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International Journal of Mediators of Inflammation
Col Shashivadhanan

Review Article

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Lumbar Degenerative Disc Disease: From Bench to Bedside

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Received date: January 23, 2018; **Accepted date:** February 12, 2018; **Published date:** February 20, 2018.

Citation: Col Shashivadhanan (2018) Lumbar Degenerative Disc Disease: From Bench to Bedside. *International Journal of Mediators of Inflammation*. Doi:10.31579/ 20.2018/ijmi/001

Abstract:

Back pain is second only to the common cold as a cause of lost time from work and results in more lost productivity than any other medical condition. Although being a common condition, the diagnosis of the pain generating structure and mechanism of pain generation remains to be completely understood. As the diagnosis is uncertain, so is the treatment. Traditional concepts for treatment of lumbar disc degeneration have aimed at symptomatic relief by removing the offending disc and limiting motion in the lumbar spine. Understanding the pathophysiological basis of disc degeneration is essential for the development of treatment strategies that target the underlying mechanisms of disc degeneration rather than the downstream symptom of pain. Researchers are working on novel treatment strategies which aim to induce disc regeneration or to replace the degenerated disc. These strategies involve stem cells, growth factors, and gene therapy. At present, treatment options for degenerative disc disease remain suboptimal, and the novel treatment strategies are not accepted as the standard of care. We are unable to morphologically differentiate between an aging and a degenerated disc. Explaining cause of pain in the absence of MRI findings is quite unsettling for the treating physician. On the other side we come across individuals with MRI showing severe degenerative changes with a patient with minimal discomfort. Like other degenerative diseases, genetic predisposition for Lumbar degenerative disc disease too should have a plausible explanation. These are some issues which need to be answered with a firm scientific conviction.

The pathophysiology of pain mechanism is so complex that formulating treatment protocol eludes standardization. The type of pain in low back pain during the acute stage is nociceptive in character. It assumes central sensitization on becoming chronic. There occurs a functional reorganization within the pain matrix of the brain. A brief outline is provided of our present understanding of, the anatomical basis of pain mechanism based on the current, available body of literature. Literature search was carried out pertaining to low back pain within the last ten years. Experience of senior physicians treating low back pain was taken and conclusions were drawn. Keeping the current scenario in the back drop, it is proposed that since the cause of low back pain is multimodal, medical care providers should adopt a multi-disciplinary model in order to provide effective pain relief. The treatment modalities should include physical therapy, pharmacotherapy, interventional local pain modulating therapy and surgical intervention.

Evolving concepts pain and treatment strategies

Despite the inherent challenge in elucidating the specific etiology of chronic low back pain, diagnostic procedures can reveal its source in up to 90% of patients. De Palma et al elucidated that three principal joints contribute to stability of the spine. Amongst the three joint each has a share in contributing to pain .Seeing each joint in isolation it has been found that percentage distribution of each joint to pain for zygapophysial joints, sacroiliac joints, and lumbar discs are 31%, 18%, and 42%, respectively
[1]. Crock was the first to propose that isolated internal disc disruption (IDD) without nerve root irritation could cause discogenic pain [2].

IDD can be found in 26%-42% patients of chronic low back pain [1, 3 &4]. Our current understanding believes IDD to be a distinct clinical entity which needs to be distinguished from other pain causing entities [5].

A recent study has classified discogenic low back pain into two types. They are annular disruption-induced low back pain (IAD) and internal endplate disruption (IED)-induced low back pain. These two distinct types have been fully supported by clinical and theoretical bases. Treatment of IAD is removal of the offending disc and that of IED is lumbar spinal fusion [6].

In addition to structural causes, psychosocial factors also play an important role in determining back pain behavior. Psychosocial factors are unlikely to predict as to who will experience back pain in the first place [7].Recent studies have shown that low back pain seems to have a genetic correlation. As on date 40 genes have been found which are involved in development of Disc [8] .

The aging process of disc follows a pattern of biochemical cascade. Am V. VO and colleagues proposed a biochemical cascade of disc aging by dividing it into three phases: (1) accumulation of damage to biomolecules, (2) aberrant cellular response to damage, and (3) loss of biologic structure and function [9].

Although a aged disc and degenerated disc has certain biochemical dissimilarities, studies have yet to prove any distinct dissimilarity in imaging morphology between an aged disc and a degenerated disc [10, 11].

Anatomy of low back pain

Bogduk and Twomey have extensively described the innervation of spinal structures [12]The dorsal rami of each spinal nerve divides into three branches. Lateral branches supply the iliocostalis lumborum muscle and the skin; intermediate branches supply the longissimus muscle and the apophyseal joints. Medial branches supply the apophyseal joints, the interspinous and multifidus muscles, and also the interspinous ligament. Each medial branch supplies the apophyseal joints at its own level and also the joint below. Vertebral body endplates have the potential to be painful as they carry sensory innervation [13]. The posterior longitudinal ligament contains an extensive plexus of nerve fibers which also have free and encapsulated endings.[14] The grey rami communicantes arises from the lumbar sympathetic trunks to join the ventral rami of the lumbar spinal nerves thereby forming a mixed nerve called the sinuvertebral nerve. The sinuvertebral nerve supplies the posterior and posterolateral annulus fibrosus, and the posterior longitudinal ligament.
De Palma and colleagues conducted studies on various pain sensitive structures and concluded that , zygapophysial joints, sacroiliac joints, and lumbar discs contributed to pain by 31%, 18%, and 42%, respectively[15]

Biochemical Pain Sensitization

There is growing evidence that pain arises from disrupted degenerated discs, but not from old dehydrated discs.

However, even the most severe degenerative changes can sometimes be observed in people who have no back pain, suggesting that pain perception depends on biochemical / central pain sensitization mechanisms which are yet to be fully established [16] . It is also possible that some individuals with degenerated and narrowed discs do not experience pain as the load bearing is transferred to neural arch.

Many patients reporting to the pain physician have an element of chronicity which implies that the pain mechanism has a nociceptive and central component. Central sensitization is defined as " an amplification of neural signaling within the central nervous system (CNS) that elicits pain hypersensitivity" [17].

A key brain area implicated in pain neuromatrix is the amygdala. The amygdala along with the hippocampus and anterior cingulate cortex are implicated in the development of pain memories.

The development of such a pain memory applies to all movements that once provoked pain. This results in protective behaviors (e.g. antalgic posture movement patterns, altered pelvic motor control and probably also, avoidance of particular movements like forward bending) [18].Even preparing for such 'dangerous' movements can evoke activation of the fear-memory center in the brain thereby eliciting pain without any peripheral nociceptive input. This will also prompt the patient to adopt a protective motor control strategy [19] .Amongst all cases of low back pain only a subgroup develop central sensitization. The exact mechanism orchestrating the same is still a mystery. Pain Neurosciences have also revealed that Glial over activity and poor sleep may play an important role in central sensitization. [20, 21] .

Contemporary pain Neurosciences aims at identifying the relevant pain mechanisms in a patient of chronic low back pain. Knowing these mechanisms will help the clinician m in devising appropriate physical therapy and postural exercises which will help in retraining the pain memories. Some of these interventions can also be directed towards targeting sleep disturbances.

Aberrant neuro vascularization

Branches of the sinuvertebral nerve, the spinal nerves, and gray rami communicants have been the targets for most pain intervention procedures. Studies have demonstrated painful discs to have increased proliferation of nerve fibers and blood vessels in the disc which is otherwise an aneural structure .Studies have shown a correlation between aberrant neuro vascularization and expression of neurotropins [22].

Studies suggest that an imbalance between the matrix metalloproteinase-3 (MMP-3) and tissue inhibitor of metalloproteinase-1 (TIMP-1) results in dehydration of disc leading to buckling of the annular lamellae. This leads to increased focal segmental mobility and shear stress to the annular wall. Delamination and fissuring within the annulus can result. Annular delamination and annular fissuring are two separate and distinct events [21, 22&23]. These degenerative disc changes affect the normal external load bearing, predisposing patient to back strain, even within physiological limits of weight bearing and motion [25].

The degenerative disc and the degenerative painful disc have a subtle difference. Early degenerative changes encompass biochemical and metabolic changes with aging without any structural failure. The term degenerative disc disease is applied to a painful degenerative disc with structural failure which may include radial tear of the annulus fibrosus, herniated intervertebral disc, calcification or damage to the end plate, and internal disc disruption [26, 27&28].

The Nociceptive Neurotransmitters

Stimulation of nociceptors in the annulus fibrosus causes nociceptive pain. Substance P, calcitonin gene-related peptide, and vasoactive intestinal polypeptide immunoreactive nerve fibers are present in the absolute outer layers of the annulus fibrosus of a normal disc and they are implicated in causation of pain during low back pain [29].Degenerative changes in the discs leading to abnormal motion amplify the pain response to nociceptors resulting in a condition called peripheral sensitization [30].

Lactic acid accumulation causes a low pH which stimulates the neurogenic and non-neurogenic pain mediator leading to provocative pain. There is abundant infiltration of mast cells in the granulation tissue zones. This triggers the inflammatory cascade within the disc and surrounding structures. It's been postulated that this inflammation induced tissue degradation, causes signal release of certain substances like tumor necrosis factor and interleukins, which go on to play a role in the development of back pain. The finding that degenerative disc contains a high concentration of Phospholipase A2 which is related to of arachidonic acid cascade, indirectly proves the above postulate [31].

External Factors

On living subjects, spinal loading depends on the precise manner in which a person moves [32] and cadaveric spine experiments show that orientation of vertebra or posture plays a vital role in weight distribution within spinal tissue[33,34&35] .This concept of 'functional pathology' explains the conventional advice on 'good' and 'bad' posture. In 2011 William Sambrook and colleagues evaluated the influence of environmental factors on disc degeneration [36]. Chemical exposure due to smoking has been postulated to influence disc degeneration, although the association is not very strong [37].Nicotine which impairs blood flow could be possible cause leading to early disc degeneration [38].

Genetic Factors

Many genes have been implicated in degenerative cascade. They include genes that code for collagens I, IX, and XI, interleukin 1 (IL-1), aggrecan, the vitamin D receptor, matrix metalloproteinase 3 (MMP-3), and other proteins [39]. It has been established that multiple gene interactions and its probable gene environmental cross interaction orchestrates the Degenerative process [40].

Diagnosis

Plain X-Ray and MRI of the lumbosacral spine indicate the health of the disc and help in identifying structural abnormality. However they fail to pinpoint the pain generator which, are generally more than one and progress in time as a dynamic entity. Crux of treatment lies in identifying these pain generators and addressing each one of them based on their pain generating potential. Provocative discography may help in identifying the culprit disc. The diagnostic criteria for IDD established by the International Association for the Study of Pain (IASP) includes, emergence of a concordant pain response during discography, internal annular disruption demonstrated by CT after discography (CTD) and at least one adjacent disc without concordant pain[41]. Validation of provocative discography remains questionable and carries the risk of accelerating the degenerative cascade [42, 43 &44].

A thorough neurological examination with imaging findings is the best tool we have as on date to identify the pain generators and formulate a treatment strategy.

Treatment Strategies

These include
1. Physical therapy and other conservative modalities
2. Minimally invasive interventions for pain management
3. Surgical interventions
4. Novel Therapies

Physical therapy

Physical Therapy, exercise, manipulation, and back schools seem to have an important role in alleviating the symptoms of back pain but their long term effects remain to be proven [45]. Exercise therapy proposed by McKenzie is a popular treatment for low back pain. Clinical studies prove McKenzie method to be more effective than manipulation for patients with chronic low back pain [46].

Minimally invasive pain interventions

The interventional pain management services have found to have a steady increase in its clientele in the past decade. From 2000 to 2011 the interventional pain management services have increase by 228%.This fact only proves that pain mitigation does not rest wholly within the realm of the spine surgeon [47].

The intervention spectrum includes
Epidural steroids
Facet interventions
Intradiscal Therapies
Vertebral Augmentation
Implantable Therapies

Epidural procedures continue to be debated regarding their effectiveness, indications, and medical necessity. Recent systematic reviews indicated that effectiveness of epidural injections for treatment of discogenic low back pain was satisfactory. It is believed that neural blockade achieved by this interventional procedures, alters or interrupts nociceptive input, the reflex mechanism of the afferent fibers, self-sustaining activity of the neurons, and the pattern of central neuronal activities .[48] As alternative treatments, percutaneous treatments directed at altering the internal mechanics or innervation of the disc by heat (intradiscal electrothermal annuloplasty, IDET, and biacuplasty) have recently been advocated), but data supporting their use does not seem very strong[49].

Surgical Intervention

The present armamentarium that exist with the spine surgeon includes minimally invasive disc volume reducing procedures, neural decompressive procedures, lumbar fusion procedures, disc arthroplasty and posterior dynamic stabilization.
The motion preserving procedures claim the benefit of preventing adjacent segment disease [50] .

Results of clinical trials evaluating disc arthroplasty with conventional fusion procedures have shown similar outcomes when compared with circumferential fusion for the treatment of discogenic pain [51]. Posterior dynamic stabilization works on the principle of limiting motion in the interspace thereby reducing discogenic pain. [52, 53] In spite of this 29 to 47% patients develop adjacent segment disease [54, 55] .

Novel therapies

Therapies directed towards disrupting the proinflammatory signalling cascade or breaking the nerve conduction pathways can transform a painful disc into an asymptomatic disc there by greatly improving the quality of life. However they fail to stop or reverse the progress of disc degeneration [56].

The newer modalities under research include biologic growth factors, stem cells, and gene transplant. They may reverse the degenerating process to some extent but fail to translate to commensurate clinical improvement [57] . Stem Cell transplantation is currently emerging as a promising treatment strategy for DDD [58] .

The stem cells being studied include the chondrocyte progenitor cells, adipocyte progenitor cells and bone marrow derived stem cells. These stem cells increase the extracellular matrix in animal experiments. In post discectomy pain it offers significant pain reduction probably by rehydrating the desiccated disc [59].The issue challenging stem cell transplantation is provisioning of nutritional supply for the transplanted cell to replicate [60].

Researchers are focusing on employing a gene vector system to effect transduction of gene which will stop degeneration or even initiate regenerative process thereby restoring normal structure and function. TGF-1B was the first gene be experimentally delivered to the IVD in an animal model so as to help in its regeneration [61].

ADAMTS5 small interference RNA was successfully used in a rabbit model to suppress degradation of NP tissue [62]. In present scenario ,growth factors, metalloproteinases inhibitors,transcription factors, can be used as targets for gene therapy[63,64,65] .In vivo studies need to validate the above findings before Gene therapy establishes as an accepted modality of treatment[66].

Conclusion

With newer insights into the pathomechanics of disc degeneration and advancement in pain neurosciences, our understanding of the painful disc has definitely improved. There seems to be no single triggering factor which initiates the Degenerative cascade. What follows is accumulation of damaged biomolecules which further instigate an aberrant cellular response to damage, leading to loss of biologic structure and function. The exact mechanism and correlation of the various cascading systems are unclear at present. These mechanisms lead to structural and biochemical changes within the disc leading to increase in the nociceptive response and spinal instability. The integration of our existing knowledge of pathophysiology still leaves many questions unanswered. But further research will help us solve the mystery of the painful disc. Treatment of low back pain requires a multidisciplinary approach.

Lack of evidence based literature does not mean lack of effectiveness of a particular modality of therapy. For pain we have no objective tests and also no controls. Identification of the pain generator and instituting appropriate strategy seems the logical approach as on date. Present understanding of pathophysiology suggests that the pain generators undergo a change in their anatomical location as well as molecular configuration with the progression of degenerative disc disease process. One must also keep in mind that when there is degeneration of disc is not an isolated phenomenon. It is often accompanied by degeneration of surrounding spine tissue. They too contribute to pain and instability. Hence the treatment strategies also need to be directed taking these factors into consideration .A musculoskeletal, vertebral or radicular pain in the acute stage may transform into neuropathic pain or over a prolonged period into chronic pain syndrome. The traditional approach of motion-eliminating fusion surgery, which may be effective for the treatment of pain in some cases, may also increase the rate of degeneration at adjacent spinal motion segments. Furthermore, this strategy does not halt the progression of the degenerative cascade of events that leads to pain and disability. So despite its undeniable significance, lumbar fusion surgery as a treatment of LBP has to be regarded suboptimal, as it targets the symptom of pain rather than its causes.

The modern molecular biology era has brought revolutionary advances in fields such as genomics, nanotechnology, stem cell biology, gene therapy, and tissue engineering, which together hold tremendous therapeutic potential for clinical applications in degenerative disorders such as DDD.

These newer modalities have the potential to become the standard of care in the near future. As on date the astute clinician must realize that winning over the painful degenerative disc disease requires a multidisciplinary approach. Sometimes you win, other times you learn.

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