Facet Joint Capsular Laxity in Degenerative Lumbar Spondylolisthesis
Associated with the Increased Expression of Fractalkine (CX3CL1)/CX3CR1 Chemokine

IN SOO OH, YOUNG HO KIM, KEE YONG HA
Department of Orthopaedic surgery, College of Medicine, The Catholic University of Korea, Seoul, Korea
Degenerative lumbar spondylolisthesis (DLS) is a disease that causes lumbar stenosis and low back pain, and the clinical features of DLS are well described.

Pathogenic mechanism and definite treatment principle of DLS are not yet established while some studies have suggested that it occurs as a result of morphologic abnormalities of the lamina and the facet joints. Studies show that degenerative changes in the facet joints is the cause of development of DLS. DLS development is associated with sagittal facet joint orientation and reduced coronal facet joint dimensions.

Fractalkine (CX3CL1) and its receptor (CX3CR1) are part of a chemokine system involved in leukocyte recruitment and adhesion in chronic inflammatory disease. From previous study the CX3CL1 and CX3CR1 activity has been investigated in ligament flavum, synovial membrane, and intervertebral discs, but not with the facet joint capsule related issue.
We hypothesize that the infiltration and accumulation of monocytes/macrophages within the facet joint capsule are prominent pathobiologic features of joint laxity, and a key chemokine known to capture and direct migration of monocytes, neutrophil and angiogenesis to sites of inflammation is CX3CL1/CX3CR1.

Correlation between facet joint capsule degeneration and increased CX3CL1/CX3CR1 activity level may reveal the interconnected cellular and molecular events which comprise DLS pathogenesis. Therefore, we evaluated the expression of CX3CL1 and CX3CR1 in patients with DLS to clarify the role of CX3CL1 and CX3CR1 in the inflammation of facet joint capsule.
MATERIALS & METHODS

- The mRNA concentrations of CX3CL1/CX3CR1 chemokine were analyzed in the surgically obtained facet joint capsule specimens from grade 1, 2 and more than grade 3 by real-time PCR.

- Grade 1 to 3 is being decided upon degree of slippage which is, less than 5mm, between 5 to 10mm, and more than 10mm.

- The localization of CX3CL1/CX3CR1 chemokine within the facet joint capsule was determined using immunohistochemical study. Plasma level of soluble fractalkine (sFKN) was measured by enzyme-linked immunosorbent assay (ELISA), respectively.
### MATERIALS & METHODS

- Table 1. Comparison of age of.

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<tr>
<th>Variables</th>
<th>Age(year)</th>
<th>P-valuea</th>
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<tr>
<td>Group 1 (n=12)</td>
<td>70.75 ± 7.64</td>
<td>0.519</td>
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<tr>
<td>Group 2 (n=12)</td>
<td>67.92 ± 5.28</td>
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<tr>
<td>Group 3 (n=11)</td>
<td>68.36 ± 5.46</td>
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1. Expression by Immunohistochemical analysis

Figure 1. Immunohistochemical stainings for CX3CL1 in DLS. Degenerations of the capsule and expression of CX3CL1 are markedly noted in the capsule of grade 3 DLS (A, C) while relatively sparse expression of FNK was observed in the grade 1 sample (B, D) (counterstain with H-E; (A, B) X100, (C, D) X400).
Figure 2. Immunohistochemical stainings for CX3CR1 in DLS. Expression of CX3CR1 are markedly noted in the capsule of grade 3 DLS (A, C) while relatively sparse expression of CX3CR1 was observed in the grade 1 sample (B, D). Arrow indicates the prominent fibroblastic and vascular proliferation in capsule of DLS (A) (counterstain with H-E; (A, B) X100, (C, D) X400).
2. Correlation of serum CX3CL1 level, mRNA Expression of CX3CL1/CX3CR1 and the degree of slippage

Figure 3. Correlations of thickness of LF with (A) mRNA expression of CX3CL1, (B) mRNA expression of CX3CR1, (C) serum level of FNK, (D) age (n = 35).
RESULTS

• The cells that shows higher CX3CL1/CX3CR1 chemokine expression ratio in the facet joint capsule are observed in tissues acquired from patients with higher degree of slippage by lumbar spondylolysis (P = 0.000, 0.000).

• In ELISA, the plasma levels of sFKN was significantly higher in the group with more severe degree of slippage (P = 0.002).

• There was greater CX3CL1/CX3CR1 expression in higher grade spondylolisthesis as quantified by RT-PCR (P = 0.000, 0.003).

• Degree of slippage in DLS patients was significantly correlated with serum CX3CL1 level (R2 = 0.451, P =0.000) and with mRNA expression of CX3CL1/CX3CR1 (R2 = 0.360, P =0.000) (R2 = 0.205, P =0.006)
Immunohistochemistry revealed substantially greater numbers of CX3CL1/CX3CR1 positive cells in the facet joint capsule of higher grade DLS individuals. Considering these findings, we hypothesized that CX3CL1/CX3CR1 might be to play an essential role in inflammatory cell migration into inflamed and lax capsular tissues.

First, unregulated expression of sFKN cooperatively augments the recruitment of mononuclear cells expressing CX3CR1 into the affected capsule, leading to inflammation, vascular injury, and angiogenesis.

Second, the elevated CX3CL1 and CX3CR1 activity can induce the degradation of the capsular matrix, and the resulting losses in elasticity and laxity are probable contributors to facet joint capsular laxity. These two pathways are not exclusive and they can comprise a vicious cycle accelerating the degenerative changes in capsule of DLS patients, although it is speculative.