Original Article

Inflammatory and Analgesic Profiles in Intervertebral Disc Herniation: Variability with Respect to Neurological Deficit

B Morkoç, O Aktan[1], HS Solak[1], E Bodur[1], J Karakaya[2], B Kaymak, S Bilgin[3]

Departments of Physical Medicine and Rehabilitation, [1]Medical Biochemistry, [2]Biostatistics, [3]Neurological Physiotherapy and Rehabilitation, Faculty of Physical Therapy and Rehabilitation, Hacettepe University, Ankara, Turkey

Abstract

Background: Disc herniation is both a mechanical and biochemical process in which contact between intervertebral discs and spinal nerves causes compression, chemical irritation, inflammation, and pain. The inflammatory process is known to vary depending on pain duration, herniation type, and pain severity, but the relationship with neurological deficits remains unknown. **Aim:** This study aimed to compare individuals with lumbar disc herniation with and without neurological deficits (WND/WOND) and healthy individuals in terms of serum levels of tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), interleukin 4 (IL-4), interleukin 1 beta (IL-1β), beta-endorphin, anandamide, and 2-arachidonoylglycerol (2-AG). **Methods:** The study included 37 lumbar disc herniation patients WND (22 female, 15 male), 37 patients WOND (22 female, 15 male), and 35 healthy individuals (18 female, 17 male). TNF-α, IL-6, IL-4, IL-1β, beta-endorphin, anandamide, and 2-AG serum levels were analyzed using commercial enzyme-linked immunosorbent assay kits. **Results:** There was no difference in TNF-α levels between the WOND, WND, and control groups ($P = 0.383$). The WOND and WND groups showed significantly higher expression of IL-1β ($P < 0.001$) and IL-4 ($P = 0.034$, $P < 0.001$) when compared with healthy controls. IL-6 expression was lower in the WND group than in the control group ($P < 0.001$). Beta-endorphin, anandamide, and 2-AG levels did not differ significantly between the WOND, WND, and control groups ($P = 0.888$, $P = 0.247$, $P = 0.433$, respectively). **Conclusion:** This study is the first to demonstrate the effect of the presence of a neurological deficit on serum biomarker levels in patients with lumbar disc herniation. Even in the presence of neurological deficit, decreased levels of proinflammatory cytokines and increased levels of anti-inflammatory cytokines indicated regression of the disc herniation. These results suggest the need to establish new and improved treatment protocols to target the inflammatory process in individuals with lumbar disc herniation.

Keywords: *Beta-endorphin, cytokines, endocannabinoids, inflammation, intervertebral disc herniation, low back pain*

Received: 28-Nov-2024;
Revision: 31-Dec-2024;
Accepted: 03-Mar-2025;
Published: 11-Apr-2025

Introduction

Low back pain is the leading cause of morbidity and disability worldwide,[1] and lumbar disc herniation (LDH) is the most common cause.[2,3] Neurological deficits associated with LDH are an important sequela and can lead to long-term disability. Neurodeficits in LDH can range from simple loss of sensation involving a single dermatome to a potentially debilitating condition such as drop foot. The presence of a neurological deficit in LDH is usually considered an indication for surgery.[4] However, the ideal timing of surgery remains

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Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_814_24

Address for correspondence: Dr. B Morkoç, Department of Physical Medicine and Rehabilitation, Hacettepe University, Ankara-06230, Turkey.
E-mail: birgul.morkoc@hacettepe.edu.tr

How to cite this article: Morkoç B, Aktan O, Solak HS, Bodur E, Karakaya J, Kaymak B, *et al.* Inflammatory and analgesic profiles in intervertebral disc herniation: Variability with respect to neurological deficit. Niger J Clin Pract 2025;28:393-400.

uncertain.[5] Studies have shown that lumbar disc herniation can be reabsorbed and symptomatic healing can occur with conservative treatment methods alone.[6] It was reported that in cases with neurological deficit, clinical recovery can occur without any morphological changes or symptomatic recovery may precede radiological changes. This finding was attributed to a gradual decrease in the pressure exerted by the herniated disc on adjacent neural structures and a progressive reduction of the inflammatory reaction.[7]

In the pathogenesis of disc herniation, in addition to mechanical factors, biochemical factors play an important role. It is not clear whether inflammation in the intervertebral disc is a cause or consequence of disc degeneration and herniation, or what may trigger the activation of different immune cells. Extracellular matrix fragments and microcrystals may elicit an internal inflammatory response, and endogenous intervertebral disc cells may produce proinflammatory mediators such as interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis factor alpha (TNF-α). The nucleus pulposus is perceived as foreign by the immune system, resulting in the induction of an immune response by macrophages, lymphocytes, and other possible inflammatory cells to destroy this foreign body.[8]

Endogenous opioids have analgesic effects in various chronic pain syndromes.[9] Beta-endorphin is a ligand of endogenous opioid receptors and acts on the descending inhibitory system, which modulates pain at the spinal cord level.[10] It has been suggested that beta-endorphin might be used as a biomarker of pain intensity in patients with chronic low back pain,[11] but its role in the pathophysiology of LDH is unclear. Anandamide and 2-arachidonoylglycerol (2-AG) are the main endocannabinoids produced from cell membrane lipid precursors.[12] Anandamide modulates inflammation by suppressing the production of proinflammatory cytokines,[13] while 2-AG is involved in downregulating macrophage activation to terminate the inflammatory response.[14] Although the effects of endocannabinoids on different systems are known, we found no study on how these effects occur in individuals with LDH.

Previous reports have focused on variations in the inflammatory processes according to pain and herniation characteristics in individuals with low back pain due to LDH. However, the presence of neurological deficits has not been investigated as a factor in the inflammatory process. In addition, the role of beta-endorphin, anandamide, and 2-AG in the pathophysiology of LDH is unclear. The present study aimed to fill these gaps in the literature by comparing the serum levels of proinflammatory cytokines (TNF-α, IL-6, and IL-1β), anti-inflammatory cytokine (IL-4), endogenous analgesic biomarker (beta-endorphin), and endocannabinoids (anandamide and 2-AG) in individuals with LDH with and without neurological deficits.

Materials and Methods

Study design

The study was conducted between February 2022 and February 2024 with 37 LDH patients with neurological deficits (WND group), 37 LDH patients without neurological deficits (WOND group), and 35 healthy individuals of similar age, height, and weight (control group). This study was performed in line with the principles of the Declaration of Helsinki. Permission to conduct the study was obtained from the Hacettepe University Clinical Research Ethics Committee (date 21/09/2021, no. 2021/23-9). Informed consent form was obtained from all participants included in the study.

Participants

Individuals aged 20–55 years who presented to the Department of Physical Medicine and Rehabilitation of Hacettepe University Hospitals with low back pain, were diagnosed with LDH by MRI, and had pain severity ≥3 on the visual analog scale (VAS) were included in the study. If patients had a positive straight leg raising test, loss of sensation, reflex abnormality, and/or motor weakness, they were included in the WND group. Those without any of these findings were included in the WOND group. The healthy control group included individuals aged 20–55 years who had no history of low back pain.

Exclusion criteria for both controls and patients were as follows: history of LDH surgery, fracture of the lumbar vertebrae, presence of lumbar scoliosis, tumor, or systemic, inflammatory, allergic, neurological, or psychiatric disease, alcohol or drug use, generalized musculoskeletal pain, pregnancy, and breastfeeding.

Clinical assessment

The participants' demographic data [age, gender, height, weight, body mass index (BMI), occupation, smoking status], disease-related information (level and type of herniation), and other clinical information (pain duration, disability, emotional state, medication use) were recorded. Occupations were classified in terms of heavy work (lifting or carrying heavy objects, forward bending), medium work (housework), and light work (sitting and constant posture).[15]

For patients with LDH, the VAS was used to assess pain at rest and during activity,[16] disability was assessed using the Oswestry Disability Index (ODI),[17] and

emotional state was evaluated with the Beck Depression Inventory (BDI)[18] and Beck Anxiety Inventory (BAI).[19]

Biochemical analysis

Serum pro- and anti-inflammatory cytokine (TNF-α, IL-6, IL-1β, IL-4) and endocannabinoid (anandamide and 2-AG) levels were measured for the inflammatory profile, and beta-endorphin levels were measured for the analgesic profile in all participants. Venous blood samples were collected into two 5 mL biochemistry tubes. The tubes were then centrifuged at 3000 rpm for 10 minutes. The serum was stored at −30°C until analysis using ELISA (enzyme-linked immunosorbent assay) kits (Reed Biotech).

Statistical analysis

Age and BMI were compared between the three study groups using analysis of variance (ANOVA). Categorical variables were compared using Chi-square test. TNF-α, IL-1β, IL6, IL-4, beta-endorphin, 2-AG, and anandamide values were compared between the three groups using Kruskal–Wallis test, followed by *post hoc* Dunn's multiple comparisons test. Mann–Whitney U test was used to compare numerical variables only between the WOND and WND groups. Correlations between numerical values were evaluated using Spearman's rho correlation coefficient. As descriptive statistics, mean and standard deviation (SD) values were given for the variables used in parametric tests, while median and range were given for nonparametric tests.

Results

A total of 79 individuals with LDH and 35 healthy controls (18 female, 17 male) were included in the study. Of the individuals with LDH, two were excluded from the study because they declined to participate and three did not meet the inclusion criteria. The remaining 74 LDH patients were divided into the WND (22 female, 15 male) and WOND (22 female, 15 male) groups based on the presence or absence of neurological deficit [Figure 1].

The demographic and clinical characteristics of the participants are shown in Tables 1 and 2.

There was no difference between the three groups in terms of age, gender, BMI, and occupation ($P > 0.05$). The number of smokers was similar in the WOND and WND groups ($P > 0.05$). None of the patients in the WOND or WND groups used medication since being diagnosed with LDH. Pain duration, pain severity during activity, disability, emotional state, and herniation levels were similar in the WOND and WND groups ($P > 0.05$). Pain severity at rest was higher in the WND group ($P < 0.05$). Patients in both the WOND and WND groups had severe restriction in activities of daily living due to low back pain (severe disability) but reported low levels of depression and anxiety. Descriptive data regarding neurological deficits of the WND group are shown in Table 3.

The mean biomarker levels of the groups are shown in Table 4. TNF-α levels did not differ between the WOND,

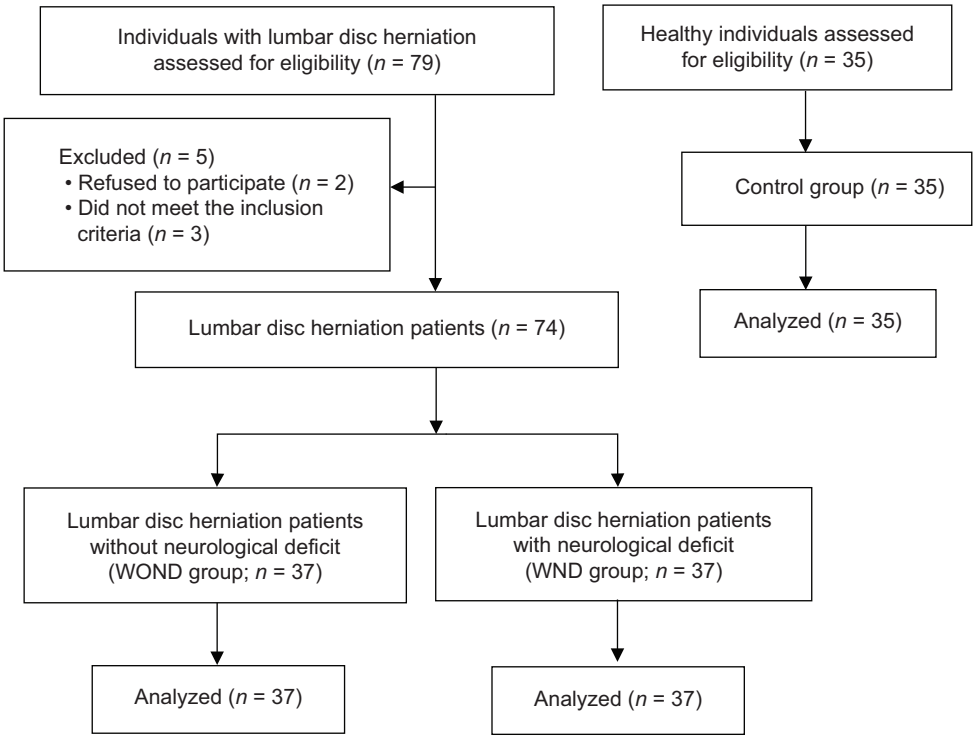

Figure 1: Flow diagram of the study

Table 1: Demographic characteristics of the study participants

	WOND group (*n*=37)	WND group (*n*=37)	Control group (*n*=35)	*P*
Age (years)	42.84 (9.56)	42.22 (8.28)	38.31 (9.49)	0.081
Gender, *n* (%)				
Male	15 (40.5)	15 (40.5)	17 (48.6)	0.732
Female	22 (59.5)	22 (59.5)	18 (51.4)	
BMI (kg/m^2)				
Normal	15 (40.5)	16 (43.2)	20 (57.1)	0.450
Overweight	18 (48.6)	14 (37.8)	11 (31.4)	
Obese	4 (10.8)	7 (18.9)	4 (11.4)	
Occupation, *n* (%)				
Light work	3 (8.1)	2 (5.4)	5 (14.3)	0.053
Medium work	23 (62.2)	18 (48.6)	10 (28.6)	
Heavy work	11 (29.7)	17 (45.9)	20 (57.1)	
Smoker, *n* (%)				
Yes	20 (54.1)	19 (51.4)	9 (25.7)	**0.029**
No	17 (45.9)	18 (48.6)	26 (74.3)	

Values in bold type were significant. WOND: Lumbar disc herniation patients without neurological deficit, WND: Lumbar disc herniation patients with neurological deficit, BMI: Body mass index. Values are presented as number (percentage) or mean (standard deviation)

Table 2: Clinical characteristics of the study participants

	WOND group	WND group	*P*
Pain duration, *n* (%)			
3–6 months	10 (27.0)	13 (35.1)	0.236
6–12 months	6 (16.2)	8 (21.6)	
12–18 months	4 (10.8)	0 (0.0)	
18–24 months	17 (45.9)	16 (43.2)	
VAS at rest	5.16 (2.48)	6.70 (2.54)	**0.004**
VAS during activity	7.92 (1.52)	8.51 (1.63)	0.063
Disability (ODI)	41.08 (12.05)	45.94 (13.90)	0.093
Emotional state			
BDI	14.08 (8.28)	11.86 (5.83)	0.344
BAI	12.03 (9.95)	7.42 (4.01)	0.092
Level of herniation, *n* (%)			
L1–L2	0 (0.0)	1 (2.7)	0.757
L2–L3	2 (5.4)	2 (5.4)	
L3–L4	2 (5.4)	2 (5.4)	
L4–L5	14 (37.8)	10 (27.0)	
L5–S1	19 (51.4)	22 (59.5)	
Herniation type, *n* (%)			
Protruded	34 (91.9)	24 (64.9)	**0.011**
Extruded	3 (8.1)	11 (29.7)	
Sequestered	0 (0.0)	2 (5.4)	

Values in bold type were significant. WOND: Lumbar disc herniation patients without neurological deficit, WND: Lumbar disc herniation patients with neurological deficit, VAS: Visual Analog Scale, ODI: Oswestry Disability Index, BDI: Beck Depression İnventory, BAI: Beck Anxiety Inventory. Values are presented as number (percentage) or mean (standard deviation)

WND, and control groups ($P = 0.383$). IL-1β expression was higher in the WOND and WND groups than in healthy controls ($P < 0.001$). However, IL-1β levels were similar in the WOND and WND groups ($P > 0.05$). IL-6 expression was lower in the WND group when compared with the control group ($P < 0.001$). There was no statistically significant difference in IL-6 between the WOND and control groups ($P = 0.388$) or between the WOND and WND groups ($P = 0.066$). IL-4 expression was higher in the WOND and WND groups than in the control group ($P = 0.034$ and $P < 0.001$, respectively) but did not differ significantly between patients in the WOND and WND groups ($P = 0.078$). There were no differences between the three groups in terms of beta-endorphin, anandamide, and 2-AG ($P = 0.888$, $P = 0.247$, $P = 0.433$, respectively).

Discussion

This study is the first to investigate inflammatory cytokines, beta-endorphin, anandamide, and 2-AG levels in individuals with LDH with and without neurological deficits and to compare these results with healthy controls. This is also the first study to analyze anandamide and 2-AG levels in patients with spinal disease. The results of the study suggest that neurological deficits are independent of the inflammatory and analgesic profiles. TNF-α levels in both LDH patient groups were similar to those of the healthy control group. However, IL-1β and IL-4 expression levels were higher and IL-6 levels were lower compared to controls. Beta-endorphin, anandamide, and 2-AG levels were also similar in patients and controls.

IL-6 is a proinflammatory cytokine that stimulates acute phase protein release and cell growth and proliferation

in response to injury.[20,21] ″TNF-α is a cytokine that can stimulate the inflammatory responses of synapses and the myelin sheath, promote cellular apoptosis via its cytotoxic effect, and induce nerve swelling and neuropathic pain″.[22] Altun[23] found that IL-1β, IL-6, and TNF-α levels were higher in individuals with intervertebral disc degeneration within the first 6 months of symptom onset compared to measurements made after 6 months. Yang *et al*.[24] found that the IL-1, IL-18, TNF-α, and IL-6 levels of individuals with lumbar intervertebral disc prolapse showed a declining trend in repeated measures performed on days 3, 7, 14, and 21.[24] Yoshida *et al*.[25] showed that TNF-α and IL-1β peaked on the first day after herniation and all cytokines reached very low levels by the fourth week. In our study, TNF-α expression did not differ between LDH patients with and without neurological deficits and was similar to that of healthy controls. While IL-6 expression was similar in patients without neurological deficits and healthy individuals, it was lower in patients with neurological deficits than in controls. The patients in our study underwent a process that started with noticing their symptoms and choosing to contact a physician and ended with the examination and diagnosis confirmation. Considering the length of this period, the proinflammatory cytokine levels of the LDH patients in the study may have started to decline as the healing process started, consistent with the literature. The lower IL-6 expression in patients with neurological deficits can also be explained by the higher levels of anandamide in this group. Anandamide is known to cause immunosuppression by reducing the expression of proinflammatory cytokines.[13,26] In our study, anandamide levels were higher in the patient group without neurological deficits compared to those with deficits and the healthy controls. Higher anandamide levels in the patients with neurological deficits may have further reduced their IL-6 levels.

IL-1β is a key mediator of the inflammatory response and an important member of the IL-1 family. It has a strong proinflammatory activity, inducing various proinflammatory mediators such as cytokines and chemokines.[27,28] Le Maitre *et al*.[29,30] reported that IL-1β and TNF-α levels were higher in people with degenerated and herniated discs compared to healthy individuals. They also noted that IL-1β release was greater than TNF-α release and concluded that IL-1β may be more dominant in intervertebral disc degeneration processes. Dadkhah *et al*.[31] also showed that IL-1β levels were higher in patients with chronic low back pain than in healthy individuals. They concluded that low back pain and pain severity were associated with high IL-1β levels. In the present study, serum IL-1β levels were increased in LDH patients with and without neurological deficits. IL-1 cytokines are involved in both acute and chronic inflammation. Increased concentrations of proinflammatory cytokines in herniated disc tissue have been shown to cause endoneural edema and nerve fiber demyelination.[24,32,33] The TNF-α and IL-6 levels observed in our study point to regression of disc herniation, but high IL-1β levels may indicate continuing chronic inflammation in the nerve. This result suggests that IL-1β inhibition could be a promising strategy for alleviating pain.

Increased production of the anti-inflammatory cytokine IL-4 ″upregulates opioid receptors[34] and may correspond to a natural analgesic system that modulates the activity and sensitivity of the endogenous opioid system. IL-4 markedly inhibits the expression and release of proinflammatory cytokines″. IL-4 can also

Table 3: Types of neurological deficits in lumbar disc herniation patients with neurological deficits

Type of neurological deficit	*n*
Sensory	10
Motor	22
Reflex	4
SLR	27

n=number of the patients, SLR=straight leg raising test

Table 4: Serum biomarker levels in lumbar disc herniation patients with and without neurological deficits and healthy controls

	WOND group (*n*=37)	WND group (*n*=37)	Control group (*n*=35)	*P*
TNF-α	4.89 (2.44–17.01)	5.05 (2.61–10.00)	4.94 (4.00–11.35)	0.383
IL-1β	2.22 (0.47–24.67)[a]	2.67 (0.48–21.17)[b]	0.57 (0.46–2.66)	**<0.001***
IL-6	0.64 (0.26–1.87)	0.51 (0.18–1.21)[b]	0.68 (0.22–1.68)	**<0.001***
IL-4	11.37 (3.70–25.86)[a]	13.63 (5.83–31.83)[b]	7.93 (4.72–21.04)	**<0.001***
BE	991.27 (168.24–2431.74)	990.67 (52.39–4878.72)	1003.73 (673.20–1338.41)	0.888
EAE	203.20 (47.41–1518.88)	204.60 (25.98–1645.95)	202.64 (69.82–205.25)	0.247
2-AG	87.35 (10.63–426.23)	100.51 (27.32–479.11)	113.64 (26.20–305.67)	0.433

Values in bold type were significant. TNF-α=Tumor necrosis factor alpha, IL-1β=Interleukin 1 beta, IL-6=Interleukin 6, IL-4=Interleukin 4, BE=Beta-endorphin, EAE=Anandamide, 2-AG=2-Arachidonoylglycerol. Values are presented as median (min-max). [a]Significant difference (P<0.05)between WOND and control groups, [b]Significant difference (P<0.05)between WND and control groups

block or suppress monocyte-derived cytokines such as TNF-α, IL-1, IL-6, and IL-8.[35] Zu *et al*.[36] showed that IL-4 levels were elevated in individuals with radicular pain due to LDH in measurements made at 1 month and decreased gradually over 12 months of follow-up. In our study, IL-4 expression was increased in the patient groups with and without neurological deficits. These findings support our conclusion that the anti-inflammatory process may have started. However, we can also conclude that the presence of a neurological deficit has no effect on serum IL-4 levels.

Beta-endorphin is one of the biomarkers that modulate the ascending and descending pain pathways.[37,38] Previous studies have suggested that low resting plasma beta-endorphin concentration may be a potential biomarker for patients with chronic pain and that increased levels correlate with a decrease in maximum pain intensity.[39,40] Most types of exercise increase circulating beta-endorphin levels, especially when exercise intensity reaches the anaerobic threshold and causes elevated serum lactate levels.[41] Although beta-endorphin levels did not differ between the groups in our study, we noted that they were lower among patients with LDH compared to healthy controls. This may be related to the intensity of pain associated with LDH. Moreover, we concluded that the presence of neurological deficits had no effect on beta-endorphin levels. Anandamide and 2-AG are lipid mediators of the endocannabinoid system and are characterized as activators of the cannabinoid receptors (CB1 and CB2).[42] The CB1 and CB2 receptors are important modulators of the immune system and induce immunosuppression.[43] Anandamide is known to suppress the production of proinflammatory cytokines such as IL-6.[13,22] In our study, we found no significant difference in anandamide levels between LDH patients with and without neurological deficits and healthy controls. This suggests that anandamide levels may have started to decrease again after suppressing proinflammatory cytokine expression. Although 2-AG levels did not differ statistically between the groups, they tended to be higher in healthy controls than in patients with LDH. This suggests that 2-AG levels may also have decreased following immunosuppression. Low levels of both anandamide and 2-AG may suggest LDH regression, consistent with our findings of low proinflammatory cytokine and high anti-inflammatory cytokine levels.

In their study comparing individuals with LDH and healthy controls, Yang *et al*.[44] showed that proinflammatory cytokine levels were the lowest in the healthy control group and increased incrementally in patients with bulging, protruded, and sequestered discs, respectively. Nygaard *et al*.[45] grouped LDH patients as those with bulging, contained, and noncontained disc herniation and found that different types of disc herniation exhibited different inflammatory properties. In the literature, sequestered and extruded discs have been associated with higher inflammatory cytokine levels.[45,46] Although in our study there was a difference in herniation types between patients with and without neurological deficits, we observed that the presence of neurological deficit had no effect on levels of pro- and anti-inflammatory cytokines, beta-endorphin, anandamide, or 2-AG.

Inflammation has been shown to be the main factor responsible for the regression of LDH. This finding reveals that inflammation is a good prognostic indicator for spontaneous regression of LDH.[47] Shamji *et al*.[48] showed that the expression levels of cytokines such as IL-4, IL-6, IL-12, and interferon gamma were high during LDH regression. In our study, the fact that proinflammatory cytokine levels in LDH patients with and without neurological deficits were similar to or lower than those of healthy controls, while levels of anti-inflammatory cytokines were higher, which may indicate regression of disc herniation. Inflammatory mediators should be considered in the evaluation and treatment of LDH. Nonsteroidal anti-inflammatory drugs and intraspinal steroids are widely used today and control pain by suppressing local inflammation, but their long-term use may prevent reabsorption of disc herniation.[49] We think that the results of this study may be useful in establishing new anti-inflammatory therapy protocols, shedding light on how measuring proinflammatory cytokine levels can guide specific medical treatment and physiotherapy programs for patients with low back pain. Current clinical treatments focus primarily on alleviating or controlling patients' symptoms but fail to retard or reverse disc defects. As a result, the condition recurs after treatment and becomes chronic. Understanding the role of inflammatory mediators, beta-endorphins, and endocannabinoids will provide more insight in regard to monitoring and improving the treatment of intervertebral discs.

This study has some limitations. First, there were no internationally accepted standard reference values for serum levels of the investigated biomarkers. Therefore, it is difficult to make sound comparisons between studies. Second, the pain duration of the LDH patients in our study was too long to demonstrate high proinflammatory cytokine levels. The literature data show that proinflammatory cytokine levels are higher closer to the onset of symptoms and lower with longer duration.

Third, the type and number of neurological deficits were not taken into account when analyzing biomarker levels. However, this study contributes valuable information to the literature regarding the immune-mediated changes that occur in patients with LDH.

Conclusion

The results of this study point to several conclusions. First, the presence of neurological deficits appears to have no significant effect on biomarker levels in individuals with LDH. In addition, the decrease in proinflammatory factors and the increase in anti-inflammatory factors in association with pain duration may be an indicator of disc herniation regression, but severe pain has an effect on other proinflammatory factors in the chronic process, and inhibition of these inflammatory agents may be beneficial in treatment. It has been shown that beta-endorphin levels are low in the presence of pain and that anandamide and 2-AG are involved in the neuroimmune process in LDH patients with and without neurological deficits.

According to the literature, suppression of proinflammatory cytokines with anti-inflammatory drug therapy is a treatment option for individuals with LDH. In our study, even in patients with a neurological deficit, it was observed that proinflammatory cytokines decreased and anti-inflammatory cytokine levels increased over time, and disc herniation started to regress without treatment. This result may suggest the need to reevaluate treatment options for individuals with LDH, even in the presence of neurological deficit. Future studies including patients with a shorter time from symptom onset and larger numbers of individuals with LDH evaluated at specific intervals would allow a more detailed investigation of the pro- and anti-inflammatory processes.

Acknowledgement

We would like to thank Jacqueline Renee Gutenkunst for English language editing.

Key Messages

The presence of neurological deficits may have a significant impact on inflammatory processes. It is thought that the balance between pro-and anti-inflammatory biomarkers may provide information about the progression and regression of the disease. Determining treatment approaches based on these biomarkers may improve patient outcomes.

Financial support and sponsorship

This study was supported by Hacettepe University Scientific Research Projects Coordination Unit (THD-2022-19859).

Conflicts of interest

There are no conflicts of interest.

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