

ORIGINAL ARTICLE

# Evaluation of The Effect of Epidural Steroid Injection on Interleukin -18 in Patients with Low Back Pain

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## Abstract

**Background:** Having lower back discomfort is common. Back tension may cause sciatica. Low back, or lumbar region, begins below the ribs. Most people will have low back discomfort. Disk damage, structural issues, and atherosclerosis also contribute. Rest, physical therapy, and medicine relieve pain. Weight management and exercise reduce low back pain risk. Epidural steroids alleviate leg and back pain (ESIs). Their extensive history makes them a good nonsurgical sciatica and back pain treatment. ESI may relieve radiculopathy. Human interleukin-18 (IL18) is an interferon-gamma-inducing factor. Gene generates inflammatory cytokine.

**The Aim:** The study was aimed at the effect of epidural steroid injection on the concentrations of IL-18 in patients with LBP.

**Materials and Methods:** Serum Interleukin-18 was measured using Elabscience® kits. In a case-control study, 36 healthy people and 22 LBP patients (13 men and 9 women) were compared (23 males and 13 females). Our research included 30 to 79-year-olds. All patients in this research were diagnosed by specialists based on their histories and clinical features. A patient's file includes ages, genders, family history, ailments (such as diabetes and hypertension), medicines, weight, height, and BMI (BMI). Participants with COVID-19, autoimmune disorders, diabetes mellitus, acute or chronic liver disease, renal disease, thyroid function abnormalities, or kidney disease were eliminated.

**Results:** Interleukin-18 (IL-18) was substantially greater in patients with LBP ( $250.87 \pm 29.72$  pg/mL) than following injection and control ( $157.94 \pm 47.23$ ), ( $132.40 \pm 22.58$ ) pg/mL, respectively. Our investigation found a very significant difference (p-value < 0.0001) in IL-18 concentrations compared to L. Also, mean values before and after injection were significantly different (p-value 0.0001). There is a significant difference in mean values before and after injection (p-value < 0.0001) and after injection and control (p = 0.0012).

**Conclusion:** Epidural steroid treatment positively impacts LBP patients by decreasing IL-18 levels, which could be played an essential role in repairing damaged tissues.

**Keywords:** interleukin-18 (IL18), Low back pain (LBP), lumbar radicular pain (LRP), Epidural steroid.

## 1 Introduction

Low back pain (LBP) and lumbar radicular pain (LRP) are common causes of physical and mental disorders as well as significant economic losses [1]. Low back pain is also referred to as sciatica, lumbar radiculopathy, lumbosacral radicular syndrome, nerve root soreness, and nerve root irritation in medical literature. The majority of individuals describe it as a backache that travels down their legs [2]. Disk disease in the spine is the major factor contributing to low back pain. The pathophysiological changes in intervertebral disk disease might result in a disk herniation, degenerative conditions including canal stenosis, or persistent instability of the affected segments. The nucleus pulposus herniation, which happens when a piece of the intervertebral disk in the lumbar area produces stenosis and inflammation, is the most frequent cause of sciatica [3, 4]. One of the most frequent causes of medical visits or missed work days is back discomfort. Back discomfort may occur in youngsters who are in school [5]. Low back pain is a significant issue worldwide, and it is largely becoming worse due to the aging and growing global population [6]. It affects people of all ages and is often linked to sedentary jobs, tobacco use, obesity, and poor socioeconomic position. Since 1990, the number of years with a handicap brought on by low back pain has grown by more than 50%, notably in low- and middle-income nations (LMICs) [7, 8]. Low back pain disability is expected to rise most in LMICs where resources are few, access to high-quality healthcare is often inadequate, and risks are only expected to rise as some people's lifestyles alter and migrate to more sedentary employment. Epidural steroid injections may be administered as pure steroids or anesthetics or as a combination of steroids and saline. These injections reduce the inflammatory response brought on by chemical and mechanical pain causes, such as a pinched nerve or a degenerative disc. Reduced immune system activity lowers the body's synthesis of inflammatory cells [9, 10]. The interleukin-18 protein, also known as the interferon-gamma inducing factor, is produced by the human interleukin-18 (IL18) gene [11]. An inflammatory cytokine is produced by this gene. Different cells, including hematopoietic and non-hematopoietic cells, have the ability to generate IL-18. It was first discovered in 1989 as a chemical that induced mouse spleen cells to produce interferon (IFN). It was discovered that Kupffer cells and liver-resident macrophages produce IL-18 initially [12, 13]. However, IL-18 is also expressed by non-hematopoietic cells such as intestinal epithelial cells, keratinocytes, and endothelial cells. Autoimmune or inflammatory illnesses may be brought on by IL-18 dysregulation, which may regulate innate

and adaptive immunity. The intracellular caspase enzyme processes the IL-18 precursor similarly to how IL-1 is handled [14–16]. Type II interferon, crucial for activating macrophages or other cells, is produced when IL-18 and IL12 interact with CD4, CD8 T cells, and NK cells [17–19]. It should be noted before we begin, throughout this review we will move to "back pain" as we explore the biochemistry literature. Wherever possible "back pain" are discussed, we will use a definition specific to the research project it is being described in at the time (and defined as acute, subacute or traumatic). If the focus is on the biochemistry and not the illness/injury then "spinal pain" will be used to describe the overall process. that cytokine research is still rather novel and we feel that it is more helpful to see all aspects to gain a better understanding of the future of cytokines in the treatment of spinal pain. Epidural steroid injections (ESIs) are a common treatment option for many forms of lower back pain and leg pain. The goals of an epidural steroid injection are to: Control pain by reducing inflammation in and around the nerve roots, Improve mobility and function in the lower back and legs, Allow the patient to participate in and make progress with a comprehensive physical therapy and rehabilitation program.

## 2 Materials and Method

### 2.1 Patients

In the period between October 2021 to June 2022, the experiments were conducted on patients diagnosed with early Low Back pain and their number was (22) patients, based on the type of therapy divided into two groups that gave them. The first group include of (22) patients, untreated group (before epidural steroid). The second group consisted of (22) patients, treated group (after epidural steroid injection). The average age of the participants in this study was between (30-75) years. They were selected and diagnosed by doctors in private clinics in Al-Diwaniyah Governorate.

### 2.2 Control

The control group of 36 healthy individuals was collected. The study's range for the average age was 30 to 75 years.

### 2.3 The setting of the study

The current research was conducted on low back pain patients in Al-Diwaniyah governorates. Also, All were carried out in the Medicinal Chemistry Laboratory.

## 2.4 Sample Collections

During the period from October 2021 to June 2022, the experimental study design was comprised of 22 patients diagnosed with LBP (13 males and 9 females) and a control consisting of 36 healthy (23 males and 13 females). Specialized doctors diagnosed all patients in this study, and the diagnosis was verified by the history of patients, clinical features. The record of patients consists of the following: ages, genders, family history, other diseases (Diabetes, hypertension), treatment (drugs), weight, height, and body mass index (BMI).

## 2.5 Inclusion criteria

Low back pain.

## 2.6 Exclusion Criteria

Patients with acute or chronic liver disease, renal disease, thyroid function problems, diabetes mellitus, hypertension, COVID-19, and autoimmune illnesses were not included in the research.

## 2.7 Human IL-18 (Interleukin-18)

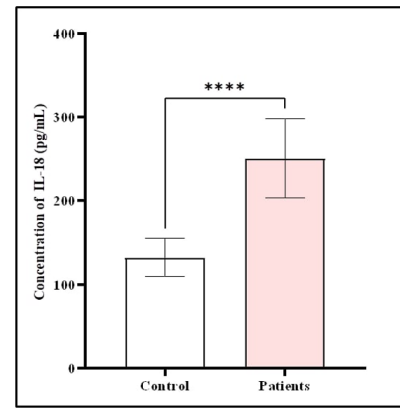
Serum IL-18 level was estimated using Elabscience kits by using ELISA.

## 2.8 Statistical Analysis

Data were summarised, analyzed, and presented using GraphPad Prism 9.2.0 and Microsoft Office Excel 2013. The mean and standard deviation were used to express numerical data. Categorical data were also expressed as numbers at the same time. In the case of regularly distributed variables, one-way ANOVA and an unpaired t-test were employed to compare the mean values between the various groups. The qualitative data were evaluated using chi-square. The Pearson correlation coefficient was used to perform a bivariate correlation. P-value was considered significant at ( $p\text{-value} \leq 0.05$ ).

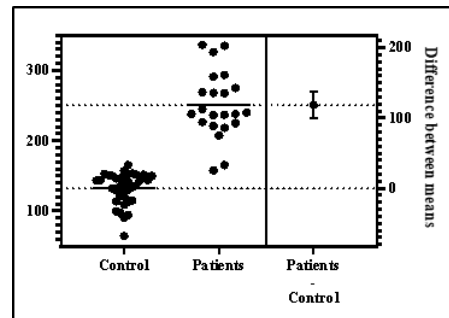
## 3 Results

The findings of this investigation indicate increased levels of Interleukin-18 (IL-18) ( $250.87 \pm 29.72$ ) pg/mL in patients with LBP as compared with treated group and control, ( $157.94 \pm 47.23$ ), ( $132.40 \pm 22.58$ ), pg/mL respectively; The results of our study showed a significant difference ( $p\text{-value} < 0.0001$ ) in the concentrations of IL-18 as compared patients with LBP and control. As shown in Figure (1).



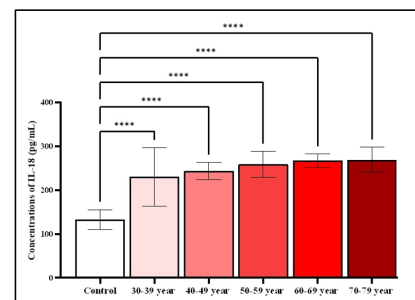
**Figure 1:** Estimating interleukin-18 [IL-18 (pg/mL)] compares patients with low back pain and control.

the significant difference ( $p\text{-value} < 0.0001$ ). Data are expressed as means  $\pm$  SD. indicates \*\*\*\* significant differences compared to the control,  $p\text{-value} < 0.0001$ .



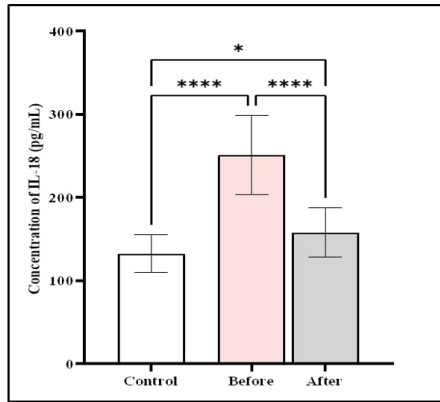
**Figure 2:** Estimation plot illustrates the presence of a significant decrease in the level of interleukin-18 [IL-18 (pg/mL)] in the patient group compared to the control

The measurement of serum interleukin-18 level (pg/ml) for patients with LBP showed that the concentration of IL-18 was significantly higher ( $P < 0.0001$ ) in the group aged (70-79) comparing the between the control group shown in Figure 3.



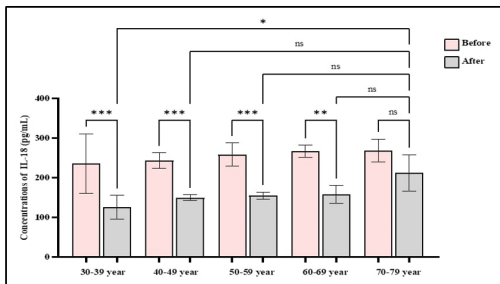
**Figure 3:** Estimation concentrations of interleukin-18 [IL-18 (pg/mL)] A comparison between control and patients among different age groups showed the presence of a significant increase ( $p\text{-value} < 0.0001$ ) in the patients group than control in all age subgroups.

Data are expressed as means ± SD. Indicates \*\*\*\* p-value <0.0001. In the measurement of serum interleukin-18 a significant difference was presented in mean values between treated group and untreated group (p-value <0.0001). Also, was a significant difference in mean values before injection and control (p-value < 0.0001), and there was a significant difference in mean values after injection and control (p-value = 0.0012), as shown in Figure 4.



**Figure 4:** Estimation of serum concentrations of interleukin-18 [IL-18 (pg/mL)] after the injection of epidural steroid treatment.

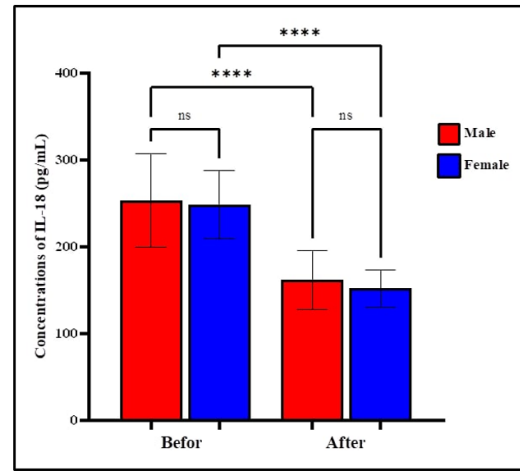
Figure 5 showed that serum interleukin-18 levels were higher in the group aged (70-79) compared to before and after the injection of epidural steroid treatment. A significantly decreased interleukin-18 level was found in the group aged (30-39) compared to the group aged (70-79). A significant decrease (p-value <0.0001) in the serum concentration of IL-18 as compared to before injection epidural. However, the concentration was significantly (p-value <0.0001) higher than the control. Data are expressed as means ± SD. Indicates \* p-value ≤0.05 and \*\*\*\* p-value ≤0.0001.



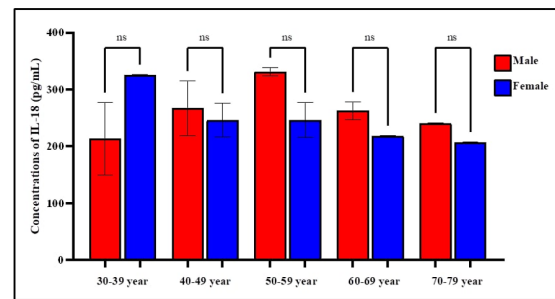
**Figure 5:** Estimation of serum concentrations of interleukin-18 [IL-18 (pg/mL)] after the epidural steroid treatment among the different age groups.

Comparing the difference between males and females, the interleukin-18 level was insignificantly in

males than in females in patients with LBP after the injection of epidural steroid treatment, as shown in Figures 6 and 7.



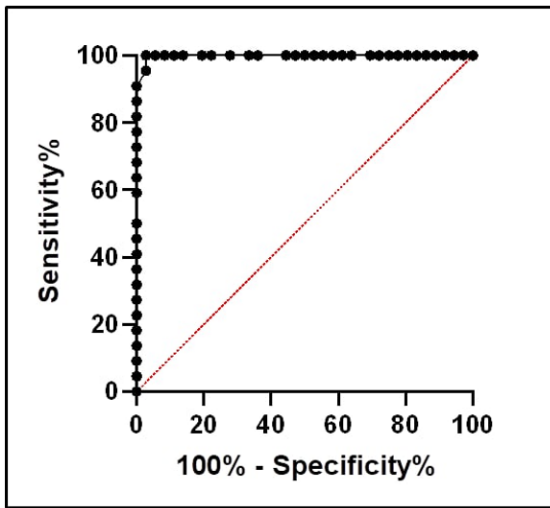
**Figure 6:** Estimation of interleukin-18 [IL-18 (pg/mL)] serum concentration before and after the injection of epidural steroid treatment.



**Figure 7:** Estimating interleukin-18 [IL-18 (pg/mL)] serum concentration of patients with Low back pain among different age groups for gender.

### 3.1 The diagnostic performance of interleukin-18 in patients with low back pain

To evaluate the diagnostic performance of cytokines markers in patients with LBP, receiver operator characteristic (ROC) curve analysis was performed, and the results are shown in Figure 8. Regarding IL-18, the cutoff value was > 157.8 pg/ml with 100% sensitivity, 97.22% specificity, and 0.9981 area



**Figure 8:** Receiver operator characteristic (ROC) curve analysis to find the best serum IL-18 (pg/mL) cutoff value that can predict a diagnosis of Low back pain.

## 4 Discussion

### Evaluation of concentrations of IL-18 in patients with low back pain the control.

Together with IL-12, IL-18 is a cytokine that contributes to the Th1 paradigm by helping to activate and differentiate diverse T cell populations. Other pro-inflammatory cytokines, such as nitric oxide generation, chemokine production, and increases in cell adhesion molecules, are hallmarks of IL-18 [19, 20] This research showed that LBP patients had higher levels of IL-18 when compared to pain-free healthy controls. These findings were corroborated by another investigation [21] that revealed individuals with low back pain had higher levels of IL-6, IL-8, and IL-18. The previous researcher claimed that IL-18 and persistent pain are related [22]. IL-18 was proposed as the primary regulatory cytokine in the upregulation of components involved in the innervation and vascularization of human deteriorated IVD in intervertebral disc (IVD) degeneration [23].

Furthermore, high levels of inflammatory mediators and IL-18 were found in degenerated and herniated IVD[24] and associated with pain development during IVD herniation and degeneration in LBP patients[25]. In contrast to our data, the findings of another study [26] which revealed levels of pro-inflammatory cytokines (IL-2, IL-6, IL-18) tumor necrosis factor-alpha), have showed no significant differences between patients with chronic back pain and pain-free healthy controls.

For over 50 years, epidural steroid injections (ESIs) have been a common therapy for low back pain with radiculopathy [1]. Compared to LBP patients before

injection and pain-free subjects, the current study results show lower levels of IL-18 in LBP patients after epidural steroid treatment. These results were consistent with a study [27] that found steroids inhibited the production of IL-18 and other secondary cytokines. Epidural steroids and corticosteroids upregulate anti-inflammatory genes, repress IL-18 genes, and reduce the production of IL-18 and pro-inflammatory cytokines [28].

Three main methods explain how glucocorticoids and ESI reduce IL-18: extragenomic effects, direct control of transcription, and inhibition of transcription effects mediated by nuclear factor B (an essential transcription factor upregulated in inflammation). It is believed that these pathways have various dose-response curves [29,30].

## 5 Conclusion

Epidural steroid treatment positively impacts LBP patients by decreasing IL-18 levels, essential in damaged tissue repair.

## Recommendations

This study could recommend the following: 1. Future basic science must at a minimum report the contents of ESI to better understand the clinical role of ESI for IVD. 2. Measurements of more inflammatory cytokines such as IL-6, IL-1, and IL-8 for more assessment for inflammatory events in patients with LBP. 3. Theories with scientific grounds for identification the common etiologies of inflammatory back pain and associated critical situations for favorable treatment.

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**Conflict of Interest:** No conflicts of interest exist between the authors and the publication of this work.

**Ethical consideration:** The study received approval from the university's ethical council at Al-Qadisiyah, Iraq.



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