Clinical Neurology and Neuroscience
2017; 1(2): 24-33
http://www.sciencepublishinggroup.com/j/cnn
doi: 10.11648/j.cnn.20170102.11

Review Article

Symptomatic Disc Herniations: A Review to Understand Pathophysiology and Prediction of Outcomes

Tagbo Ilozue[1], Mohamed Abdelsadg[2], Avinash Kumar Kanodia[3, *], Kismet Hossain-Ibrahim[2]

[1]Department of Neurosurgery, Royal Victoria Infirmary, Newcastle, UK

[2]Department of Neurosurgery, Ninewells Hospital, Dundee, UK

[3]Department of Radiology, Ninewells Hospital, Dundee, UK

Email address:

avinash.kanodia@nhs.net (A. K. Kanodia)

[*]Corresponding author

To cite this article:

Tagbo Ilozue, Mohamed Abdelsadg, Avinash Kumar Kanodia, Kismet Hossain-Ibrahim. Symptomatic Disc Herniations: A Review to Understand Pathophysiology and Prediction of Outcomes. *Clinical Neurology and Neuroscience*. Vol. 1, No. 2, 2017, pp. 24-33.
doi: 10.11648/j.cnn.20170102.11

Received: February 28, 2017; **Accepted**: March 24, 2017; **Published**: April 10, 2017

Abstract: Lumbar disc herniation is a common condition with a significant impact on health and economics worldwide. Although deemed unrequired in the majority of cases; surgery has a cardinal role in the management of this disease. Most patients will experience symptomatic improvement following conservative treatment, in fact some will experience complete recovery of their symptoms. Nonetheless the mechanism behind this spontaneous improvement is currently poorly understood, yet it offers the potential to inform therapeutic options that might promote more rapid recovery and prevent the establishment of long-term complications. This review summarises the available literature on the pathophysiological events occurring following lumbar disc herniation, with some relevant reflections on the clinical picture. Also the review highlights the current gaps in our knowledge, and stresses some of the debatable concepts in managing the disease, in order to identify areas where future research might help explain the process of spontaneous recovery from symptomatic lumbar disc herniations and also suggest direction of further research to have a positive impact about outcomes.

Keywords: Lumbar Disc Herniation, Disc Prolapse, Pathophysiology, Radiculopathy

1. Introduction

Disc herniation is a patho-anatomical abnormality defined by localised displacement of disc material beyond the limits of the intervertebral space [1]. Although this definition formally includes the "Schmorl's nodes" created by herniation into the endplates of the vertebrae, the term tends to be reserved for herniations that displace disc contents posteriorly into the spinal canal [1, 2]. In this more restricted formulation the condition affects 15-45% of the general population [3, 4]. However, the majority of these individuals will never discover their condition [5]. Disc herniations occur most commonly in the lower lumbar discs [6]. Thus, in the patients that are symptomatic, the typical clinical syndrome is a lower limb radiculopathy [7]. The syndrome continues to be designated 'sciatica', despite recent criticism of the persistent use of this 'archaic' term, which is derived from the Greek word for hip pain and thus does not adequately describe the problem [7, 8, 9]. It has a point prevalence of 1.6%, and affected individuals often experience symptoms during their working life, amplifying the economic consequences of the disease [10, 11].

Surgical intervention to remove the herniated disc material offers the potential of a more rapid relief from symptoms, but long-term outcomes for surgery and conservative treatment are equivalent [12]. Current guidelines recommend an initial period of conservative treatment before surgery is considered, even for the largest herniations, in the absence of red flags [13, 14]. In practice, this means that up to 90% of affected patients never require surgery to remove the herniated disc material that is thought to cause their symptoms [3, 7, 8]. Understanding why the majority of these patients recover offers guiding therapy to hasten recovery and enable more patients to avoid surgery. Furthermore, such understanding

may inform therapeutic options for up to 30% of patients who never fully recover from their symptoms [15]. Even amongst those undergoing surgery, more than 15% of patients experience recurrent radiculopathy or persistent lower back pain [16]. The development of these chronic symptoms after an acute herniation enormously augments the health and economic impact of the disease [11].

This paper provides a descriptive review of the literature that aims to establish our current level of understanding about the pathophysiological mechanisms responsible for spontaneous recovery from symptomatic lumbar disc herniations and proposes potential directions for future research into the phenomenon.

2. Review of Literature

2.1. Spontaneous Resorption of Herniated Discs

Multiple studies have attributed spontaneous clinical recovery to the resorption of herniated disc material (figure 1) [17]. Disc resorption was initially inferred from findings in cadaver specimens at autopsy [18], but the advances of CT and MRI enabled the process to be observed in living patients [14, 19, 20]. Herniations can be classified by whether the displaced material is 'contained' by annulus fibrosis, 'uncontained' due to a defect in the annulus, or 'sequestered' when a fragment has broken away within the spinal canal [1]. Greater resorption tends to be seen in larger herniations and in uncontained and sequestered fragments, and evidence of resorption is usually apparent within 6 months [14, 15, 20, 21]. The mechanism of this resorption has been debated and early speculation about a role for desiccation or physical retraction of the disc material has been replaced by consensus opinion that an inflammatory and phagocytic mechanism is likely to be responsible for the process [19, 21, 22, 23].

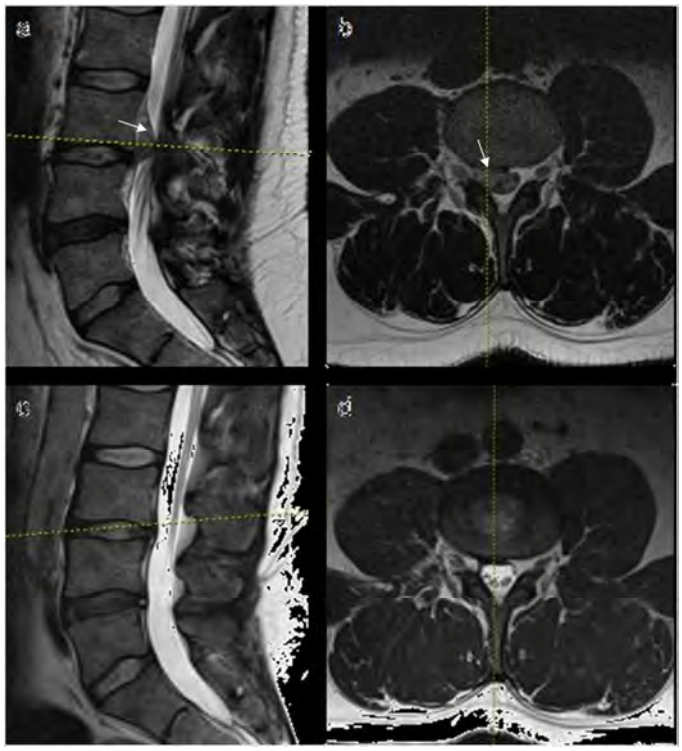

Figure 1. *a-b) large right L3/4 sequestered disc herniation (white arrow); c-d) resolution of the disc herniation after 11 months.*

2.1.1. The Nature of Inflammatory Response in Disc Herniation

The disc interior has been described as an immune privileged site due to its avascular nature and to nucleus pulposus expression of fas ligand, which promotes immune privilege by inducing apoptosis of fas-expressing cells such as activated T cells [24]. The exposure of nucleus pulposus tissue after disc herniation is therefore thought to initiate a foreign body reaction that triggers an adaptive immune response [25, 26]. However, others argue that the characteristics of the cellular infiltrate observed on histology and localisation of the inflammatory reaction to the site of herniation are not consistent with an antigen-specific response, suggesting instead that the pattern of inflammation is more consistent with wound healing [21, 27, 28]. Thus, while there is consensus about the importance of inflammation for disc resorption, there is ongoing debate over whether the inflammatory response is based on an auto-immune reaction [29].

In a rabbit model of disc herniation based on transplanting disc material into the epidural space, application of lipopolysaccharide to promote inflammation generated a more rapid decrease in the size of the disc material than suppression of inflammation with steroids [30]. Discs in the lipopolysaccharide group exhibited greater neovascularisation and a larger infiltrate of inflammatory cells and both these features are understood to be key components of the process

that leads to disc resorption [17]. Neovascularisation has been shown to be the most important prognostic determinant of whether resorption will occur [31]. The likelihood of resorption correlates directly with the degree of neovascularisation, identified on MRI by gadolinium-DTPA enhancement [32] (Figure 2). Contained discs, which are less likely to regress, are also less likely to exhibit such neovascularisation and may be less likely to exhibit a cellular infiltrate [33]. Whenever an infiltrate is observed, however, it is consistently dominated by macrophages [22, 34, 35]. These cells have a demonstrated capacity to engulf the cellular components of herniated discs and also stimulate production of matrix metalloproteinases (MMPs), which mediate extracellular matrix degradation [23, 36]. MMPs are normally produced by disc chondrocytes as part of the homeostatic turnover of the matrix, but are upregulated in herniated discs [37, 38]. Their catabolic effects are likely to contribute to the process of resorption [39].

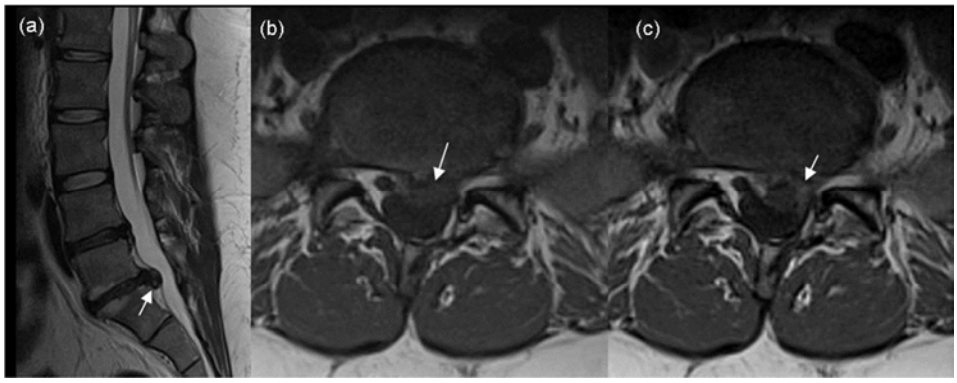

Figure 2. *Left paracentral disc extrusion at L5/S1. (a) T2 weighted sagittal, (b) T1 precontrast axial, (c), T1 post contrast axial. The arrow shows disc extrusion showing peripheral enhancement on contrast (c), thereby suggesting presence of an inflammatory reaction around it.*

Much of the available data on the post-herniation inflammatory changes in human discs are based on immunohistochemical experiments performed on tissue resected at surgery. Thus, by definition, the material was obtained from patients that failed to recover spontaneously from their symptoms. It might therefore be proposed that the data is of limited value for understanding the spontaneous improvement in patients who never need surgery, and instead reflects the chronic inflammatory process associated with a failure of symptom resolution (see below). This proposition appears to be supported by the dominance of macrophages in the cellular infiltrate: macrophages have a strong association with chronic inflammation, while acute inflammatory reactions are typically characterised by neutrophils [40, 41]. However, macrophages remain the dominant cell type whether discs are resected less than 3 weeks or more than 6 months after the onset of pain, and inflamed animal disc tissue resected just days after the onset of inflammation is also dominated by macrophages [42, 43]. Moreover, macrophages are not merely the cell type of chronic inflammation, but also have a central role in the resolution of inflammation and the remodelling associated with wound healing [44]. Thus, the spatial and temporal localisation and function of macrophages is consistent with their active contribution to the process of spontaneous disc resorption. Macrophage activity may also be implicated in the process of healing after surgery: the presence of an inflammatory infiltrate in resected disc tissue is associated with improved outcomes following discectomy [35, 45]. However, it takes a few weeks for leg pain to improve for the majority of patients [46] and, as we shall now discuss, before such recovery occurs inflammation is likely to exacerbate the painful symptoms caused by herniation.

2.1.2. The Chemical Contribution to Lumbar Radiculopathy

The physical presence of herniated discs within the spinal canal is not the sole cause, and may not even be necessary, for the symptoms of radiculopathy [47, 48]. Many people with no symptoms are found to have herniated discs and approximately 20% of patients with radiculopathy have no anatomical abnormalities apparent on imaging [49, 50]. However, note that negative scans might be false negatives resulting from imaging in a supine position rather than the axially loaded and dynamic postures that are more likely to produce symptoms [51, 52]. Nevertheless, dissociation between clinical symptoms and herniation is also apparent from studies documenting spontaneous disc resorption: resolution of symptoms typically takes place weeks or months before resorption occurs and there is not always a clear correlation between the degree of resorption and clinical improvement [10, 14, 15]. The invasive treatment of chemonucleolysis provides further evidence of this dissociation. The technique is efficacious in treating the symptoms associated with non-sequestered herniation, and relief typically occurs immediately, whilst the resultant reduction in the size of herniated material and reduction in disc height are not apparent for a month or more [53]. Similarly, relief of intradiscal pressure by inversion therapy results in a significant reduction in the need for surgery in patients with single level lumbar discogenic disease, despite the lack of MRI evidence for physical disc retraction [54]. Even when clinical recovery is mediated by surgery, many patients continue to show anatomical evidence of herniation [16].

Controlled animal studies have revealed that the exposure of nerve roots to nucleus pulposus tissue in the absence of

compression is sufficient to cause neural tissue injury similar to that seen in radiculopathy [55, 56]. This reaction is felt to be a result of the pro-inflammatory activity of the cells of the nucleus pulposus, which release mediators such as tumour necrosis factor α (TNF-α), interleukin 1β (IL-1β), and nitric oxide (NO), and promote the infiltration of inflammatory cells [37, 57]. Interaction between macrophages and disc tissue upregulates the production of the pro-inflammatory cytokines, and these chemicals have a pathological effect on nerve roots resulting in symptoms associated with radiculopathy [58, 59]. The clinical relevance of these data is reflected in the upregulation of such cytokines in local tissue samples obtained from patients with painful radiculopathy [60, 61, 62]. Furthermore, direct evidence has been provided to show that chemical radiculitis is a feasible cause of human radiculopathy in the absence of anatomical abnormalities. For example Peng et al [63] reported on 42 patients with radiculopathy without visible disc herniation, in these patients, evidence of nerve root injury was established via electromyography and motor nerve conduction measurements. An association between the nerve root lesions and the location of annular tears visualised in discography was observed, suggesting that the symptoms were a result of chemical irritation of the nerve roots following leakage of material from the nucleus pulposus [63] (Figure 3). Thus chemical irritation may be sufficient to cause some degree of pathology in the absence of mechanical compression [48]. However, to our knowledge, none of the studies advocating the existence of a purely chemical radiculitis in humans have confirmed the lack of herniation in weight-bearing and dynamic imaging.

In the genuine clinical context, chemical and mechanical effects typically co-exist. Experimental work carried out to explore their interaction, such as the observation that mechanical compression can cause an upregulation of cytokine receptors in the dorsal nerve root ganglia [64], indicates that the two features have a synergistic effect [47].

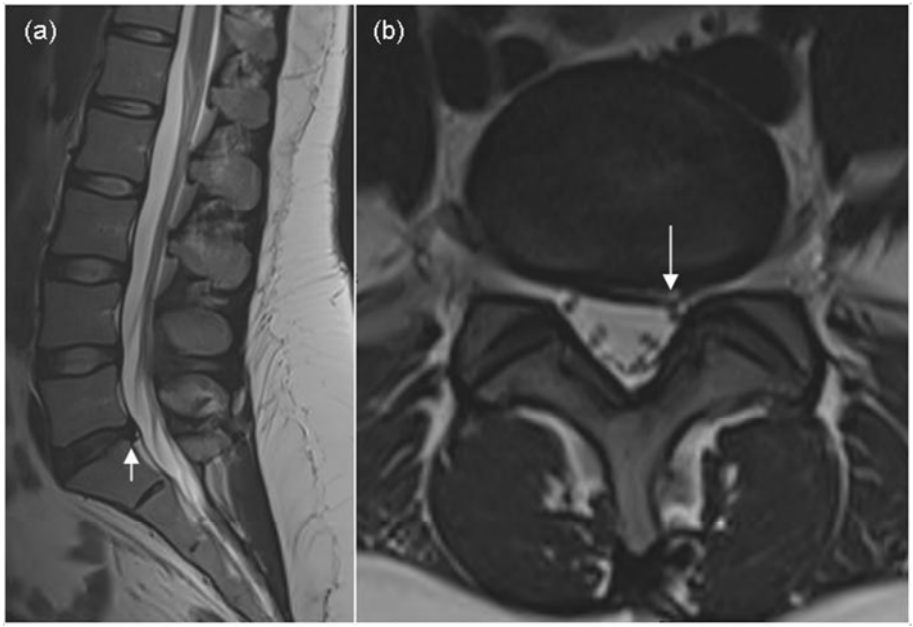

Figure 3. *T2 sagittal (a) and T2 axial (b). Arrows shows annular fissuring on left paracentral aspect, abutting the left S1 root, thereby bringing nucleus pulposus in contact with the root.*

2.1.3. A Double Role for Inflammation

The preceding discussion has demonstrated how the inflammation associated with lumbar disc herniation is understood to occupy a central role in both the initial symptomatology and the subsequent resolution of the condition. A study from 2002 by Autio et al [31] highlights these dual effects. The researchers acquired contrast-enhanced MRI scans from 148 patients with radiculopathy and compared the clinical symptoms with the degree of rim enhancement seen around the herniated disc material. Greater enhancement of L5-S1 lesions was associated with nerve dysfunction, as assessed by the Achilles tendon reflex, but also correlated negatively with the duration of symptoms [31]. Thus a single index of the inflammatory process was shown to relate to both the negative effect of neural dysfunction and the positive effect of recovery from symptoms following herniation. Despite the correlation that has been reported between disc resorption and symptom resolution, we remain ignorant about the mechanisms underlying clinical improvement [15, 32]. Regression of the herniation is an unsatisfactory explanation for symptomatic recovery because patients that spontaneously recover do not consistently exhibit disc resorption [8, 65] and, in discs that do regress, the magnitude of the regression does not relate to the degree of improvement (14); moreover, symptom relief is typically observed some time before resorption has taken place [32]. Thus, although the tissue damage associated with herniation typically generates a nociceptive inflammatory reaction leading to a recruitment of macrophages and upregulation of proteases that eventually mediate resorption of the herniated material, there must be an additional, transitional stage in the

inflammatory process that is directly related to the recovery from symptom. Furthermore, in some patients this transitional stage must be an end in itself because it never progresses to disc resorption. Accordingly the mechanism underlying the progression from the initial inflammatory reaction to this transitional stage is the mechanism that we seek in order to explain the clinical improvement that the majority of patients experience with conservative treatment.

2.1.4. The Inflammatory Process and Symptom Relief

The nucleus pulposus evidently has an important role in the chemical contribution to pain in disc herniation, so some authors have speculated that restoration of a barrier between the nucleus pulposus and spinal canal might be part of the mechanism for achieving symptom improvement [8, 66]. Work in animal model systems demonstrates that healing of the annulus fibrosus can occur following experimentally induced injury [67, 68]. We have no clear evidence of whether a similar process of healing occurs in human discs, but the granulation tissue seen in surgically resected samples may indicate that it does [69, 70]. Furthermore, some of the chemical factors associated with healing, such as transforming growth factor β (TGF-β), have been detected in herniated tissue [71]. TGF-β is a growth factor known to have a role in attracting tissue repair cells and promoting collagen production from fibroblasts, leading to the formation of granulation tissue and regeneration of damaged tissue [72]. It is also produced as part of the inflammatory process associated with painful disc degeneration and there is *in vitro* evidence that human annulus fibrosus cells proliferate in response to TGF-β stimulation [73, 74].

The example of TGF-β, and related agents such as lipoxins, resolvins and protectins, highlights the important role physiological anti-inflammatory factors have in the natural history of inflammation, by actively mediating resolution of the inflammatory process [41, 75]. Multiple studies have reported the lack of a relationship between the degree of disc inflammation and the clinical symptoms reported by patients [76, 77, 78]. However, these investigations have focussed on pro-inflammatory factors or cells, and it is plausible that a more comprehensive analysis incorporating the dynamics in the entire network of pro and anti-inflammatory factors and cell infiltrates might more reliably reflect the clinical condition. Specific targets could then be modulated to determine their individual contribution to the global inflammatory cascade and the natural history of symptoms. Due to obvious ethical constraints, such a study would be untenable in humans. Thus, although animal models have only a limited relevance to the human clinical context, they offer the sole practicable way of investigating the issue [79].

Some studies have already explored the post-herniation evolution of the inflammatory cascade, but often with a focus on its pathological effects alone. For example Takada et al. transplanted disc tissue into the back muscle of living rats and showed that TNF-α, IL-1β, IL-8, cyclo-oxygenase 2 (COX2) and nerve growth factor (NGF) mRNA expression peaked after a day and then subsequently declined, with TNF-α and IL-1β expression decreasing at a slower rate than the remaining factors. In contrast IL-6 and monocyte chemotactic protein 1 (MCP-1) exhibited a slower rise in expression, reaching a peak at day 3 post transplantation before a subsequent rapid decline. They provided an indirect correlation with symptoms by recording changes in the mechanical threshold for pain withdrawal after autografting disc tissue into a ligated L5 spinal nerve. An elevated pain response was seen at day 1, subsequently increasing to a maximum at day 5, at least 2 days after all the proinflammatory cytokine mRNA levels in the muscle discs had reached their peak [58]. In an alternative model of disc herniation, which is arguably more representative of the clinical disease, Yoshida et al [17] used an anterior surgical approach to puncture the entire depth of rabbit discs and compressed the anterior aspect of the discs to generate posterior herniation of nucleus pulposus material into the spinal canal. The technique is distinctive amongst animal models of disc herniation because it avoids a surgical incision in the region of disc herniation and thereby avoids the confounding effects of the inflammatory reaction induced by surgical trauma. In the study, protein expression levels of TNF-α, IL-1β and MCP-1 were examined by immunohistochemistry and TNF-α and IL-1β were seen to peak at day 1 following herniation and decrease rapidly thereafter, whereas MCP-1 peaked at day 3 and remained elevated for 1 week, before subsequently decreasing. A corresponding assessment of the size of the herniated material was performed and a 70% reduction in size was documented, but not until many weeks after the levels of the three measured cytokines had dropped to very low levels. Unfortunately no data on symptoms or nerve function was provided [17].

2.2. Potential for Therapeutic Agents

Efforts to establish the potential therapeutic efficacy of individual anti-inflammatory drugs such as TNF-α inhibitors have been equivocal in human studies [80, 81]. It is plausible that a broader approach, targeting multiple factors at clearly defined time-points in the inflammatory process might be more successful. Future analyses of the dynamics of inflammatory and anti-inflammatory agents, infiltrating cells, and symptoms, which include the time of symptomatic improvement within the period of observation, should enable the construction of a comprehensive picture of the evolution of the inflammatory process and its correlation with changes in pain-related behaviour. Hopefully this strategy will reveal characteristic cellular and molecular features of the inflammatory process that are robustly associated with the recovery from symptoms and thus could plausibly have a mechanistic role in mediating recovery. At present we can only speculate about what these mechanisms might be. However, some further insight might be gained from considering reasons why the relief from symptoms may never be achieved.

The use of epidural steroids was promoted by Olmarker, who described a beneficial effect of epidural steroids (methylprednisolone) on nucleus pulposus- induced nerve

root injury [82]. He reported nerve root morphological changes and significant delay in the nerve conduction velocities in animal models following mere application of nucleus pulposus material on nerves, which were prevented by early administration of steroids [82].

The use of epidural steroids in managing lumbar radiculopathy remains a debatable topic and the reports of it are conflicting. While several studies reported that epidural steroids administration minimizes the immediate postoperative pain and peri-dural fibrosis on the longer term [83, 84, 85, 86]. On the other hand, other reports have discouraged the use of steroids following increased risks of steroids related complications mainly those of infection [87, 88]. Two systematic reviews were conducted to assess the efficacy of epidural steroids on adults undergoing lumbar spine surgery for degenerative spinal disease [89, 90].

There was a trend toward benefit with epidural steroids in immediate post op pain score, together with a lower analgesic consumption post operatively. Nonetheless these results should be considered with caution, accounting for the heterogeneity of the studies included in the reviews, the variation in the type of operation, difference in the steroids preparations and application method, etc. The considerable variation between the trials makes it difficult to make undisputed conclusions. Nevertheless, currently it appears that there is some evidence supporting the use of epidural steroids in lumbar disc surgery, by being effective in reducing pain in the early stage and reducing the consumption of postoperative analgesia without an increased risk of complications. However there is a definite need of a large multicenter trial with validated outcome measures that are recorded at fixed time intervals to address the topic.

2.3. The Trigger for Chronicity

The chronic pain following initial disc-related radiculopathy is likely to be the result of a chronic inflammatory process driven by an ineffective healing response [89, 90, 73]. There are several theories explaining this disease chronicity.

2.3.1. Trigger for Chronicity: Poor Angiogenic Response

The inherently avascular nature of the disc endows it with a poor nutritional supply and low metabolic activity that undermine its ability to self-repair after injury [93, 94]. The neovascularisation seen in response to the injury associated with herniation is positively associated with the rate of recovery from radiculopathy [77, 95]. Thus, patients who do not recover may fail to do so because they generate an inadequate angiogenic response following herniation, causing the injured disc tissue to remain damaged and continue to produce inflammatory stimuli, leading to the establishment of chronic inflammation [67, 96]. This theory predicts that agents promoting angiogenesis have a therapeutic benefit. An experimental herniation model has demonstrated faster disc resorption with induction of neovascularisation, using Midkine (MK) (a nonglycosylated protein, strongly induced during oncogenesis, inflammation and tissue repair). Nonetheless this has not been correlated with a pain response [97].

2.3.2. Trigger for Chronicity: Repetitive Trauma

Another theory explaining the chronicity of the inflammatory process is through repeated mechanical trauma that undermines the repair process. This is supported by the persisting inflammation seen in an animal model of repeated disc injury and is in keeping with general principles of wound healing in other tissues [66, 98]. However, it predicts that a period of rest promotes symptom resolution and is inconsistent with studies demonstrating that physical activity enhances recovery from radiculopathy and associated low back pain [99, 100].

2.3.3. Trigger for Chronicity: Low Grade Infection

A third theory postulates an infectious agent as the stimulus for the chronicity of symptoms following disc herniation. In 2001 an association was described between sciatica and bacterial infection in herniated discs, particularly with the organism Propionibacterium acnes [101]. 53% of 36 patients with severe sciatica produced positive isolates from disc tissue obtained at microdiscectomy and 84% of the positive samples were propionibacterium. In contrast, 100% of 14 patients with other spinal disorders (scoliosis, trauma, myeloma, and degenerative disc disease) produced negative disc sample cultures. The authors hypothesised that a break in the mechanical integrity of the spinal disc from minor trauma allowed low virulence microorganisms to enter and initiate a chronic inflammatory response. Other studies have replicated the findings [102], and one study has demonstrated the clinical relevance of the putative infective process by recording significant symptomatic improvement in a specific group of patients with chronic low back pain treated with 100 days of antibiotics [103]. The authors propose that the neovascularization accompanying the inflammatory reaction to herniation enables bacteria to gain access to the a vascular disc space after transient bacteraemias, an ideal environment for anaerobes such as propionibacterium acnes [103]. If this theory is correct, then increasing angiogenesis could either have the detrimental effect of increasing the risk of bacterial infection or could produce a more aerobic environment within the disc that would undermine the ability of anaerobic infections to become established. Further studies are required to establish whether the treatment can be generalized beyond the highly selected group of patients included in the single investigation conducted so far.

2.3.4. Trigger for Chronicity: Genetic Predisposition

One final potential explanation for the switch to chronicity can be derived from the strong genetic predisposition for disc degeneration demonstrated by familial epidemiological studies [104, 105]. Genetic variation in some of the mediators involved in disc inflammation has been implicated in endowing a propensity for degenerative disease. For example: a polymorphism that influences the expression levels of matrix metalloproteinase 3 has been correlated with MRI evidence of degeneration [106]. Cartilage intermediate layer

protein, which is a factor thought to influence disc degeneration through its inhibitory interaction with TGF-β, exhibits a single nucleotide polymorphism that has been associated with variation in the level of its inhibitory effect [107]. Allelic variation in the interleukin 1 gene has been associated with the severity of low back pain [108]. We can speculate that the patients who fail to recover from disc herniation might possess genetic characteristics that cause them to mount an inappropriate inflammatory cascade within the disc, promoting chronic reactivity rather than resolution. Dynamic analysis of the evolution of these factors with symptom correlation would contribute to elucidating this theory.

3. Summary and Conclusion

We have reviewed the body of literature investigating the pathophysiology of intervertebral disc herniation. The trauma of herniation generates an inflammatory reaction, characterised by the release of multiple inflammatory mediators from the nucleus pulposus cells. These mediators stimulate accumulation of a cellular infiltrate dominated by macrophages, which are understood to phagocytose the herniated tissue and promote up-regulation of factors that degrade the extracellular matrix, leading to disc resorption. There is a correlation between resorption and symptomatic improvement, but this is not consistent enough to properly explain symptom resolution. Thus, further studies are required to reveal the features of the inflammatory process that correspond directly to the recovery that the majority of patients experience with conservative treatment. The ultimate aim is to understand how this recovery might be therapeutically promoted in contrast to the persistent inflammatory cycle that is likely to underlie chronic pain. Important insights could be gained by investigating the post-herniation dynamics of the entire network of chemical and cellular inflammatory mediators implicated in the condition and correlating these with symptoms. Further answers might also be obtained by exploring the role of neovascularisation, to establish whether this key component of the physiology of healing can be manipulated to therapeutic benefit.

Authors' Contributions

While all authors made significant contributions, Tagbo Ilozue and Mohamed Abdelsadg contributed prominently and equally and justify to be called joint first authors.

References

[1] Fardon DF, Milette PC. Nomenclature and classification of lumbar disc pathology: recommendations of the combined task forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. Spine 2001; 26: E93–E113.

[2] Milette PC. Classification, diagnostic imaging, and imaging characterization of a lumbar herniated disk. Radiol Clin North Am 2000; 38: 1267–1292.

[3] Mixter WJ, Barr JS. Rupture of the intervertebral disc with involvement of the spinal canal. N Engl J Med 1934; 211: 210–225.

[4] Cheung KMC, Karppinen J, Chan D, Ho DWH, Song Y-Q, Sham P, et al. Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. Spine 2009; 34: 934–940.

[5] Boos N, Semmer N, Elfering A, Schade V, Gal I, Zanetti M, et al. Natural history of individuals with asymptomatic disc abnormalities in magnetic resonance imaging: predictors of low back pain-related medical consultation and work incapacity. Spine 2000; 25: 1484–1492.

[6] Battié MC, Videman T, Parent E. Lumbar disc degeneration: epidemiology and genetic influences. Spine 2004; 29: 2679–2690.

[7] Koes BW, van Tulder MW, Peul WC. Diagnosis and treatment of sciatica. BMJ 2007; 334: 1313–1317.

[8] Valat J-P, Genevay S, Marty M, Rozenberg S, Koes B. Sciatica. Best Pract Res Clin Rheumatol 2010; 24: 241–252.

[9] Fairbank JC. Sciatica: An archaic term. BMJ 2007; 335: 112.

[10] Konstantinou K, Dunn KM. Sciatica: review of epidemiological studies and prevalence estimates. Spine 2008; 33: 2464–2472.

[11] Frymoyer JW. Back pain and sciatica. N Engl J Med 1988; 318: 291–300.

[12] Jacobs WCH, van Tulder M, Arts M, Rubinstein SM, van Middelkoop M, Ostelo R, et al. Surgery versus conservative management of sciatica due to a lumbar herniated disc: a systematic review. Eur Spine J 2011; 20: 513–522, 2011.

[13] Koes BW, van Tulder M, Lin C-WC, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. Eur Spine J 2010; 19: 2075–2094.

[14] Benson RT, Tavares SP, Robertson SC, Sharp R, Marshall RW. Conservatively treated massive prolapsed discs: a 7-year follow-up. Ann R Coll Surg Engl 2010; 92: 147–153.

[15] Benoist M. The natural history of lumbar disc herniation and radiculopathy. Joint Bone Spine 2002; 69: 155–160.

[16] Barzouhi el A, Vleggeert-Lankamp CLAM, Lycklama à Nijeholt GJ, Van der Kallen BF, van den Hout WB, Jacobs WCH, et al. Magnetic resonance imaging in follow-up assessment of sciatica. N Engl J Med 2013; 368: 999–1007.

[17] Yoshida M, Nakamura T, Sei A, Kikuchi T, Takagi K, Matsukawa A. Intervertebral disc cells produce tumor necrosis factor α, interleukin-1β, and monocyte chemoattractant protein-1 immediately after herniation: an experimental study using a new hernia model. Spine 2005; 30: 55–61.

[18] Lindblom K, Hultqvist G. Absorption of protruded disc tissue. J Bone Joint Surg Am 1950; 32: 557–560.

[19] Teplick JG, Haskin ME. Spontaneous regression of herniated nucleus pulposus. AJR Am J Roentgenol 1985; 145: 371–375.

[20] Saal JAJ, Saal JSJ, Herzog RJR. The natural history of lumbar intervertebral disc extrusions treated nonoperatively. Spine 1990; 15: 683–686.

[21] Ikeda T, Nakamura T, Kikuchi T, Umeda S, Senda H, Takagi K. Pathomechanism of spontaneous regression of the herniated lumbar disc: histologic and immunohistochemical study. Journal of Spinal Disorders & Techniques 1996; 9: 136–140.

[22] Doita M, Kanatani T, Harada T, Mizuno K. Immunohistologic study of the ruptured intervertebral disc of the lumbar spine. Spine 1996; 21: 235–241.

[23] Tsuru M, Nagata K, Ueno T, Jimi A, Irie K, Yamada A, et al. Electron microscopic observation of established chondrocytes derived from human intervertebral disc hernia (KTN-1) and role of macrophages in spontaneous regression of degenerated tissues. The Spine Journal 2001; 1: 422–431.

[24] Takada T, Nishida K, Doita M, Kurosaka M. Fas ligand exists on intervertebral disc cells: a potential molecular mechanism for immune privilege of the disc. Spine 2002; 27: 1526–1530.

[25] Grönblad M, Habtemariam A, Virri J, Seitsalo S, Vanharanta H, Guyer RD. Complement membrane attack complexes in pathologic disc tissues. Spine 2003; 28: 114–118.

[26] Geiss A, Larsson K, Rydevik B, Takahashi I, Olmarker K. Autoimmune properties of nucleus pulposus: an experimental study in pigs. Spine 2007; 32: 168–173.

[27] Minamide A, Hashizume H, Yoshida M, Kawakami M, Hayashi N, Tamaki T. Effects of basic fibroblast growth factor on spontaneous resorption of herniated intervertebral discs: an experimental study in the rabbit. Spine 1999; 24: 940.

[28] Kawaguchi S, Yamashita T, Yokogushi K, Murakami T, Ohwada O, Sato N. Immunophenotypic analysis of the inflammatory infiltrates in herniated intervertebral discs. Spine 2001; 26: 1209–1214.

[29] Fadda A, Oevermann A, Vandevelde M, Doherr MG, Forterre F, Henke D. Clinical and pathological analysis of epidural inflammation in intervertebral disk extrusion in dogs. J Vet Intern Med 2013; 27: 924–934.

[30] Minamide A, Tamaki T, Hashizume H, Yoshida M, Kawakami M, Hayashi N. Effects of steroid and lipopolysaccharide on spontaneous resorption of herniated intervertebral discs: an experimental study in the rabbit. Spine 1998; 23: 870–876.

[31] Autio RA, Karppinen J, Niinimäki J, Ojala R, Kurunlahti M, Haapea M, et al. Determinants of spontaneous resorption of intervertebral disc herniations. Spine 2006; 31: 1247–1252.

[32] Komori H, Shinomiya K, Nakai O, Yamaura I, Takeda S, Furuya K. The natural history of herniated nucleus pulposus with radiculopathy. Spine 1996; 21: 225–229.

[33] Virri J, Grönblad M, Seitsalo S, Habtemariam A, Kääpä E, Karaharju E. Comparison of the prevalence of inflammatory cells in subtypes of disc herniations and associations with straight leg raising. Spine 2001; 26: 2311–2315.

[34] Grönblad M, Virri J, Seitsalo S, Habtemariam A, Karaharju E. Inflammatory cells, motor weakness, and straight leg raising in transligamentous disc herniations. Spine 2000; 25: 2803–2807.

[35] Woertgen C, Rothoerl RD, Brawanski A. Influence of macrophage infiltration of herniated lumbar disc tissue on outcome after lumbar disc surgery. Spine 2000; 25: 871–875.

[36] Doita M, Kanatani T, Ozaki T, Matsui N, Kurosaka M, Yoshiya S. Influence of macrophage infiltration of herniated disc tissue on the production of matrix metalloproteinases leading to disc resorption. Spine 2001; 26: 1522–1527.

[37] Kang JD, Georgescu HI, McIntyre-Larkin L, Stefanovic-Racic M, Donaldson WF III, Evans CH. Herniated lumbar intervertebral discs spontaneously produce matrix metalloproteinases, nitric oxide, interleukin-6, and prostaglandin E2. Spine 1996; 21: 271–277.

[38] Goupille P, Jayson MI, Valat J-P, Freemont AJ Matrix metalloproteinases: the clue to intervertebral disc degeneration? Spine 1998; 23: 1612–1626.

[39] Haro H, Komori H, Kato T, Hara Y, Tagawa M, Shinomiya K, et al. Experimental studies on the effects of recombinant human matrix metalloproteinases on herniated disc tissues--how to facilitate the natural resorption process of herniated discs. J Orthop Res 2005; 23: 412–419.

[40] Mantovani A, Biswas SK, Galdiero MR, Sica A, Locati M. Macrophage plasticity and polarization in tissue repair and remodelling. J Pathol 2013; 229: 176–185.

[41] Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. Nat Immunol 2005; 6: 1191–1197.

[42] Habtemariam A, Grönblad M, Virri J, Karaharju E. A comparative immunohistochemical study of inflammatory cells in acute-stage and chronic-stage disc herniations. Spine 1998; 23: 2159–2165.

[43] Kikuchi T, Nakamura T, Ikeda T, Ogata H, Takagi K. Monocyte chemoattractant protein-1 in the intervertebral disc. A histologic experimental model. Spine 1998; 23: 1091–1099.

[44] Sonnemann KJK, Bement WMW: Wound repair. toward understanding and integration of single-cell and multicellular wound responses. Annu Rev Cell Dev Biol 2011; 27: 237–263.

[45] Rothoerl RD, Woertgen C, Brawanski A. Pain resolution after lumbar disc surgery is influenced by macrophage tissue infiltration. A prospective consecutive study on 177 patients. Journal of Clinical Neuroscience 2002; 9: 633–636.

[46] Peul WC, van Houwelingen HC, van den Hout WB, Brand R, Eekhof JAH, Tans JTJ, et al. Surgery versus prolonged conservative treatment for sciatica. N Engl J Med 2007; 356: 2245–2256.

[47] Mulleman D, Mammou S, Griffoul I, Watier H, Goupille P. Pathophysiology of disk-related sciatica. I.-Evidence supporting a chemical component. Joint Bone Spine 2006; 73: 151–158.

[48] Byun WM, Ahn SH, Ahn MW. Value of 3D MR lumbosacral radiculography in the diagnosis of symptomatic chemical radiculitis. American Journal of Neuroradiology 2012; 33: 529–534.

[49] Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med 1994; 331: 69–73.

[50] van Rijn JC, Klemetso N, Reitsma JB, Majoie CBLM, Hulsmans FJ, Peul WC, et al. Symptomatic and asymptomatic abnormalities in patients with lumbosacral radicular syndrome: Clinical examination compared with MRI. Clinical Neurology and Neurosurgery 2006; 108: 553–557.

[51] Zou J, Yang H, Miyazaki M, Wei F, Hong SW, Yoon SH, et al. Missed lumbar disc herniations diagnosed with kinetic magnetic resonance imaging. Spine 2008; 33: E140–E144.

[52] Tarantino UU, Fanucci EE, Iundusi RR, Celi MM, Altobelli SS, Gasbarra EE, et al. Lumbar spine MRI in upright position for diagnosing acute and chronic low back pain: statistical analysis of morphological changes. J Orthop Traumatol 2013; 14: 15–22.

[53] Gibson JNA, Waddell G. Surgical interventions for lumbar disc prolapse: updated Cochrane Review. Spine 2007; 32: 1735–1747.

[54] Prasad KSM, Gregson BA, Hargreaves G, Byrnes T, Winburn P, Mendelow AD. Inversion therapy in patients with pure single level lumbar discogenic disease: a pilot randomized trial. Disabil Rehabil 2012; 34: 1473–1480.

[55] Yabuki S, Onda A, Kikuchi S, Myers RR. Prevention of compartment syndrome in dorsal root ganglia caused by exposure to nucleus pulposus. Spine 2001; 26: 870–875.

[56] Olmarker K, Blomquist J, Strömberg J, Nannmark U, Thomsen P, Rydevik B. Inflammatogenic properties of nucleus pulposus. Spine 1995; 20: 665–669.

[57] Katsuno R, Hasegawa T, Iwashina T, Sakai D, Mikawa Y, Mochida J. Age-related effects of cocultured rat nucleus pulposus cells and macrophages on nitric oxide production and cytokine imbalance. Spine 2008; 33: 845–849.

[58] Takada T, Nishida K, Maeno K, Kakutani K, Yurube T, Doita M, et al. Intervertebral disc and macrophage interaction induces mechanical hyperalgesia and cytokine production in a herniated disc model in rats. Arthritis & Rheumatism 2012; 64: 2601–2610.

[59] Murata Y, Onda A, Rydevik B, Takahashi I, Takahashi K, Olmarker K. Changes in pain behavior and histologic changes caused by application of tumor necrosis factor-alpha to the dorsal root ganglion in rats. Spine 2006; 31: 530–535.

[60] Takahashi H, Suguro T, Okazima Y, Motegi M, Okada Y, Kakiuchi T. Inflammatory cytokines in the herniated disc of the lumbar spine. Spine 1996; 21: 218–224.

[61] Genevay S, Finckh A, Payer M, Mezin F, Tessitore E, Gabay C, et al. Elevated levels of tumor necrosis factor-alpha in periradicular fat tissue in patients with radiculopathy from herniated disc. Spine 2008; 33: 2041–2046.

[62] Andrade P, Hoogland G, Garcia MA, Steinbusch HW, Daemen MA, Visser-Vandewalle V. Elevated IL-1β and IL-6 levels in lumbar herniated discs in patients with sciatic pain. Eur Spine J 2013; 22: 714–720.

[63] Peng B, Wu W, Li Z, Guo J, Wang X. Chemical radiculitis. Pain 2007; 127: 11–16.

[64] Schäfers M, Sorkin LS, Geis C, Shubayev VI. Spinal nerve ligation induces transient upregulation of tumor necrosis factor receptors 1 and 2 in injured and adjacent uninjured dorsal root ganglia in the rat. Neuroscience Letters 2003; 347: 179–182.

[65] Jensen TS, Albert HB, Sorensen JS, Manniche C, Leboeuf-Yde C. Magnetic resonance imaging findings as predictors of clinical outcome in patients with sciatica receiving active conservative treatment. Journal of manipulative and physiological therapeutics 2007; 30: 98–108.

[66] Adams MA, Stefanakis M, Dolan P: Healing of a painful intervertebral disc should not be confused with reversing disc degeneration: implications for physical therapies for discogenic back pain. Clin Biomech (Bristol, Avon) 2010; 25: 961–971.

[67] Hampton D, Laros G, McCarron R, Franks D. Healing potential of the anulus fibrosus. Spine 1989; 14: 398–401.

[68] Osti OL, Vernon-Roberts B, Fraser RD. 1990 Volvo Award in experimental studies. Anulus tears and intervertebral disc degeneration. An experimental study using an animal model. Spine 1990; 15: 762–767.

[69] Coventry MB, Ghormley RK, Kernohan JW. The Intervertebral Disc: Its microscopic Anatomy and Pathology Part II. Changes in the Intervertebral Disc Concomitant with Age. J Bone Joint Surg Am 1945; 27: 233–247.

[70] Peng B, Wu W, Hou S, Li P, Zhang C, Yang Y. The pathogenesis of discogenic low back pain. J Bone Joint Surg Br 2005; 87: 62–67.

[71] Ahn S-H, Cho Y-W, Ahn M-W, Jang S-H, Sohn Y-K, Kim H-S. mRNA expression of cytokines and chemokines in herniated lumbar intervertebral discs. Spine 2002; 27: 911–917.

[72] Martin P. Wound healing-aiming for perfect skin regeneration. Science 1997; 276: 75–81.

[73] Peng B, Hao J, Hou S, Wu W, Jiang D, Fu X, et al. Possible pathogenesis of painful intervertebral disc degeneration. Spine 2006; 31: 560–566.

[74] Gruber HE, Fisher EC Jr, Desai B, Stasky AA, Hoelscher G, Hanley EN Jr. Human intervertebral disc cells from the annulus: three-dimensional culture in agarose or alginate and responsiveness to TGF-beta1. Exp Cell Res 1997; 235: 13.

[75] Buckley CD, Gilroy DW, Serhan CN, Stockinger B, Tak PP. The resolution of inflammation. Nat Rev Immunol 2013; 13: 59–66.

[76] Andrade P, Visser-Vandewalle V, Philippens M, Daemen MA, Steinbusch HWM, Buurman WA, et al. Tumor necrosis factor-α levels correlate with postoperative pain severity in lumbar disc hernia patients: opposite clinical effects between tumor necrosis factor receptor 1 and 2. Pain 2011; 152: 2645–2652.

[77] Autio RA, Karppinen J, Kurunlahti M, Kyllönen E, Vanharanta H, Tervonen O. Gadolinium diethylenetriaminepentaacetic acid enhancement in magnetic resonance imaging in relation to symptoms and signs among sciatic patients: a cross-sectional study. Spine 2002; 27: 1433–1437.

[78] Rothoerl RD, Woertgen C, Holzschuh M, Rueschoff J, Brawanski A. Is there a clinical correlate to the histologic evidence of inflammation in herniated lumbar disc tissue? Spine 1998; 23: 1197–1200.

[79] Alini M, Eisenstein SM, Ito K, Little C, Kettler AA, Masuda K, et al. Are animal models useful for studying human disc disorders/degeneration? Eur Spine J 2008; 17: 2–19.

[80] Ohtori S, Miyagi M, Eguchi Y, Inoue G, Orita S, Ochiai N, et al. Epidural administration of spinal nerves with the tumor necrosis factor-alpha inhibitor, etanercept, compared with dexamethasone for treatment of sciatica in patients with lumbar spinal stenosis: a prospective randomized study. Spine 2012; 37: 439–444.

[81] Korhonen T, Karppinen J, Paimela L, Malmivaara A, Lindgren K-A, Bowman C, et al. The treatment of disc-herniation-induced sciatica with infliximab: one-year follow-up results of FIRST II, a randomized controlled trial. Spine 2006; 31: 2759–2766.

[82] Olmarker K, Byrod G, Cornefjord M, Nordborg C, Rydevik B. Effects of methylprednisolone on nucleus pulposus- induced nerve root injury. Spine 1994; 19: 1803–1808.

[83] Jones KG, Barnett HC. The use of hydrocortisone in spinalsurgery. South Med J 1955; 48: 617–623.

[84] King JS. Dexamethasone—a helpful adjunct in management after lumbar discectomy. Neurosurgery 1984; 14: 697–700.

[85] Naylor A, Flowers MW, Bramley JE. The value of dexamethasone in the postoperative treatment of lumbar disc prolapse. Orthop Clin North Am 1977; 8: 3–8.

[86] Watters WC III, Temple AP, Granberry M. The use of dexamethasone in primary lumbar disc surgery. A prospective, randomized, double-blind study. Spine 1989; 14: 440–442.

[87] Lowell, Troy D., Thomas J. Errico, and Mark S. Eskenazi. "Use of epidural steroids after discectomy may predispose to infection." Spine 2000; 25 (4): 516-519.

[88] Yang, Scott, et al. Preoperative epidural injections are associated with increased risk of infection after single-level lumbar decompression. *The Spine Journal* 2016; 16. 2: 191-196.

[89] Ranguis SC, Li D, Webster AC. Perioperative epidural steroids for lumbar spine surgery in degenerative spinal disease: a review. Journal of Neurosurgery: Spine 2010; 13 (6): 745-757.

[90] Jamjoom BA, Jamjoom AB. Efficacy of intraoperative epidural steroids in lumbar discectomy: a systematic review. BMC Musculoskeletal Disorders 2014; 15 (1): 146.

[91] Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? Spine 2006; 31: 2151–2161.

[92] Lotz JC, Ulrich JA. Innervation, inflammation, and hypermobility may characterize pathologic disc degeneration: review of animal model data. J Bone Joint Surg Am 2006; 88: 76–82.

[93] Nerlich AG, Schaaf R, Wälchli B, Boos N. Temporo-spatial distribution of blood vessels in human lumbar intervertebral discs. Eur Spine J 2007; 16: 547–555.

[94] Urban JPG, Smith S, Fairbank JCT. Nutrition of the intervertebral disc. Spine 2004; 29: 2700–2709.

[95] Kobayashi S, Meir A, Kokubo Y, Uchida K, Takeno K, Miyazaki T, et al. Ultrastructural analysis on lumbar disc herniation using surgical specimens: role of neovascularization and macrophages in hernias. Spine 2009; 34: 655–662.

[96] Roy S, Sen CK. miRNA in wound inflammation and angiogenesis. Microcirculation 2012; 19: 224–232.

[97] Ulrich JA, Liebenberg EC, Thuillier DU, Lotz JC. ISSLS prize winner: repeated disc injury causes persistent inflammation. Spine 2007; 32: 2812–2819.

[98] Zhou G, Dai L, Jiang X, Ma Z, Ping J, Li J, et al. Effects of human midkine on spontaneous resorption of herniated intervertebral discs. International Orthopaedics (SICOT) 2010; 34: 103–108.

[99] Dahm KT, Brurberg KG, Jamtvedt G, Hagen KB. Advice to rest in bed versus advice to stay active for acute low-back pain and sciatica. Cochrane Database Syst Rev 2010; CD007612–CD007612.

[100] Malmivaara A, Häkkinen U, Aro T, Heinrichs M-L, Koskenniemi L, Kuosma E, et al. The treatment of acute low back pain—bed rest, exercises, or ordinary activity? N Engl J Med 1995; 332: 351–355.

[101] Stirling A, Worthington T, Rafiq M, Lambert PA, Elliott TS. Association between sciatica and Propionibacterium acnes. Lancet 2001; 357: 2024–2025, 2001.

[102] Agarwal VJ, Golish R, Kondrashov D, Alamin TF. Results of Bacterial Culture from Surgically Excised Intervertebral Disc in 52 Patients Undergoing Primary Lumbar Microdiscectomy at a Single Level. The Spine Journal 2010; 10: S45–S46, 2010.

[103] Albert HB, Sorensen JS, Christensen BS, Manniche C. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. Eur Spine J 2013; 22: 697–707.

[104] Battié MC, Videman T. Lumbar disc degeneration: epidemiology and genetics. J Bone Joint Surg Am 2006; 88 Suppl 2: 3–9.

[105] Paesold G, Nerlich AG, Boos N. Biological treatment strategies for disc degeneration: potentials and shortcomings. Eur Spine J 2007; 16: 447–468.

[106] Takahashi M, Haro H, Wakabayashi Y, Kawa-Uchi T, Komori H, Shinomiya K. The association of degeneration of the intervertebral disc with 5a/6a polymorphism in the promoter of the human matrix metalloproteinase-3 gene. Journal of Bone & Joint Surgery, British Volume 2001; 83: 491–495.

[107] Seki S, Kawaguchi Y, Chiba K, Mikami Y, Kizawa H, Oya T, et al. A functional SNP in CILP, encoding cartilage intermediate layer protein, is associated with susceptibility to lumbar disc disease. Nat Genet 2005; 37: 607–612.

[108] Solovieva S, Leino-Arjas P, Saarela J, Luoma K, Raininko R, Riihimäki H. Possible association of interleukin 1 gene locus polymorphisms with low back pain. Pain 2004; 109: 8–19.