

Prediction and Mechanisms of Spontaneous Resorption in Lumbar Disc Herniation: Narrative Review

Zili Zeng¹⁾, Jun Qin¹⁾, Liang Guo¹⁾, Takashi Hirai²⁾, Zhiheng Gui²⁾, Tao Liu²⁾, Chen Su²⁾, Daiyang Yu²⁾ and Mengmeng Yan²⁾

1) Department of Orthopedics, University-Town Hospital of Chongqing Medical University, Chongqing, China

2) Department of Orthopaedic and Spine Surgery, Tokyo Medical and Dental University, Tokyo, Japan

Abstract:

The major symptoms of lumbar disc herniation (LDH) are low back pain, radiative lower extremity pain, and lower limb movement disorder. Patients with LDH suffer from great distress in their daily life accompanied by severe economic hardship and difficulty in self-care, with an increasing tendency in the aging population. PubMed and the Cochrane Central Register of Controlled Trials were searched for relevant studies of spontaneous resorption or regression in LDH after conservative treatment and for other potential studies, which included those from inception to June 30, 2023. The objective of this narrative review is to summarize previous literatures about spontaneous resorption in LDH and to discuss the mechanisms and influencing factors in order to assess the probability of spontaneous resorption by conservative treatment. Spontaneous resorption without surgical treatment is influenced by the types and sizes of the LDH, inflammatory responses, and therapeutic factors. If the lumbar disc herniated tissue comprises a higher percentage of cartilage or modic changes have been shown on magnetic resonance imaging (MRI), resorption in LDH is prevented. The bull's eye sign on enhanced MRI, which is a ring enhancement around a protruding disc, is a vital indicator for easy reabsorption. In addition, the type of extrusion and sequestration in LDH could forecast the higher feasibility of natural reabsorption. Moreover, the higher the proportion of protrusion on the intervertebral disc tissue within the spinal canal, the greater the likelihood of reabsorption. Therefore, which illustrates the feasibility of conservative treatments for LDH. Nonsurgical management of LDH with clinical symptoms is recommended by the authors.

Keywords:

Spontaneous resorption, Lumbar disc herniation (LDH), Mechanisms of resorption, Conservative treatment

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Introduction

Low back pain (LBP) is a chief factor of morbidity around the world and the most popular clinical symptom occurring mainly in middle-aged and elderly people¹⁾. A common cause of LBP is lumbar disc herniation (LDH)²⁾. LDH is the most common degenerated spine disease and a major cause of LBP and restricted mobility without or with sciatica, including lower extremity pain, paresthesia, sensory deficits, muscle weakness, and other neurologic signs³⁻⁶⁾. An estimated 5%-10% of patients worldwide experience immense pain in their daily life, accompanied by severe economic hardship and difficulty in self-care, with an increasing tendency as the population ages^{7,8)}. The major cases of LDH are disc degeneration related to aging, biomechanical fac-

tors, genetic predisposition, sedentary lifestyle, and trauma⁹⁾. Obesity, smoking status, axial overloading of the sciatic nerve, or sedentary professions for a long time had the greatest influence on the presence of intervertebral disc (IVD) pathology¹⁰⁾. LDH was thought to be associated with fibrous ring rupture, extrusion or protrusion of the disc nucleus, tension of the posterior longitudinal ligament from its normal anatomical location, and compression of the nearby nerve roots¹¹⁾. However, disruption of the lamina terminalis closure is more likely to be the primary cause of lumbar herniation than fibrous ring rupture¹²⁾.

The current treatments for LDH are divided into conservative and surgical treatments. Individualized treatment plans should consider the advantages, disadvantages, and risks of different therapeutic schedules¹³⁾. Conservative therapy has

Corresponding author: Liang Guo, guoliang@hospital.cqmu.edu.cn, 462986302@qq.com

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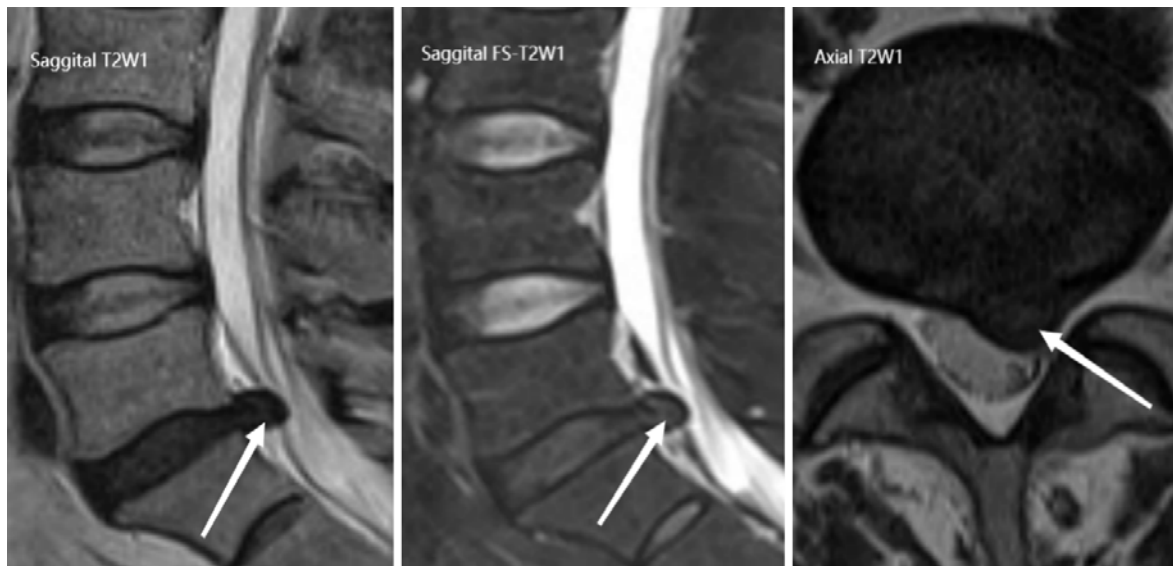


Figure 1. Magnetic resonance images of the University-Town Hospital of Chongqing Medical University at the initial visit. L5/S1 LDH on sagittal T2-weighted images, fat-suppressed T2-weighted images, and an axial T2W1 image as indicated by the white arrow.

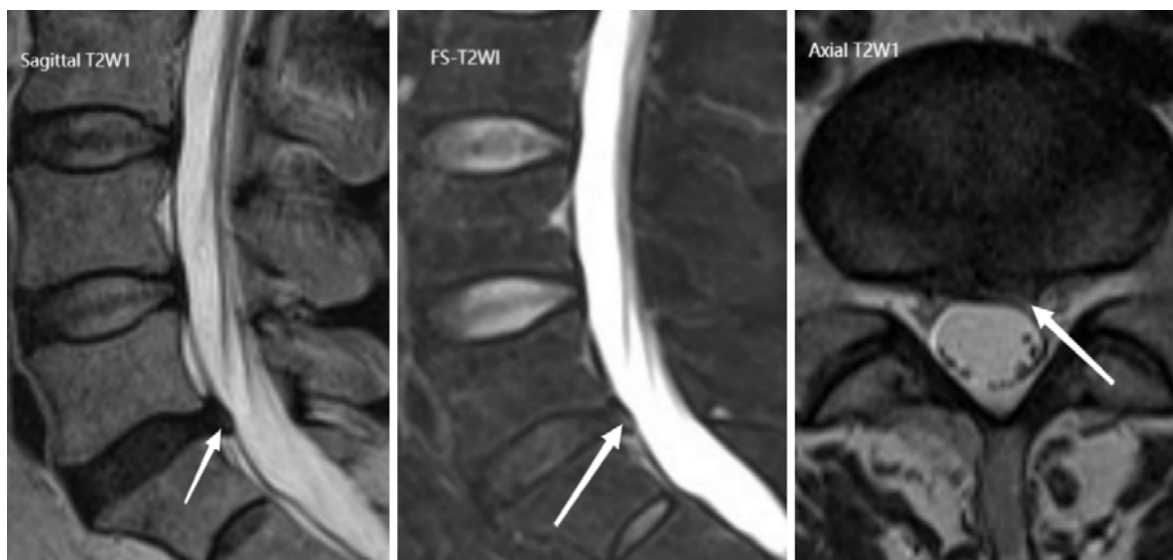


Figure 2. Follow-up magnetic resonance images at 5 months after conservative treatment. The herniated disc tissue L5/S1 spontaneously and completely disappears, L1/S1 shows degenerative changes on sagittal T2 weighted, fat-suppressed T2-weighted images, and an axial T2W1 image as indicated by the white arrow.

successfully treated the majority of cases, resulting in a significant alleviation of symptoms between 3 and 6 months^{4,6,14}. Approximately 60%-90% of patients with LDH will experience improvements with conservative treatment^{15,16}. Only 2%-10% of all LDH cases require surgery due to a failure in conservative measures. Therefore, nonsurgical therapy is the major method of choice for LDH^{17,18}. Conservative therapy relies on the body's natural capability for the spontaneous reabsorption of fragments from IVD herniation as a "self-healing" phenomenon (Fig. 1, 2). The herniated disc tissue spontaneously shrinks or even completely disappears, which is called LDH resorption^{19,20}.

Methods

As this is a narrative review, we searched PubMed and the Cochrane Central Register of Controlled Trials (from inception to June 30, 2023). Search terms included those related to LDH, herniated IVD, herniated lumbar disc, regression, resorption, nonsurgical treatment, conservative treatment, and their variants. There were restricted language in English literature studies. Randomized controlled trials, non-randomized studies, and case reports were eligible for inclusion. Experimental studies on the relevant mechanisms of lumbar disc resorption have also been included. Lastly, studies on the relationship between modic changes (MCs) and

the resorption in LDH were included. The following studies were excluded: 1) Studies on the follow-up results of any surgery for LDH; 2) Studies on the resorption in cervical and thoracic discs; 3) Studies that did not report the morphological changes in LDH by conservative treatment. There were 10695 papers on the treatment of LDH, 44 papers on LDH, resorption, and conservative treatment, 62 papers on regression, LDH, and conservative treatment, and 7 papers on MCs, LDH, resorption, and conservative treatment.

We reviewed the previous literature and discussed the mechanisms and influence factors of spontaneous resorption in LDH in order to assess the probability of resorption by conservative treatment. We tried to cite the original literature as much as possible and selected articles from journals with higher impact factors of science citation index, such as JAMA, Lancet, N Engl J Med, and Spine.

Imaging and Clinical Evidence of Spontaneous LDH

In 1984, the first case of spontaneous resorption in an IVD herniation after conservative treatment was reported by Guinto²¹. With the increasingly popular technology of computed tomography (CT) and magnetic resonance imaging (MRI), there have been new reports on reduced or disappearing IVDs in patients with LDH after conservative treatment²²⁻²⁵. Previous studies have shown that all adjusted outcomes significantly improved after both nonsurgical and surgical treatments, and surgical treatment has short-term advantages over conservative treatment^{26,27}. However, the results of patients with LDH who underwent surgical or conservative treatment after 6-12 months and 10 years are similar^{28,29}. Even though the precise mechanism of action is in dispute, the current research suggests that the spontaneous reabsorption of LDH was achieved early at 3 months, and 67%-100% of cases occurred 1 year after conservative management, which includes taking gabapentin for treatment, acupuncture, and avoiding the intake of anti-inflammatory medication^{30,31}.

Anatomical Features of IVD and LDH

IVDs, which are located within two vertebrae, are comprised of three primary complexes: the inner nucleus pulposus (NP), the outer annulus fibrosus (AF), and the vertebral and cartilaginous endplates (EP) on the inferior and superior surfaces. NP is a highly hydrated, gelatinous, and proteoglycan-rich tissue. AF is a highly structured fibrous tissue consisting of concentric sheets of inclined collagen fibers with dispersed proteoglycans. Both NF and AF are segregated from contiguous vertebrae through the EP. Under normal conditions, both NP and AF provide jointly to the mechanical behavior of IVD to sustain a high-stress loading on the centrum, resist spinal compression, and limit movement between the vertebrae³².

IVD degeneration is usually associated with LBP and is a

complex event covering diversified morphological, biochemical, and functional alterations. LDHs are the main forms of IVD degeneration³³. LDH results in LBP as well as pain in the buttocks and the lower limbs, or neurological dysfunction^{1,2,34}. LDH refers to the displacement of the NP in the lumbar IVD through the ruptured AF, thereby increasing pressure on spinal cord and nerve roots. LDH symptoms range from mild back pain and hip pain to the inability to ambulate and cauda equina syndrome.

Mechanisms and Influence Factors of Spontaneous Resorption in LDH

Spontaneous resorption of IVD tissue has been documented in many clinical literatures^{21-31,35,36}. However, its underlying mechanism is unclear. As far as we know, researchers have proposed the following mechanisms to interpret the spontaneous resorption of IVD herniation tissue.

Mechanical traction

The tension exerted by the fibrous ring causes the disc fragments to shrink into the IVD space. This mechanism can interpret a situation in which a fibrous ring of a lumbar herniated disc is complete, but it cannot adequately interpret that the cases of regression of a free fragment are complete^{12,37}. Changes of the herniated NP tissue retract in median (78.5%), posterolateral (66.6%), and lateral herniations (57.1%) under the effect of a traction³⁸. Lumbar traction, which decreases the size of the herniated disc tissue with the use of a CT for measurement, is effective in alleviating symptoms³⁹.

Dehydration reaction

The dehydration reaction of the protruding nuclear tissue is the first mechanism used to explain core absorption⁴⁰. The NP is 70%-90% water, and the IVD tissue itself is hyperpermeable, so the protruding IVD will absorb water and expand after contact with the epidural spinal fluid, leading to further enlargement and bulging of the protruding IVD. The proteoglycans in the protrusion of the gelatinous core degenerate, causing dehydration of the gelatinous core tissue, and the fragments of the IVD protrusion shrink due to contraction and gradual dehydration. This may explain why MRI scans show that the signal intensity of the responsible spinal disc decreases in some studies, and it is also consistent with the phenomenon that the higher T2-W1 signal intensity, the higher the rate of absorption⁴¹. Many reports have demonstrated that the segregated NP is more easily absorbed than the protruded NP, because the segregated NP may be due to directly contacting with the blood supply and easily triggering a local immune response after the IVD ruptures through the ligamentum flavum⁴².

Neovascularization in LDH resorption

There are barely blood vessels in the maturation stage of IVD. However, the hyperplasia of new blood vessels has

been discovered at the edge of the herniated tissue, which is considered to be the main determining factor for the spontaneous resorption of LDH⁴³. Some molecular mediators, including tumor necrosis factor- α (TNF- α), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF), are believed to partake in the neovascularization of LDH⁴⁴. Doita showed that 68.8% of patients with ruptured LDH and 60% of patients with isolated LDH had capillary growth and inflammatory cell infiltration at the edge of the herniated disc⁴⁵. In addition, the degree of MRI peripheral enhancement correlated significantly with the degree of displacement of the prominent medullary tissue and was most pronounced in the case of a complete sequestration⁴⁶.

Neovascularization of herniated disc fragments: protrusion of the IVDs into the epidural space causes neovascularization and an inflammatory reaction characterized by degradation mediated by immune cells, and the more severe the protrusion, the more intense the inflammatory response⁴⁷. Subsequently, the blood supply around the protruding NP increases, and it can be observed that the protruding the gadolinium contrast agent peripherally strengthens NP. Kobayashi⁴⁸ found that new microvessels enters the epidural space and grow around the IVD tissue, and local inflammatory reactions and extensive macrophage infiltration can be observed under light and electron microscopy. The bull's eye sign is related to the formation of blood vessels and inflammatory granulation tissue in LDH⁴⁹, and inflammatory reaction and the neovascularization in LDH are the critical factors for reabsorption⁵⁰.

MCs affect resorption

LDH is also closely related to endplate changes, with the bony endplate changes being even more common than annulus rupture in patients with disc herniation¹². MCs are variations in signal intensity in the vertebral body region adjacent to the endplate visible on MRI and are believed to be related to degenerative disc disease⁵¹. In MRI imaging, type 1 MCs refers to the increased angiogenesis and vertebral body marrow edema, type 2 MCs indicates lipidosis in, and type 3 MCs manifests subchondral osteosclerosis⁵². Despite the initial classification, research has supported the view that MCs have transitional properties. In addition, type 1 MCs are closely related to inflammation and severe LBP, while types 2 and 3 are inclined to be more stable and exhibit less intractable pain. MCs-related pain could be associated with the neovascularization and neurogenesis owing to the boost in VEGF expression by vascular cells, IVD cells, and inflammatory cytokines⁵³. With a close relation to LBP, knowing the pathogenesis of MCs is vital to an optimal treatment protocol⁵⁴.

The probability of spontaneous resorption was obviously lower in patients with disc herniation with MCs than those with non-MCs⁵⁵. In patients with MCs, the herniated disc tissue is predominantly cartilaginous endplates with relatively little NP⁵⁶. However, cartilage endplates only cause a

weak inflammatory response, leading to a small amount of tissue degradation and resorption and inhibiting cardiovascular production⁵⁷. It is known that proteoglycans inhibit blood vessels and nerve growth. In contrast, cartilage endplates accompanying disc herniation reduce the degree of proteoglycan loss in the disc tissue, thereby inhibiting the inflammatory response and tissue edema⁵⁸.

Autoimmune inflammatory response induced by IVD herniation tissue

The IVD is the biggest nonvascular organ in the body, and it has been deemed a isolated part of the body's immune system⁵⁹. The IVD is sufficiently isolated from the body's immune system not only because it is located in two cartilage endplates and the AF of the dense collagen fiber structure, but also because the expression of Fas ligand (FasL) on IVD cells resist immune system invasion, which is a feature of immune privileged sites⁶⁰. FasL belongs to the TNF family, which is considered to induce cell apoptosis through binding with its Fas receptor. At sites of immune privilege, FasLs from stromal cells combine to Fas receptors expressed on infiltrating immunocytes. The ligand-receptor induces apoptosis of infiltrating immunocytes and keeps the immune privileged status of the tissue²⁴. The immune privileged status of IVDs is the theoretical support for the inflammatory response behind the spontaneous absorption of lumbar disc tissue. The theory is that extrusion of disc tissue entering the epidural space causes an autoimmune reaction, leading to immune cell infiltration⁴⁵.

Increasing evidence show that sustaining immune histology and inflammatory processes are potential mechanisms responsible for material absorption in IVD herniation. Notably, macrophages are vital immune cells in the absorption process of IVD herniation by immunohistochemistry^{13,60}. Moreover, macrophage phagocytosis and neovascularization were more common in free discs than in herniated discs in histological samples of herniated discs^{13,61}. Immune cells interact with IVD cells to secrete various cytokines, including TNF- α , Interleukin-1 (IL-1), matrix metalloproteinases (MMPs), and bFGF, which initiate the resorption process of LDH. TNF- α is a powerful inducer of MMP-1/3 and VEGF, which is associated with the neovascularization of herniated discs and mediates the inflammatory response, and both VEGF and bFGF play a positive role in neovascularization⁶². Similarly, histological analysis of herniated human IVD tissue has revealed the presence of infiltrating T cells¹³. This suggests that lymphocytes are also involved in the spontaneous immune response of the herniated disc, and the exact mechanism remains to be explored in further studies. In addition, disc cells can produce inflammatory mediators such as MMPs, IL-4/6/12, nitric oxide (NO), prostaglandin E2 (PGE2), and interferon- γ ⁶².

These may be conducive to collecting other immunocytes to the herniated disc, particularly monocyte chemoattractant protein (MCP)-1, which is a cytokine that helps activate and recruit monocytes. These inflammatory factors stimulate

IVD cells to generate MCP-1, resulting in macrophage infiltration of the tissue in LDH. Meanwhile, soaking monocyte-derived macrophages also generate MCP-1 and recruit growing monocytes to the IVD⁶³. The activation of protein hydrolases is also a key factor of the spontaneous resorption in herniated discs. MMPs are important extracellular matrix (ECM) enzymes for degradation, involving cartilage degradation, mediating cellular degradation and reconstruction⁶⁴. When the activity and production of MMPs is enhanced, the corresponding tissue inhibitors of metalloproteinases are reduced, resulting in an imbalance between the synthesis and degradation of ECM. This complex series of changes can degrade the herniated disc and promote the resorption of the herniated disc tissue. Current investigators have demonstrated the presence of IL-1b and TNF-a in herniated disc tissue⁶⁵. When MMP-1/3 are excited by IL-1 α/β and TNF, the production of MMP-1/3 is reactively enhanced, prompting the protruding IVD tissue to resolve. Recent research also indicated that the autograft in rat IVD guided extensive macrophage infiltration *in vivo*, rising the mRNA production of IL-6/8, TNF- α , and COX-2. TNF- α is necessary to produce IL-6 and PGE2⁶⁶.

Relationship between the Time of Spontaneous Resorption of Herniated Material and the Types of LDH

According to the classifying system of LDH introduced by the North American Spine Society, North American Spine Radiology, and the North American Society of Neuro-radiology, disc herniations are classified as follows: bulging, focal herniation, broad basal herniation, extrusion, and sequestered⁶⁷. Different types of herniated discs have different volume sizes, different free distances, and different volumes of NP tissue exposed to the circulation, resulting in different probabilities of resorption of the herniated disc. Reabsorption is a natural procedure, and the larger the herniation, the greater the possibility and degree⁵⁶. Many studies have shown that enormous ruptured tissue in LDH is resorbed more easily, whereas small ruptured tissues took longer³⁶. Recently, researchers reported that the spontaneous regression rate of sequestration, extrusion, protrusion, and bulging was 96%, 70%, 41%, and 13%, respectively. As time passed, the rate of complete resorption in LDH was 43% for sequestration and 15% for extrusion²¹. The majority of massive LDHs resolved at variable points between 3 and 21 months⁴⁶. The average time for spontaneous resorption was 9 months, which occurred the earliest in giant disc herniation than in other types of herniation²⁶⁶.

Resorption time depends on the types of LDH and the treatment modality^{20,31}. The type of extrusion and sequestration in LDH predicts the probability of natural reabsorption because of favorable conditions for macrophage infiltration and new angiogenesis⁶⁸. If MCs were shown on MRI or if the tissue of IVD herniation includes a higher ratio of cartilage, it is unfavorable for macrophage infiltration and

growth of blood vessels, inhibiting the occurrence of reabsorption on IVD tissue⁵⁶. This may be influenced by several factors: the destructive degree of the fibrous rings and cartilage endplates and the exposing degree and extent of the various components in the NP. The type and magnitude of autoimmune reactions caused by different influencing factors may vary. In the initial stages of disc degeneration, disruption of the cartilage endplates and the fibrous rings can act as triggers, and a downstream cascade of inflammatory responses will accelerate the pathological process of the autoimmune response. These effects take a significant role in inducing, accelerating, and predicting degeneration of the lumbar IVD⁶⁹. As can be seen, the degree of spontaneous resorption on herniated discs is greatly influenced by the components of herniated tissue, which also impacts subsequent treatment options and the patient's recovery⁴⁶.

Conservative Treatments of LDH

Diagnosis is achieved with a thorough medical history, comprehensive checkup in conjunction with the patient's symptoms, and advanced imaging⁶¹. The current treatments for LDH include conservative and surgical treatments. The surgical treatment of LDH includes disadvantages, such as high cost and surgical trauma. In recent years, many studies have shown that surgical and conservative treatment of LDH have similar outcomes in long-term follow-up^{56,70}. Hence, to relieve pain and improve the patients' prognosis, the relationship between conservative treatment and spontaneous IVD resorption was studied^{26,71}.

Conservative management includes the prescription of effective nonsteroidal anti-inflammatory drugs and muscle relaxants according to current guidelines⁷². Other conservative treatment modalities include such things as lumbar support, bed rest, physiotherapy, epidural steroid injections, behavioral therapy, and manual manipulation of the spinal column. The main causes of spontaneous resorption in lumbar herniated discs should lie in the types of herniated disc rather than in the specific interventions used in conservative treatment⁷³. Conservative treatment and radiological follow-up may be the most appropriate initial treatment option for patients without progressive neurological dysfunction, rectal bladder impairment, or refractory pain. This helps to improve patient prognosis, decrease the financial burden on patients, and ultimately reduce national healthcare costs.

Conclusion

Conservative treatment for LDH significantly alleviates symptoms for the majority of cases, mainly due to LDH resorption. Spontaneous resorption without surgical treatment is influenced by the types and sizes of disc herniation, inflammatory responses, and therapeutic factors. The higher the proportion of protrusion of IVDs within the spinal canal, the more likely it is to be absorbed. The type of extrusion and sequestration in LDH could predict the possibility of

natural reabsorption. Controlling the inflammation to an appropriate level will be a major challenge in the conservative treatment of patients with herniated discs in alleviating their symptoms without affecting the reabsorption of LDH.

With the help of follow-up imaging, if MCs were shown on MRI or if the tissue of IVD herniation includes a higher ratio of cartilage, reabsorption is prevented. If herniated discs break through the posterior longitudinal ligament and enhance peripheral signal intensity of the disc, disc resorption easily occurs. The bull's eye sign on enhanced MRI, which is an enhanced ring around a protruding disc, is a vital indicator for easy resorption. A large number of reports have indicated that the probability of spontaneous reabsorption in LDH with conservative therapy is higher. As a result, these can be perceived as factors for the diagnosis and treatment of LDH.

Further work is needed to study the relationship between the clinical effects and LDH spontaneous regression by conservative treatment. Advanced techniques of susceptibility-weighted MRI should be probed to draw these changes in IVD and to rule the ability of alterations to forecast particular phenotypes and spontaneous resorption progress of LDH. We will research the objectives and perfect the evaluation criteria to guide clinicians in making a detailed diagnosis and formulate personalized treatment plans for patients by combining the physiological and pathological principles of spontaneous resorption in LDH and by collecting demographic factors such as the age and gender of patients.

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

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Author Contributions:

1. Liang Guo proposed the concepts and design of the article and wrote "Relationship between the time of spontaneous reabsorption of herniated material and the type of disc herniation";
2. Zili Zeng collected literatures and wrote the "Diagnosis and Treatments";
3. Jun Qin gave administrative support, collected literatures, prepared Fig. 1, 2 and wrote the "Conclusion";
4. Takashi Hirai wrote the "Abstract";
5. Zhiheng Gui wrote the "Introduction";
6. Mengmeng Yan, Tao Liu, and Liang Guo wrote the "Mechanisms and influence factors of spontaneous resorption in lumbar disc herniation";
7. Chen Su wrote the "Imaging and clinical evidence of spontaneous LDH";
8. Daiyang Yu wrote the "Anatomical features of intervertebral disc and lumbar disc herniation";
9. Zili Zeng and Jun Qin are co-first authors;

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