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Review Article

Clarifying the nomenclature of intervertebral disc degeneration and displacement: from bench to bedside

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Abstract: As a significant determinant of low back pain, intervertebral disc degeneration (IDD) has attracted more and more attention of both investigators and physicians. Disc herniation, termed as intervertebral disc displacement, is amongst the most prevalent spinal diseases closely linked with IDD. Due to the same origins and similar pathophysiology, the ambiguity regarding the similarity and difference of IDD and intervertebral disc displacement thus remains. The aim of this study was to clarify the nomenclature of IDD and disc herniation in terms of molecular etiology, pathophysiology, nature history and clinical outcomes. Collectively, IDD is a type of multifaceted, progressive spinal disease with or without clinical symptoms as back pain, characterized by extracellular matrix and the integrity of NP and AF lost, fissures formation. Disc herniation (termed as intervertebral disc displacement) is a type of spinal disease based on IDD or not, with local pain and/or sciatica due to mechanical compression and autoimmune cascades upon the corresponding nerve roots. Clarifying the nomenclature of intervertebral disc degeneration and displacement has important implications both for investigators and for physicians.

Keywords: Nomenclature, intervertebral disc, degeneration, displacement

Introduction

Low back pain has an impact on 80% of the population with overwhelming health-care and socioeconomic burden globally [1]. There are numerous determinants of low back pain [2-4], the chief of which is intervertebral disc degeneration (IDD). During the past decade, studies addressing IDD intensified considerably in terms of both clinically and basically [5-7]. The basic studies of IDD can be divided into three major subsets, i.e, the etiology of IDD ranging from genetics [8, 9], microRNAs (miRNAs) [10-13], molecular alterations to cellular function within the disc [14, 15], stem cell repair strategies [16], artificial biomaterials mimic the natural hallmarks of the disc [17-20].

Despite more and more novel findings have been unraveled by the worldwide investigators, the nomenclature of IDD has not been well documented and clarified so far. On the other hand, disc herniation termed as intervertebral disc displacement, is amongst the most prevalent spinal diseases closely linked with IDD. Due to

the same origins and similar pathophysiology, the ambiguity regarding the similarity and difference of IDD and intervertebral disc displacement thus remains.

Normal intervertebral disc and immune privilege

The intervertebral disc plays important roles in the support, durability and flexibility of the spine by acting as mechanical stress absorber and transmitter on the basis of its unique structural feature. The disc is composed of 3 distinct but interlinked subparts: the outer layer as annulus fibrosus (AF), the central core as nucleus pulposus (NP) and the cartilage endplates connecting the disc to the adjacent vertebral bodies.

The structure of cells and tissues conforms to the requirements of their function. Within the harsh environment of the disc, there are large amounts of extracellular matrix but small amounts of highly specialized cells [21]. AF cells are elongated and polarized [22] in support of concentric lamellae consisting of both type-I

and type-II collagen; whereas NP cells in adults are small, rounded and chondrocyte-like in support of extracellular matrix rich in type-II collagen and proteoglycans [23]. As localized within a nest under electron microscopy or capsule under light microscopy, both NP cells and AF cells are phagocytic in terms of autophagy and clearance of extracellular matrix and apoptotic cells [23-26].

Increasing evidence indicates that intervertebral disc belongs to immune privileged sites, owing to its avascular feature as well as molecular basis, FasL expression of NP [27-32]. In parallel with the findings of local expression of FasL and Fas in human NP cells, we further demonstrate that FasL expression in NP cells contribute for the maintenance of the immune privilege of the disc by interacting with immunocytes and vascular endothelial cells via both bound and soluble FasL-Fas machinery [33-35].

Intervertebral disc degeneration

With disc degeneration, the increasingly lost NP proteoglycans leads to reduced hydrodynamic transfer of axial stresses to the outer AF. Concurrently, the integrity of the AF is despoiled with radial fissures. The endplates undergo an ossification process and further reduce the nutritional supply to the disc.

IDD is multifaceted, the etiology of which including genetics [9], mechanical loading [14, 36, 37], aberrant expression profiles of miRNAs [10, 13] and other molecules, such as CK8, link-N [15, 38]. Accumulating evidence based on the Twin Spine Study indicates that heredity plays a much bigger role than environmental factors [39]. It is noteworthy that small non-coding RNAs, miRNAs, attract more and more attention in a variety of physiologic and pathologic processes. miRNAs are key post-transcriptional regulators by interacting with 3'-UTRs of their repressed genes. We addressed the expression profiles of miRNAs in IDD and further demonstrated that miR-155 promotes Fas-mediated apoptosis in human IDD by targeting *FADD* and *CASP3* [10]. Despite a few studies addressed several other miRNAs in IDD, including miR-10b [13], the upstream regulation of miRNAs and their interaction with cytokines remain elusive.

As for the classification of IDD, there are clinical and histological schemes. Clinically, MRI is the current gold standard to assess the integrity of the disc. According to Pfirrmann and Boos [40], IDD can be classified as Grade I to V. As IDD progresses, the patients might complain low back pain rather than sciatica; whereas histological classification is proposed on the basis of degenerative hallmarks, such as cell clusters, fissures extents and morphology of AF [41-43].

In 2012, IDD was introduced into the PubMed as a MeSH term with an OMIM code as 603932. However, the term has not been widely accepted and used in the literature. A variety of other terms have been used, including IVDD, DDD (degenerative disc disease), LDD (lumbar disc degeneration), IVD degeneration etc. Unifying the term and nomenclature might be critical for global investigators and physicians.

The nomenclature of intervertebral disc degeneration

Therefore, IDD is a type of multifaceted, progressive spinal disease with or without clinical symptoms as back pain, characterized by extracellular matrix and the integrity of NP and AF lost, fissures formation. Moreover, IDD can exist in any part of the spine, including the cervical and thoracic spine. The most frequent region with IDD is at C5/6 (men: 51.5%, women: 46%), T6/7 (men: 32.4%, women: 37.7%), and L4/5 (men: 69.1%, women: 75.8%) [44].

As IDD develops, there are several types of outcome. One is intervertebral disc displacement, or disc herniation with clinical symptoms as sciatica. The other might be the decreased disc height which eventually results in spontaneous fusion of the spinal level without clinical symptoms.

The nomenclature of intervertebral disc displacement

As a MeSH term, the intervertebral disc displacement indicates the NP protrudes through the surrounding AF. Due to the anatomic hallmarks of posterior longitudinal ligament [45] and the range of motion, disc herniation most frequently occurs in the lower lumbar region. Since the fissures in AF often develop in the posterolateral region [46], intervertebral disc displacement might protrude posterolaterally

Nomenclature of intervertebral disc degeneration and displacement

Table 1. Intervertebral disc degeneration and disc herniation

Diseases	Intervertebral disc degeneration	Disc herniation
MeSH term	Intervertebral disc degeneration	Intervertebral disc displacement
OMIM	603932 intervertebral disc disease	603932 intervertebral disc disease
Onset	Slow, progressive	Acute or sub-acute
Etiology	Multifaceted	Nucleus pulposus protrusion
Pathophysiology	Loss of integrity of the disc	Mechanical compression and immune cascades upon affected nerve roots
Region	Lower lumbar spine most frequently	Lower lumbar spine most frequently
Natural history	Progression to herniation Or lost of disc height until fusion	Immune absorption Or progression to sequestration
Classification	MRI grading system Histological grading system	Location based classification Degree of protrusion based classification
Clinical symptoms	Slight to moderate: no symptoms Severe: local regional pain without sciatica	Local regional pain with sciatica
Diagnosis	Clinical symptoms and MRI	Clinical symptoms and radiographic images
Treatment	Slight to moderate: observation and physical exercises Severe: anterior fusion	Slight to moderate: rest, traction and physical therapy Severe: posterior discectomy

to the adjacent nerve roots in the epidural region, resulting in sciatica. In addition to the compressive factors derived from the protrusion contributing to sciatica, the exposure of the immune-privileged NP triggers an autoimmune response involving macrophages, neutrophils, T cells and B cells as well as proinflammatory cytokines, including interleukins and TNF-alpha [47-51]. Early clinical trials using TNF-alpha antagonists have been proven as a promising treatment option [52]. Patients with long term of herniation history might complain of numbness and motor weakness due to the immune cascades [53] in the region.

It should be stressed that intervertebral disc displacement can derive not only from elder patients with considerably IDD, but also from adolescent patients with minimal IDD. Therefore, IDD and disc herniation are different but somewhat linked diseases. Patients with severe IDD complaining of low back pain usually undergo fusion from anterior approach; whereas patients with severe disc sequestration usually undergo posterior discectomy. The ambiguity regarding the nomenclature of these two disorders in the literature still remains. Future studies using disc specimens should clarify the disc derivation as IDD or intervertebral disc displacement to avoid conceptual confusion and misleading.

Summary

IDD is a type of multifaceted, progressive spinal disease with or without clinical symptoms

as back pain, characterized by extracellular matrix and the integrity of NP and AF lost, fissures formation. Disc herniation (termed as intervertebral disc displacement) is a type of spinal disease based on IDD or not, with local pain and/or sciatica due to mechanical compression and autoimmune cascades upon the corresponding nerve roots (Table 1). Clarifying the nomenclature of intervertebral disc degeneration and displacement has important implications both for investigators and for physicians.

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Disclosure of conflict of interest

None.

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