of OA in facet joints, with a p-value of 0.043 (p < 0.05) and a weak positive correlation strength (0.330). Meanwhile, the IL-1β/IL-10 ratio showed a weak positive correlation (0.490) with a p-value of 0.002. ODI exhibited a positive correlation with a strength of (0.393) and a p-value of 0.015. A statistically significant relationship was found for IL-1β with a p-value of 0.039, and IL-10 with a p-value of 0.031 (p > 0.05). The correlation strengths were positive for IL-1β (0.327) and negative for IL-10 (-0.336).

Conclusion: There was a relationship between the IL-1β/IL-10 ratio, the degree of pain, and the levels of CTX-II with the histopathological features of facet joint osteoarthritis in patients with lumbar spinal canal stenosis.

Keywords: CTX-II, IL-1β/IL-10, lumbal spinal canal stenosis, osteoarthritis.


INTRODUCTION

Osteoarthritis of the facet joint is the final stage of spinal degeneration that begins with the degeneration process in the intervertebral discs. This degenerative process is characterized by a decrease in the water content of the intervertebral discs, tears in the annulus fibrosus, thickening of the ligaments supporting the spine, damage to the cartilage of the facet joints, and thickening of the facet joint capsule. The decreased water content in the intervertebral discs triggers the release of pro-inflammatory and anti-inflammatory mediators.

The prevalence of pain due to facet joint osteoarthritis in the lumbar region is reported to vary in the literature, ranging from below 5% to more than 90% of patients complaining of back pain.¹,² Age is strongly associated with the prevalence of lumbar facet joint arthropathy. According to a study, moderate to severe lumbar facet joint arthropathy was found in 36% of adults under the age of 45, 67% of adults aged 45-64, and 89% of adults aged 65 and above.³ Another study using lumbar CT scans and X-rays found that women aged 50 and above are at a higher risk of experiencing osteoarthritis of the facet joints compared to men.⁴

Cytokines are believed to play a crucial role in degenerative joint diseases. Several cytokines are considered to be involved in the pathogenesis of osteoarthritis of the facet joints. Tsuchida et al., in an observational study measuring the levels of IL-6 and IL-8 in synovial fluid, concluded that these cytokine levels increase in OA patients’ blood and synovial fluid. A study conducted by Igarashi et al. in 2004, examining the levels of IL-1β in facet joints, found approximately 11% in lumbar disc herniation (LDH) and 21.7% in lumbar spinal canal stenosis (LSCS).⁵ It is important to note that not only pro-inflammatory cytokines and
cartilage-degrading enzymes but also anti-inflammatory cytokines and inhibitors of cartilage-degrading enzymes, including IL-10, play a role in the degenerative process of facet joints. IL-10 is highly effective in suppressing the ability of macrophages to release TNF-α, although the induction of some other cytokines (such as IL-1 and GMCSF) also occurs. Histopathological examinations are not routinely performed in Lumbar Spinal Canal Stenosis (LSCS) cases. However, the degree of facet joint damage based on histopathological findings has recently begun to be investigated.

Other biochemical markers, such as the C-terminal telopeptide of type II collagen (CTX-II), serve as indicators of joint cartilage degradation. They represent the end result of cutting the C-terminus ¼ fragment composed of six non-helix amino acid groups.

Researchers are interested in investigating the relationship between the IL-1β/IL-10 ratio, the degree of pain, and the levels of CTX-II with the histopathological features of facet joint osteoarthritis in patients with lumbar spinal canal stenosis. This will allow researchers to determine the significant levels of the IL-1β/IL-10 ratio and CTX-II in causing facet joint osteoarthritis.

Based on the above description, a study will be conducted on the relationship between the IL-1β/IL-10 ratio, the degree of pain, and the levels of CTX-II with the histopathological features of facet joint osteoarthritis in patients with lumbar spinal canal stenosis.

**METHODS**

The research design used is a Cross-Sectional design employing consecutive sampling methods. The study was conducted at Prof. Dr. I.G.N.G Ngoerah Teaching Hospital in Denpasar, Bali. Clinical and laboratory data were obtained from secondary data in patient medical records. The research period was from March 2023 to September 2023.

This study involves patients diagnosed with lumbar spinal canal stenosis according to the hospital's standard operating procedure from January 2023 to September 2023. Inclusion criteria for this study include patients with lumbar spinal canal stenosis and facet joint osteoarthritis based on clinical and diagnostic (MRI) examinations, aged over 18 years, normal BMI, willing to participate in the study, and complete data. Exclusion criteria for this study include patients currently experiencing acute or chronic infections confirmed by physical and laboratory examinations, those who have undergone bilateral ovary removal, those using hormonal medications or hormone replacement therapy, corticosteroid use, malignancy or cancer history, and a history of lumbar-sacral spine trauma.

Lumbar spinal canal stenosis refers to the narrowing of the spinal canal or intervertebral foramen with neural impingement causing neurogenic claudication or radiculopathy. This is confirmed by reading MRI results by a radiology specialist. Facet joint osteoarthritis is a pathological process involving synovial facet joint damage. Degenerative changes begin with cartilage degradation, leading to erosion and joint space narrowing, ultimately resulting in subchondral bone sclerosis.

CTX-II is the cytokine level of CTX-II examined using the Enzyme-Linked Immunosorbent Assay (ELISA) method with the Biomeureaux ELISA manual tool and BT Lab CTX-II reagent, expressed in pg/mL. Interleukin-10 (IL-10) is the plasma IL-10 cytokine level examined using the Enzyme-Linked Immunosorbent Assay (ELISA) method with the Biomeureaux ELISA manual tool and Quantikine IL-10 reagent with catalog number D10000B, expressed in pg/mL. Low IL-10 levels refer to IL-10 levels ≤ the median IL-10 level of all samples.

Histopathology is a microscopic examination of cells and tissues through staining under a microscope, differentiated based on grading (grades 1-4). Oswestry Disability Index (ODI) is an instrument used to measure pain intensity experienced by patients on a scale of 1-10, categorized as mild (ODI 1-3), moderate (ODI 4-6), and severe (7-10). IL-1β levels are the plasma IL-1β cytokine levels examined using the Enzyme-Linked Immunosorbent Assay (ELISA) method with the Biomeureaux ELISA manual tool and BT Lab IL-1β reagent, expressed in pg/mL.

**RESULTS**

The subjects of this study consist of a total of 38 samples, where each sample has undergone Oswestry Disability Index (ODI) questionnaire completion and tissue collection in the form of facet joints for laboratory examinations in the Clinical Pathology and Anatomic Pathology laboratories. Measurements of IL-10, IL-1β, CTX-II levels, and the degree of Facet Joint Osteoarthritis (OA) were conducted through histopathological examinations.

A total of 38 samples were gathered for this study, and Table 1-3 shows the demographic features of these samples. Regarding gender, the proportion of men was higher than that of women (52.6 vs. 47.4%). The average age of the participants, as determined by age, was 58 years, with the youngest being 40 years old and the oldest being 82 years old. 5 (7.9%) had grade 2 facet joint osteoarthritis, 14 (36.8%) had grade 3 osteoarthritis, and 21 (55.3%) had grade 4 osteoarthritis, according to the histological results.

The association between CTX-II levels, the IL-1β/IL-10 ratio, and ODI scores with the Histological Degree of Osteoarthritis (OA) in facet joints was examined in this study using a Pearson correlation analysis. A modest positive correlation strength of 0.330 and a p-value of 0.043 (p < 0.05) indicated a statistically significant link between CTX-II and the histological degree of OA in facet joints based on the tests conducted. In the meantime, a weak positive association (0.490) with a p-value of 0.002 was seen in the IL-1β/IL-10 ratio. Table 4 shows that the ODI showed a positive connection with a strength of (0.393) and a p-value of 0.015.

Next, a Spearman correlation analysis...
assessed the relationship between IL-1β levels, ODI scores, and the Histological Degree of Osteoarthritis (OA) in facet joints. Based on Table 5 and the analysis performed, a statistically significant relationship was found for IL-1β with a p-value of 0.039 and IL-10 with a p-value of 0.031 (p > 0.05). The correlation strengths were positive for IL-1β (0.327) and negative for IL-10 (-0.336).

**DISCUSSION**

**Relationship between ODI Degree and Facet Joints in Lumbar Spinal Canal Stenosis**

In this study, strong evidence supported a positive correlation between the degree of pain and the histopathological manifestation of osteoarthritis (OA) in the facet joints of lumbar spinal canal stenosis. These findings are consistent with previous research indicating that structural changes, such as cartilage damage and inflammation, directly correlate with the intensity of pain patients perceive. Data analysis indicates that patients with more severe histopathological features tend to experience more significant pain. A deep understanding of the histopathological mechanisms contributing to pain highlights the crucial role of cartilage damage, inflammation, and structural changes in facet joint health. Inflammatory processes, such as releasing inflammatory mediators, can trigger nerve sensitivity and an increase in nociceptor activity, thereby enhancing pain perception.

This aligns with the study conducted by Splettstober in 2017, observing a statistically significant positive correlation between ODI scores and lumbar spinal stenosis at the L4/5 and L5/S1 levels, bilaterally (p<0.01). According to the ODI score in this study, patient symptoms and disabilities ranged from a minimum score of 0% to a maximum score of 91.11%. The average score was 34.06% ± 16.89%. The majority of patients (48.39%) exhibited moderate functional disabilities (21%-40%). Regarding gender, there was no statistically significant difference in ODI scores: males 32.47% ± 16.55% and females 35.58% ± 16.55%.


![Figure 1. Grade 2 Osteoarthritis Histopathology.](image)

The two main histological features of facet joint osteoarthritis in patients with lumbar spinal stenosis that we found were substantial de novo bone formation and macrophage-rich tissue infiltration of subchondral bone marrow.
associated with clinical symptoms, but only 17.5% of participants with severe central stenosis experienced symptoms.

The results of this study provide a foundation for the development of more targeted therapies. These therapies have the potential to directly intervene in specific histopathological mechanisms to manage pain in patients with lumbar spinal canal stenosis and facet joint osteoarthritis.

The relationship between the levels of IL-1β and facet joints in lumbar spinal canal stenosis

Interleukin (IL) is a pro-inflammatory factor that plays a role in the pathophysiology of osteoarthritis, including osteoarthritis of the facet joints. In a study conducted by Martel-Pelletier and his colleagues, there was an increase in the levels of IL-1 (IL-1R1) receptor in joint cartilage cells suffering from osteoarthritis, indicating an increased level of IL-1β during the inflammatory process in the joint.

Activation of the IL-1 signaling pathway is initiated by several proteins such as myeloid differentiation primary response gene 88 (MyD88), interleukin-1 receptor-activated protein kinase (IRAK1), and tumor necrosis factor receptor-associated factor (TRAF6), which form a complex with IL-1 and IL-1R1. Additionally, one of the enzymes involved is chondrocyte-expressed caspase-1, acting as the IL-1β converting enzyme (ICE), aiding in the transformation of pro-IL-1β into its active form. Interleukin 1β also produces IL-1β through a positive feedback mechanism.

Active IL-1β has a catabolic effect on chondrocytes, which results in higher regulation of matrix metalloproteinase (MMPs) and aggrecanase, increased production of inflammatory mediators, and decreased chondrogenic extracellular matrix synthesis in the joint cartilage. Mitogen-activated protein kinase (MAPK) pathways can be triggered by interleukin-1β. These pathways include p38, c-Jun-N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), nuclear factor k-light-chain-enhancer of activated B cells (NF-κB), and other inflammatory mediators. Numerous inflammatory mediators participate in the inflammatory cascade, leading to synovial inflammation and chondrocyte degradation. These mediators include wingless-type protein (Wnt)-mediated signaling, Notch-1-mediated effects, toll-like receptor (TLR)-signaling, PLC/IP3/Ca2+-signaling, interleukin 6 (IL-6), tumor necrosis factor (TNF), leukemia inhibitory factor (LIF), PGE2, nitric oxide (NO), and cyclooxygenase-2 (COX2).

Interleukin-1β plays a very broad role in each bone cell, synovium, and inflammatory mediator. In osteoblasts, IL-1β stimulates the production of estrogen and enhances osteoblast proliferation. In contrast, IL-1β also increases the expression of MMP-2, MMP-3, MMP-9, ADAMTS-4, ADAMTS-5, and RANKL, supporting the degradation of bone matrix and the catabolism of cartilage by damaging collagen type II and aggrecans. This mechanism can explain the occurrence of osteophytes and cartilage degradation in osteoarthritis.

Inhibition of interleukin activity and production is believed to be one useful therapeutic approach in managing osteoarthritis. Antagonists against the IL-1 receptor, especially IL-1β, have been extensively researched and proven effective in reducing catabolic processes in joint cartilage. These antagonist treatments include IL-1 antagonists, soluble IL-1 receptors, monoclonal antibodies against IL-1 and its receptor, and genetic therapy to inhibit the formation of active IL-1β and activate cellular signaling pathways. However, as of now, the effectiveness of IL-1β antagonist treatments remains inconclusive.

The relationship between IL-10 levels and facet joints in lumbar spinal canal stenosis

This study deepens the understanding of the relationship between interleukin-10 (IL-10) levels and the histopathological profile of osteoarthritis (OA) in facet joints, particularly in patients with lumbar spinal canal stenosis. IL-10, as an anti-inflammatory cytokine, has been a focus of research due to its role in regulating inflammatory responses in various disease conditions, including OA.

Research findings indicate a significant correlation between IL-10 levels and histopathological characteristics in facet joints. Patients with higher IL-10 levels tend to exhibit milder histopathological features, with signs of reduced inflammation and less prominent tissue damage. This supports the hypothesis that IL-10 may play a role in alleviating the inflammatory process in facet joints, inhibiting cartilage damage, and ultimately influencing the severity of OA.

The results of this study align with Efendioglu, who evaluated IL-10 levels in patients with lumbar canal stenosis. Through 64 involved samples, IL-10 levels in the patient group were significantly higher statistically compared to the control group (p=0.017; p<0.05).

The expression of IL-10, an anti-inflammatory cytokine, increases during cytokine storms and can facilitate self-protection. Immunosuppression in sepsis is directly related to the high levels of IL-10 associated with inflammation. Degeneration of intervertebral discs and stenosis are also associated with changes in IL-10 levels in the lumbar ligament. Based on research conducted by Duan, it
is shown that there is higher expression of IL-6, IL-10, LEP, and TNF-α in the hypertrophic human ligamentum flavum tissue.\textsuperscript{16}

The findings contrast with the research conducted by Weber on 107 patients with low back pain due to lumbar canal stenosis, where IL-10 levels were found to be 0.23 ± 0.018. In the control group of 26 patients, the IL-10 value was 0.25 ± 0.040, with no significant difference in IL-10 levels (p = 0.71).\textsuperscript{17}

The interpretation of these findings provides important insights into the potential role of IL-10 as a prognostic marker in the development of OA in lumbar spinal canal stenosis. In a clinical context, monitoring IL-10 levels can be a useful noninvasive approach to assessing disease progression and planning more effective management strategies.

**The relationship between the IL-1β/IL-10 ratio and facet joints in lumbar spinal canal stenosis**

In this study, the exploration of the relationship between the ratio of interleukin-1β (IL-1β) to interleukin-10 (IL-10) and the histopathological picture of osteoarthritis (OA) in facet joints in the context of lumbar spinal canal stenosis provides a profound understanding of the balance between pro-inflammatory and anti-inflammatory roles in the development of this disease.

The research findings indicate that patients with a high IL-1β/IL-10 ratio tend to exhibit more severe histopathological features. This ratio reflects an imbalance between pro-inflammatory cytokines and the anti-inflammatory capacity of IL-10, with a dominance of IL-1β indicating higher inflammatory activity compared to the anti-inflammatory capacity of IL-10. This illustrates the crucial role of IL-1β in stimulating inflammation and potentially contributing to tissue damage in facet joints.

The interpretation of these findings provides a foundation for developing therapeutic strategies that can target the balance of pro-inflammatory and anti-inflammatory cytokines. For example, therapies aimed at reducing the IL-1β/IL-10 ratio could be considered a potential approach to controlling inflammation and protecting the integrity of joint tissues in patients with lumbar spinal canal stenosis and OA in facet joints.

However, it should be noted that the IL-1β/IL-10 ratio can also be influenced by other factors, including individual responses to therapy and genetic factors. In a clinical context, this understanding can lay the groundwork for more targeted and personalized treatment approaches.

**Ethical Approval**

Ethical approval for this study (Ethical Clearance number I473/UN14.2.2.VII.14/LT/2023) was provided by the Research Ethics Committee of the Faculty of Medicine, Udayana University, Bali, Indonesia on 5th June 2023. A copy of the ethical clearance letter is available for review by the Editor-in-Chief of this journal on request.

**Conflict of Interest**

There is no conflict of interest in this study.

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**References**


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