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Original Article

Orthopaedics Section

Association of Interleukin-6 in Degenerative Lumbar Disorder: A Systematic Review

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ABSTRACT

Introduction: Degenerative disorder of lumbar spine, lumbar spondylosis is characterised by disc degeneration and osteophyte formation. Low Back Pain (LBP) is exacerbated by chronic degeneration, which leads to inflammation, elevated cytokine production and activation of inflammatory pathways. Interleukin-6 (IL-6) and other cytokines worsen disc degeneration and discomfort and increased levels of IL-6 is associated with the severity of this condition.

Aim: To find out the association between IL-6 levels and degenerative lumbar disorders and its related conditions.

Materials and Methods: The present systematic review was conducted following PRISMA guidelines and the protocol was registered in PROSPERO (Registration No.: CRD42024479518). An extensive search of four databases i.e., PubMed, Scopus, Web of Science and Embase from October 2023 to May 2024 was carried out. Studies with cohort, case-control, cross-sectional, human research designed were considered for this review. Two independent reviewers extracted the data and evaluated the methodological quality and risk of bias using National Heart Lung and Blood Institute (NHLBI) scale. Disagreement between the two primary investigators during the evaluation process was resolved by a second pair of reviewers through discussion.

Results: Out of total 106 articles, six studies met the inclusion criteria and were included in the qualitative synthesis. No studies were eligible for quantitative meta-analysis due to heterogeneity in study design and outcome reporting. The outcome of included studies consistently showed elevated IL-6 levels in patients with lumbar spondylosis or disc degeneration and related disorders. Increase IL-6 expression was associated with enhanced inflammatory activity and greater severity of clinical symptoms.

Conclusion: The present review suggests a significant strong association between IL-6 and degenerative lumbar disorders, indicating that IL-6 plays a vital role in the pathophysiology of this condition.

Keywords: Degenerative disc disease, Inflammatory cytokines, Lumbar spondylosis, Spinal osteoarthritis

INTRODUCTION

Lumbar Spondylosis is a degenerative joint condition affecting the lumbar spine and intervertebral discs. Spondylosis denotes the presence of osteophyte formation along with degeneration of the lumbar spine and discs, often leading to nerve-related pain [1]. Terminology used to characterise the changes seen in the spine and discs includes lumbar Osteoarthritis (OA), disc degeneration, degenerative disc disease and spondylosis. These changes entail the development of osteophytes, deterioration of the lumbar spine and discs and associated nerve-related symptoms culminating in pain. One of the most common causes of disc degeneration involves multiple signalling pathways [2]. Several studies have demonstrated that elevated levels of cytokines are produced during the course of disc degeneration and the inflammatory reactions triggered by these cytokines worsen the onset and progression of disc degeneration, ultimately leading to back pain [3]. The mechanisms underlying the onset and progression of Intervertebral Disc Degeneration (IDD) are highly complex. Lumbar IDD is strongly associated with metabolic abnormalities within the stroma, cellular senescence and an increased inflammatory response [4-7]. Numerous clinical studies have demonstrated that activation of the immune response promotes inflammation via different pathway [8-12]. The inflammatory response is significantly upregulated by cytokines such as IL-6,which modulate cellular activity via diverse signalling pathways i.e., Janus kinase signal transducer and activator of transcription pathways (JAK-STAT), Ras and phosphoinositide 3 kinase pathways (Ras-MAPK and PI3K), thereby amplifying the pro-inflammatory cascade in IDD [10,12]. In addition, the inflammatory response raises blood levels of pro-degenerative inflammatory cytokines, such as IL-6 and C-Reactive Protein (CRP) [11].

Several molecular biology studies have demonstrated that degenerative intervertebral discs exhibit increased expression of pro inflammatory markers like IL-6, CRP and IL-1β, crucial in disc degeneration as they not only mediate extracellular matrix degeneration and inflammation but also serve as potential biomarkers of disease severity and risk stratification [12-14]. The ability of IL-6, IL1β and IL-10 to affect inflammatory responses and hasten the deterioration of the lumbar intervertebral disc has been validated in later studies [15,16]. IL-6 is an important cytokine involved in inflammation and immune responses [12]. Researchers have examined the relationship between IL-6 levels and advancement of lumbar spondylosis, a degenerative disease of the spine. It is imperative to consult the latest scientific literature for an up-to-date and comprehensive understanding of the association between IL-6 and lumbar spondylosis, as research in this field is ongoing. Determining the relationship between IL-6 levels and the existence or severity of the illness may provide medical professionals with an important prognostic and diagnostic tool. In degenerative lumbar spondylosis, IL-6 is produced by discs cells and in herniated discs with chronic pain. IL-6 with soluble IL-6 receptors (sIL6R) enhances the catabolic effects of IL-1 and Tumour Necrosis Factor (TNF) on nucleus pulposus cells [12]. This reduces the production of proteoglycans (important for disc health) and increases substances like Prostaglandin 2 (PGE2) and Matrix Metalloproteinase 13 (MMP-13) that damage the disc. IL-6 also increases TNF and causes nerve cell death in the Dorsal Root Ganglia (DRG), leading to pain sensitivity (allodynia) and increase pain response (hyperalgesia) [12]. Others studies also confirm that higher IL-6 level is associated with lumbar degeneration and may correlate with disease severity and LBP intensity [15-17].

Investigating the association between IL-6 and lumbar spondylosis aims to clarify the inflammatory pathway involved in the disease, identify reliable diagnostic and prognostic biomarkers, evaluate the severity of pathology and support the development of targeted therapeutic strategies. Such evidence not only helps in clinical decision making and enhance disease management but also contributes to a deeper understanding of lumbar degenerative pathophysiology. Furthermore, by identifying inconsistencies or gaps in the current literature, systematic reviews in this domain can direct future research priorities and highlight areas that require more comprehensive investigation.

MATERIALS AND METHODS

This systematic review was conducted following PRISMA guidelines and the protocol was registered in PROSPERO (Registration No.: CRD42024479518. Information was collected from four online electronic databases. These databases were systematically searched for relevant literature for this study between October 2023 and May 2024 from Embase (http://www.embase.com/info/), Web of Science (http://wok.mimas.ac.uk/), PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Scopus (http://www.scopus.com).

Research question: Research question of this review is given below:

Is there a association between serum IL-6 levels and degenerative lumbar disorders?

Inclusion and Exclusion criteria: The inclusion criteria for this review focused on studies demonstrating a relationship between IL-6 and lumbar spine disorders including lumbar spondylosis, disc degeneration, or herniation. Eligible studies were limited to observational studies, specifically case-control and cross-sectional studies conducted on human subjects with Lumbar Disc Degeneration (LDD) diagnosed based on clinical, pathological or radiological examination to ensure accuracy and consistency. In contrast, studies such as reviews, editorials, conference abstracts, case reports and animal studies were excluded. By applying these criteria, the review aimed to include high-quality observational studies focusing on the relationship between IL-6 and degenerative lumbar spine disorders in human subjects while excluding studies that did not meet these specific criteria or could potentially introduce bias into the analysis. To guide the eligibility criteria and search strategy, PICO framework was applied as follows:

PICO Framework

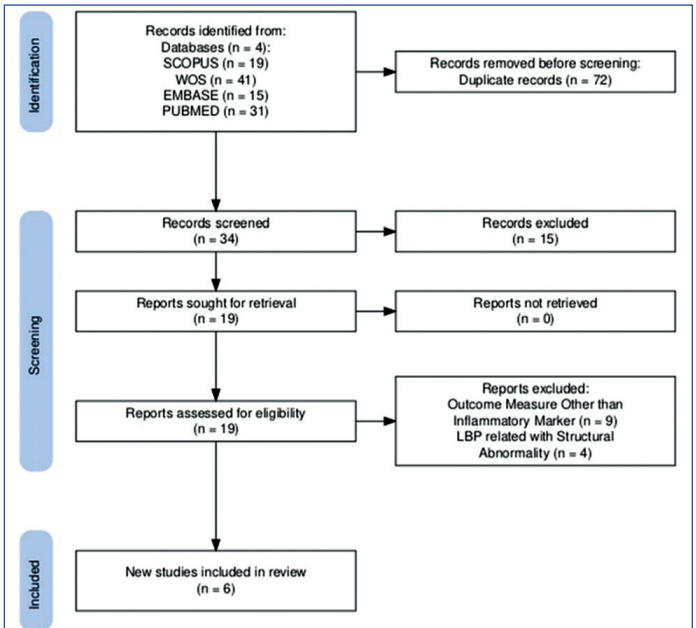
- P-Population: Human subjects diagnosed with lumbar spondylosis, LDD, or lumbar disc herniation, confirmed through clinical, pathological or radiological examination.
- I-Intervention: Measurement or presence of IL-6 levels in relation to lumbar spine disorders.
- C-Comparison: Not mandatory, but may include comparison between affected and unaffected individuals (e.g., case control design).
- O-Outcome: Association or corelation between IL-6 and the presence, severity or progression of lumbar degeneration or lumbar spondylosis.

Literature search strategy: The search strategy used in this study for all databases is presented in [Table/Fig-1]. A mix of free terms and Medical Subject Headings (MeSH) terms was used to extract relevant papers published in the last 15 years. Boolean operators "AND" and "OR" were applied with combination of MeSH terms.

Selection process: The screening process included: 1) pre-screening; 2) screening titles and abstracts; and 3) full-text screening as shown in the [Table/Fig-2]. An initial screening process was implemented by two independent reviewers (1st & 2nd Author) manually scrutinised the bibliographies of relevant articles as per inclusion/exclusion criteria. Any discrepancy was sorted by a third reviewer (3rd Author). After thoroughly reviewing titles and abstracts to eliminate duplicate studies. The remaining articles were subjected to an extensive full-text screening process to guarantee that the final selection consisted of original and pertinent studies that satisfied the predetermined inclusion criteria. This systematic approach was used to enhance the precision and reliability of the selected studies.

Database	Date searched	Search string	Filters applied	Results retrieved
Scopus	22/10/2024	(("Interleukin-6"[Mesh] OR "interleukin-6" OR IL-6 OR "IL 6" OR "interleukin 6")) AND (("Low Back Pain"[Mesh] OR "Spinal Diseases, Degenerative"[Mesh] OR "Intervertebral Disc Degeneration"[Mesh] OR "degenerative lumbar disorder*" OR "lumbar spondylosis" OR "lumbar spine" OR "low back pain" OR "lumbar degenerative disease" OR " LDD" OR "lumbar disc disease" OR "degenerative disc disease")) AND (association OR association OR relationship OR link OR "related to" OR predictor OR biomarker)	None initially (filters: English, Article, Review, Observational, case-control design, human trial, studies published between October 2023-May 2024)	19
Web of Science	30/10/2024			41
Embase	05/11/2024			15
PubMed	10/11/2024			31

[Table/Fig-1]: Search strategy.



[Table/Fig-2]: PRISMA diagram of selection process.

Data Collection Process

The two reviewers (1st & 2nd Author) methodically extracted the eligible article as listed in [Table/Fig-3] in accordance with the predefined criteria. In the event of any discrepancies encountered during the extraction process, the next two authors (3rd & 4th) re-evaluated the articles collaboratively. Following mutual discussion, they reached a consensus to ensure the accuracy and consistency of the extracted information across all the included studies. This meticulous approach aimed to enhance the reliability of the data-extraction process.

Data items: The following data items were extracted and summarised in [Table/Fig-3] i.e., author name, year of publication, title of research, sample size, research nation, subject age, study design, IL-6 levels and results of studies. The main outcome measure related to this review is serum level of IL-6 [18-23].

Author (Year)	Title	Country	Sample Size (n)	Age (Mean±SD)	Study design	IL-6 Levels (Mean±SD)	Remarks
Naponen-Hietala N et al., [18] (2005)	Genetic variations in IL-6 associate with intervertebral disc disease characterised by sciatica.	Finland	334	For case group 44±13 For control group 39±13	Case-control	This study didn't report serum IL-6 level, focusing exclusively on genetic variations rather that circulating IL-6 concentration.	Findings support the role of IL-6 in disc degeneration.
Kraychete DC et al., [19] (2010)	Serum cytokine levels in patients with chronic low back pain due to herniated disc: analytical cross-sectional study	Brazil	33	For chronic LBP group 42.8±7.0 For healthy control group 39.5±4.5	Cross-sectional study	For chronic LBP Group 4.1±3.0 pg/mL For Healthy control Group 0.9±0.4 pg/mL in healthy controls	IL-6 levels highly elevated in chronic Low Back Pain (LBP) patients as compared to healthy controls.
Li Y et al., [20] (2016)	Inflammation in low back pain may be detected from the peripheral blood: suggestions for biomarker.	China	70	For case group 45-70 For control group 45-70	Case-control	This study didn't report IL-6 serum concentrations but assesses IL-6 expression at cellular level by RT-PCR	This study found a significant increase in IL-6 expression in CLBP patients compared to healthy controls.
Huang X et al., [21] (2017)	Interleukin 6 (IL-6) and IL-10 promoter region polymorphisms are associated with risk of lumbar disc herniation in a northern Chinese Han population.	China	567	For case group 44.05±9.02 For control group 41.85±11.02	Case-control	This study focused solely on IL-6 genetic polymorphism and promotor region, did not present any IL-6 level measurements as concentrations.	This study demonstrated that IL-6 is associated with lumbar disc herniation risk.
Zhu Y et al., [22] (2017)	Association between IL4, IL-6 gene polymorphism and lumbar disc degeneration in Chinese population	China	961	For case group 50.27±12.53 For control group 50.65±11.79	Case-control	This study did not report any quantitively IL-6 concentration but focused on SNP genotype associated with Lumbar Disc Degeneration (LDD)	IL-6 levels significantly elevated in LDD.
Pratma DGK et al., [23] (2019)	High IL-6 levels as a marker of lumbar Osteoarthritis (OA) in patients older than 55 years with low back pain	Indonesia	48	For case group Male 67.7±10.4 Female 74.4±10.5 For control group Male 67.7±6.3 Female 64.9±6.1	Case-control	Case group For men-6.17±5.51 pg/mL For women-12.08±4.91 pg/mL Control group For men-5.12±2.78 pg/mL For women-7.43±5.32 pg/mL	Probability of lumbar OA in LBP patients with high IL-6 levels (>6.60 pg/mL) is five times greater than in those with low IL-6 levels (p=0.009), with women facing a 6.9-fold greater risk than men (p=0.03).

[Table/Fig-3]: Study characteristics [18-23].

Methodological Quality Assessment

The methodological quality of the included studies was evaluated using the NHLBI quality assessment tools for case-control and cross-sectional studies as shown in the [Table/Fig-4,5] [24]. These tools provide structured checklists tailored to different study designs, including randomised controlled trials, observational cohort and cross-sectional studies, case-control studies, case series, before-after studies and diagnostic accuracy studies. The tool consists of a series of questions addressing key methodological domains such as research question clarity, study population, comparability of groups, measurement of exposures and outcomes, blinding, confounding control, attrition and appropriateness of statistical analyses. Responses are categorised as "Yes", "No", "Cannot Determine", "Not Reported", or "Not Applicable" and an overall quality rating (Good, Fair, or Poor) is assigned based on the reviewer's judgment of the potential risk of bias. Disagreement between the two primary investigators during the evaluation process was resolved by a second pair of reviewers through mutual discussion until they came to an agreement. Using this procedure, the methodological quality assessment of all included studies was guaranteed to be dependable and consistent.

Risk of Bias Assessment

Based on NHLBI tools total ratings, studies were classified as follows: good (low-risk of bias), fair (moderate-risk of bias) or poor

S. No.	Criteria	Noponen-Hietala N et al., [18]	Li Y et al., [20]	Huang X et al., [21]	Zhu Y et al., [22]	Pratma DGK et al., [23]
1.	Was the research question or objective in this paper clearly stated and appropriate?	Y	Y	Y	Y	Y
2.	Was the study population clearly specified and defined?	Y	CD	Y	Y	Y
3.	Did the authors include a sample size justification?	N	N	N	N	N
4.	Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	Y	Y	Y	Y	Y
5.	Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable and implemented consistently across all study participants?	Y	Y	Y	Y	Y
6.	Were the cases clearly defined and differentiated from controls?	Y	N	Y	Y	Y
7.	If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	CD	N	N	CD	CD
8.	Was there use of concurrent controls?	Y	Y	Y	Y	Y
9.	Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	Y	N	Y	Y	Y
10.	Were the measures of exposure/risk clearly defined, valid, reliable and implemented consistently (including the same time period) across all study participants?	Y	Y	Y	Y	Y
11.	Were the assessors of exposure/risk blinded to the case or control status of participants?	CD	NR	CD	NR	CD

12.	Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	N	Y	Y	N	N
	Overall quality	Fair	Fair	Good	Good	Fair
	Risk of Bias	Moderate	Moderate	Low	Low	Moderate

[Table/Fig-4]: Quality Assessment of included studies according to National Heart Lung and Blood Institute (NHLBI) of case control studies [18,20-23].
{Y: Yes; N: No; NR: Not reported; CD: Cannot determine; NA: Not applicable; Risk of bias rating (Low (75-100%), Moderate (25-75%), or High (0-25%))}

S. No.	Criteria	Kraychete DC et al., [19]
1.	Was the research question or objective in this paper clearly stated?	Y
2.	Was the study population clearly specified and defined?	Y
3.	Was the participation rate of eligible persons at least 50%?	Y
4.	Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y
5.	Was a sample size justification, power description, or variance and effect estimates provided?	Y
6.	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	N
7.	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	N
8.	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	N
9.	Were the exposure measures (independent variables) clearly defined, valid, reliable and implemented consistently across all study participants?	Y
10.	Was the exposure(s) assessed more than once over time?	N
11.	Were the outcome measures (dependent variables) clearly defined, valid, reliable and implemented consistently across all study participants?	Y
12.	Were the outcome assessors blinded to the exposure status of participants?	NR
13.	Was loss to follow-up after baseline 20% or less?	NA
14.	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	N
	Overall quality	**Fair**
	Risk of bias	**Moderate**

[Table/Fig-5]: Quality assessment of included studies according to National Heart Lung and Blood Institute (NHLBI) of cross-sectional studies [19].
{Y: Yes; N: No; NR: Not reported; CD: Cannot determine; NA: Not applicable; Risk of bias rating (Low (75-100%), Moderate (25-75%), or High (0-25%))}

(high-risk of bias) as shown in the [Table/Fig-4,5]. This process ensures reliable and consistent risk of bias classification across all included studies. The Preferred Reporting Items for Systematic Review and Meta-Analyses Guidelines (PRISMA guidelines; http://www.prisma-statement.org/) was followed in the conduct of this systematic review [17]. The protocol of this review was published in PROSPERO (registration number CRD42024479518).

RESULTS

Initially, a total of 106 items were identified. There were 34 researches left after deleting duplicates, review articles, conference papers and case reports. Fifteen publications were eliminated during the title screening process because they addressed conditions other than LBP, did not assess inflammatory biomarkers, were part of genetic studies or placed a strong emphasis on interventions or treatments for LBP. Nineteen studies were included in additional reviews. Nine studies were removed during the abstract screening process because they either didnot quantify inflammatory biomarkers, were primarily concerned with managing LBP rather than researching it, or were unrelated to LBP (e.g., inflammatory back disease, structural back pathology, or cervical spine concerns). Four more studies were eliminated following full-text screening because their primary focus was on particular structural abnormalities linked to LBP as outcome measures, or because their data could not be separated for result synthesis. As a result, six publications i.e., Noponen-Hietala N et al., 2005 [18], Kraychete DC et al., 2010, Li Y et al., 2016, Huang X et al., 2017 and Zhu Y et al., 2017 and Pratama DGK et al., 2019, were included in the final quality synthesis as shown in the [Table/Fig-2] [19-23].

Study Characteristics

The included studies are summarised in [Tables/Fig-3]. Five case-control studies; Noponen-Hietala N et al., Li Y et al., Huang X et al., Zhu Y et al. and Pratama DGK et al. and one cross-sectional research by Kraychete DC et al., were published between 2004 and 2019 [18-23]. Three articles were carried out in China [20-22] and rest were from Finland [18], Brazil [19] and Indonesia [23]. The participants in all trials ranged in age from 39 to 74 years and both men and women were included. To date, no study has demonstrated precise inclusion and exclusion criteria for the selection of instances of lumbar spondylosis linked to IL-6. Because the pathophysiology is characterised by the degeneration of two or more disks and vertebrae, we chose studies of lumbar OA, lumbar intervertebral disc disease, LDD, lumbar disc herniation and presence of persistent LBP. While the included studies examinations of the inflammatory biomarkers differed, every study included a similar biomarker IL-6. Sample size justification was not mentioned in the majority of the research [18-22]. However, one study examined a sample size (n=20) [19]. In five trials, the major confounders of age, sex, weight and height were not considered [18-22]. The majority of studies did not clarify whether the risk assessors were blinded to the participants case or control status or whether the researchers could verify that the risk or exposure occurred before the occurrence of the condition or event that classified a participant as a case.

IL-6 and Findings

Six research assessing the association between IL-6 and lumbar spondylosis, disc degeneration, disc herniation, disk/intervertebral degeneration, degenerative lumbar illness and chronic back pain found a positive relationship. According to a study by Pratma DGK et al., women with high IL-6 levels have a 6.9-times higher probability of developing lumbar degenerative changes than men (p=0.03) and the probability of lumbar degeneration in LBP patients with high IL-6 levels (>6.60 pg/mL) is five times greater than in those without lumbar degeneration (p=0.009) [23]. Another study by Noponen-Hietala N et al., provided evidence that IL-6 plays a role in discogenic pain (p=0.0033) [18]. Disc degeneration is associated with inflammation, discomfort and tissue destruction, all of which are mediated by IL-6. IDD is associated with several pro-inflammatory cytokines, although IL-6 is probably the most important mediator of pain in intervertebral disc disease.

Li Y et al., also discovered comparable outcomes [20]. Although this study doesn't specifically discuss lumbar degenerative condition, it was included since it focuses on IL-6 expression in chronic LBP patients in 45-70 years of age, which is a common symptom of such conditions. Using RT-PCR, this study found a substantial increase in IL-6 concentration in the plasma samples (p<0.05) of chronic LBP patients compared to healthy controls. According to Zhu Y et al., there is a association between IL-6 and the risk of LDD in the Chinese population [22]. One important inflammatory

cytokine that causes inflammation and joint degeneration is IL-6, which is released by activated lymphocytes and macrophages, is an important pro-inflammatory cytokine that causes inflammation and joint degeneration. IL-6 can cause lumbar discomfort by interfering with the structure and function of important macromolecules, which can reduce fibre-ring protection and nucleus protrusion. This is achieved by suppressing the enzymes involved in matrix breakdown within intervertebral discs. Research by Burke J et al., has also demonstrated how the pro-inflammatory properties of IL-6, which is released by ruptured intervertebral disc cells, contribute to this pain [25]. Additionally, Huang X et al., study on IL-6 shows that, in northern Chinese Han group, lumbar disc herniation risk is correlated with genetic variations in the IL-6 promoter areas ($p<0.01$) [21]. In a similar vein, Kraychete DC et al., cross-sectional investigation demonstrated a favourable association ($p=0.01$) between IL-6 levels and persistent LBP caused by disc herniation [19].

DISCUSSION

One of the most frequent problems stated by senior adults seeking medical care is LBP. Up until the age of fifty, its frequency is the same, but after that, it is more common in women. LBP is more common in women between the ages of 40 and 80 years and tends to get worse as they get older [26,27]. The morphology and molecular makeup of intervertebral discs alter significantly with age and this can lead to disorders such as disc degeneration and consequent LBP. The primary component of intervertebral discs in the aged is fibrocartilage, which ages and grows denser and more irregular [28]. This aging-related change is frequently linked to disc degeneration, which is a primary reason why older people experience back discomfort [27]. Moreover, growing older is a known risk factor for degenerative diseases like OA. OA is most common in the older population in the lumbar spine. Even though cytokines and OA have been the subject of much research, most of the studies have concentrated on OA that affects the knees and hips, leaving a significant knowledge vacuum in OA or degenerative condition i.e., spondylosis that especially affects the lumbar spine.

Our systematic review examined the association between the inflammatory biomarker IL-6 and lumbar spondylosis, disc degeneration and OA. Six moderate-quality studies published between 2004 and 2019 were included. Despite variations in study designs and populations, all studies consistently reported a positive association between elevated IL-6 levels in these degenerative conditions.Evidence suggests that IL-6 plays a significant role in the pathogenesis of lumbar spondylosis and its related conditions.

In the study by Pratma DGK et al., results found significant age-related differences only among female patients [23], aligning with Hoy D et al., 2012 study, which showed LBP is most prevalent in women aged 40-80 years [27]. As people age progress, intervertebral discs change, becoming dense and irregular, often leading to back pain. Age is a risk factor for degenerative diseases like lumbar OA. Lumbar OA can be asymptomatic and LBP duration doesn't always reflect its pathophysiology. Higher levels of IL-6 were significantly associated with a greater likelihood of lumbar OA in LBP patients, consistent with studies on knee and hip OA. Elevated IL-6 levels were linked to IDD, joint space narrowing, lumbar instability and OA of the facet joints. Weber KT et al., suggested that circulating pro-inflammatory cytokines play a key role in disc diseases, similar to the process in knee and hip OA [29].

Study by Naponen-Hietala N et al., suggests that IDD is a multifactorial disorder which develops by several factors, including occupational stress, trauma, obesity and genetic alterations in matrix components [18]. These factors can weaken disc structure, potentially causing herniation and leading to sciatica and pathological disc changes. Inflammation is also important in IDD progression. Pro-inflammatory cytokines like IL-6, IL-1α, IL-1β and TNF-α are synthesised by various cells, including activated macrophages, fibroblasts and chondrocytes and are released due to cell or tissue injury. IL-6 is produced at the site of lumbar disc herniation and increased production of these cytokines leads herniated discs to produce MMPs, nitric oxide and prostaglandin E2, which mediate pain or enhance sensitivity to pain. Research shows that genetic variations in IL-6 are associated with IDD-related radiculopathy [18]. IDD and associated sciatica are characterised by tissue destruction, inflammation and pain, which are related to IL-6 functions. While IL-6 is not the only pro-inflammatory cytokine in IDD pathogenesis, it likely plays a significant role in pain mediation in IDD.

Subjects with chronic LBP experienced pain for at least one year without any other disease evidence. To investigate the molecular basis of elevated IL-6 and decreased IL-10 levels, study by Li Y et al., conducted an in vitro analysis by culturing monocytes and converting them into M1 pro-inflammatory or M2 anti-inflammatory macrophages using specific growth factor conditions [20]. This study found that M2 macrophages had a significantly reduced capacity to secrete the opioid peptide β-endorphin. Additionally, mRNA expression of β-endorphin was significantly decreased in subjects with LBP, suggesting a transcriptional blockade affecting the release of endogenous peptides alongside an increase in pro-inflammatory monocytes. Due to the challenges of obtaining Dorsal Root Ganglion (DRG) biopsies, the study focused on the peripheral blood to demonstrate the imbalance between pro-and anti-inflammatory environments in blood cells and differentiated macrophages. The findings suggest potential peripheral markers for LBP, including: (i) Assessing CD14 and CD16 monocytes; (ii) Evaluating the IL-10 and IL-6 balance; (iii) Peripheral differentiation of M1/M2 macrophages and transcriptional regulators; and (iv) Endogenous opioid peptide release [20]. These markers could serve as reliable indicators of LBP.

IL-6 is a 184 amino acid glycoprotein and a key pro-inflammatory cytokine produced by activated inflammatory cells such as lymphocytes and macrophages. It plays a crucial role in rheumatoid arthritis and OA, acting as a mediator of joint destruction and inflammation. IL-6 may inhibit enzymes that degrade the intervertebral disc matrix, affecting the structure and function of proteoglycans, collagen and elastin. This weakening of the disc's protective fiber-ring can lead to nucleus protrusion [22]. A similar research by Burke J et al., showed that herniated intervertebral disc cells secrete pro-inflammatory mediators, including IL-6, which are associated with lumbar pain [25]. This study highlights the importance of considering both mechanical compression and inflammatory cytokine stimulation in treating lumbar disc herniation. It suggests that treatment plans should integrate surgery with postoperative strategies to inhibit inflammatory cytokine secretion and consider long-term follow-ups to monitor serum levels of IL-4 and IL-6.

In study by Huang X et al., investigated the association of IL-6 and IL-10 genetic variants with the risk of developing lumbar disc herniation in a North China Han population [21]. The results showed that the IL-6 GG genotype and G allele were more frequent in the case group than in the control group, while the CC genotype was less frequent in the case group. Individuals with the IL-6 GG/GC genotype had a 1.69 times higher risk of developing lumbar disc herniation compared to those with the CC genotype. The CG/GG genotype had 1.55 and 4.48 times higher risks, respectively, compared to the CC genotype. Additionally, the IL-10-1082 AG genotype was significantly more common in the case group, whereas the AA genotype was less common. The relative risk for individuals with the IL-10-1082 GG/GA genotype was 2.69 times higher than for those with the AA genotype for developing lumbar disc herniation.

Individuals with herniated lumbar intervertebral disc disease have higher serum levels of TNF-alpha and IL-6 compared to healthy individuals. This condition causes nerve root impingement, leading to overexpression of cytokines and a network of biochemical reactions that modify transcription factors, expand nearby glial cells and cause neuronal hyperexcitability. The increased concentrations of cytokines in herniated disc tissue suggest they may contribute to endoneural edema and nerve fiber demyelination. Cytokines also excite nociceptors, indicating their role in peripheral hyperalgesia and pain behavior, suggesting that these molecules are involved in systemic inflammatory reactions. While elevated IL-6 levels have been observed in individuals with sciatic pain following discectomy, they have not been found in those with disc herniation and sciatica. Pro-inflammatory cytokines exhibit circadian rhythms and variations, influenced by factors such as blood sample timing, stress responses, cytokine release sequences, receptor internalisation and stimulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis. A dysfunctional HPA axis may lead to elevated serum cytokine levels. Research indicates that different types of disc herniation have distinct inflammatory properties. Recent findings show that intervertebral disc cells can produce TNF-alpha and IL-1 beta shortly after disc herniation onset [19]. Increasing serum levels of pro-inflammatory cytokines correlate with rising pain intensity in chronic pain patients. High cytokine levels are associated with inflammatory and infectious diseases and correlate with disease severity [30].

IL-6 is a key pro-inflammatory cytokine involved in the inflammatory cascade, contributing to tissue destruction and pain. The studies reviewed highlighted IL-6's ability to inhibit enzymes involved in matrix degradation within intervertebral discs, leading to structural and functional disruption and resulting in pain. Studies have been conducted in diverse geographical locations, including China, Brazil, Finland and Indonesia, indicating that the association between IL-6 and lumbar degenerative conditions is not limited to a specific population. However, variability in genetic backgrounds, lifestyle factors and environmental exposures might influence the observed associations and warrant further investigation.

While the current evidence suggests a role for IL-6 in the pathogenesis of lumbar spondylosis and related conditions, high-quality longitudinal studies are needed to confirm these findings and evaluate the magnitude of these associations. Future research should include well-defined inclusion and exclusion criteria, adequate sample size justification and adjustment for potential confounders. Additionally, exploring the mechanistic pathways by which IL-6 influences disc degeneration and pain could provide insights into targeted therapeutic interventions.

Limitation(s)

This study had several limitations like most of the studies didn't included sample size justification. Also, majority of the study have not mentioned about confounders, such as age, sex, weight, and height, and there correlation. The lack of blinding of assessors and uncertainty regarding the timing of IL-6 elevation relative to disease onset also pose challenges in the interpretation of the findings.

CONCLUSION(S)

The findings of the present systematic review support the notion that elevated IL-6 levels are associated with lumbar spondylosis, disc degeneration and OA. This highlights the potential of IL-6 as a biomarker for these conditions and suggests that targeting IL-6 could be a promising strategy for managing inflammatory processes in degenerative spinal diseases. However, further research is essential to validate these associations and to develop effective IL-6-targeted therapies.

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