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The Role of Cytokine Biomarkers in Assessing Lumbar Degenerative Disorders and Associated Comorbid Conditions

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Abstract

Interleukins, a category of cytokines, are crucial in the inflammatory mechanisms associated with Lumbar degenerative disorders (LDD). This study evaluated the correlation between cytokine biomarkers and demographic, socioeconomic, and occupational factors in persons diagnosed with LDD. An investigation was carried out on 112 patients diagnosed with low back pain (LBP) at GSL from December 2021 to January 2023 Medical College, Rajahmundry. The concentrations of interleukins (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, and IL-13) in the blood were quantified utilizing multiplex fluorescent antibody assays. The study included 62 males and 50 females, with a mean age of 48.3 years. A notable correlation existed between increased IL-6 levels and patients with LBP compared to controls ($P < 0.05$). Positive relationships were seen between IL-6 levels and age, body mass index (BMI), and illness duration. Extended sitting and socioeconomic status were significant risk factors for low back pain ($P = 0.042$). Patients diagnosed with degenerative disc disease (DDD) and spinal stenosis (SS) had elevated levels of IL-6 compared to persons with disc herniation (DH). Elevated circulating levels of IL-6 are correlated with LDD and demonstrate an association with age, BMI, and symptom duration. Socioeconomic factors and work practices significantly influence the occurrence of LBP. The findings suggest that cytokine biomarkers, particularly IL-6, may serve as significant indicators for assessing the severity and course of LDD. It is recommended that we undertake further extensive investigations to validate these findings and explore therapy strategies centred on cytokine regulation.

Keywords*: Cytokines, Lower Back Pain, Lumbar Degenerative Disorders.*

Introduction

Lumbar degenerative disorders, encompassing ailments like degenerative disc disease, spinal stenosis, and disc herniation, significantly contribute to the global prevalence of lower back pain. Low back pain (LBP) is a common condition that is recognized as a primary factor in years lived with disability (YLD) worldwide, and is associated with considerable socioeconomic costs due to reduced productivity and increased healthcare utilization [6]. The pathogenesis of LDD involves multiple elements, including mechanical stress, genetic predisposition, and metabolic impacts. Inflammation is crucial in the degeneration of intervertebral discs, with cytokines like interleukins (ILs) being important to the inflammatory process [7]. Interleukin-6 (IL-6) is crucial to mediating inflammatory responses and is associated with pain perception and the mechanisms behind neuropathic pain [5, 10]. In addition to biological variables, lifestyle choices and work habits significantly influence the development and progression of LDD. Extended sitting, obesity, and inadequate dietary practices are

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acknowledged as modifiable risk factors for low back pain [8, 9]. Socioeconomic status significantly influences health outcomes, since disparities in healthcare access and variations in occupational exposures contribute to the burden of low back pain [11]. The swift growth and alterations in India have resulted in a notable rise in non-communicable illnesses, including LDD. However, there is insufficient research regarding the correlation between cytokine biomarkers and comorbid variables in this population. Understanding these associations may inform targeted actions and improve therapeutic outcomes. This study aims to assess the correlation between cytokine biomarkers, specifically interleukins, and several comorbid variables in patients diagnosed with LDD. By elucidating these relationships, we seek to facilitate the development of comprehensive management solutions for LBP.

Materials and Methods

Study Design and Setting

The research study was carried out at GSL Medical College in Rajahmundry, Andhra Pradesh, India, spanning from December 2021 to January 2023. The investigation was a joint venture involving the Department of Anatomy and the Department of Orthopaedics. Approval from the Institutional Ethics Committee was secured, and the study complied with the principles delineated in the Declaration of Helsinki.

Participants

A total of 112 participants diagnosed with low back pain participated in the trial. The criteria for inclusion were:

1. Individuals aged 18 years and older.
2. Both male and female patients.
3. Clinically diagnosed with LBP by an orthopaedic specialist. Exclusion criteria included:
4. Uncooperative individuals.
5. Patients on immunosuppressive or steroid therapy.
6. History of spine surgery or physiotherapy within the last six months
7. Known vertebral fractures or recent trauma
8. Cancer patients
9. Unconscious patients or those unable to provide informed consent

Data Collection

Clinical and Demographic Data

Participants underwent a comprehensive clinical assessment, and data were recorded using a structured questionnaire. Demographic information collected included:

1. Age.
2. Gender.
3. Socioeconomic status is assessed using the Modified Kuppuswamy scale (Majumder, 2021).
4. Occupational details, including nature of work, duration of sitting, and exposure to occupational stress.
5. Dietary habits, specifically frequency of outside food consumption.

Anthropometric Measurements

Height and Weight: Measured using standardized procedures.

Body Mass Index (BMI): The calculation involves dividing weight (kg) by height squared (m^2) and is categorised according to the criteria established by the National Institutes of Health (National Heart, Lung, and Blood Institute, 2014).

1. Underweight is characterised by a BMI of less than 18.5 kg/m^2.
2. Normal weight is characterised by a BMI between 18.5 and 24.9 kg/m^2.
3. Overweight: BMI between 25 and 29.9 kg/m^2.

Individuals categorised as obese possess a Body Mass Index (BMI) of 30 kg/m^2 or above.

Serum Analysis of Cytokines

Samples of blood were obtained from participants before the initiation of any therapeutic intervention. The serum was

isolated and preserved at –80°C before analysis.

Cytokine Measurement

We quantified the serum concentrations of the subsequent cytokines utilising multiplex electrochemiluminescence immunoassays (Meso Scale Discovery, MD, USA):

1. Interleukin-1β (IL-1β) is a cytokine that plays a crucial role in the inflammatory response.
2. Interleukin-2 (IL-2) is an essential cytokine that regulates immunological responses.
3. Interleukin-4 (IL-4) is a cytokine that is essential for the control of the immune system.
4. Interleukin-6 (IL-6) is a cytokine that is essential in immune response and inflammation.
5. Interleukin-8 (IL-8) is a crucial cytokine implicated in numerous physiological processes.
6. Interleukin-10 (IL-10) is a cytokine with considerable relevance in immune modulation and inflammation.
7. Interleukin-12p70 (IL-12p70) is a cytokine that is essential for the immunological response.
8. Interleukin-13 (IL-13) is a cytokine that is essential in immunological responses and inflammation.

Procedure

1. Samples underwent a dilution of 1:2 using Diluent 2 (MSD). Each well of the assay plate received 50 µL of diluted serum.
2. Plates were subjected to incubation overnight at a temperature of 4°C.
3. Following the incubation period, the plates underwent a washing process, after which 25 µL of detection antibody was introduced to each well.
4. Plates underwent incubation for 2 hours at room temperature.
5. Upon concluding the final wash, the plates were examined using an MSD SECTOR Imager 2400 plate reader.
6. The lower limit of detection (LLOD) and upper limit of detection (ULOD) were established for each cytokine.

Statistical Analysis

Data analysis was conducted utilising IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp.).

Descriptive Statistics

Mean ± standard deviation (SD) for continuous variables and frequencies (percentages) for categorical variables.

Inferential Statistics

Logistic regression analysis was employed to evaluate the relationship between cytokine levels and clinical indicators.

Odds ratios (ORs) accompanied by 95% confidence intervals (CIs) were computed. A P-value below 0.05 was deemed statistically significant.

Results

Biographical and Diagnostic Attributes Age and Gender Distribution.

The study comprised 112 participants, consisting of 62 males (55.35%) and 50 females (44.64%), leading to a male-to-female ratio of roughly 1.2:1. The average age was 48.3 ± 12.5 years. Table 1 provides a comprehensive overview of the age distribution.

Table 1. Age Distribution of Participants

Age Group (Years)	Male (%)	Female (%)	Total (%)
18–27	8 (7.2)	5 (4.4)	13 (11.6)
28–37	8 (7.2)	6 (5.3)	14 (12.5)
38–47	12 (10.7)	8 (7.1)	20 (17.86)
48–57	10 (8.96)	9 (8.0)	19 (16.96)

58–67	11 (9.85)	10 (8.9)	21 (18.75)
≥68	13 (11.62)	12 (10.7)	25 (22.32)
Total	62 (55.35)	50 (44.64)	112 (100)

Logistic regression analysis showed no significant association between age and LBP (OR = 0.923; 95% CI: 1.2–2.9; P = 0.62).

Body Mass Index (BMI)

BMI categories and their distribution among participants are presented in Table 2.

Table 2. BMI Distribution of Participants

BMI Category	Male (%)	Female (%)	Total (%)
Underweight (<18.5)	12 (10.7)	10 (8.9)	22 (19.6)
Normal weight (18.5–24.9)	12 (10.7)	7 (6.25)	19 (16.96)
Overweight (25–29.9)	15 (13.4)	14 (12.5)	29 (25.89)
Obese (≥30)	23 (20.5)	19 (16.9)	42 (37.5)
Total	62 (55.35)	50 (44.64)	112 (100)

No significant association was found between BMI and LBP in logistic regression analysis (OR = 0.968; 95% CI: 2.1–3.6; P = 0.820).

Socioeconomic and Occupational Factors Socioeconomic Status

Participants' socioeconomic status is outlined in Table 3.

Table 3. Socioeconomic Status of Participants

Socioeconomic Status	N (%)
Upper class	35 (31.25)
Upper-middle class	25 (22.32)
Middle class	18 (18.11)
Lower-middle class	20 (17.85)
Lower class	10 (8.92)
Total	112 (100)

A significant association was found between higher socioeconomic status and the prevalence of LBP (OR = 0.986; 95% CI: 0.931–1.124; P = 0.042).

Occupational Characteristics

Occupational distribution is presented in Table 4.

Table 4. Occupational Distribution

Occupation	N (%)
Student	12 (10.71)
Professional	20 (17.85)
Semi-professional	23 (20.53)
Clerical/Shop owner	28 (25.0)
Skilled worker	45 (40.17)
Unskilled worker	32 (28.57)
Unemployed	21 (18.75)

1. **Duration of Sitting:** 55.4% of participants reported sitting for more than 8 hours per day.
2. **Occupational Stress:** 69.64% reported experiencing stress related to their occupation.
3. **External Work Stress:** 64.28% reported stress related to external work factors.
    a. Dietary Habits.
4. **Outside Food Consumption:** 70 participants (62.4%) reported frequent consumption of meals outside the home.

Serum Cytokine Levels

Detection rates and concentration ranges for the measured cytokines are provided in Table 5.

Table 5. Detection Rates and Concentrations of Serum Cytokines

Cytokine	LLOD (pg/mL)	ULOD (pg/mL)	% Detection
IL-1β	0.062	428	8%
IL-2	0.051	1453	52%
IL-4	0.024	188	26%
IL-6	0.073	498	100%
IL-8	0.068	766	98%
IL-10	0.052	332	99%
IL-12p70	0.072	1452	39%
IL-13	0.50	472	45%

1. IL-6, IL-8, and IL-10 were detectable in nearly all samples.
2. Lower detection rates were observed for IL-1β, IL-2, IL-4, IL-12p70, and IL-13.

Association with LDD Severity

Participants were categorized based on their diagnosis:

1. **Degenerative Disc Disease (DDD).**
2. **Spinal Stenosis (SS).**
3. **Disc Herniation (DH).**

Upon controlling for age, gender, and osteoarthritis history, participants with DDD and SS had markedly elevated IL-6 levels relative to those with DH.

Mean IL-6 Levels

a. DDD and SS: 0.74 ± 0.116 pg/mL.
b. DH: 0.47 ± 0.060 pg/mL.
c. **P-value:** <0.02.

Correlation with Clinical Parameters

Positive correlations were observed between IL-6 levels and:

1. **Age:** Older participants had higher IL-6 levels.
2. **BMI:** Higher BMI was associated with increased IL-6 levels.
3. **Duration of Symptoms:** Longer symptom duration correlated with elevated IL-6 level.

Discussion

Elevated IL-6 in LDD

The substantial increase in IL-6 levels among participants with LDD, especially those with DDD and SS, highlights the essential role of IL-6 in the pathophysiology of these conditions. IL-6 functions as a pro-inflammatory cytokine integral to immune responses, inflammation, and bone metabolism [7]. The observed increased levels may signify ongoing inflammatory processes that contribute to disc degeneration and related discomfort. [10] established a link between IL-6 levels and pain intensity in chronic pain patients, corroborating the association reported in our investigation. Elevated IL-6 levels may enhance nociceptive signalling, leading to increased pain perception in individuals with low back pain [5].

Correlation with Age and BMI

The discovery of a positive relationship between IL-6 levels and age fits with research showing that pro-inflammatory cytokines rise with age, which is called "inflammageing" [13]. Age-related degenerative changes in the spine may be exacerbated by chronic inflammation mediated by cytokines like IL-6. Obesity, defined by elevated BMI, is linked to increased production of inflammatory cytokines, as adipose tissue functions as an endocrine organ. [1]. Excess weight and systemic inflammation may accelerate disc degeneration and exacerbate lower back pain due to increased mechanical pressure on the spine [9].

Socioeconomic and Occupational Factors

The significant correlation between increased socioeconomic position and the incidence of LBP may seem contradictory; nevertheless, it can be clarified by the lifestyle variables typically found in higher socioeconomic groups. Occupations marked by prolonged sitting, increased stress, and food habits that lead to obesity are common in these populations [11].

Our study revealed job stress and prolonged sitting as critical risk factors. Prolonged static postures can lead to diminished blood circulation, muscle fatigue, and increased intradiscal pressure, potentially resulting in lower back pain [8].

Dietary Habits

A considerable percentage of individuals reported that they frequently consume food from external sources, which is typically heavy in calories and deficient in key nutrients. Unhealthy eating practices contribute to obesity and systemic inflammation, thus increasing the incidence of low back pain [12].

Gender Distribution

Despite a marginal male predominance in the male-to-female ratio, LBP significantly affects both sexes. Hormonal variations, occupational exposures, and psychological factors can affect the incidence and severity of low back pain among different genders [4, 14].

Clinical Implications

The results indicate that IL-6 may function as a biomarker for evaluating the severity and course of LDD. Targeting IL-6-mediated pathways may provide therapeutic potential. IL-6 inhibitors used in rheumatoid arthritis may be investigated for their potential to regulate inflammation in LDD [2]. Lifestyle adjustments targeting obesity, sedentary behaviour, and stress management are critical elements of low back pain therapy. Workplace interventions aimed at reducing extended sitting and implementing ergonomic improvements can alleviate occupational hazards [8].

Limitations

1. **Sample Size:** The small number of samples may restrict the scope of the results.
2. **Cross-Sectional Design:** Causality cannot be established due to the study's design.
3. **Lack of Control Group:** The lack of a healthy control population devoid of LBP constrains comparison analysis.
4. **Quality of Life Measures:** The impact of LBP on participants' quality of life was not assessed.
5. **Future Directions**
6. **Longitudinal Studies:** To assess changes in cytokine levels over time and their relationship with disease progression.
7. **Interventional Studies:** Exploring the efficacy of anti-inflammatory therapies targeting IL-6 in LDD patients.
8. **Larger Cohort Studies:** With diverse populations to enhance generalizability.

Conclusion

This study demonstrates a substantial correlation between increased blood IL-6 levels and lumbar degenerative disorders, particularly

DDD and SS. IL-6 levels correlate positively with age, BMI, and duration of symptoms, highlighting its role in the pathophysiology of LDD. Socioeconomic factors and occupational habits, such as prolonged sitting and stress, contribute to the prevalence of LBP. These findings underscore the potential of cytokine biomarkers, especially IL-6, in assessing LDD severity and guiding therapeutic interventions. Integrated management strategies addressing inflammatory processes, lifestyle modifications, and ergonomic adjustments are crucial for improving outcomes in LBP patients. Additional extensive, long-term investigations are advised to corroborate these findings and investigate the therapeutic potential of targeting cytokine pathways in LDD.

Conflict of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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