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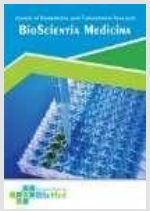

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The Relationship between CC Ligand 5 Plasma Levels and Modic Changes in Low Back Pain Patients' Severity

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A B S T R A C T

Background: Low back pain (LBP) is one of the global health problems. The most common cause of LBP is disc degeneration. Modic changes (MC) are the most common MRI features in patients with disc degeneration. As a result of cartilage and disc tissue damage, CCL 5 is released and modulates pain responses in the dorsal root ganglion. This study aims to determine the relationship between CCL5 levels and the description of Modic changes on MRI with pain levels in patients with low back pain. **Methods**: This study is a cross-sectional study. The research subjects were LBP patients who were treated at the Neurology Polyclinic, Dr. M. Djamil General Hospital, Padang, in the range of March 2021-December 2021, who meets the inclusion and exclusion criteria. Subjects will be taken blood to assess CCL5 plasma levels, pain assessment using the McGill Pain Questionnaire, and undergo an MRI examination. **Results:** A total of 52 subjects consisted of 23 men and 29 women with an age range of 34-77 years. Most of the Modic changes were found in the type 2 group. Based on the pain scale, there were two groups with mild pain and moderate pain. On examination of plasma CCL 5 levels, the median value of plasma CCL5 levels was 303,271 ng/L. There was a significant relationship between plasma CCL5 levels and pain levels in patients with low back pain (p = 0.004). There was no significant relationship between Modic changes and the severity of pain. **Conclusion:** Plasma CCL5 levels are associated with pain levels in patients with low back pain, while Modic changes are not associated with pain severity.

1. Introduction

Low back pain (LBP) is one of the global health problems with high morbidity and disability rates and has an economic impact.[1] The Global Burden of Disease reports that at least 80% of people have experienced LBP during their lifetime.[2] The incidence of LBP is estimated to increase with increasing life expectancy. The cause of LBP is mostly caused by mechanical factors (80-90%), namely disc degeneration. Disc degeneration is one of the sources of pain in LBP cases. This condition is common, especially in the elderly.[3] The Longitudinal Assessment of Imaging and Disability of the Back (LAIDBack) study showed that 29 of the 29 study samples aged 65 years all experienced disc degeneration, and as many as 24 of 31 people under 45 years (77%) also experienced disc degeneration

through MRI examination.[4] Modic changes (MC) are the most common MRI features in patients with intervertebral disc degeneration. There are 3 types of MC. Type I, which shows spinal cord edema. Type II, which is a common degeneration, and type III, which is subchondral sclerosis.[5] Modic changes cause cytokines, growth factors, and chemokines to stimulate nerve fibers and trigger pain. However, Modic changes do not affect the occurrence of pain. One of the markers of disc degeneration is the chemokine CC ligand motif 5 (CCL5).[6] CCL5 is produced by joint chondrocytes. As a result of cartilage and disc tissue damage, CCL 5 is released and modulates pain responses in the dorsal root ganglion. An increase in CCL5 goes hand in hand with an increase in pain and is also associated with disability.[7] This study aims to determine the relationship between CCL5 levels and the description of Modic changes on MRI with pain levels in patients with chronic low back pain.

2. Methods

This research is a cross-sectional study. A total of 52 research subjects participated in this study, which was low back pain patients who were treated at the Neurology Polyclinic, Dr. M. Djamil General Hospital, Padang, in the range of March 2021-December 2021 who meet the inclusion and exclusion criteria. The inclusion criteria include patients who have been diagnosed with low back pain, are willing to undergo a lumbar MRI examination.**,** have never undergone spinal surgery before, are willing to be the subject of the study, and signed the research consent letter. At the same time, the exclusion criteria were suffering from autoimmune diseases, immunocompromised malignancy, history of spinal trauma, history of rheumatoid arthritis, and uncooperative patients at the time of examination. This study has been approved by the Health Research Ethics Committee of Dr. M. Djamil General Hospital, Padang, Indonesia (No. 34/KEPK/2021).

Each subject will take 3 cc of venous blood and then centrifuge to separate plasma and serum. Examination of plasma CCL5 levels using the ELISA technique according to the ELISA Kit CCL5 (Cloud Clone®) manual. Pain assessment using the McGill Pain Questionnaire. The study subjects underwent an MRI examination, and the reading of Modic changes was performed by a neurologist.

Data analysis was carried out with the help of SPSS version 25 software. Univariate analysis was carried out to present the frequency distribution data for each variable. Bivariate analysis was carried out using a T-test or Mann-Whitney test if the data were numerical, and the analysis was carried out using Chi-square if the data were categorical. The p-value is set at 5% or 0.05, where if the p-value is <0.05, it is stated that there is a difference between the test groups.

3. Results

The basic characteristics of the research subjects are presented in table 1. The study subjects consisted of 23 males and 29 females with an age range of 34-77 years and a mean age of 53 years ± 10,62, with the highest age group being 46-65 years as many as 31 people (59.6%). As for gender, there was no significant difference between men and women. Most of the research subjects experienced low back pain for more than 1 year, as many as 37 people (65.4%). Overview of fashionable changes Most were found in the type 2 group, as many as 27 people (51.9%) (Table 2). Based on the pain scale, there were two groups of subjects with mild pain (53.8%) and subjects with moderate pain (46.2%), and there were no subjects with severe pain (table 3).

Table 1. Basic characteristics of LBP patients

	Frequency	Percentage (%)
Gender		
Male	23	44.2
Female	29	55.8
Age		
26 - 45 years	13	25
46 - 65 years	31	59.6
> 65 years	8	15.4
Onset		
Less than 6 months	7	13.46
6 months – 1 year	8	15.39
More than 1 year	37	71.15

Table 2. Modic changes profile of LBP patients

	Frequency	Percentage (%)
Modic changes profile		
Type 1	18	34.6
Type 2	27	51.9
Type 3	7	13.5

Table 3. Degree of pain in LBP patients

	Frequency	Percentage (%)
Degree of pain		
Mild pain	28	53.8
Moderate pain	24	46.2

On examination of plasma CCL5 levels, the mean plasma CCL5 level was 348.46 ng/L with a standard deviation of ±114.99 ng/L. The results showed that plasma CCL5 levels in the group of subjects with mild pain were lower than plasma CCL5 levels in the group of subjects with moderate pain, as presented in table 4. Then a normality test was carried out on CCL5 levels, and the results of the data distribution were not normal, so a test was carried out by Mann-Whitney. The results of the data analysis obtained a p-value <0.05 (p = 0.004), so from this test, it is known that there is a significant relationship between plasma CCL5 levels and the degree of pain in LBP patients.

Table 4. Relationship of CCL5 plasma levels with the degrees of pain

Variable	Degree of pain		p-value
	Mild pain	Moderate pain	
N	28	24	0.004*
CCL5 Plasma Level, ng/L. Mean (±SD)	317.87(±95.2)	384.15(±127.3)	

*Mann-Whitney test, p=0.05

Modic changes type 2 is the most common type found in this study, as many as 27 people, of which 16 people (59.3%) complained of mild pain. Statistical data analysis used is the chi-square test, as presented in table 5. Found p>0.05 (P=0.9), which indicates there is no significant relationship between Modic changes and the severity of pain.

Table 5. Relationship of Modic changes with the degree of pain

Modic changes	Degree of pain		p-value
	Mild (n)	Moderate (n)	
Type 1	9	9	0.7*; 0.5**; 0.3***
Type 2	16	11	
Type 3	3	4	
Total	28	24	

*Chi square test; Modic changes Type 1 VS Type 2; **Fischer exact test; Modic changes Type 1 VS Type 3; ***Fischer exact test; Modic changes Type 2 VS Type 3, p=0.05

4. Discussion

Inflammatory cytokines and chemokines such as TNF-α, IL-1 α/β, IL-6, IL-17, CCL5, and CXCL6 cause matrix degradation in the vertebrae. The unbalanced matrix catabolism and anabolism process causes degeneration of the vertebrae, which will then cause radicular and disc herniation.[8] CCL5 acts as a chemotactic against T cells, eosinophils, and basophils and plays a role in bringing leukocytes to sites of inflamed tissue.[9] Another study showed no association between CCL 5 expression and herniation of the nucleus pulposus.[10] Another study showed that only 17% of LBP cases with herniated nucleus pulposus expressed CCL5.[11] Another study showed that CCL5 is expressed in painful intervertebral disc conditions. Expression CCL5 was found to be consistent with the severe discussion breakdown condition.[12]

CCL5 is produced by articular chondrocytes. Plasma CCL5 levels were higher in cases of LBP with disc displacement than in those without displacement.[13,14] When the disc has degenerated, CCL5 actively diffuses to the endplate and annulus fibrosus.[15] CCL5, together with 1L-1β cytokines, then inhibits the formation of disc extracellular matrix, increases the production of degradation enzymes, and triggers other cytokines to the site of inflammation. This study did not take control samples.[16] However, several previous studies have shown plasma CCL5 levels to be in the range of 2.1-33 ng/ml. This value is higher than the plasma CCL5 level obtained from the results of this study.[17] Other studies have found similar results, where levels of inflammatory cytokines and chemokines decreased compared to the control group. It is possible that changes in these chemokines occur due to several factors such as chronic disease processes, drug therapy, depression, physical activity, alcohol, and nicotine consumption.[18]

This study found a significant relationship between plasma CCL5 levels and pain severity as measured by the McGill Pain Questionnaire (MPQ) pain scale (p=0.004). From the results of the study, there were only 2 degrees, namely mild and moderate. Another study showed that patients with LBP found an increase in CCL5 in line with the pain experienced.[19] This study did not find a significant relationship between Modic changes and pain severity (p=0.69). Differences in the results of this study were also found in other studies that state that pain sensation is influenced by multifactorial such as the use of NSAID therapy, the experience of pain from each subject which can be different and psychosocial factors. Type 1 Modic changes are generally the most painful form because there is severe edema and inflammation, in contrast to types 2 and 3 where the inflammation and edema process is generally reduced. Giving anti-inflammatory can reduce the sensation of pain felt even though it does not change the degree of Modic changes.[20]

5. Conclusion

Plasma CCL5 levels were associated with the severity of low back pain, but Modic changes were not associated with the severity of pain.

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