ORIGINAL RESEARCH PAPER

Orthopaedics

# A STUDY OF RELATIONSHIP BETWEEN SERUM PROTIEN IL6 AND SEVERITY OF PAIN IN PATIENT OF LUMBAR DISC HERNIATION

KEY WORDS:

**Dr. Rupesh Kadam** Senior Resident , B.J.Govt.Medical College, Pune.

**Dr. Sushant Ghumare*** Assistant Professor , B.J.Govt.Medical College, Pune. *Corresponding Author

**Dr. Nitin Dawre** Senior Resident, B.J.Govt.Medical College, Pune.

**Dr. Abhay Patil** Junior Resident , B.J.Govt.Medical College, Pune.

**ABSTRACT**

A herniated disk is a condition that can occur anywhere along the spine, but most often occurs in the lower back. It is sometimes called a bulging, protruding, or ruptured disk. It is one of the most common causes of lower back pain, as well as leg pain or "sciatica. In patients with disc herniation, increase in the levels of total proteins and injury markers have been detected in cerebrospinal fluid (9) . IL-6 is one of such important inflammatory cytokine in Lumbar disc herniation. The present study is to find out a co-relation between serum IL-6 and lumbar disc degeneration. **METHODS:** Our study includes 100 patients with lumbar disc degeneration to evaluate for co-relation with serum IL-6. Demographic data, clinical, radiological and laboratory investigations were done to find a co-relation between serum IL-6 and severity of symptoms. **RESULTS:** In our study, VAS Scores in low VAS (<5) group are positively correlated to serum IL6 levels. Pearson's correlation coefficient is 0.404 and is found significant (p=0.011). VAS Scores in high VAS (> 5) for back pain group were positively correlated to serum IL6 levels. Pearson's correlation coefficient is 0.508 and is found highly significant (p< 0.001). **CONCLUSION:** , our study has shown a strong correlation between the levels of IL-6 and lumbar disc herniation. VAS Scores in low VAS (<5) group as well as high VAS group are positively correlated to serum IL6 levels.

## INTRODUCTION

Displacement of the content of the intervertebral disc via external membrane i.e. the fibrous ring, usually in the posterolateral region comprises Lumbar disc herniation. It is clinically represented by the pain known as sciatica which arises due to compression and irritation of the lumber nerve roots and the dural sac. The intensity of compression depends on the volume of the herniated material. The sciatic pain originates via involvement of many factors which include mechanical stimulation of the nerve ends of the external portion of fibrous ring, nerve root compression which might be with or without ischemia along with various inflammatory responses.

The origin of sciatic pain is probably multifactorial, involving mechanical stimulation of the nerve ends of the external portion of the fibrous ring, direct compression of the nerve roots (with or without ischemia) and a series of inflammatory phenomena induced by the extruded nucleus–(1). The pain in nerve roots caused by disc herniation is induced by both chemical and mechanical factors(2, 3). Chemical factors arise due to leakage of substances from nucleus pulposus (NP) which is considered inner part of disc after the rupture of annulus fibrosus (4)(5). Experimentally it has been found that nucleus pulposus can induce inflammatory-like reactions around the nerve roots along with increase in vascular permeability, changes in myelin (6). Various inflammatory mediators like cytokines, phospholipase A2 and nitric oxide have been found to be important in pathophysiology of NP-induced injury of nerve roots (7, 8). In patients with disc herniation, increase in the levels of total proteins and injury markers have been detected in cerebrospinal fluid (9). IL-6 is one of such important inflammatory cytokine in Lumbar disc herniation. Neuro-inflammation has been found to play a crucial role in the generation of chronic pain. Various in vitro and animal models of pain studies have demonstrated such data (10-14). It has been shown in human patients also that local and systemically expressed proinflammatory cytokine are mediators of pain (15)(16). Role of TNF-$\alpha$, IL-1$\beta$ and IL-6 seems to be more important because of their hyperalgesic effects after nerve damage. At the end of the study the primary outcome will be to establish a relationship between levels of serum protein IL6 and severity of lumbar radicular pain in patient lumbar disc herniation. We also wish to study the clinical characteristics in patients with lumbar disc herniation with increased levels of IL6 and the study will also help in establishing relationship between increased levels of IL6 with worsening of neurological functions in these patients.

## AIMS AND OBJECTIVES

- To establish a relationship between levels of serum protein IL6 and severity of lumbar radicular pain in patient lumbar disc herniation
- To study the clinical characteristics in patients with lumbar disc herniation with increased levels of Il6
- To establish relationship between increased levels of IL6 with worsening of neurological functions in patients of lumbar disc herniation

## METHODOLOGY

### Inclusion criteria

1) Patients with degeneration of lumbar intervertebral disc leading to disc bulge/protrusion/extrusion on MRI compressing spinal cord

2) Patients with chronic back pain with features of lumbar myelopathy such as pain , numbness , loss of sensation , loss of power , increase in tone in lower limbs.

### Exclusion criteria

1) Patients with diagnosed neurological dysfunction such as-
   a) STROKE leading to monoparesis /monoplegia /paraparesis /paraplegia /quadriparesis /quadriplegia
   b) PERIPHERAL NEUROPATHIES
2) Patients with traumatic lumbar spine injury.
3) Patients with congenital spine deformities
4) Patients with fractures in lower limb
5) Patients with known psychological dysfunction
6) Tuberculosis of spine and other infections of spinal cord

**Ethics approval:** An observational cross-sectional study conducted at a tertiary care centre of B. J. Medical College and Sassoon Hospital, Pune, and approved by the regional ethical committee.

**Study Area:** Department of Orthopaedics, B.J. Govt medical college & Sassoon General Hospital, Pune with Lumbar Disc Herniation related complaints and willing to participate in the research of this shall constitute the study sample.

**Study procedure**

I. Detail history regarding onset and progression of symptoms.
II. History of trauma to be taken.
III. Detail neurological examination.
IV. Xray lumbar spine AP and LATERAL view
V. MRI lumbar spine-. Degree of the spinal cord compression and other findings related to degeneration were recorded.

**IL6 Estimation.**

IL6 esimation was done from an external lab.The methodology was a kit based analysis and the reference values were used as per annexure format.

**History**

1. History of poor posture at work
2. History of NSAIDs consumption
3. H/O work Mechanical stress
4. Numbness or tingling in a foot or leg

**Sample Size Calculation:** Consecutive type of non-probability sampling was used for selection of cases. A total of 100 cases with lumbar disc herniation diagnosed on MRI coming in the department of orthopaedics fulfilling inclusion and exclusion criteria were selected for the study.

**OBSERVATIONS AND RESULTS**

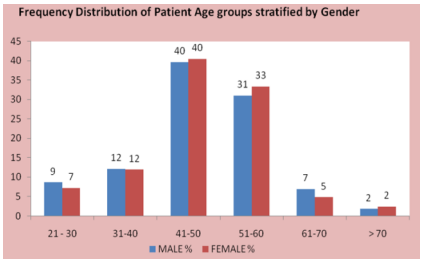


**Table 1 : Frequency Distribution of Patient Age groups stratified by Gender**

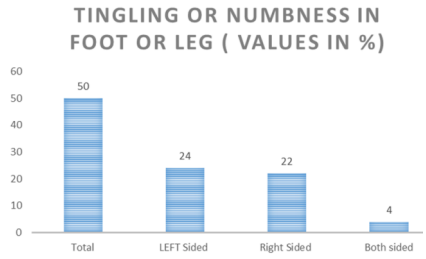


**Table 2 : Numbness or tingling in a foot or leg**

I. 50 % cases reported having experienced numbness or tingling in foot or leg.

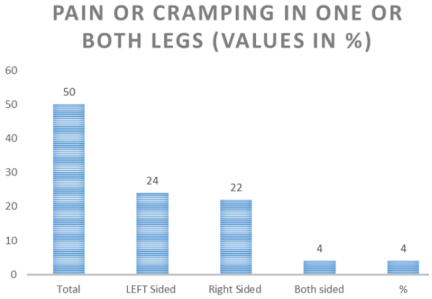


**Table 3: Pain or cramping in one or both legs Error! Not a valid link.**

I. 36 % cases reported pain or cramping in either one or both legs.

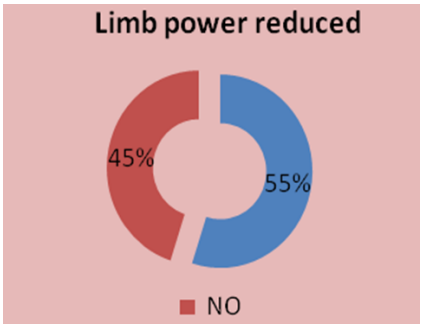


**Table 04: Limb power reduced**

I. Limb power was found reduced in 55 % of the cases.

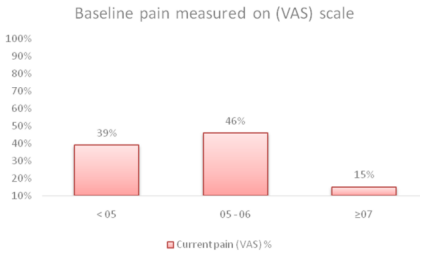


**Table 5 : BACK PAIN assessed by (VAS) (0-10 scale) at Baseline assessment**

Based on intensity of back pain on a visual analog scale (VAS, 0–10 cm) it was noted that

I. 39 % cases had the score lesser than 5.
II. 46% cases had VAS scores ranging between 5 and 6.
III. 15 % cases had severe pain (vas >07)

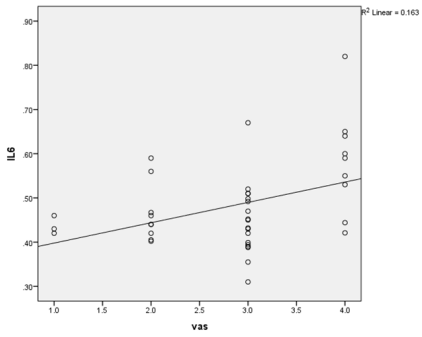


**Table 6: Correlation of Low VAS Score (<5) for back pain group with IL6 values**

Scatter Diagram of IL6 values in low VAS Score patients.

VAS Scores in low VAS (<5) group are positively correlated to serum IL6 levels. Pearson's correlation coefficient is 0.404 and is found significant (p=0.011)

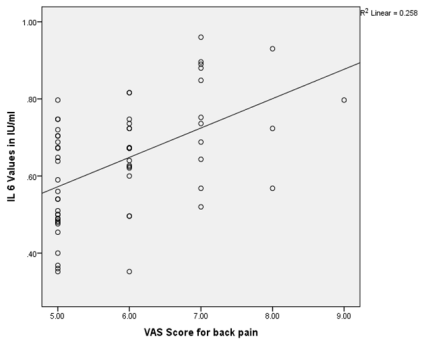


**Table 7 : Correlation of High VAS Score (≥ 5) for back pain group with IL6 values.**

VAS Scores in high VAS (> 5) for back pain group were positively correlated to serum IL6 levels. Pearson's correlation coefficient is 0.508 and is found highly significant ($p < 0.001$

## DISCUSSION

This study primarily demonstrates the presence of IL-6 in serum of patients with lumbar disc herniation and co-relation of these levels with intensity of pain. IL-6 is a 184-amino acid-long glycoprotein and an important pro-inflammatory cytokine produced by activated inflammatory cells, including lymphocytes and macrophages. By detecting pro-inflammatory cytokines in serum of above-said groups of patients, this study supports the idea that lumbar disc herniation is a condition that is accompanied by a chronic, local inflammation. Previous data suggest that high serum levels of IL-6 when the patients arrive the hospital, may predict a less favorable recovery[17]. In this study, we recruited patients with lumbar disc herniation (N= 100) with an average age of 50 ± 30 years and gender distribution of 58 % male (n = 58) and 42 % female (n= 42) (Table 1). Maximum (40 %) patients in both the genders fell in the age group 41-50 years.31% males and 33 % females were in the age group 51-60 years.

All the participants had the problem of lower back ache and nearly 50% of the patients had the Numbness or tingling in a foot or leg . 29% of total participants had increased tone in lower limb; however 71% of patients did not show such symptoms. 64% patients had cramping in one or both legs and 55% had reduction in limb power. Based on intensity of pain on a visual analog scale(VAS, 0–10 cm) at 12 months follow-up, the patients were divided into two groups, i.e., the high- and low-pain group with VASP ≥ 5 and VAS <5, respectively. 61 % of the investigated patients still had a pain intensity score on VASP ≥ 5 at 12 months follow-up. The mean VAS score decreased over time for the low-pain group, but was more stable over time for the high-pain group. The levels of IL-6 were not much increased in group with VAS <5. Data is represented as ±SD. It was observed that in the low-pain group, there was no significant change in the serum levels of IL-6 from inclusion upto 12 months of follow-up. VAS Scores in low VAS (<5) group are positively correlated to serum IL6 levels. Pearson's correlation coefficient is 0.404 and is found significant ($p=0.011$) In the majority of the patients, reduced pain and a drop in the serum cytokine levels were observed from inclusion to 6 weeks which further dropped after 12 months of follow up. We observed very high levels of Il-6 in high VAS group after 6 weeks which had fallen sharply after 12 months of follow-up.The fall in IL-6 over time was, however, only observed in the high-pain group. VAS Scores in high VAS (> 5) group are positively correlated to serum IL6 levels. Pearson's correlation coefficient is 0.508 and is found highly significant ($p< 0.001$). In the present study, however, we have demonstrated that chronic pain patients have increased serum levels of IL-6 in the follow-up period, that is, 6 weeks and12 months after disc herniation. This suggests that this cytokines may be associated with the mechanisms underlying development of chronic pain after disc herniation. However, the reduced IL-6 levels from inclusion to 6 weeks may also be a reflection of early benefits of establishing and activating a treatment plan.IL-6 may act on both peripheral and the central nervous system. Supporting the relevance of these cytokines, we showed that the serum levels of IL-6 were associated with long-lasting pain in patients with disc herniation. Earlier data have shown similar results in patients with chronic widespread pain[16]– indicating a relationship between the levelof IL-6 in plasma and the extent of pain. The elevated serum levels of IL-6 observed in the presentstudy may reflect a local inflammatory process near the site ofthe disc herniation. After disc herniation, endothelial cells, fibroblastsand chondrocytes close to the nerve roots also express IL-6(Takahashi et al., 1996). It has also been shown in rat models of radicular pain, pain inhibitors significantly reduced expression of IL-6 in tissues and suppressed the degree of the pain, indicating that IL-6 exerts vital function to give rise to radicular pain. Moreover, an animal experiment [12] showed that IL-1, IL-6, and TNF-α may lead to significant hyperalgesia, with the degree of hyperalgesia positively correlated with the dose of IL-6.

It has also been investigated whether serum interleukin-6 (IL-6) expression levels were associated with the onset and progression of intervertebral disc degeneration (IDD). A comprehensive meta-analysis of the scientific literature from numerous electronic databases was performed, in order to obtain published studies associated with the topic of interest. Relevant case-control studies that had previously assessed a correlation between IL-6 expression levels and IDD were identified using predetermined inclusion and exclusion criteria.

A study aimed at providing an overview of the literature addressing the role of genetic factors and biomarkers predicting pain recovery in newly diagnosed lumbar radicular pain (LRP) patients. Previous studies revealed that inflammatory cytokines are not only closely related to other cytokines and chemical mediators but also play an important role in lumbar disc herniation (Habtemariam et al., 1996; Kang et al., 1996). In particular, interleukin 6 (IL-6) and IL-10 were shown to be highly expressed and activated in herniated disc and surrounding tissues, which presented as important pro- and anti-inflammatory cytokines, respectively, in the human body (Sommer and Kress, 2004). Burke et al. (2002) showed that herniated intervertebral disc cells secreted a number of pro-inflammatory mediators and cytokines, including IL-6, that causes lumbar pain. Kang et al. (1996) demonstrated that IL-6 was expressed in both normal and herniated discs, but was significantly induced in the herniated discs. Furthermore, Ahn et al. (2002) demonstrated that IL-10 inhibited expression of IL-1, IL-6, tumor necrosis factor-a (TNF-a), and other inflammatory mediators, as well as matrix metalloproteinase (MMP), to regulate the pathogenesis of intervertebral disc degeneration. A recent study profiled inflammatory proteins in the sera of patients with disc herniation to predict lumbar radicular pain within a year (Moen et al., 2016).

Burke et al. (2002) showed that herniated inter-vertebral disc cells were able to secrete a number of proinflammatory mediators and cytokines, including IL-6, and this was associated with lumbar pain, although Kanemoto et al. (1996) argued that IL-6 might cause the loss of proteoglycan in the extracellular matrix of the nucleus pulposus, thereby inhibiting fibroblast synthesis of collagen.

## SUMMARY

This prospective observational cross sectional study was conducted in tertiary care academic hospital over the period of 2017 till 2019. A cohort of 100 Patients with lumbar disc herniation were selected from the orthopaedic surgery department. The primary objective of the study was to establish a relationship between levels of serum protein IL6 and severity of lumbar radicular pain in patient lumbar disc herniation. The study also aimed to study the clinical characteristics in patients with lumbar disc herniation with increased levels of Il6.

The findings of the study are summarized as follows.

I. Average age of the study group was 46.9 years with standard deviation of 10.03 years.
II. There were 58 males and 42 females in the study group.
III. 22 % Males and 24 % females were in the obese category while 29 % Males and 40 % females were in the overweight category.
IV. 18 % of the cases reported that during their work the posture was improper.
V. 29 % patients reported that their occupation contributed to mechanical stress.

VI. 12 % of the cases were found to have diabetes mellitus history. All of these cases were receiving oral medications.
VII. 15 % of the cases in our study were found to have chronic history of consuming non streroidal anti-inflammatory drugs for pain due lumbar disc herniation.
VIII. 50 % cases reported having experienced numbness or tingling in foot or leg.
IX. 36 % cases reported pain or cramping in either one or both legs.
X. Based on intensity of back pain on a visual analog scale (VAS, 0–10 cm) it was noted that39 % cases had the score lesser than 5., 46% cases had VAS scores ranging between 5 and 6., 15 % cases had severe pain (vas >07)
XI. VAS Scores in low VAS (<5) group are positively correlated to serum IL6 levels. Pearson's correlation coefficient is 0.404 and is found significant (p=0.011)
XII. VAS Scores in high VAS (> 5) for back pain group were positively correlated to serum IL6 levels. Pearson's correlation coefficient is 0.508 and is found highly significant (p< 0.001)

## CONCLUSION

In conclusion, our study has shown a strong correlation between the levels of IL-6 and lumbar disc herniation. VAS Scores in low VAS (<5) group as well as high VAS group are positively correlated to serum IL6 levels. Moreover, the intensity of pain also affected the levels of IL-6 in lumbar disc herniation patients, which indicate that as the disease becomes chronic; the levels of IL-6 also increase simultaneously, indicating that IL-6 could be a marker for progressive disease in case of lumbar disc herniation. Further case controlled studies with bigger sample size can provide greater details regarding precise role of IL6 in lumbar disc herniation.

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