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General

Prevalence, clinical predictors, and mechanisms of resorption in lumbar disc herniation: a systematic review

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Study design

Systematic review

Background

Conservative treatment is clinically preferred for lumbar disc herniation (LDH), and surgery is considered when patients' life quality is still affected by LDH symptoms after three months' conservative treatment. Spontaneous resorption of nucleus pulposus (NP) is common during conservative treatment. However, the current understanding for the mechanism of NP spontaneous resorption is lacking.

Purpose

The aim of this study was to elucidate the rate of NP spontaneous resorption, the evidence of predicting spontaneous resorption, and the pathophysiologic mechanisms of spontaneous resorption in the conservative management of LDH based on existing evidence from literature.

Methods

Studies related to NP spontaneous resorption of LDH were retried from PubMed, Embase, and Cochrane databases. Based on the studies conforming to inclusion criteria, a systematic review was generated for describing the proportion of NP spontaneous resorption, evidence of predicted resorption, and pathophysiologic mechanisms of spontaneous resorption.

Results

We reviewed a total of 34 articles dealing with the percentage of LDH resorption. The percentage of NP spontaneous resorption after conservative treatment was 76.6% (1684/2199), ranging from 20% to 96.2%. A total of 25 papers were reviewed, involving evidence of predicting resorption using predictors including NP size, inflammatory response to NP herniation, NP prolapse, the percentages edge-enhancing area and posterior longitudinal ligament coverage of the herniation measured by enhanced MRI. Moreover, we analyzed a total of 22 papers describing the pathophysiologic mechanisms of NP spontaneous resorption, where main mechanisms include inflammatory response, neovascular growth, macrophage infiltration, immune intervention, and matrix degradation.

Conclusions

A percentage of 76.6% in LDH patients undergo NP resorption. Prolapsed NP has a greater contact surface with blood system, which is easily to trigger immune response and thus promote spontaneous resorption. The mechanism of NP spontaneous resorption is mainly due to macrophage infiltration leading to immune response.

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INTRODUCTION

Lumbar disc herniation (LDH) is characterized as the rupture of fibrous annulus of the intervertebral disc, resulting in herniation or prolapse of nucleus pulposus (NP), which compresses spinal nerves and cauda equina nerve roots and thus causes clinical symptoms.[1] LDH, as the leading cause of lumbago, is the most common degenerative disease of the lumbar spine, which brings extreme pain and economic burden to patients.[2] Currently, conservative treatment is preferred for the initial diagnosis of LDH, including physical rehabilitation therapy, administration of opioids and non-steroidal anti-inflammatory drugs, and local injection of steroids.[3] When long-term conservative treatment fails and doesn't improve life quality, surgical treatment is feasible. Surgical treatment mainly removes the herniated portion of the responsible disc.[4] However, the satisfaction and recurrence rates vary between individuals, with re-herniation occurring in approximately 2%-25% of patients undergoing discectomy.[5] Postoperative recurrence is a common clinical complication, and additional complications especially nerve root injury or dural tear may occur when receiving revision surgeries.[6]

Most of the symptoms of LDH can be relieved by conservative treatment that can shrink the herniated portion and thus reduce compression.[7] As shown in Figure 1, in some patients with conservative treatment, the shrinkage or even disappearance of the herniated portion of the disc has been observed by magnetic resonance imaging (MRI). In 1984, the spontaneous resorption of NP in LDH without surgical intervention was first reported.[8], followed by a popular discussion among researcher in the 1990s [9-17] According to a recent meta-analysis, spontaneous resorption occurs in more than 60-70% of patients from adolescents to the elderly, suggesting no direct association between spontaneous resorption and age.[18] However, the percentage of herniated discs where spontaneous resorption occurs is controversial. On one hand, it is difficult to evaluate the overall population suffering from LDH. On the other hand, we know little about follow-up information of NP spontaneous resorption after conservative treatment, including the occurrence and timing of resorption, predictive indicators and mechanisms of resorption. Therefore, it is necessary to extend the existing evidence to further elucidate the clinical characteristics of NP spontaneous resorption.

In this systematic review, we expected to uncover the following three questions: 1) What is the percentage of spontaneous resorption in the conservative management of LDH? 2) How do we predict that spontaneous resorption may occur in LDH patients? 3) What are the molecular mechanisms of NP spontaneous resorption in LDH patients?

MATERIAL AND METHODS

This study was approved by the Ethics Committee of Union Hospital of Tongji Medical College, Huazhong University of Science and Technology. All data were obtained from published studies, so informed consent was waived. This systematic study was conducted in strict accordance with the Preferred Reporting Items for Systematic Evaluation and Meta-Analysis (PRISMA).

LITERATURE SEARCH AND SELECTION

A comprehensive literature search was conducted on October 01, 2023 in Pubmed, Embase, and Cochrane databases using a combination of the following keywords: "disc herniation", "spontaneous", "resorption", "regression", "disappearance", "imaging", "therapeutic strategy", and "mechanism", with no other restrictions.

Inclusion criteria: (1) prospective or retrospective studies; (2) correlation studies of LDH typology; and (3) imaging-related studies of LDH. Exclusion criteria: (1) non-English literature; (2) case reports or reviews; (3) studies that included repeat patients; and (4) studies that lacked valid data or full text.

DATA COLLECTION

For the included studies, the following variables were extracted: author information, study design, country, sample size, resorption proportion, sex of patients, mean age of patients, duration of follow-up, factors of predicting resorption, and description of the molecular mechanisms including neovascular growth, inflammatory response, vital factors, and immune response.

LEVEL OF EVIDENCE

The quality of the included studies was evaluated independently by two authors using GRADE. Each study was rated as high, moderate, low, or very low quality according to the GRADE criteria based on scores in five aspects: risk of bias, inconsistency, indirectness, imprecision, and other considerations. Kappa coefficients were calculated to determine inter-rater reliability for two-author ratings.

STATISTICAL ANALYSIS

All analyses for this systematic review were performed using SPSS 22.0 software. Continuous variables were presented as "mean ± standard deviation". Categorical variables were presented in the form of "number/percentage". Considering the significant heterogeneity of the included studies and the small sample size, Meta-analysis was not used and only a narrative review was performed.

RESULTS

LITERATURE SEARCH AND QUALITY ASSESSMENT

As shown in Figure 2, a total of 236 publications were searched from Pubmed, Embase, and Cochrane databases. After removing duplicates, a total of 180 studies were re-

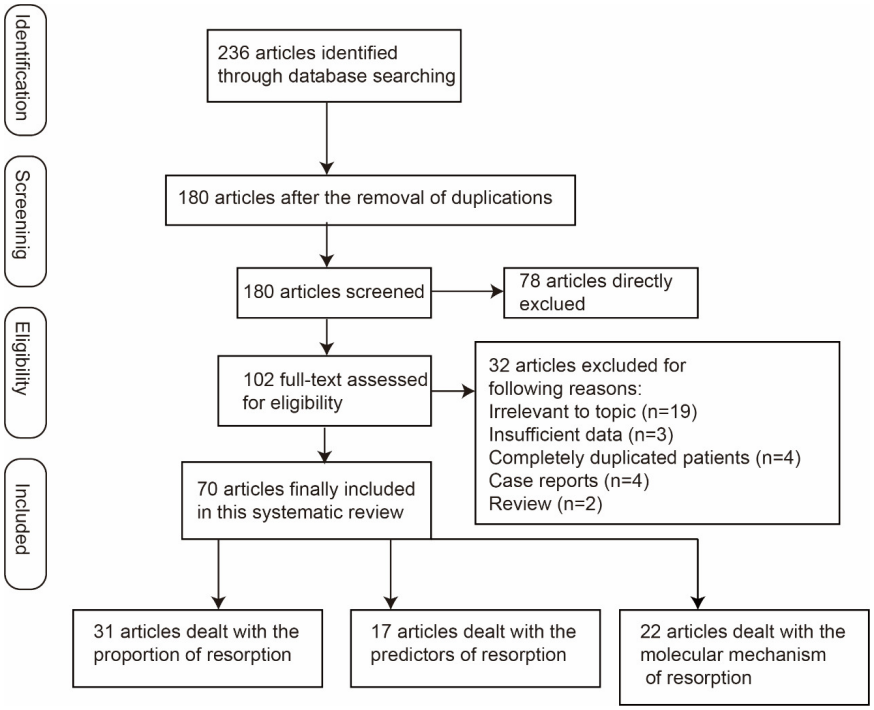

Figure 1. Flow chart for literature search and selection.

mained further evaluation. Of the 180 studies, 78 studies were directly excluded based on the contents of title or abstract. By going throughout the full text of the remaining 102 studies, 32 studies were further excluded following the below reasons: irrelevant topic (n = 19), insufficient data (n = 3), complete duplication of patients (n = 4), case reports (n = 4), and reviews (n = 2). 70 studies were ultimately included in this systematic review, of which 31 dealt with the proportion of resorption, 17 with predictors of resorption, and 22 with molecular mechanisms of resorption. GRADE was used to evaluate the quality of the included studies, and all included studies were of low or very low quality. Kappa's correlation showing the consistency between the two authors for quality evaluation of the included studies was 0.93.

PREVALENCE OF RESORPTION IN LDH

As shown in Table 1, a total of 31 studies were included, including 2,199 patients who received conservative treatment. We found that the overall incidence of NP resorption was 76.6%, and the incidence of resorption was higher in ruptured disc herniations than in inclusive disc herniations. The incidence of resorption differed significantly between countries. The resorption process occurred mainly within 3-6 months of conservative treatment.

PREDICTING SIGNS OF SPONTANEOUS RESORPTION

Spontaneous resorption of herniated discs is difficult to predict as no specific clinical symptoms are associated with it.[9] Researchers have attempted to predict the likelihood of spontaneous resorption through imaging typing and signal differences.[41] Treatment decisions for LDH require are based on a combination of factors including types, sizes, compositions, and enhancement around the herniation.[42-45] The integrity of annulus fibrosus and posterior longitudinal ligament where whether NP breaks through them are key factors in NP spontaneous resorption (Figure 3). However, Seo et al.[46] showed that the integrity of the disc suggested by MRI can lead to a higher rate of resorption. We believe that this may not be spontaneous resorption, but rather dehydration and atrophy of the disc leading to degeneration pulling on the posterior protrusion. Similarly, Ahn et al.,[35] found fibrous annulus integrity to be a factor in resorption, as all cases of closed herniation showed either partial or complete disappearance of LDH, but this may also be due to dehydration and atrophy of the disk. Recently, Lee et al.[22] revealed that dissociative herniation is the optimal sign of resorption, as it exposes NP to the intradiscal vasculature. Zou et al.[18] reiterated these results in a systematic review and meta-analysis, where they reported that the probability of NP resorption was as high as 96% for a dislodged NP. Therefore, the integrity of the posterior longitudinal ligament is also relevant in predicting whether NP resorption can occur. The current theory of NP resorption is that protruding NP may be more susceptible to resorption when it is exposed to epidural vessels through the ruptured posterior longitudinal ligament. A recent study by Hornung et al.[41] found that larger herniations were more readily resorbed compared with smaller herniations, which was contrary to clinician's decision to intervene surgically based on the size of the herniation. Interestingly, Hornung et al. uncovered that there was also a relationship between NP spontaneous resorption and sagittal parameters of the lumbar spine, which indirectly proved

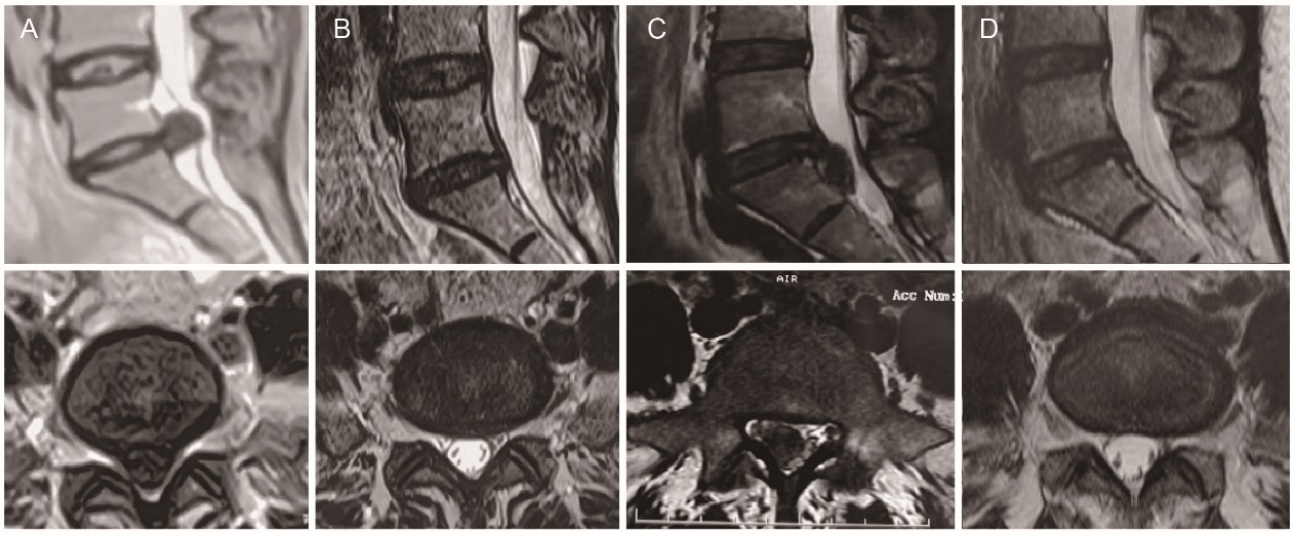

Figure 2. Sagittal and axial MRI scans demonstrating resorption of herniation at 3-month follow-up. (A) Baseline MRI. (B) MRI at 3-month follow-up. (C) Baseline MRI. (D) MRI at 3-month follow-up. MRI=magnetic resonance imaging.

the influence of patient's posture to resorption.[41] In addition, the composition of the herniation such as annulus fibrosus, endplate cartilage, and NP may affect resorption.[47] When the prominence contains mostly loosen NP, resorption may be preferred. If a loosen NP is also present anterior to the posterior longitudinal ligament, and there is a possibility of protrusion of the loosen NP after resorption of herniated NP, the new protrusion may be mistaken for a lack of resorption during follow-up. Resorption may be inhibited when the herniation contains endplate cartilage.[48] so that herniations with Modic changes have a decreased chance of resorption (Figure 4). Moreover, cartilage denudation is often present at endplate sites with combined Modic changes, and the low rate of healing at the site of cartilage denudation is the main reason for the recurrence,[15,47,49,50] Marginal enhancement of disassociated NP indicates the formation of neovascularization and inflammatory granulation tissue that are both responsible for resorption.[36] Enhanced MRI is commonly used for patients with disassociated NP, which can detect a typical image called "bull's-eye sign". In a 2006 study by Autio et al.[31] individuals with higher rim enhancement thickness were more likely to undergo spontaneous resorption than those with lower rim enhancement thickness. A higher degree of signal enhancement suggests a greater likelihood of spontaneous resorption, which is also considered an important factor in assessing spontaneous resorption of LDH. Therefore, the circumferential enhancement around a herniated disc, "bull's-eye sign", is an important predictor of resorption (Table 2).

MOLECULAR MECHANISMS OF SPONTANEOUS ABSORPTION OF LDH

Despite the extensive literature on disc spontaneous resorption, the exact mechanism remains incompletely elucidated. In general, four pathophysiologic mechanisms are widely recognized, including (1) cascading inflammatory response, (2) neovascularization, (3) macrophage infiltration-mediated immune response, and (4) matrix protease activation for degradation (Figure 5). The secretion of inflammatory factors promotes the production of a series of matrix-degrading enzymes, accelerates the breakdown of extracellular matrix, and enhances the recruitment of immune cells to this region, thereby maintaining and promoting inflammation.[54,55] Inflammatory factors are mainly derived from immune cells, of which CD4+ T cells are present around NP.[56] When NP is extruded into the epidural space, an autoimmune response is elicited, leading to infiltration of immune cells, and the recruited immune cells interact with the disc cells to secrete a variety of factors to promote NP resorption.[57] The normal intervertebral disc is an avascular one with a unique structure isolating NP from the host immune system, and therefore it inhibits the infiltration of immune cells and cytokines.[7] This is mainly attributed to the blood-NP barrier and the local expression of Fas ligands. FasL-Fas interaction induces apoptosis of immune cells and vascular endothelial cells through a complex signaling pathway that maintains immune immunity and prevents angiogenesis in the disc.[58] In the case of disrupted blood-NP barrier, such as NP exposing to the immune microenvironment, an autoimmune response is triggered, leading to the development of a variety of pathological processes such as neovascularization and immune infiltration.[59] NP and intervertebral discs are avascular structures and are waived from immunity. Several studies have suggested that neovascularization, detected by histology at the site of disc herniation, may be a key determinant of LDH resorption.[60] In addition, enhanced MRI has shown resorption of herniations fully exposed to the epidural space, which is positively correlated with vascularization, as it is often found at the margins of herniated discs.[36] The main mediators that induce formation around

Table 1. The incidence of spontaneous resorption of LDH.

Study	Country	Study design	Number of patients (total/ resorption)	Prevalence of resorption (%)	Age	Sex
Sucuoglu et al., 2021 [19]	Turkey	Prospective	55/49	89.1	25-67	23/32
Ma et al., 2021 [3]	China	Retrospective	409/189	59.1	14-70	245/ 164
Dai et al., 2020 [20]	China	Prospective	66/46	73.0	25-67	46/20
Kesikburun et al., 2019 [21]	Turkey	Prospective	40/36	90	39.7-66.7	21/15
Lee et al., 2017 [22]	Korea	Retrospective	505/486	96.2	NA	306/ 199
Demirel et al., 2017 [23]	Turkey	RCT	20/18	90	NA	10/10
Hong et al., 2016 [24]	Korea	Retrospective	28/24	85.7	26-78	NA
Yu et al., 2014 [25]	China	Prospective	83/42	50.6	16-60	NA
Barzouhi et al., 2013 [1]	Netherlands	RCT	95/88	92.7	18-65	NA
Iwabuchi et al., 2010 [26]	Japan	Prospective	34/21	66.8	NA	NA
Benson et al., 2010 [27]	UK	Prospective	28/28	100	25-62	NA
Cribb et al., 2007 [28]	UK	Retrospective	15/14	93.3	24-73	NA
Jensen et al., 2006 [29]	Denmark	Prospective	139/65	46.8	18-65	84/70
Erly et al., 2006 [30]	USA	Retrospective	36/25	69.4	NA	NA
Autio et al., 2006 [31]	Finland	Retrospective	74/68	91.9	19-78	NA
Splendiani et al., 2004 [32]	Italy	Prospective	72/25	34.7	21-68	NA
Ahn et al., 2002 [33]	Korea	Prospective	17/13	76.5	19-73	15/7
Takada et al., 2001 [34]	Japan	Prospective	42/37	88.1	16-64	28/14
Ahn et al., 2000 [35]	Korea	Prospective	17/13	76.5	19-73	15/7
Komori et al., 1998 [36]	Japan	Prospective	48/32	66.7	20-75	NA
Yukawa et al., 1996 [37]	Japan	Retrospective	30/16	53.3	14-69	NA
Komori et al., 1996 [38]	Japan	Retrospective	77/49	63.6	18-86	NA
Matsubara et al., 1995 [39]	Japan	Prospective	32/20	62.5	16-52	11/21
Gallucci et al., 1995 [40]	Italy	Prospective	15/11	73.3	27-62	11/4
Ellenberg et al., 1993 [14]	USA	Prospective	14/111	78.6	28-67	10/4
Maigne et al., 1992 [13]	France	Prospective	48/39	81.3	26-75	NA
Delauche et al., 1992 [12]	France	Prospective	21/14	66.7	20-64	15/6
Bush et al., 1992 [11]	UK	Prospective	111/71	63.9	17-72	NA
Bozzao et al., 1992 [10]	Italy	Prospective	21/14	66.7	20-64	15/6
Saal et al., 1990 [9]	USA	Prospective	11/9	81.8	NA	NA
Teplick et al., 1985 [8]	USA	Retrospective	55/11	20	NA	NA

the herniation are tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF), where VEGF is an important mediator of angiogenesis.[61] The activity of different types of macrophages and pro-angiogenic mediators they secrete are the main regulators

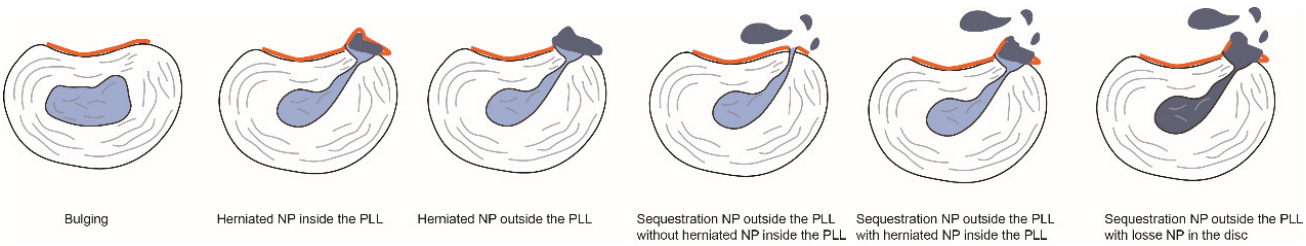

Figure 3. The depictions of LDH includes bulging, herniated NP inside the PLL, herniated NP outside the PLL, sequestration NP outside the PLL without herniated NP inside the PLL, sequestration NP outside the PLL with herniated NP inside the PLL and sequestration NP outside the PLL with loss NP in the disc space.

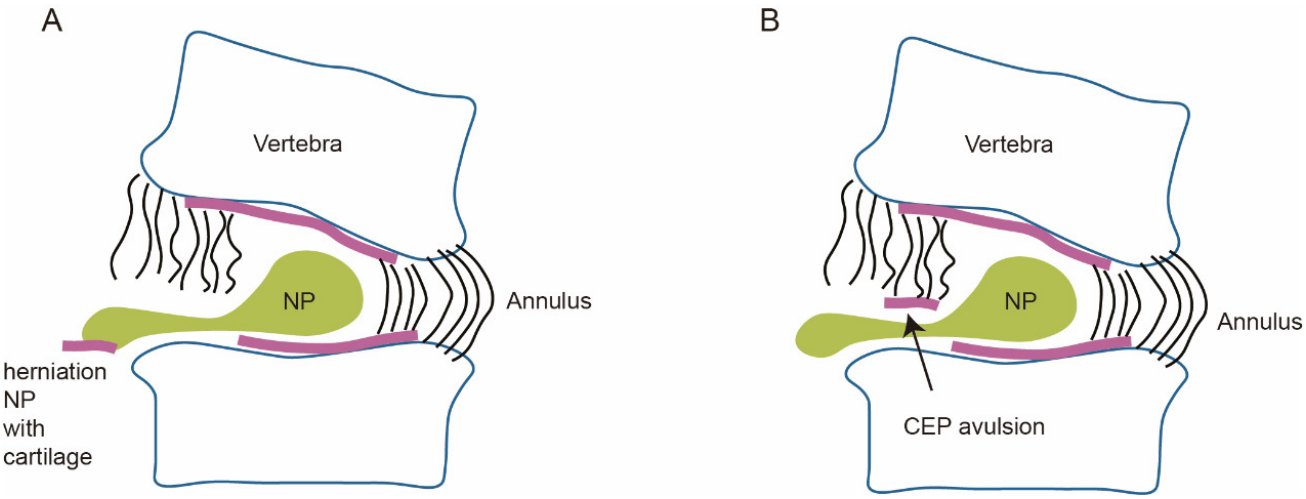

Figure 4. (A) Cartilage endplate (CEP) is avulsed from bone, herniating with the NP materials. The absorption is difficult. (B) CEP is avulsed from bone, allowing disc material to escape. Endplate junction failure is the most common cause of clinical disc herniations reoccur.

of neovascularization in the inflammatory response. The activated macrophages are divided into M1 and M2 types which co-orchestrates in regulating angiogenesis.[62] Theoretically, NP in LDH is recognized by the immune system and an inflammatory response occurs, which results in the involvement of monocytes in the NP resorption. Studies have shown that disc cells stimulate the production of many pro-inflammatory cytokines such as TNF-α, IL-1β and IFN-γ, where TNF-α is a strong inducer, leading to the production of MCP-1.[63] Then MCP-1 recruits more monocytes, accumulating signals for the transformation of monocytes into macrophages, which in turn triggers the release of more MCP-1, leading to an amplification of the inflammatory response, i.e., the inflammatory cascade response.[64] Macrophages appear to be key immune cells involved in this process, and many histologic studies have demonstrated the presence of macrophages in tissues with herniated NP. Electron microscopy has suggested that macrophages appear to remove associated cellular debris from NP by phagocytosis. Macrophage infiltration and activation are critical steps in the resorption process, and macrophage infiltration in disc herniations has been widely demonstrated.[65] Macrophages are classified to classically activated M1-type and alternatively activated M2-type according to different phenotypes.[66] M1-type macrophages are characterized by the production of high levels of pro-inflammatory cytokines, such as TNF-α and IL-1β, which are closely associated with inflammatory neuralgia and can modulate pain-mediated inflammatory response. Meanwhile, these inflammatory factors stimulate the production of chemokines that induce activation of MMP and indirectly promote neovascularization, a response known as the functional inflammatory response that is beneficial for the resorption. M2-type macrophages function as anti-inflammatory and wound healing promoters, exerting effects on tissue repair, fibrosis and tissue regeneration by modulating functional inflammatory response. Immunohistochemical detection of prolapsed nucleus pulposus tissue suggested M1/M2 macrophage infiltration (Fig6). There is evidence that M2-type macrophages secrete anti-inflammatory cytokines, such as IL-4 and IL-10, which promote herniation resorption by promoting phagocytosis, as well as attenuating the inflammatory response.[67] Macrophages related inflammatory factors stimulate the production of chemokines that induce activation of MMPs to promote herniation resorption.[68,69] Doita et al.[65] demonstrated that the production of increased MMP-3 in the herniated disc contributes to NP degradation. Likewise, Haro et al.[70,71] investigated the role of MMP in the resorption of disc herniation, and they found that MMP-3 and MMP-7 expression

Table 2. Predictive clinical features spontaneous resorption of LDH.

Study	Country	Clinical Features	Sample Size	Age	Sex
Hornung et al., 2023 [41]	USA	Size; L4 posterior body height; Sacral slope	93	NA	45/47
Gupta et al., 2020 [44]	USA	Size	368	NA	NA
Kawaguchi et al., 2018 [51]	Japan	Modic change	71	21-73	49/29
Lee et al., 2017 [22]	Korea	Modic change	505	NA	306/199
Seo et al., 2016 [46]	Korea	Size；Disruption of PLL	43	19-65	19/24
Shan et al., 2014 [48]	China	Modic change	85	22-66	52/33
Iwabuchi et al., 2010 [26]	Japan	Plain MRI	34	NA	21/12
Benson et al., 2010 [27]	UK	Size	37	NA	NA
Autio et al., 2006 [31]	Finland	Rim enchancement	160	19-65	NA
Erly et al., 2006 [30]	USA	Size	123	NA	NA
Jensen et al., 2006 [29]	Danmark	Sequestration	154	19-73	84/70
Splendiani et al., 2004 [32]	Italy	Size	75	21-68	NA
Kawaji et al., 2001 [52]	Japan	Enhanced MRI	21	21-69	13/8
Ahn et al., 2000 [35]	Korea	Sequestration；Disruption of PLL	36	17-74	19/17
Komori et al., 1998 [36]	Japan	Contrast-enhanced MRI	48	20-75	31/17
Carreon et al., 1997 [53]	Japan	Annulus fibrosus; Cartilage	24	NA	NA
Bozzao et al., 1992 [10]	Italy	Size	65	23-65	NA

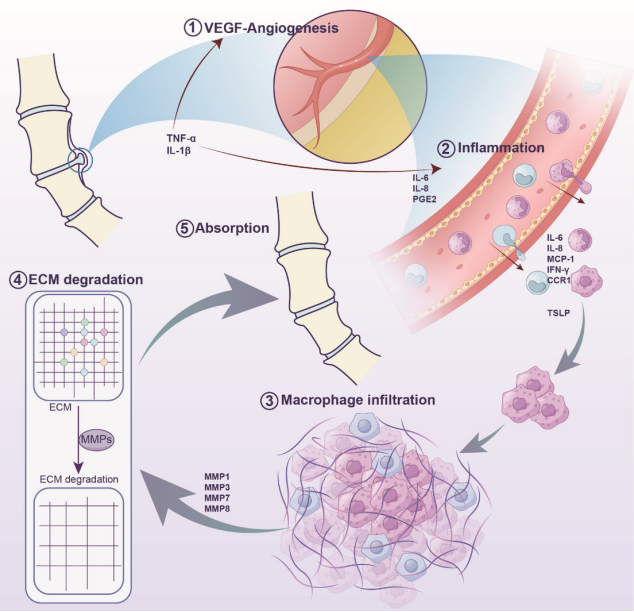

Figure 5. The main mechanism of spontaneous resorption of LDH.

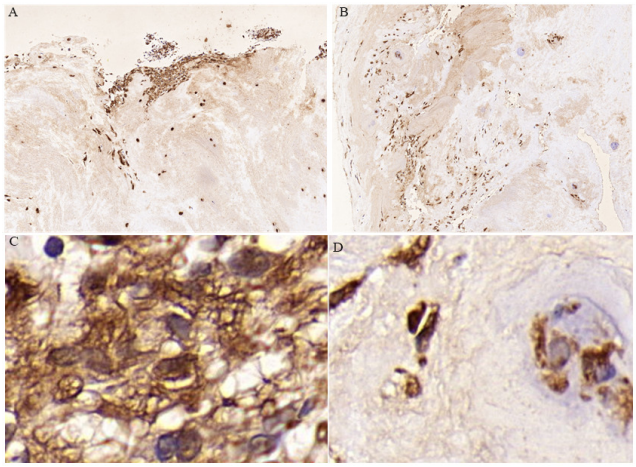

Figure 6. Immunohistochemical detection of nucleus pulposus. A. CD 86(+), X10; B. CD 163 (+), X10;C. CD 86(+), X 100 ; D. CD 163 (+), X 100.

was upregulated in herniated NP samples, where MMP-3 is essential for the degradation of NP tissue. (Table 3).

DISCUSSION

Clinically, surgical treatment is mainly for those patients with urinary dysfunction, persistent or worsening manifestations of neurological damage (dysfunction or sensory abnormalities), and intractable pain that severely affects quality of life.[85] Typically, conservative treatment is preferred for LDH,[86,87] including medication, physical therapy, or other physiotherapy, which benefit for a number of patients, although the comparison of conservative and surgical treatment remains controversial. A follow-up comes with conservative treatment to determine if the disc will resorb or require surgical intervention. Therefore, resorption

Table 3. Molecular Mechanisms of spontaneous absorbption of LDH.

Study	Country	Journal	Species	Identified Cellular modulators
Ohba et al., 2020 [64]	Japan	JOR Spine	Human	TWEAK, Fn-14, TSLP
Tsarouhas et al., 2017 [72]	Greece	Molecular Medicine Reports	Human	VEGF, PDGF-C, PDGF-D
Takada et al.,2012 [73]	Japan	Arthritis rheumatism	Rat	TNF-a, IL-6, IL-8, and PGE2
Hedgewald et al., 2012 [74]	Japan	Arthritis and Rheumatism	Human	CXCL10 and CXCL1
Shamji et al., 2010 [75]	Canada	Arthritis and Rheumatism	Human	IL-4, IL-6, IL-12, and IFN-r
Yoshida et al., 2005 [76]	Japan	Spine	Rabbit	TNF-a, IL-b, and MCP-1
Zhou et al., 2010 [77]	China	International Orthopaedics	Human	Midkine
Haro et al., 2005 [78]	Japan	Journal of orthopaedic research	Rabbit	MMP-7
Takada et al., 2004 [79]	Japan	Spine	Rat	IL-6
Haro et al., 2002 [61]	Japan	Journal of orthopaedic research	Human	VEGF
Burke et al., 2002 [80]	Ireland	Spine	Human	IL-8 and MCP-1
Ahn et al., 2002 [33]	Korea	Yonsei Medical Journal	Human	IL-8, TNF-a, IL-1a, RANTES, and IL-10
Doita et al., 2001 [65]	Japan	Spine	Human	MMP-1 and MMP-3
Haro et al., 2000 [70]	Japan	The journal of clinical investigation	Mice	MMP-7
Haro et al., 2000 [71]	Japan	The journal of clinical investigation	Mice	MMP-3
Haro et al., 1999 [81]	Japan	Journal of Spinal Disorders	Human	MMP-7 and MMP-8
Haro et al., 1997 [63]	Japan	Journal of orthopaedic research	Human	MCP-1
Haro et al., 1997 [82]	Japan	Spine	Human	Stromelysin-1
Kang et al., 1997 [83]	USA	Journal of Orthopaedic Research	Human	IL-6, NO, PGE2, MMP-3, and MMP-2/ MMP-9
Ito et al., 1996 [60]	Japan	Spine	Human	Macrophages, vasculiarized
Haro et al., 1996 [84]	Japan	Spine	Human	MCP-1, MIP-1 a
Habtemariam et al., 1996 [56]	Finland	Spine	Human	Immunocytochemical localization

of a herniated disc is an important indicator of the efficacy of conservative treatment.

The current first-line regimen for pain management in LDH patients is nonsteroidal anti-inflammatory drugs (NSAIDs), but new research questions the use of NSAIDs or glucocorticoids for LDH treatment due to the potential for these drugs to limit the pathophysiologic process of spontaneous resorption of herniated NP. For example, in the study by Minamide et al,[88] spontaneous resorption of NP was more likely to occur in the inflammatory group compared to the control group, suggesting that inflammation plays an important role. In addition, we have clinically observed that systemic inflammatory responses in LDH patients, promoting by novel coronavirus 19 (COVID-19), facilitates spontaneous resorption of herniated NP.

Pain relief by controlling inflammation is a key strategy in the treatment of LDH, but the administration of anti-inflammatory drugs may be detrimental to NP resorption. Based on the inflammatory mechanism in NP resorption, the early inflammatory response involves the recruitment of macrophages and the induction of factors that promote resorption. Currently, commonly used NSAIDs control pain by suppressing local inflammation, but long-term use of these drugs may hinder NP resorption. A prospective study dug out that anti-inflammatory drugs impede LDH resorption. Future studies should focus on modulating M1 and M2 macrophages to rationally control the inflammatory response and promote angiogenesis.[89] Moreover, the autophagic pathway was more active in spontaneous resorption of the extruded disc after LDH,[90] there is a need to develop new clinical treatments, increase safety studies, and explore the growth factors required to promote disc resorption and their optimal characterization. In addition, randomized, double-blind, controlled trials are necessary to demonstrate the efficacy of new treatments in promoting LDH resorption.

NP resorption often occurs during the first 6 months of conservative treatment, and the available evidence suggests an overall resorption incidence of 76.6%, with a higher incidence in ruptured LDH than in inclusive LDH. The greater the area of NP exposed, the greater the likelihood of spontaneous resorption. Recurrence after spontaneous resorption depends mainly on the nature of loose NP anterior to the posterior longitudinal ligament. At present,

we mainly use imaging features to initially determine the possibility of resorption. The future development of more advanced MRI technology is promising for determining NP resorption. So far, many guidelines have reached a consensus that conservative treatment is the first choice for LDH patients without severe neurologic injury, and that inflammation subsidence and NP resorption are the key processes of conservative treatment.

Nevertheless, some limitations should be considered when interpreting our results. First of all, a limited population were included in this systematic review, which may be due to insufficient follow-up of conservative treatment. Second, all included studies were retrospective in design with low or very low levels of evidence, which undoubtedly reduced the reliability of our findings. Third, spontaneous absorption of disc herniation relies mainly on imaging, which may affect the accuracy of the diagnosis. Despite these limitations, we have systematically described for the first time the problems associated with NP resorption in LDH, and we therefore believe that the present systematic review may provide additional valuable suggestions for the management of NP spontaneous resorption in conservative treatment.

CONCLUSIONS

NP spontaneous resorption in disc herniation is a clinical phenomenon, and its mechanisms may involve multiple inflammatory and neovascular pathways, which are not fully elucidated. Although a number of clinical features and factors associated with NP resorption have been summarized, much of the evidence is conflicting and has not been extensively validated. The main treatment for LDH is conservative treatment, and NSAIDs are the main therapeutic agents. The future spread of MRI technology is crucial in exploring the disc contours, relationship to the periphery, and nature of NP, which also helps determine the need for LDH intervention in the clinic.

CONFLICTS OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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