Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2020 Feb 05; 8(B):6-10.
https://doi.org/10.3889/oamjms.2020.4114
eISSN: 1857-9655
Category: *B - ClinicalSciences*
Section: *Rheumatology*

Association between Serum Levels of High Sensitivity C-Reactive Protein, Interleukin-1, and Interleukin-6 with Pain Intensity in Patients with Low Back Pain without Sciatica

Khairul Putra Surbakti*, Iskandar Nasution

Department of Neurology, Faculty of Medicine, Universitas Sumatera, Utara, Medan, Indonesia

Edited by: Sasho Stoleski
Citation: Surbakti KP, Nasution I. Association between Serum Levels of High Sensitivity C-Reactive Protein, Interleukin-1, and Interleukin-6 with Pain Intensity in Patients with Low Back Pain without Sciatica. Open Access Maced J Med Sci. 2020 Feb 05; 8(B):6-10. https://doi.org/10.3889/oamjms.2020.4114.
Keywords: High sensitivity C-reactive protein; Interleukin-1; Interleukin-6; Visual analog scale score; Association
***Correspondence:** Khairul Putra Surbakti, Department of Neurology, Faculty of Medicine, Universitas Sumatera, Utara, Medan, Indonesia. E-mail: khairulputra@yahoo.com
Received: 29-Nov-2019
Revised: 20-Jan-2020
Accepted: 31-Jan-2020

Funding: This research was funded by the Research Institute of Universitas Sumatera Utara under the contract of Universitas Sumatera Utara TALENTA Research, fiscal year of 2019 No. 4176/UN5.1.R/PPM/2017, April 1, 2019
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: A strictly mechanical and pathoanatomical explanation for low back pain (LBP) and sciatica has proved inadequate; therefore, the role of biochemical and inflammatory factors remains under investigation.

AIM: The aim of this study is to evaluate whether there is any association between serum levels of high sensitivity C-reactive protein (hs-CRP), interleukin-1 (IL-1), and IL-6 with pain intensity in a patient with LBP without sciatica.

METHODS: Venous blood serum levels of hs-CRP, IL-1, and IL-6 were measured on 50 patients with LBP who had a negative Lasègue test on physical examination. The pain intensity was measured using a visual analog scale (VAS).

RESULTS: There were 50 patients with LBP without sciatica with mean of age of46.72 ± 10.79-year-old participated in this study comprised 8 (16%) men and 42 (84%) women. The mean serum levels of hs-CRP, IL-1, and IL-6 were 0.50 ± 0.61 mg/dL, 55.02 ± 49.73 ng/L, and IL-6 39.43 ± 38.56 ng/L, respectively. The mean of VAS score was 49.3±9.6 mm. There was no significant correlation ($r = 0.05$; $p = 0.72$) between hs-CRP serum levels and VAS scores. There was found a weak negative non-significant correlation ($r = −0.10$, $p = 0.47$) between IL-1 serum levels and VAS score. There was found a weak negative non-significant correlation ($r = −0.17$, $p = 0.23$) between IL-6 serum levels and VAS score as well.

CONCLUSION: There was no significant correlation between serum levels of hs-CRP, IL-1, and IL-6 with VAS scores in patient with LBP without sciatica.

Background

Non-infectious diseases that rarely receive special attention are degenerative diseases because they are thought to occur due to the aging process. One disease that is considered a degenerative disease is low back pain (LBP). Lower back pain is a health problem that is often found in industrialized countries and developing countries, where the recovery of a low back can be resolved with only needing a few days or a few weeks, except about 6–10% can develop or become chronic [1]. Lower back pain is a very common world health problem that causes limit activity and also absence from work. Lower back pain does not cause death but involves individuals who experience it to be unproductive so that it will create a huge economic burden for individuals, families, communities, and governments [2].

In this era of globalization, humans are required to work faster to fulfill their need for life so that it can cause static work cycle in the long term, such as sitting in front of a computer for hours and not paying attention to the position of the body that works well. This can cause complaints of low back pain and decrease work productivity [3]. The increasing prevalence of musculoskeletal pain including LBP has become an epidemic. An estimated 70–85% of the entire population has experienced an episode of LBP.

C-reactive protein (CRP) is an acute-phase reactant protein substance whose levels increase dramatically during the process of infection/inflammation that occurs in the body. This increase in CRP occurs due to increasing in the levels of interleukin-6 (IL-1) in the plasma that is produced by macrophages around the intervertebral disc tissue. Therefore, CRP is usually used as a parameter to evaluate infection/inflammation of the first jam after infection/inflammation [4], [5]. Like in osteoarthritis, degenerative changes are the cause of lower back, thereby it is suggested that the severity of pain is associated with high sensitivity CRP (hs-CRP) levels [6]. Subclinical increases hs-CRP probably due to local inflammation of soft tissue resulting in pain and increases levels of hs-CRP. Besides acute infections and unknown systemic inflammatory conditions, characteristic factors such as age, body mass index, smoking, diabetes, and alcohol consumption are known or affect hs-CRP levels. Therefore, to interpret the relationship between pain and hs-CRP these characteristic factors must be taken into account.

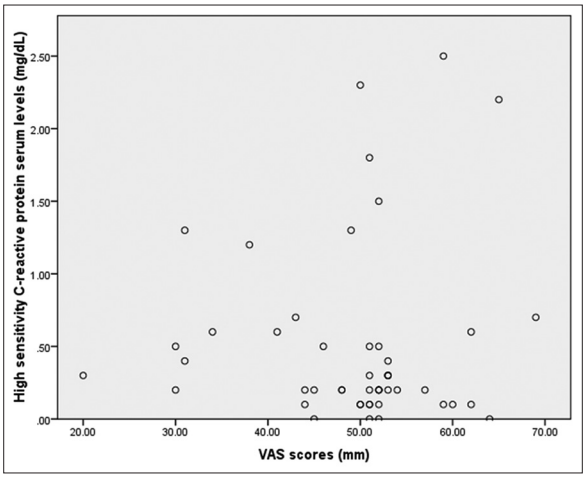

Figure 1: Scatter diagram of the correlation between high sensitivity C-reactive protein levels (mg/dL) and visual analog scale score (mm)

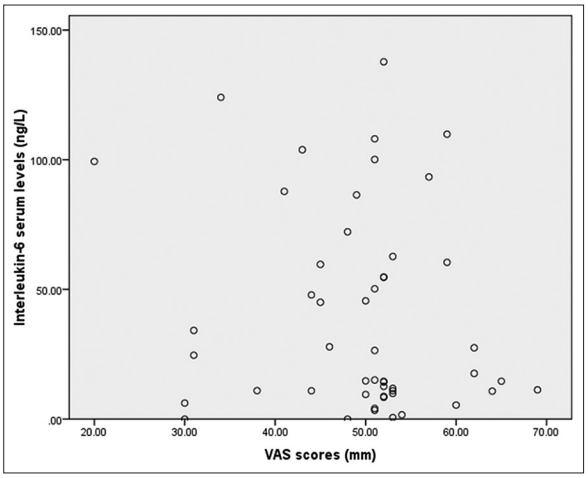

Figure 3: Scatter diagram of a correlation between serum interleukin-6 (ng/L) levels and visual analog scale scores (mm)

The relationship between chronic LBP and increased CRP is still controversial (Figures 1-3) [7]. The previous studies have examined aspects of inflammatory pathologies such as disc herniation, inflammation of the nerve root, and sciatica showing a positive correlation [8]. Other studies have not found an association and reported constant levels of hs-CRP [9],[10]. Chronic LBP usually

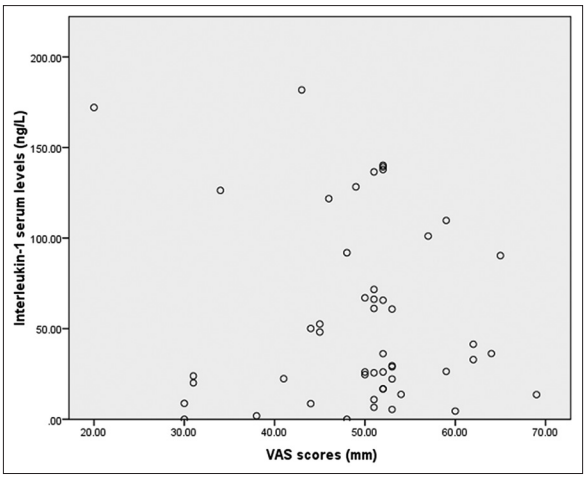

Figure 2: Scatter diagram of a correlation between serum interleukin-1 (ng/L) levels and visual analog scale scores (mm)

results from failure of spinal surgery, degenerative disease of the intervertebral discs in the lumbar, arthritis, or spinal stenosis. If the nerve roots that come out of the spinal column are compressed, LBP that radiates to the legs will be known as lumbar radiculopathy. Inflammation plays a major role in the onset of radiculopathy. When inflammation occurs, the nerves become sensitive to pressure, even if only by movement or light pressure [11]. The local inflammation is caused by inflammatory mediators such as IL-6 produced by macrophages and monocytes at the site of inflammation. The high concentration of inflammatory mediators can cause a systemic inflammatory reaction [12]. It is therefore believed that hs-CRP levels are increased in patients with LBP.

The cause of chronic back pain is often assumed to be due to degenerative conditions of the spine, but studies with controls have shown that the correlation of clinical symptoms with signs of degeneration found in radiology is very minimal or nonexistent. In fact, arthropathic inflammation, bone metabolic conditions, and fibromyalgia are reported as other causes of chronic pain conditions related to the spine. Although intervertebral disc herniation has long been recognized as a radicular pain from the spine, asymptomatic intervertebral disc hernias are often seen on computed tomography scans and magnetic resonance imaging. Besides that there is no clear relationship between the presenting of disc protrusion with the degree of severity of clinical symptoms. Degenerative and traumatic changes in the structure of the spine produce back pain and legs with great variety. Strict mechanical or pathoanatomic explanations for LBP have been shown to be inadequate; therefore, the role of biochemistry and inflammatory factors is currently being studied. Uncertainty in the pathoanatomic mechanism of the onset of pain has led to the difficulty of treating LBP to date [13].

By observing the above conditions, it was proposed by the authors to examine the relationship between the intensity of low back pain as measured using visual analog scales (VAS) and serum hs-CRP levels in LBP patients without sciatica. The reason for choosing the subject of lower back pain without sciatica is because the prevalence of lower back pain without sciatica is higher than lower back pain with sciatica and the relationship of LBP without sciatica with CRP levels is still unclear, so research is still needed. An estimated 5–10% of LBP is caused by sciatica, while the lifetime prevalence of LBP is reported to be around 49–70% [14]. In addition, the relationship between increased hs-CRP and low back pain with sciatica in the previous studies has been reported [6]. The sciatica diagnosis is mainly made on the basis of history and physical examination [15]. The characteristic of sciatica pain is the pain that spreads to the legs following the

dermatome pattern. The most important neurological examination on sciatica is Crossed Lasègue. It was reported that the specificity of the Crossed Lasègue test reached 88% and sensitivity of 29% [16]. Therefore, to rule out sciatica pain in the subject of this study, a neurological clinical examination was done with the Crossed Lasègue test.

From the description above, it can be seen that there is no clear relationship between mechanical and pathoanatomic factors with the onset of pain in patients with LBP. Therefore, the role of biochemical factors and inflammatory factors is still under research. This study aims to determine the relationship of serum CRP, IL-1, and IL-6 levels with pain intensity in patients with LBP without sciatica. The results of this study are expected to help achieve a more accurate diagnosis so that the management of LBP can be done optimally.

Methods

The design of this research is descriptive analytics with cross-sectional sampling method. We studied 50 sufferers of LBP with a negative Lasègue test on a neurological physical examination. The characteristics of the research subjects are in Table 1. The study subjects were taken from outpatients in the General Polyclinic of the Department of Neurology, H. Adam Malik Hospital Medan, who visited from April 2019 to July 2019. The inclusion criteria in this study were patients with lower back pain that lasted more from 2 months both women and men aged ≥18 years and signed informed consent to join the study. Patients were excluded from this study if: Focal neurological deficits were found related to back pain, patients with cancer, patients with chronic disease, patients with diabetes, patients using corticosteroids, and if the patient did not follow the entire study procedure to completion.

Table 1: Frequency distribution of 50 LBP patients without sciatica

Characteristics	Frequency
Sex	
Men, n (%)	8 (16)
Women, n (%)	42 (84)
Mean of age, (±SD)	46.72±10.79
Serum levels, (±SD)	
hs-CRP (mg/dL)	0.50±0.61
IL-1 (ng/L)	55.02±49.73
IL-6 (ng/L)	39.43±3.56
The mean of VAS score, (±SD)	49.3±9.6

N: Number of patients, mean (±SD): Standard deviation, IL: Interleukin, VAS: Visual analog scale, hs-CRP: High sensitivity C-reactive protein, LAB: Low back pain.

This study was approved by the Medical Research Ethics Committee FK-USU Medan. The informed consent form was signed by the subjects after they were given an explanation of the research objectives and procedures. Subjects who met the inclusion and exclusion criteria had their blood sample taken for assay of serum hs-CRP, IL-1, and IL6 levels. Pain intensity was measured using a VAS score. Patients were asked to indicate the severity of pain experienced on a horizontal line along 100 mm marked from the number 0 (no pain at all) to 100 (very painful). VAS scores are measured in millimeters from the left (number 0) to right (number 100) after being cross-marked by the patient. The method of testing is for the patient to mark himself with a pencil on the value of pain in accordance with the intensity of pain he feels after being given an explanation of the meaning of each scale. Determination of the VAS score is done by measuring the distance between the ends of the lines that show no pain to the point indicated by the patient.

VAS score is an instrument used to assess pain intensity using a 10 cm line with a scale reading of 0–100 mm with the following interpretation:

- 0–<10 mm: No pain
- ≥10–<30 mm: Mild pain
- ≥30–<70 mm: Moderate pain
- ≥70–<90 mm: Severe pain
- ≥90–100 mm: Very heavy pain.

hs-CRP levels were measured using Cobas 6000 while IL-1 levels were used using the Human IL-1 Kit, and IL-6 using the Human IL-6 Kit with the Chemwel 2910 analyzer.

Statistical analysis

Variables hs-CRP, IL-1, IL-6, and VAS scores are presented in the mean and standard deviation, while for numerical data, the mean and standard deviation values are displayed.

To determine the relationship between levels of hs-CRP, IL-1, and IL-6 with pain intensity, the Pearson Correlation test was used. A significant value is stated if the value α is <0.05.

Results

A total of 50 LBP patients without sciatica who come to the Neurology Polyclinic of H. Adam Malik Hospital participated in this study consisting of 8 (16%) men and 42 (84%) women with an average age of 46.72 ± 10.79 years. Mean serum hs-CRP was 0.50 ± 0.61 mg/dL, mean IL-1 was 55.02 ± 49.73 ng/L, mean IL-6 was 39.43 ± 3.56 ng/L, and mean VAS score was 49.3 ± 9.6 (Table 1).

From the Pearson correlation test, the VAS score was found to have a weak positive relationship (r = 0.05) association with serum hs-CRP levels which was nonsignificant (p = 0.72). The VAS score was found to have a weak negative association with IL-1 serum levels (r = −0.10) which was nonsignificant (p = 0.47).

Serum IL-6 levels also had a non-significant negative relationship (r = −0.17; p = 0.23) with VAS scores (Table 2).

Table 2: Relationships between serum hs-CRP, IL-1, and IL-6 levels with VAS scores

	hs-CRP (mg/dl)	hs-CRP (mg/dl)	hs-CRP (mg/dl)
VAS			
r	0.05	−0.10	−0.17
p	0.72	0.47	0.23
n	50	50	50

p<0.05 (Pearson correlation test). IL: Interleukin, hs-CRP: High sensitivity C-reactive protein, VAS: Visual analog scale.

Discussion

The results of this study did not find a significant correlation between hs-CRP serum levels and VAS scores in patients with LBP without sciatica. Inflammation is closely related to the perception of pain, which is more likely in those with increased CRP levels. In a study of 99 twin pairs, it was reported that high CRP levels were associated with lower pain thresholds and increased pain perception [17]. Previous studies have examined aspects of inflammatory pathologies such as disc herniation, inflammation of the nerve root, and sciatica showing a positive correlation [8]. Other studies have not found an association and reported constant levels of hs-CRP [9], [10].

IL-1 has a weak and insignificant negative correlation with VAS scores in this study. Kraychete *et al*., 2010, also did not find an increase in levels of IL-1 in patients with chronic LBP but found an increase in levels of TNF-α, soluble TNF-α, and IL-6 [18].

In this study, VAS scores were found to have a weak but not significant negative correlation with IL-6. Licciardone *et al*., 2012, in one study, reported that IL-6 correlated with the severity of LBP [19]. A number of triggers for LBP including mechanical trauma, deformity, genetic predisposition, infection, and smoking can induce proinflammatory signaling in degenerative cells of intervertebral discs. The activity of immune cells infiltrates into the disc along with nerve compression; all sensitization contributes to pain through this mechanism if it is not triggered by inflammation. Because inflammation contributes to the pathogenesis of LBP, proinflammatory cytokines may be used as molecular biomarkers of pathological processes associated with disc degeneration, disc herniation, and LBP. Such proinflammatory cytokines can be measured in the systemic blood of patients with LBP [20]. In this study, serum levels of hs-CRP, IL-1, and IL-6 did not show a significant correlation with pain intensity as measured by VAS scores in patients with LBP without sciatica. Thus, the serum levels of hs-CRP, IL-1, and IL-6 cannot be used as molecular biomarkers in diagnosing LBP without sciatica.

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