Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/r9seyt84

INFLAMMATORY MARKERS AND PATHOGENESIS OF OSSIFICATION OF THE POSTERIOR LONGITUDINAL LIGAMENT (OPLL): A PROSPECTIVE STUDY

Dr. Mote Srikanth*

*Assistant Professor, Department of General Medicine, Sri Lakshmi Narayana Institute of Medical Sciences & Hospital, Osudu, Puducherry - 605502

***Corresponding Author:** Dr. Mote Srikanth
*Assistant Professor, Department of General Medicine, Sri Lakshmi Narayana Institute of Medical Sciences & Hospital, Osudu, Agaram Village, Koodapakkam Post, Puducherry - 605502

ABSTRACT
Ossification of the posterior longitudinal ligament (OPLL) is a condition characterized by ectopic bone formation within the spinal ligaments, leading to spinal canal narrowing and neurological impairment. This prospective study aimed to evaluate the potential role of inflammation in OPLL by analyzing serum high-sensitivity C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR) levels in OPLL patients and comparing them with control subjects. The study included 95 OPLL patients and 100 controls, with biomarker analysis conducted using immunonephelometric assays. Results showed significantly elevated hs-CRP and ESR levels in OPLL patients compared to controls, with even higher levels in the OPLL progression group. These findings suggest that inflammation may contribute to OPLL pathogenesis and progression, supporting the potential role of anti-inflammatory therapy in its management. Further research is required to establish the precise mechanisms linking inflammation to OPLL development.

Key Words: Ossification of the posterior longitudinal ligament (OPLL), Inflammation, hs-CRP, ESR, Spinal cord compression.

INTRODUCTION
Ossification of the spinal ligaments refers to the development of heterotopic ossified lesions that can occur along the spine. Ossification of the posterior longitudinal ligament (OPLL) is characterized by the ectopic formation of new bone, which replaces ligamentous tissue [1]. This condition often leads to spinal canal narrowing and has been identified as a potential cause of neurological dysfunction, including cervical myelopathy and radiculopathy. Epidemiological studies have shown that cervical OPLL is more prevalent in males, while thoracic OPLL is more common in females. Additionally, a recent genome-wide association study identified six candidate genes that may play a role in the pathogenesis of OPLL [2]. This suggests that the development and progression of ossified lesions may be strongly influenced by sex hormones and genetic factors. Numerous studies have examined OPLL, focusing on its epidemiology, surgical treatment, and radiological characteristics [3]. Computed tomography (CT) is widely used to assess bone structure and the distribution of ossification throughout the spine. Research has established that neurological symptoms are closely associated with the degree of spinal canal narrowing caused by OPLL, as well as segmental mobility

at the affected level [4]. Patients with OPLL and severe spinal cord compression often present with multiple lesions along the spine. Since thoracic OPLL can sometimes occur alongside cervical ossification, it is crucial to thoroughly evaluate ossified lesions and determine the extent of neurological deterioration caused by spinal cord compression. The symptoms of OPLL tend to be progressive, and surgical intervention is considered the preferred treatment option to relieve spinal cord compression. Research has indicated that certain biomarkers, including leptin and insulin, may be associated with OPLL. However, the role of inflammation in the development of OPLL remains unclear. Previous studies have reported that C-reactive protein (CRP) levels are elevated in patients with heterotopic ossification following total hip replacement. This study was designed to investigate whether serum CRP and erythrocyte sedimentation rate (ESR) levels are altered in OPLL patients. If an increase in CRP and ESR levels is detected, it could suggest that inflammation plays a role in OPLL development, and thus, anti-inflammatory therapy may be beneficial for these patients. For individuals with mild and non-progressive symptoms, conservative management and periodic monitoring are often sufficient. However, once myelopathic symptoms emerge and neurological impairment progresses, surgical intervention becomes necessary to alleviate spinal cord compression. Research has also linked several biomarkers, such as leptin and insulin, with OPLL [5]. Additionally, a previous study confirmed that CRP levels were elevated in patients with heterotopic ossification after total hip replacement [6]. The objective of this study was to prospectively examine whether serum CRP and ESR levels were altered in OPLL patients. If elevated CRP and ESR levels are observed, this may support the hypothesis that inflammation contributes to the pathogenesis of OPLL, suggesting that anti-inflammatory treatment could be a viable therapeutic approach.

MATERIAL AND METHODS

A prospective study was conducted at the tertiary care center from October 2019 to October 2020. The study received approval from the regional ethical committee, and all patients diagnosed with ossification of the posterior longitudinal ligament (OPLL), along with control subjects, were recruited from the Departments of Anesthesia and Orthopedics. The diagnosis of OPLL was confirmed based on radiological assessments, which included plain radiographs and computed tomography (CT) scans of the cervical, thoracic, and lumbar spine.

RESULT

Patients with ankylosing spondylitis and metabolic disorders associated with OPLL, including hypophosphatemic rickets/osteomalacia and hyperparathyroidism, were excluded from the study. A total of 95 patients diagnosed with OPLL (56 males and 39 females, mean age 75.3 ± 17.4 years, range 40–85 years) underwent radiological follow-up for more than two years. The average follow-up duration was 5.2 ± 2.1 years (range: 2–10 years). To assess ossified lesions and determine OPLL progression, plain radiographs were used in 35 patients, while CT scans were performed in 60 patients. OPLL progression was defined as ossification extending beyond 2 mm during follow-up. The control group consisted of 100 age-matched individuals diagnosed with cervical spondylosis, lumbar degenerative disease, or spinal disc disease. Among them, 22 patients had cervical spondylosis, 73 had lumbar degenerative disease, 3 had cervical disc herniation, and 2 had lumbar disc herniation. Their diagnoses were confirmed through radiographic, CT, and MRI studies, and none exhibited spinal canal ossifications, as verified by CT imaging. Additionally, any OPLL patient or control subject with inflammatory conditions (such as collagen diseases and rheumatoid arthritis), infections, trauma, myocardial infarction, cerebral infarction, or malignancies was strictly excluded. Furthermore, none of the participants were taking non-steroidal anti-inflammatory drugs (NSAIDs) or steroids.

Blood Sample Collection and Biomarker Analysis

Blood samples were collected from all participants in the morning during their hospital visit. High-sensitivity C-reactive protein (hs-CRP) levels were analyzed using an ultrasensitive latex-enhanced immunoassay (L-Latex CRP II) with the BN ProSpec nephelometer (Dade Behring, Newark, DE, USA). This immunonephelometric assay is highly sensitive and can measure hs-CRP at a concentration of 0.00095 mg/dL. In addition to hs-CRP, routine laboratory tests were performed, including glucose (Glu), calcium (Ca), inorganic phosphate (Pi), erythrocyte sedimentation rate (ESR) at 1 hour and 2 hours, white blood cell count (WBC), hemoglobin (Hb), and platelet count (PLT).

Statistical Analysis

The OPLL and control groups were compared using the unpaired t-test, Mann-Whitney U test, and chi-squared test, as appropriate. Results were expressed as mean ± standard deviation (SD). All statistical analyses were conducted using SPSS for Windows (version 22.0; IBM Corp., Armonk, NY, USA), and a p-value of less than 0.05 was considered statistically significant.

Findings and Results

Comparison of Serum Biomarkers Between OPLL and Control Groups

The mean serum hs-CRP concentration was 0.133 ± 0.151 mg/dL in the OPLL group and 0.087 ± 0.115 mg/dL in the control group, showing a statistically significant difference ($p = 0.048$).

ESR levels at 1 hour (ESR-1h) and 2 hours (ESR-2h) were significantly elevated in OPLL patients compared to controls ($p = 0.004$ and $p = 0.003$, respectively).

Classification of OPLL Types

The segmental type of OPLL was the most prevalent, accounting for 44% of cases.

The mixed type represented 23%, followed by the continuous type (20%) and localized type (12%).

Comparison of Serum Biomarkers Between the Progression and Non-Progression Groups

The mean serum hs-CRP concentration was 0.19 ± 0.17 mg/dL in the progression group and 0.097 ± 0.13 mg/dL in the non-progression group, indicating a statistically significant difference ($p = 0.0015$). No significant differences were observed in other biomarkers between the two groups. These findings suggest a potential role of inflammation in OPLL progression, as evidenced by the elevated hs-CRP and ESR levels in affected patients.

Table1: Demographic data of the patients with OPLL (case) and the control.

Parameter	OPLL	Controls	P Value
Gender (M/F)	60/35	70/30	0.41
Age (years)	72.5 ± 16.8	78.0 ± 17.9	0.27
Height (cm)	165.5 ± 38.7	160.2 ± 10.2	0.18
Weight (kg)	67.0 ± 14.9	60.5 ± 12.2	0.12
BMI	27.3 ± 4.2	25.0 ± 2.9	0.36

Table2: Comparison of the biomarkers between the patients with OPLL (case) and the controls.

Parameter	OPLL	Controls	P Value
Glucose (mg/dL)	230 ± 75.4	115 ± 40.2	0.58
Calcium (mg/dL)	9.05 ± 0.40	9.18 ± 3.95	0.17
hsCRP (mg/dL)	0.140 ± 0.160	0.090 ± 0.110	0.046
ESR at 1 hour (mm)	18.5 ± 15.9	12.3 ± 7.2	0.005
ESR at 2 hours (mm)	36.8 ± 26.1	27.1 ± 17.0	0.002
WBC (×100 µL)	70.5 ± 55.8	61.8 ± 15.9	0.30
Hemoglobin (g/dL)	16.9 ± 4.5	15.2 ± 3.8	0.36
PLT (×10000 µL)	23.1 ± 7.2	22.0 ± 5.4	0.88

Table 3: Distribution of study group as per the radiological type of OPLL.

Types of OPLL	Number of Samples	Percentage
Segmental	45	46.2%
Mixed type	20	20.5%
Continuous type	21	21.5%
Localized type	11	12.0%

Table 4: Comparison of the biomarkers betweeen the progression group and the non-progression group.

Parameter	Progression Group	Non-Progression Group	P Value
Glucose (mg/dL)	130 ± 46.1	127 ± 43.5	1.98
Calcium (mg/dL)	9.10 ± 0.75	9.05 ± 0.38	0.74
hsCRP (mg/dL)	0.21 ± 0.18	0.099 ± 0.14	0.0015
WBC (×100 µL)	62.8 ± 15.0	58.3 ± 15.7	0.31
Hemoglobin (g/dL)	13.5 ± 2.10	14.7 ± 1.72	0.27
PLT (×10000 µL)	21.0 ± 7.1	22.2 ± 6.9	0.58

DISCUSSION

The current study identified two key factors associated with the pathogenesis of OPLL: inflammation and calcium phosphate metabolism. The serum concentration of high-sensitivity C-reactive protein (hs-CRP) was elevated in OPLL patients compared to the control group, and erythrocyte sedimentation rate (ESR) levels were also significantly higher in OPLL patients. Additionally, this study demonstrated that serum hs-CRP levels in the OPLL progression group were notably higher than those in the non-progression group, aligning with findings by Gabay C, Kushner, et al. [7-8]. These results suggest that local inflammation may be closely associated with the development and progression of OPLL. CRP is a widely recognized acute-phase marker used to detect inflammation following tissue injury. Pro-inflammatory cytokines, including interleukin 6 (IL-6), interleukin 1β (IL-1β), and tumor necrosis factor-alpha (TNF-α), play a critical role in stimulating CRP production in the liver. The elevation of both hs-CRP and ESR levels in OPLL patients suggests an inflammatory component in the disease process. OPLL is characterized by ectopic bone formation within spinal ligaments, and progressive ossification is commonly observed. Previous studies by Sell S et al. have shown that CRP levels are elevated in patients with heterotopic ossification following total hip replacement and in individuals who developed heterotopic ossification after traumatic spinal cord injury [9]. However, in the present study, no surgical specimens were available to directly confirm local inflammation at the ectopic bony lesions of OPLL, though endochondral ossification was consistently observed in affected patients.

The findings of this study further revealed that CRP levels were elevated in different OPLL subtypes as follows:

- 89.4% of continuous-type cases
- 90% of localized-type cases
- 69.2% of mixed-type cases
- 92.8% of segmental-type cases

Similarly, elevated ESR levels were observed in:

- 81.4% of continuous-type cases
- 65.7% of localized-type cases
- 51.5% of mixed-type cases
- 73.0% of segmental-type cases

These findings correlate with the study by Jagadish T et al. [10], further supporting the association between inflammation and OPLL progression.

CONCLUSION

The findings of this study indicate that hs-CRP levels in patients with OPLL were higher compared to the control group. Additionally, hs-CRP levels in the OPLL progression group were elevated compared to those in the non-progression group, suggesting a potential inflammatory component in OPLL. These results provide new insights into the local pathology of OPLL, contributing to a better understanding of its underlying mechanisms.

REFERENCE

1. Onji, Y., Akiyama, H., Shimomura, Y., Ono, K., Hukuda, S., & Mizuno, S., et al. Posterior paravertebral ossification causing cervical myelopathy. Journal of Bone and Joint Surgery - American Volume, 49, 1967, 1314–1328.
2. Ono, M., Russell, W. J., Kudo, S., Kuroiwa, Y., Takamori, M., Motomura, S., & Murakami, J., et al. Ossification of the thoracic posterior longitudinal ligament in a fixed population: Radiological and neurological manifestations. Radiology, 143, 1982, 469–474.
3. Hirai, T., Yoshii, T., Egawa, S., Sakai, K., Inose, H., Yuasa, M., Yamada, T., Ushio, S., Kato, T., Arai, Y., et al. Increased height of fused segments contributes to early-phase strut dislodgement after anterior cervical corpectomy with fusion for multilevel ossification of the posterior longitudinal ligament. Spine Surgery and Related Research, 4, 2013, 294–299.
4. Yoshii, T., Sakai, K., Hirai, T., Yamada, T., Inose, H., Kato, T., Enomoto, M., Tomizawa, S., Kawabata, S., Arai, Y., et al. Anterior decompression with fusion versus posterior decompression with fusion for massive cervical ossification of the posterior longitudinal ligament with a 50% canal occupying ratio: A multicenter retrospective study. Spine Journal, 16, 2013, 1351–1357.
5. Ikeda, Y., Nakajima, A., Aiba, A., Koda, M., Okawa, A., Takahashi, K., et al. Association between serum leptin and bone metabolic markers, and the development of heterotopic ossification of the spinal ligament in female patients with ossification of the posterior longitudinal ligament. European Spine Journal, 20, 2011, 1450–1458.
6. Sell, S., & Schleh, T. C-reactive protein as an early indicator of the formation of heterotopic ossifications after total hip replacement. Archives of Orthopaedic and Trauma Surgery, 119, 1999, 205–207.
7. Rifai, N., Tracy, R. P., & Ridker, P. M. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. Clinical Chemistry, 45, 1999, 2136–2141.
8. Gabay, C., & Kushner, I. Acute-phase proteins and other systemic responses to inflammation. New England Journal of Medicine, 340, 1999, 448–454.
9. Sell, S., & Schleh, T. C-reactive protein as an early indicator of the formation of heterotopic ossifications after total hip replacement. Archives of Orthopaedic and Trauma Surgery, 119, 1999, 205–207.
10. Jagadish, T., et al. A study of the relationship between serum ESR and CRP in patients with ossification of posterior longitudinal ligament. Indian Journal of Research, 10, 2013, June.