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Review

AN ANALYSIS OF PREDICTIVE FACTORS AND POTENTIAL MECHANISMS UNDERLYING LUMBAR DISC HERNIATION RESORPTION

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Abstract

Spontaneous resorption of lumbar disc herniation (RLDH) is a frequently observed phenomenon in imaging studies. However, the predictors of this process are difficult to control, posing a major clinical challenge. Moreover, the underlying biological mechanisms of RLDH remain incompletely understood. This limitation hinders clinicians from optimizing non-surgical treatments of lumbar disc herniation (LDH) in clinical practice. This review summarized the existing literature on the resorption of LDH, aiming to elucidate the predictive factors and potential biomechanical processes underlying this disease. Additionally, existing therapeutic approaches designed to promote resorption were also summarized. By providing insights into the dynamics of LDH resorption, this review offers the possibility of enhancing diagnostic accuracy and facilitating the development of targeted treatment strategies.

Keywords: Lumbar disc herniation, resorption, mechanisms, predictive factors, macrophages.

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Introduction

Lumbar disc herniation (LDH) refers to the displacement of the nucleus pulposus (NP) through a compromised annulus fibrosus (AF), leading to the compression of neural elements. Clinically, this condition manifests with symptoms such as numbness, pain, as well as dermatomal and myotomal weakness [1,2]. This process results in increased pressure and stimulation of the lumbosacral nerve root and cauda equina, thereby inducing an inflammatory response [3]. The prevalence of radicular pain attributable due to disc herniation ranges from 2 % to 4 %, with a higher incidence exhibited in males and individuals aged 30 to 50 years [4]. The primary manifestations of LDH are pain and neurological dysfunction, with over 60 % of patients experiencing persistent low back pain or frequent recurrences of the pain within a year [4]. Initial management strategy typically involves the use of non-steroidal anti-inflammatory drugs (NSAIDs) [5]. Consequently, there is an increasing need for expeditious and precise clinical diagnostics methods, accompanied by targeted therapeutic interventions.

Currently, computed tomography (CT) and magnetic resonance imaging (MRI) are the most efficient methods for the diagnostic imaging of disc herniation. In 1984, Guinto *et al.* [6] reported for the first time the resorption phenomenon in patients with LDH, which was observed on CT images after 18 weeks of non-surgical treatment. Additionally, in 2016, resorption was observed using MRI as well in a 29-year-old woman with a herniated intervertebral disc (IVD) [7]. Existing research indicates that the resorption rate of LDH is approximately between 60 % and 70 %, with significant inter-country variability [8,9]. The resorption rates of LDH are significantly high, with reported values including 66.98 % in Japan, 61.66 % in USA, 83.52 % in Korea, 60.68 % in China, 78.30 % in UK, 56.70 % in Italy,

and 83.68 % in Turkey [10]. The underlying mechanism of resorption may be associated with various factors, including vascularization of prominent tissues, immune response, and nucleus pulposus dehydration.

The treatment strategies for LDH comprise surgical and non-surgical interventions. Lumbar discectomy is the most common surgical procedure for the treatment of low back and lower extremity symptoms in USA; however, its efficacy compared to non-surgical treatments remains a topic of ongoing debate. Short-term results from several large-scale randomized controlled trials indicate that surgical treatments exhibit significant effects for pain relief [11–14]. However, with extended follow-up periods, especially in assessing medium- and long-term outcomes, the difference between surgical and non-surgical treatments is not significant [15]. Additionally, not all patients with current surgical indications prefer surgical intervention. Recent advancements in non-surgical treatments have exhibited promising results, with a majority of LDH patients experiencing symptom relief or complete recovery without requiring surgical intervention. Currently, the spontaneous resorption of lumbar disc herniation (RLDH) has extensively been observed via imaging, however, its underlying mechanism remains incompletely understood. Consequently, it is crucial to investigate which factors can accurately predict the RLDH, as well as the optimal conditions that can induce or facilitate the resorption mechanism. This review comprehensively summarizes the predictive factors of recurrent RLDH and the key mechanisms contributing to its development, with the aim of providing valuable insights to improve clinical treatments. While numerous studies have identified correlations between LDH resorption and various factors, most of these studies insufficiently investigate the causal mechanisms in depth. Subsequently, there remains a gap in literature regarding the understanding of these LHD resorption mechanisms [3,16]. This review aims to critically assess the existing findings, highlighting their limitations, and addressing the gaps in our understanding of the underlying mechanisms of LDH resorption.

Predictive Factors of RLDH

The natural history of LDH is influenced by various factors, including type and location of the herniated disc, patient's anatomical characteristics, composition of the herniated material, biochemical properties of the herniated tissue, patient's clinical presentation, and patient-related factors [3]. Researchers have identified a significant correlation between these factors and the natural history of RLDH. Consequently, the focus of our study is to investigate the predictive factors of RLDH.

Tissue Components of LDH

Disc herniation is primarily composed of varying proportions of NP, AF, and cartilaginous endplate (CEP). Studies using the MRI technology indicate that the lumbar intervertebral discs consist of components such as NP, AF, mucoid tissue, proliferating granulation tissue, and CEP [17–19]. The NP, predominantly composed of water, is particularly susceptible to absorption. This susceptibility is associated with the extrusion of NP into the extradural space, thereby facilitating macrophage infiltration and neovascularization, which facilitates absorption. The AF, characterized by good tensile strength, can effectively boost absorption in instances where it remains intact and the herniated disc material does not exhibit extrusion or displacement. However, protruding CEP fragments may impede the RLDH, with Modic type 2 changes the most predominant observation [20]. According to a study conducted by Lama *et al*. [21], CEP fragments exhibit negligible swelling, loss of proteoglycans, or invasion of inflammatory cells in a saline environment, resulting in a slow absorption rate. Conversely, NP and AF tissues experience rapid swelling in physiological saline environment, which enlarges the pore size, causing a significant loss of proteoglycans, as well as hindrance of vascular growth. Additionally, CEP protrusion is strongly correlated with Modic changes. Research has demonstrated that protruding tissues exhibiting Modic changes contain a greater quantity of CEP fragments, which further impede their absorptive capacity [22,23]. Conversely, herniated tissues that are devoid of Modic changes demonstrate increased neovascularization and macrophage infiltration, thereby boosting their absorptive capacity [24]. This observation may be due to the inhibitory effects of CEP fragments or Modic changes on neovascularization and inflammatory cells phagocytosis, consequently delaying or preventing absorption. Hence, the absorptive capacity of the IVD tissue is determined by its components: NP exhibits higher water content and AF exhibits good tensile strength that enhance the absorption, while CEP fragments and Modic changes may impede neovascularization and inflammatory cells phagocytosis, thereby delaying or blocking absorption. The potential of herniated IVD tissue components to facilitate RLDH is primarily influenced by their propensity to foster neovascularization and inflammatory cells phagocytosis. Future studies should aim to delineate the components of herniated tissue and identify molecular markers to predict LDH prognosis, which will significantly impact clinical decision-making.

The Types of LDH

A comprehensive review focusing on RLDH has revealed significant findings on the incidence of disc resorption. The overall disc resorption incidence was reported to reach a high figure of 70.39 %. Notably, the rates varied based on the type of herniation with 87.77 % for sequestrated discs, 66.91 % for extruded discs, 37.53 % for protruded discs, and 13.33 % for bulged discs. Furthermore, the observed resorption rates varied depending on the degree of disc herniation reduction. Resorption occurred in 40.19 % of patients with 25–50 % herniation reduction,

43.62 % with greater than 50 % reduction, and 36.89 % with complete (100 %) resorption [10]. These findings highlight varying outcomes of disc resorption in RLDH based on various clinical presentations. Particularly, free and sequestrated types of LDH demonstrate a higher potential of undergoing resorption, with this propensity attributable to the fact that these types of herniated materials rupture the AF and enter the spinal canal, thereby interacting with the extradural venous plexus's rich blood supply. This interaction causes hematoma formation, which potentially precedes the natural resorption process. Enhanced blood supply induces more immune cells to infiltrate into the LDH and can lead to the secretion of more growth factors, which facilitate repair and waste removal. Moreover, free and sequestrated herniations exhibit a tendency to extrude extra-disc material and they involve more active autophagic pathways, facilitating the resorption of the herniated area [25]. In a prospective cohort study [26], findings demonstrated that sequestered LDH tends to undergo spontaneous regression, with this regression observed in the majority of patients who received conservative treatment for non-surgical isolated LDH, typically occurring around the sixth month after an MRI evaluation. Furthermore, the development of RLDH is associated with the location of the LDH. The herniation of the NP into the spinal canal triggers an inflammatory response, which promotes the natural resorption of the herniated disc.

In summary, RLDH is frequently observed in sequestered and extruded discs, which are characterized by the ability of NP to rupture the fibrous ring, intrude the blood-rich spinal canal, and potentially induce a strong inflammatory response. The inflammatory response, body's self-protection and repair mechanism against the protrusion, can further stimulate angiogenesis, recruiting immune cells and repair factors to the damaged area. Sequestered and extruded particles can trigger a robust inflammatory response, thereby stimulating the self-repair mechanism and leading to a high self-absorption rate. Further research should be conducted to explore the intrinsic association between LDH types and RLDH mechanisms to maximize patient benefits.

MRI Signal Enhancement around LDH

When the NP of the IVD protrudes through the dura mater, it triggers an autoimmune response leading to inflammation and granulation tissue formation. This process is observable on imaging as a ring enhancement pattern, with the unaffected IVD at the center, forming an image known as the "bull's-eye" sign (Fig. 1) [3]. This "bull's-eye" sign indicates vascularization and formation of inflammatory granulation tissue in LDH [27]. Concurrently, the immune response fosters neovascularization in the protruding IVD tissue [28]. On T2-weighted MRI (T2WI), areas of high-intensity ring enhancement in the posterior AF at the site of the LDH can be observed [29]. According to Shen *et al*. [27], a thicker edge enhancement indicates a higher degree of ring enhancement signal, thereby increasing the likelihood of resorption. Additionally, ring enhancement around the IVD on MRI significantly correlates with inflammatory histopathological features, including detectable CD3+ T lymphocytes and various degrees of neovascularization [30]. Notably, these imaging manifestations are influenced by MRI principles; specifically, the number of hydrogen ions affects the size of the ring enhancement. Therefore, a positive "bull's-eye" sign serves as an imaging indicator of neovascularization and inflammation in protruding tissues and represents a novel predictor of resorption.

MRI is the definitive tool for diagnosing LDH, as well as an emerging tool for predicting RLDH [31]. Although recent advancements in MRI methods detect subtle chemical changes in the IVD matrix, predicting resorption remains a challenging task. Besides, it is insufficient to solely rely on advanced imaging to diagnose resorption. Clinical judgment and a comprehensive understanding of resorption are required as well. Additionally, factors such as the patient's economic condition and MRI side effects complicate the application of these new MRI methods. Moreover, these advancements have enabled the detection of subtle chemical changes within the disc matrix, which offer significant clinical insights. Advancements in MRI technology, including T2WI, have enabled the detection of subtle chemical changes and morphological alterations within the IVD matrix, such as height and water-intensity loss [32]. These techniques facilitate the observation of alterations in the microenvironment associated with LDH resorption, thereby aiding in the evaluation of its potential.

In summary, the development of new detection and treatment methods is ongoing, emphasizing the importance of spinal orthopedic surgeons recognizing the resorption phenomenon. Acknowledging this process allows for an integrated approach that combines both symptomatic and imaging data, ultimately improving the clinical decision-making process.

The Degree of LDH

Research indicates that the likelihood of a protruding IVD absorption increases with the size of the protrusion and the extent of the protrusion into IVD space [33]. This observation can be attributed to the fact that when the protrusion is large or the NP extends beyond the IVD space, it interacts with a greater number of surrounding tissues and immune cells [25]. This interaction triggers an inflammatory response, promoting neovascularization and absorption of the NP structure. However, small and enclosed IVD protrusions pose significant challenges in non-surgical treatments and natural history of the condition. Additionally, if the protruding IVD tissue has enough space to contact blood circulation, its metabolism and cell renewal become more active, facilitating IVD tissue absorption. Therefore, large protrusions or those where the NP structure extends beyond the IVD space are increasingly likely to be absorbed.

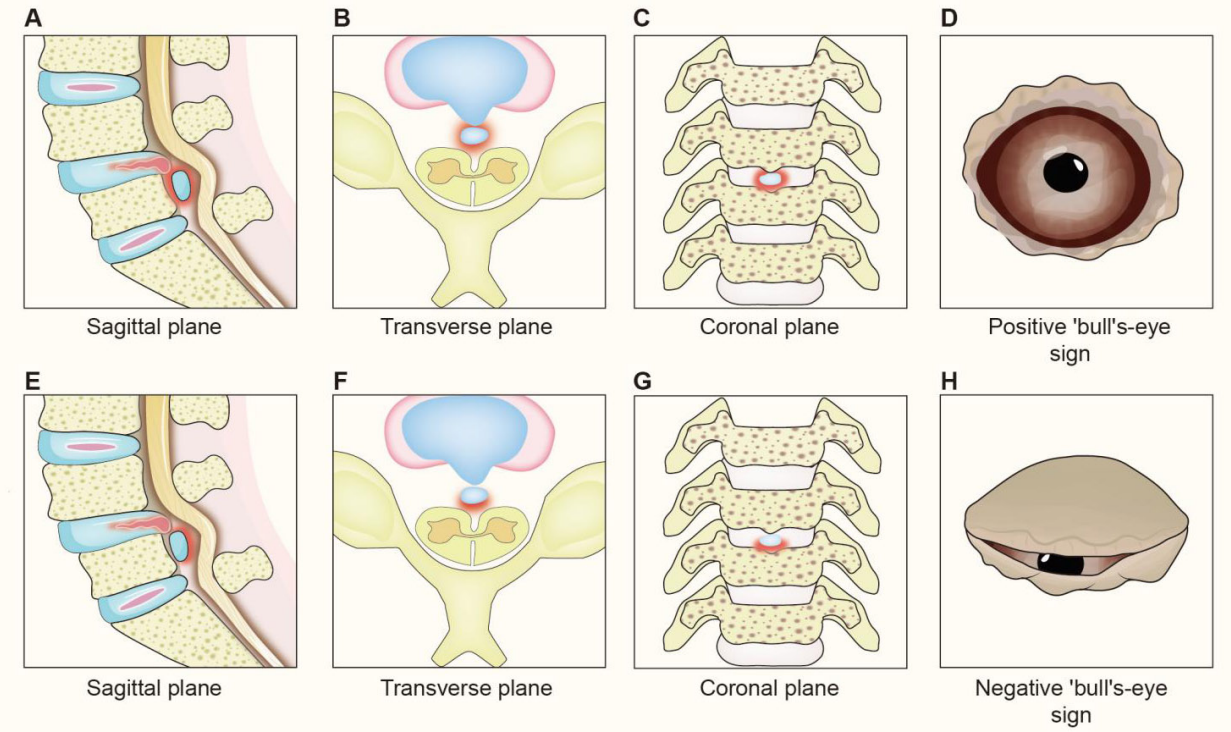

Fig. 1. The "bull's-eye" sign. The image depicts a positive "bull's-eye" sign with circular enhancement signals encircling the prominence in the sagittal plane (**A**), transverse plane (**B**), and coronal plane (**C**) positions, bearing resemblance to an open cow's eye (**D**). In contrast, a negative "bull's-eye" sign devoid of enhancement signals encircling the prominence is discernible in the sagittal plane (**E**), transverse plane (**F**), and coronal plane (**G**) positions, bearing resemblance to a slightly closed cow's eye (**H**).

While the severity and destructiveness of such protrusions often necessitate surgery, the challenge occurs in making clinical decisions, especially regarding waiting for absorption or opting for timely surgical intervention. Gunzburg *et al*. [34] revealed that the degree of IVD protrusion is not a primary surgical indication; instead, the patient's pain symptoms should be the main consideration. This finding is corroborated by an observational study of 409 patients with massive LDH, which revealed that only about 22 % (89/409) of the patients underwent surgical treatment [9]. The study further emphasized that patients with massive LDH are less likely to experience progressive nerve damage and cauda equina syndrome, rendering non-surgical treatment a viable option. Therefore, the likelihood of IVD absorption is directly associated with its size and the extent of displacement from the IVD space. In the future, doctors and researchers should explore all treatment options, including non-surgical interventions, and base their decisions on the patient's symptoms and quality of life to reduce the economic burden and side effects of LDH surgery.

Other Predictive Factors

Numerous clinical factors, including age, smoking habits, and disease duration, have been found to potentially impact RLDH. Research indicates that younger LDH patients are more likely to experience disc reabsorption [35]. This finding can be attributed to the heightened cell activity within young patients' discs, which are typically more elastic and water-rich. Consequently, the younger patients are better equipped to self-repair when the disc protrudes, leading to the absorption of the extruded disc tissue. Furthermore, among patients with a smoking history exceeding a decade, smokers exhibit higher hemoglobin levels compared to non-smokers, indicating that chronic smoking induces hypoxia due to increased carboxyhemoglobin formation. This reduction in oxygenation impairs the natural resorption process of IVDs [36]. This hypoxic is attributed to nicotine-induced vasoconstriction in smokers, leading to diminished blood flow to the IVD, hindering cellular activity within the disc, thereby reducing the nutritional supply essential for disc health. Additionally, patients with a shorter symptom duration exhibit a higher rate of disc reabsorption. Research has shown that early resorption can occur in 24.7 % of LDH patients at around 3 months [16], a period that serves as a crucial opportunity to determine the optimal treatment option [2,37]. During the early stage of LDH, the immune inflammatory response around the protrusion is intense, representing an optimal opportunity for reabsorption to occur. Ultimately, factors such as age, smoking status, and symptom duration play a significant role in disc reabsorption. Moreover, the 3-month post-onset period represents an optimal opportunity to make clinical decisions on the application of surgical intervention.

In summary, exploring various factors influencing disc protrusion absorption—such as the degree of protrusion, the composition of the protruding tissue, patient age, smoking habits, symptom duration, and genetic factors—enable informed decision on optimal treatment strategies. These factors significantly impact the mechanisms of recurrent RLDH, influencing inflammatory phagocytic responses and neovascularization. Although the existing studies have identified predictive factors for RLDH, they exhibit several limitations. Most studies use small sample sizes and lack the longitudinal data necessary to establish causality. To address these gaps, future studies should involve larger cohorts and long-term follow-up to validate these predictive factors and explore the underlying mechanisms in depth. Additionally, future studies should focus on optimizing models that simulate the biomechanical conditions and microenvironment of human disc herniation. Such models will be instrumental in identifying key factors influencing absorption, thereby facilitating a deeper understanding of the process and the development of more effective intervention strategies for the treatment of RLDH.

Potential Mechanisms

Inflammatory Phagocytosis

The IVD, the largest avascular structure in the human body, is composed of the peripheral AF, central NP, and the CEP [38,39]. The IVD acts as an immunologically privileged organ under healthy conditions [2], effectively isolating the NP from the host's immune system. This protective isolation is facilitated by the blood-NP barrier, a structure composed of AF, CEP, and immune-suppressive molecular factors [40,41]. Additionally, the local expression of Fas ligand (FasL, a protein modulating cell death) prevents neovascularization within the IVD [42]. Collectively, elements like AF, CEP, and FasL render the IVD a unique, immunologically privileged structure. The proteoglycans and collagen within the NP, both capable of inducing an immune response, are antigenic. In circumstances where the disc tissue protrudes or extrudes from the AF, breaking the blood-NP barrier, an immune response is elicited by the NP [43]. This process is attributed to the expression of monocyte chemotactic protein-1 by IVD cells, which stimulates the recruitment of macrophages that induce IVD proteolysis. Consequently, the interaction between these macrophages and IVD cells induces inflammatory factors, leading to local inflammation. This cascade of immune response causes continuous degradation of the antigenic substances until the protruding tissue is resorbed and inflammation resolves. A previous observation study identified a higher proportion of regulatory T cells and macrophages in LDH tissue using bioinformatics analysis, further validating the involvement of the immune response in the disc resorption process [30].

Macrophages play a pivotal role in the context of RLDH. Recognized as the primary immune regulators inducing RLDH, the infiltration and activation of macrophages are at the core of the resorption process [44]. Numerous studies have validated the presence of macrophages in protruding IVDs [43,45]. Notably, these macrophages undergo a transition from M1 macrophages to M2 macrophages during resorption [46]. The pro-inflammatory M1 macrophages secrete cytokines that promote matrix metalloproteinases (MMPs) expression and induce apoptosis of protruding IVD nucleus cells, thereby initiating angiogenesis. Additionally, M1 macrophages produce nitric oxide, fostering cell autophagy and apoptosis under oxidative stress conditions [47]. The M2 macrophages secrete anti-inflammatory cytokines that facilitate the resorption of protruding IVD fragments, thereby reducing the volume and intensity of nerve compression. Moreover, M2 macrophages limit inflammation to alleviate pain, eliminate residual tissue, promote angiogenesis, and contribute to tissue remodeling and repair. However, excessive polarization of either M1 or M2 macrophages leads to negative health outcomes. Overactivation of M1 macrophages is associated with tissue damage, inflammation, and autoimmune diseases, whereas excessive polarization of M2 macrophages can enhance repair and immune tolerance, potentially resulting in fibrosis [48]. Therefore, maintaining a balance between M1 and M2 macrophages emerges as a potential therapeutic approach for RLDH. This observation underscores the need for researchers to explore whether modulating the M1/M2 macrophage balance can offer an effective treatment for RLDH. For instance, converting macrophages from an M1-dominant to an M2-dominant state could reduce excessive inflammation, while shifting from an M2-dominant to an M1-dominant state might decrease fibrosis. These new strategies warrant further investigation. To corroborate these findings, Kim *et al*. [49] demonstrated the feasibility of reprogramming M1 to M2 macrophages in rheumatoid arthritis treatment. Their findings revealed that the cartilage destruction associated with rheumatoid arthritis was associated with the overactivation of M1 macrophages. However, the use of M2-derived exosomes successfully redirected macrophages toward M2 macrophage polarization, effectively mitigating the effects of the disease [49]. Therefore, the infiltration and activation of macrophages are vital in mediating the inflammatory response, facilitating angiogenesis, and activating MMPs.

Matrix metalloproteinases are pivotal in the inflammatory cascade response associated with RLDH. The MMPs stimulate the degradation and remodeling of damaged tissues and modulate the inflammation process [28]. Le Maitre *et al*. [50] evaluated the human IVD tissue obtained either at surgery or at post-mortem examination, and found that the proportion of matrix metalloproteinase-3 (MMP-3) positive cells was significantly higher in degenerate discs compared to that in non-degenerate discs. Moreover, this proportion was directly proportional to the degree of protrusion. Concurrently, Haro *et al*. [51,52] reported increased

expression levels of MMP-3 and matrix metalloproteinase-7 (MMP-7) in mice experiments. Collectively, these findings indicate that MMP-3 is a potential key mediator of IVD resorption. Additionally, Le Maitre *et al*. [50] and Haro *et al*. [51] demonstrated that MMP-3 can trigger the production of macrophage chemotactic factors, thereby promoting more monocyte chemoattractant protein-1 (MCP-1) release. This release facilitates macrophage infiltration and proteoglycan loss, as well as the absorption of IVD protruding tissues. Current, research indicates that the presence of tumor necrosis factor-alpha (TNF-α) in IVDs can induce a comparatively mild inflammatory response, impede the formation of the cartilage matrix and stimulate the production of MMPs, potentially influencing the protrusion and absorption of IVD [53].

In summary, the protrusion and subsequent breach of the IVD tissue's isolation barrier induce an immune response, causing local inflammation and absorption of the protruding tissues. Macrophages, which could polarize from the M1 to the M2 macrophage phenotype, play a crucial role in the resorption process by facilitating the degradation and absorption of protruding IVD tissues. Similarly, MMPs significantly contribute to this process by facilitating tissue degradation and regulating inflammation. Three potential approaches have been proposed to induce the inflammatory response to promote RLDH [3]: first is the interaction of the structural elements and compounds in IVD cell membranes and matrix; second, the direct contact between NP and the immune system could also stimulate this response; finally, secondary response to an autoimmune reaction.

Angiogenesis

In addition to the inflammatory response, a distinguishing feature of RLDH is neovascularization in the IVD protruding tissue absorption area, which correlates with the degree of protrusion reduction and prognosis [54]. Clinically, vascular invasion which is a key marker of neovascularization has been observed in the deeper tissues of the IVD [55]. Within the IVD protrusion area, the primary cytokines that initiate neovascularization include TNF-α, vascular endothelial growth factor (VEGF), basic fibroblast growth factor, and platelet-derived growth factor [56]. Additionally, the role of infiltrated macrophages in disc degeneration extends beyond inflammatory response, encompassing the process of neovascularisation, where M2-type macrophages promote the pro-angiogenic capacity of endothelial cells, thereby facilitating conditions conducive for disc resorption [57,58]. Notably, although the mature IVD lacks blood supply system, the exposure of protruding NP tissue to the vascular environment in the extradural space initiates inflammatory responses and vascularization in protruding NP tissues. This induces macrophage activity and immune responses, eventually leading to the shrinkage or disappearance of the protruding NP tissue.

These studies underscore the important role of neovascularization in the RLDH process and its significant influence in the absorption and prognosis of IVD protruding tissues. Mediators such as fibroblast growth factor and VEGF are the primary drivers in this process. Notably, macrophage-based therapy has shown promising results in the treatment of intervertebral disc herniation. The envisaged clinical therapy consists of a minimally invasive autologous adoptive cell transfer, in which monocytes are isolated from the patient's peripheral blood, polarized *in vitro*, and returned to the same patient similar to the protocol used for dendritic cells and T-cells cancer immunotherapies. This therapy relies on the potentiation of the physiological hernia regression mechanisms. Further development of this macrophage-based therapy for clinical application is warranted [43].

NP Dehydration

Dehydration of the NP of the IVD is hypothesized as a potential mechanism for LDH reabsorption. A normal NP is a gelatinous structure with high viscosity and elasticity, comprised of proteoglycans and intermolecular water, which accounts for up to 80 % of its composition [59]. Persistent pressure on the IVD leading to protrusion, results in high osmotic pressure of the IVD matrix that causes the protruding part to further expand upon contact with an aqueous solution. During this process, water and glycosaminoglycans permeate into the surrounding tissues, resulting in disc swelling. Conversely, when the load decreases or disappears, these substances gradually re-enter the disc from surrounding tissues, reducing the disc's volume and height, a process termed as NP dehydration, which facilitates reabsorption. This theory was initially proposed by Bozzao *et al*. [60], who observed that the initial high signal IVD fragments on T2-weighted MRI scans are secondary to an increase in water content or vascular reconstruction post-protrusion in 69 LDH patients. Despite these observations, additional evidence is needed to substantiate the role of NP dehydration in the RLDH process.

Mechanical Traction

Mechanical traction is another potential mechanism of the RLDH. This concept suggests that the protruding IVD could retract into the IVD gap. However, theoretically, this process may only be viable when the AF remains intact and the protruding IVD has not been extruded or migrated. According to Kilitci *et al*. [61], the primary reason for the retraction of IVD protrusion is primarily due to the pressure exerted by the posterior longitudinal ligament. Another hypothesis posits that during the spinal load-bearing process, parts of the AF endure tensile stress, thereby inducing an elongating effect [62]. This traction force decreases the transverse dimension of the intact AF, elongates it longitudinally, and transforms the IVD from a short convex shape to a narrow and slightly concave shape. This defor-

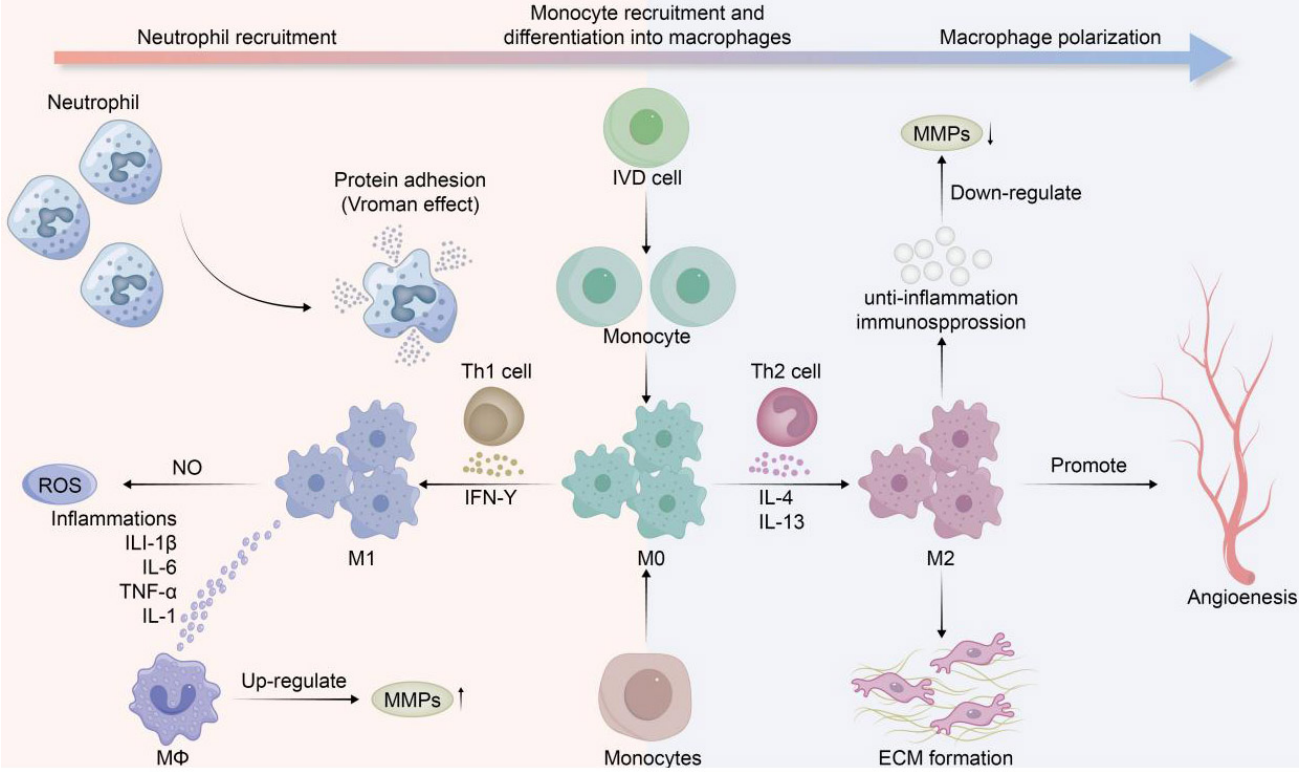

Fig. 2. The main mechanism of RLDH. The process of RLDH involves macrophage infiltration of disc tissue, interactions between macrophages and disc cells, and the differentiation of M0-type macrophages into M1 and M2 types. This leads to the release of various cytokines, including TNF-α, VEGF, IL-1, IL-1β, IL-4, and IL-13, which interact to regulate reactive oxygen species (ROS) and MMPs, as well as to promote disc herniation resorption. IVD, intervertebral disc; MMPs, matrix metalloproteinases; TNF-α, tumor necrosis factor-alpha; RLDH, resorption of lumbar disc herniation; VEGF, vascular endothelial growth factor; IFN, interferon; NO, nitric oxide; IL, interleukin.

mation potentially generates a pressure differential within and outside the ring, inducing an internal negative pressure that contributes to the reabsorption of the protruding NP part. Based on this principle, traction and operational techniques have been used to promote IVD reabsorption. Theoretically, there is a potential for RLDH, however, this possibility is not manifested in every patient. Consequently, given the insufficient research supporting this mechanism, further studies should be conducted to verify the feasibility of the mechanical traction method.

In summary, RLDH results from a sequential occurrence and interaction of various biological processes (Fig. 2). Currently, research indicates that inflammatory response and the formation of new blood vessels are primary drivers of this phenomenon, synergistically reinforcing each other in the RLDH process. The inflammatory response allows immune cells like macrophages to invade the protruding NP tissues and triggers angiogenesis, providing the necessary physical and biological conditions for reabsorption. Similarly, angiogenesis amplifies the inflammatory response, thereby facilitating the absorption of the protruding NP tissues. The potential mechanisms underlying RLDH, including inflammatory phagocytosis and angiogenesis, remain largely speculative based on the existing research [63]. Although these mechanisms provide a plausible explanation for the process of resorption, they are mainly inferred from correlative data. Consequently, further experimental validation is needed to establish causality. Future therapeutic strategies should aim to mediate the microenvironment of RLDH, effectively regulate the polarization of macrophages, determine the optimal degree of the inflammatory response, and promote angiogenesis to facilitate reabsorption.

First-Line Therapies of RLDH

The RLDH is intrinsically associated with inflammation, facilitated by the biological mechanisms of inflammation and neovascularization. During RLDH, neovascularization and the upregulation of inflammatory factors in protruding tissues lead to heightened oxidative stress, evidenced by an increase in reactive oxygen species (ROS) within NP cells. The increase of ROS levels initiates excessive autophagy, altering the function of protruding NP cells, ultimately facilitating reabsorption. Existing research indicates that inflammation is the primary catalyst for RLDH, rendering it as a reliable prognosis indicator [43]. Despite the National Institute for Health and Care Ex-

cellence (NICE) guidelines recommending NSAIDs as the first-line treatment for sciatica, it is crucial to consider individual risk factors—such as age—and monitor for potential gastrointestinal, liver, and cardio-renal toxicity when prescribing these medications [64]. The lowest effective dose should be used for the shortest duration, alongside appropriate clinical assessment and gastroprotective treatments. While NSAIDs and corticosteroids are commonly prescribed, their impacts on the inflammatory process in RLDH pose challenges for the resorption process, which is essential for healing. Recent studies suggest that anti-inflammatory medications such as NSAIDs and corticosteroids potentially interfere with the body's natural mechanisms for RLDH [65–67]. This finding highlights a significant limitation in our current therapeutic approach, as the suppression of inflammation, which is a significant feature of RLDH, may inadvertently hinder the resorption process.

Advancements in basic research on the RLDH have highlighted the disc reabsorption mechanism, leading to the exploration of novel treatments that preserve inflammation. These treatments, including regenerative medicine, epigenetics, genomics and cell-based therapy, offer unique therapeutic benefits. Regenerative medicine, including epidural injection of pro-angiogenic factors can promote new blood vessel formation and induce macrophage phagocytosi [3]. While regenerative medicine exhibits promise for disc repair, its clinical application remains in the early stages, and further research is necessary to evaluate long-term safety and efficacy. Epigenetic modulation presents a promising therapeutic strategy for LDH by influencing macrophage polarization, particularly promoting the shift towards M2 macrophages phenotype, which plays a key role in tissue repair and inflammation resolution. As highlighted by Hou *et al*. [68], epigenetic mechanisms, such as deoxyribonucleic acid (DNA) methylation and histone modifications, can regulate macrophage phenotypes, potentially reducing inflammation and facilitating the reabsorption of the NP. This approach offers a targeted alternative to the traditional anti-inflammatory drugs, which exhibit several limitations and adverse side effects. However, challenges remain in the application of epigenetic mechanisms, including the complexity of epigenetic regulation, the risk of unintended effects, and the need for efficient drug delivery systems to target the affected disc. Despite these challenges, epigenetic modulation exhibits promise as a personalized, targeted therapy for LDH, warranting further research to evaluate its safety, efficacy, and clinical application. In genomics, Wang *et al*. [30] identified critical genes and NP cell subclusters in LDH tissues. Their study reveals that transforming growth factor beta (TGF-β) and mitogen-activated protein kinase (MAPK) signaling pathways play a pivotal role in the immune infiltration of NP tissues and may serve as diagnostic markers for IVD degeneration and herniation [30]. These findings underscore the importance of macrophage polarization in RLDH pathogenesis and the potential for gene-targeted therapies to alleviate inflammation and promote tissue repair. However, challenges in optimizing delivery methods for targeting specific NP cell subclusters persist. Additionally, the identified hub genes and the associated sub-clusters of NP cells elucidate the molecular landscape of LDH. These findings have potential applications in developing targeted diagnostic tools and therapeutic strategies to modulate these signaling pathways, thereby alleviating inflammation and promoting tissue repair in LDH [30]. However, significant challenges remain. Targeting the TGF-β and MAPK pathways may exert unintended effects on other cellular processes, and their long-term safety profile and efficacy need to be further investigated. Furthermore, optimizing delivery methods for targeting specific NP cell subclusters and immune cells is essential for realizing the clinical potential of these strategies. Their findings suggest that the TGF-β and MAPK signaling pathways may serve as diagnostic markers, highlighting the role of specific gene expressions in IVD degeneration and herniation. In their pivotal study, Ribeiro-Machado *et al*., 2023 [43] investigated the crucial role of macrophages in RLDH using a rat model, in which they compared the effects of systemic macrophage depletion with the therapeutic injection of bone marrow-derived macrophages into the affected discs. The results revealed a 44 % reduction in herniation size after macrophage injection, while depletion of macrophages led to increased herniation, underscoring their essential role in RLDH. Additionally, the study identified cytokine modulation—specifically interleukin-4 (IL-4), IL-17a, IL-18, lipopolysaccharide-induced CXC chemokine (LIX), and the Regulated upon Activation, normal T cell expressed and presumably secreted (RANTES)—as key factors in promoting tissue resorption and repair. These findings enhance our understanding of the pathophysiology of LDH and offer promising insights into the development of targeted macrophage-based therapies for this prevalent condition. However, the study exhibited limitations that must not be overlooked, including species differences in the model, the lack of long-term efficacy and safety data, and the complexity of macrophage subtypes [43].

While basic research into the mechanisms of RLDH, such as the roles of inflammatory phagocytosis, angiogenesis, and macrophage polarization, has unveiled promising therapeutic strategies, translating these insights into clinical practice is vital. The major challenges include developing personalized treatment strategies that consider the patient's unique clinical presentation, genetic profile, and response to therapy. Against this background, multiple therapies, including those targeting macrophage polarization and inflammation, are increasingly being investigated for potential clinical translation, and improve the implementation of personalized treatment approaches for RLDH patients. Regenerative medicine, including epidural injection of pro-angiogenic factors, has shown significant potential to repair damaged disc. To unlock its full clinical value, it is crucial

to identify specific IVD hernia patients who are most likely to benefit from this therapeutic approach, and hence improve personalized treatment. To achieve this, several targeted analyses must be conducted. These analyses should focus on profiling the most effective pro-angiogenic factors to be administered, optimizing the injection timing, route, and dosage, and ensuring the safety of the therapy. Additionally, the establishment of advanced diagnostic tools, such as MRI and biomarkers, is necessary. These tools will help determine the optimal treatment timing and dosage, thereby enhancing treatment outcomes and minimizing associated side effects. Notably, lumbar disc degeneration (LDD) has a close causal relationship with LDH, with its progression linked to the development of LDH [69,70]. In patients with LDD, the height of the IVD gradually decreases and the biomechanics of the spinal segments are altered, leading to degeneration of the adjacent segments and other spinal structures (ligaments, joints, muscles, etc.), or even rupture of the lumbar disc AF. Moreover, the NP protrudes into the spinal canal compressing the nerves, causing LDH. In cases where the herniation degree of LDH is large or the type of LDH is disc sequestration and extrusion, RLDH may occur. LDD represents the early stage of the disease, in which the internal environment of the IVD is still stable, with only a small number of disc cells undergoing degeneration or necrosis. In contrast, the condition is severer when RLDH develops, and in response to strong stimuli such as contact of the herniated material with the blood transport and high cytokine aggregation, numerous disc cells undergo necrosis, and the internal environment of the disc is destabilized, resulting in the occurrence of disc resorption. Macrophages play an important role in LDD, LDH, and RLDH, and influence the pathological process of the lumbar intervertebral disc by regulating the inflammatory response and promoting apoptosis and autophagy. Epigenetic modulation provides a targeted approach for modulating immune responses by shifting macrophage polarization, making it a novel strategy for treating LDD. Regarding clinical translation, these findings indicate that agents targeted at macrophage polarization through epigenetic mechanisms like DNA methyltransferase 1 (DNMT1) inhibition may be promising treatments for LDD [68]. In the early stage of disc herniation, epigenetic modulation can inhibit disc degeneration, and when applied early enough, it can prevent, reverse or inhibit further progression of the disease. For patients with RLDH who present with severe clinical symptoms and significantly herniated tissue in the MRI images, epigenetic modulation's intervention can promote resorption of the herniated tissue and treat the disease at the pathogenesis level. To address the gap between basic research and clinical application, future studies should focus on evaluating the safety, efficacy, and long-term outcomes of such therapies in human patients. Personalized treatment approaches are vital in addressing this challenge, tailoring therapies based on individual factors such as the stage of disc degeneration, inflammatory profiles, and immune responses. Advanced diagnostic tools including MRI and biomarkers could help guide therapy, monitor treatment efficacy, and optimize therapeutic outcomes. This will promote the formulation of individualized treatment plans, thereby improving the precision and effectiveness of LDD therapies. Integrating epigenetic modulation into regenerative therapies offer significant benefits for LDD patients, addressing both the underlying pathology and promoting long-term healing and pain relief. Genomics and macrophage-based therapies represent a promising frontier in RLDH treatment. These therapies target the molecular mechanisms underlying RLDH; however, effective clinical translations require the development of methods to deliver these therapies directly to the IVD or surrounding tissues. Liu *et al*. [71] present glypican-3-targeted macrophages delivering drug-loaded exosomes, which enhance tumor targeting and immune modulation. Genomic analyses may facilitate identification of patients most likely to benefit from such therapies, allowing for the integration of targeted macrophage injections into personalized treatment strategies. This approach can effectively reduce tumor size and promote healing, offering a more precise, individualized therapeutic strategy applicable to both solid tumors and conditions such as disc degeneration. However, these therapies are still in the experimental stages, necessitating large-scale clinical trials to determine the most effective patient profiles and delivery techniques. In summary, while each treatment strategy offers unique advantages, successful clinical translation of RLDH therapies depends on the design of personalized treatment plans that consider patient-specific factors. These strategies can be combined to maximize therapeutic efficacy, such as integrating genomics with regenerative therapies or combining epigenetic modulation with macrophage-based treatments. Personalized medicine represents the future of RLDH treatment, and continued research will be pivotal in refining these approaches and validating their clinical benefits through large-scale, prospective trials.

Based on these findings, clinical translation of RLDH treatments requires a careful integration of various therapeutic strategies. The LDH resorption is often compared to inflammation and tumor regression, with cellular autophagy playing a complex, "double-edged sword" role in disc reabsorption. Each treatment strategy—NSAIDs, regenerative medicine, epigenetics, genomics, and cell-based therapy—offers distinct advantages but with specific challenges. Despite the promise of these therapies, future large-scale, prospective randomized trials are crucial for accurately assessing their clinical benefits. Progressive refinement of these strategies and integration of personalized treatments based on patient-specific factors are crucial to optimize patient outcomes in RLDH management.

Conclusions

This study provides a comprehensive review of the factors influencing RLDH and underlying biological mechanisms, highlighting the significant roles of variables such as MRI signal characteristics, patient age, smoking habits, and symptom duration in the resorption process. It has been identified that patients with specific MRI signal features, such as a positive "bull's-eye" sign, exhibit higher rates of resorption. Additionally, younger patients, non-smokers, and those with shorter symptom durations experience greater natural resorption of LDH. Biologically, the resorption of LDH is influenced by inflammatory macrophages and angiogenesis. Specifically, the shift from M1 to M2 macrophage polarization, alongside the involvement of MMPs in tissue remodeling and inflammation modulation, plays a pivotal role in the natural resorption of LDH.

Despite the identification of several predictive factors for RLDH, significant gaps remain in understanding the causal mechanisms of RLDH. Most studies are limited by small sample sizes and the absence of longitudinal data, thereby restricting their generalizability. Moreover, the proposed mechanisms, including inflammatory phagocytosis and angiogenesis, remain largely speculative and are primarily based on correlative data, thereby insufficient to infer any causality. These limitations underscore the need for large-scale, long-term, and randomized controlled trials to validate these findings and further elucidate the complex interactions between inflammation, autophagy, and tissue repair.

The effect of individual patient variability on the RLDH needs to be further dissected, with a particular focus on the key biological mechanisms, such as inflammatory responses and angiogenesis. The development of advanced diagnostic tools and targeted therapeutic strategies—particularly those capable of selectively modulating inflammation and promoting disc repair—would significantly benefit non-surgical treatment approaches for LDH. Regarding clinical translation, the application of these findings to clinical practice is crucial. This includes developing personalized treatment plans that are tailored for patient-specific factors such as the extent of disc degeneration, inflammatory profiles, and response to prior treatments. Additionally, incorporating advanced imaging techniques and biomarkers for monitoring therapeutic outcomes will be essential for optimizing treatment regimens and improve clinical outcomes. This study provides valuable insights into the pathophysiology of RLDH and lays the foundation for future clinical advancements, with the aim to improve the management and long-term outcomes of LDH through individualized, regenerative therapies.

List of Abbreviations

RLDH, resorption of lumbar disc herniation; LDH, lumbar disc herniation; NP, nucleus pulposus; AF, annulus fibrosus; CT, computed tomography; MRI, magnetic resonance imaging; CEP, cartilaginous endplate; IVD, intervertebral disc; MMPs, matrix metalloproteinases; MMP-3, matrix metalloproteinase-3; MMP-7, matrix metalloproteinase-7; MCP-1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; ROS, reactive oxygen species; NICE, National Institute for Health and Care Excellence; NSAIDs, non-steroidal anti-inflammatory drugs; DNA, deoxyribonucleic acid; TGF-β, transforming growth factor beta; MAPK, mitogen-activated protein kinase; DNMT1, DNA methyltransferase 1; LDD, lumbar disc degeneration; T2WI, T2-weighted MRI; FasL, Fas ligand; RANTES, normal T cell expressed and presumably secreted; IFN, interferon; NO, nitric oxide; IL, interleukin; LIX, lipopolysaccharide-induced CXC chemokine.

Availability of Data and Materials

Not applicable.

Author Contributions

LY contributed to the design of this work. YY contributed to the interpretation of data. LP analyzed the data. LY and ZYX drafted the work. HSJ and GQC revised critically for important intellectual content. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

All authors declare no competing interests.

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