Discogenic Pain

4

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Introduction

The intervertebral disc (IVD) is one of the main constituents of spine biomechanics. The IVD allows spinal segments freedom and mobility, which enables spinal flexibility. In addition, the IVD provides stability to the spine by dissipating compressive loads and unifying adjacent bony vertebrae into a functional unit. Degenerative changes of mechanical and chemical etiology occur with increasing age and may begin as early as the third decade [1–8]. The etiology is multifactorial and includes demographic risk factors, such as age and gender, along with genetic, environmental, and mechanical factors. In office, physicians may find difficulty differentiating between discogenic neck pain and other etiologies of neck pain. This can be attributed to the varied presentations of discogenic pain—some individuals may find discogenic pain unbearable, while for others it is a benign process. Furthermore, there are no specific pathologic findings on history or physical exam. Imaging may be misleading, as many patients can have degenerative disc findings and with no symptomatology.

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This chapter reviews the biomechanics, pathophysiology, presenting signs and symptoms, imaging findings, and treatment of discogenic pain in the cervical spine [9].

Biomechanics/Pathophysiology

The normal adult IVD is an avascular structure between two bony vertebrae. The IVD can be divided into three distinct anatomic substructures—the cartilaginous endplate (EP), the nucleus pulposus (NP), and the annulus fibrosis (AF). The NP located at the core of the IVD is formed from the remnants of the notochord. The amount of water in the disc matrix of the NP is regulated by meshwork of proteoglycans and collagen. The proteoglycans facilitate the binding of water. The increased content of proteoglycans in the IVD allows for it to function as a liquid and dissipate forces. This differs from the AF, a stiff fibrocartilaginous structure composed of type I or type II collagen, oriented in concentric rings. The outer component of the AF densely organized, resulting in increased stability. The AF also has a small amount of elastin to provide elasticity with stretching. The inner AF has a small amount of proteoglycan in addition to its cartilage, lending to slightly higher water content and minimal ability to dissipate forces. The cartilaginous endplate is a thin calcium layer situated on each end of the vertebral body. It allows for diffusion of nutrients into the IVD [10].

There are three clinical and biomechanical stages of spine degeneration described by Kirkaldy-Wallis and Farfan: dysfunction, instability, and stabilization [11]. If one component of the spine's three joint complex is damaged, the effects are experienced by the other two joints in the complex. The most classic example of this concept is disc degeneration—the disc desiccates, providing the initial dysfunction of one component. The result is modified orientation of the superior and inferior facets. Sequelae include inconsistent facet loading, facet hypertrophy, abnormal translation, osteophyte formation, and ligamentous hypertrophy [11–13]. Each of these sequelae are potential pain generators with varying treatments but have vague presentation. To add uncer-

tainty, identification of the presence of disc degeneration on MRI or facet hypertrophy may not be the origin of the patient's pain.

As previously mentioned in this chapter, disc degeneration begins in the NP. In the second decade of life, proliferative chondrocytes replace the residues of notochordal cell aggregates that have been present in the NP since infancy [4]. As the disc continues to age, proteoglycan synthesis decreases and the NP has decreased ability to absorb water, leading to decreased ability to disperse compressive forces. Once the NP becomes dry, granulation tissue appears. In the third decade, the AF begins to replace the fibrous connective tissue network with increasingly hyalinized collagen fibers. Ensuing cellular proliferation death leads to invasion of blood vessels along tears and clefts. General inflammatory pathways are activated as an attempt to repair tears in the AF. As degeneration progresses, other types of collagens may be produced in the AF. The result is a more fibrous and stiff AF unable to handle the compressive forces [13, 14].

Discogenic pain has multiple etiologies. The natural history of degeneration can be affected by comorbidities and prior trauma. Disc space narrowing occurs with increased age and more frequently in women than men, but men are more prone to osteophyte formation [15]. Environmental factors include smoking, obesity, occupational factors. Prior animal studies have demonstrated smokers likely experience impaired blood flow to the disc, leading to decreased synthesis of proteoglycans and collagen [16]. Disc degeneration scores in groups of identical twins discordant for cigarette smoking found smokers had scores 18% higher than nonsmokers [17]. Excessive body weight in obese and overweight individuals was found to lead to a 14-fold greater prevalence of disc degeneration than underweight or normal individuals [18]. This process may begin as early as childhood [19]. Related metabolic disorders, such as diabetes mellitus, can also change the properties of the disc leading to increased prevalence of disc degeneration compared to the general population [20].

The development of disc degeneration depends on nutrient availability as well. The cells of the IVD are very sensitive to extracellular oxygen and pH. As the pH lowers with lactic acidosis from inefficient anaerobic metabolism, proteoglycan synthesis

decreases. This decrease in proteoglycans also inhibits the ability of waste products to exit the disc space, contributing to buildup of waste and degeneration. Furthermore, in a healthy individual, nutrients, such as oxygen, will pass through the porous endplate into the disc. If the endplate is impermeable due to calcifications, then nutrients also cannot pass through [13, 21–23].

The genes associated with the development of disc degeneration are categorized into four subtypes. Collagen type I alpha1 gene (COLIA1) is related to disc structure. Certain phenotypes of COLIA1 have been associated with low mineral density, increased bone loss, higher bone turnover, and increased risk of fracture, leading to increased risk of IVD degeneration. Collagen type II alpha2 gene (COL11A2), a gene coding for collagen XI, is also associated with increased risk of IVD degeneration, and subsequent disc bulges and degenerative stenosis. Matrix degrading enzymes have been demonstrated to have a genetic component and can lead to increased risk of disc degeneration. Specifically, IL-1 and IL-6 are associated in the production of inducing enzymes that destroy collagen [19, 24–26].

Aggrecan is a proteoglycan that binds hyaluronic acid, which is another component of the NP that helps to dissipate compressive loads. Polymorphisms of aggrecan may change its properties, resulting in less effective dissipation of compressive loads [27]. MMPs are known to be crucial to the homeostasis of the IVD and matrix turnover. Polymorphisms can lead to increased MMPs and accelerated proteoglycan degradation [28, 29].

Polymorphisms of the gene for the Vitamin-D receptor (VDR) have also been demonstrated to contribute to degenerative disc disease, as VDR plays a significant role in mineralization and remodeling of bones [30, 31]. Other genes, such as SOX9, SPARC, have demonstrated potential to increase risk of disc degeneration, but further research is needed [32, 33].

The inflammatory cascade plays a crucial role in discogenic pain. Degenerated discs have increased amounts of inflammatory mediators [34]. NO and cytokines are produced in the IVD as a response to increased mechanical stress. In patients with disc herniations, there is greater presence of TNF-alpha, IL1B, IL-6 compared to controls. In addition, IL-1, Il-6, NO, MMPs, TNF-alpha,

PGE2, and cytokines are all present in the environment of a degraded IVD [35]. These inflammatory mediators lead to decreased matrix synthesis and increased matrix degradation. The disc will load abnormally due to smaller and fewer proteoglycans limiting the ability to disperse mechanical forces. In this process, there is increased production of waste, which congests the nutrient and waste transport system causing increased cell death and apoptosis. Each of these components contributes to IVD degeneration [33].

Presentation

Cervical discogenic pain can present as acute herniated disc or chronic disc degeneration. In any disc herniation, the patient may present with at level pain because the torn annulus fibrosis has sensory innervation. In addition, an extruded NP can impinge on surrounding neurological structures, causing radiculopathy if the nerve roots are affected and myelopathy if the spinal cord is affected [36]. A detailed motor and sensory exam can identify the level of the lesion [37].

Spondylosis includes degeneration of the disc and may present with vague and overlapping symptomatology, as it is associated with end plate stress, spur and osteophyte formation, and facet arthropathy. Most patients presenting to a physician with degenerative discogenic pain are over 40 years old [37]. The reported symptoms are often poorly localized, such as axial neck pain exacerbated by movement associated with occasional headache. The pain may refer to other areas, such as the shoulder, interscapular zone, or anterior chest wall [38].

Patients presenting with neck pain should always have red flag symptoms ruled out. Pain associated with trauma should be evaluated for fracture and/or instability. If the patient has history of cancer, pain predominantly at night, and/or unexplained weight loss, constitutional symptoms, or failure to improve with reasonable duration of therapy, then consider neoplastic disease. If evidence of systemic inflammatory disease, consider rheumatology referral to evaluate for arthritides. In patients with current

or history of intravenous drug use, immunosuppression, or ongoing systematic infection, consider discitis or osteomyelitis. Prior spinal surgery may indicate pseudoarthrosis. Cervical myelopathy should also be referred to a neurosurgeon or orthopedic surgeon [39].

In addition to the general exam questions, the physician may administer the "Neck Disability Index" questionnaire. This investigates 10 areas of activities of daily living with the potential to be affected by neck pain [9, 40].

Imaging

Changes in cervical discs are not uncommon in asymptomatic individuals. One study reported asymptomatic disc degeneration in 86–89% of people over 60 years old [41]. Therefore, imaging should be clinically correlated. Issues exist with imaging in acute cervical disc herniations as well. Boden et al. reported abnormal disc findings in 14% of people who were less than 40 years old, and 28% of people who were older than 40 years. Of these, the disc was degenerated or narrowed at one level or more in 25% of those less than 40 years and almost 60% in those older than 40 years [42].

Spondylosis will have loss of disc height on imaging. CT is superior to MRI in differentiating the contribution of bone hypertrophy to stenosis. However, MRI is superior when assessing for disc bulges and herniations, as surrounding soft tissues can be distinguished from the herniated disc. In addition, mass effect from herniation or bulges on nerve roots and the spinal cord are evident on MRI, whereas they are not usually seen on CT [43]. To evaluate for spondylosis, T2-weighted MRI is most useful, as the normal discs will have intermediate to bright signal. Spondylosis is the most common indication for MRI in the cervical spine. The primary findings will be decreased signal within the cervical discs and focal outpouchings [9]. Whenever reviewing a cervical spine MRI, a physician should also scan for evidence of nerve root or central cord compression [44].

Discography is a diagnostic test involving injection of contrast into an IVD under fluoroscopy. This type of imaging can discern discogenic back pain at specific vertebral levels. During discography, the patient is not sedated and will endorse if the injection pressure at a specific level correlates with his/her pain. The goal of this intervention is to identify specific levels associated with the patient's symptomatology when multiple levels could be involved. As MRI has become more common and spondylosis is identified more frequently, discography has become more common, especially when planning cervical fusion. Discography can also be helpful in patients with prior fusion who have unresolved or recurrent back pain. The true diagnostic value is controversial, as the false positive rate is 10–50% [45–47]. As with MRI, patients with no symptoms may have positive findings on discography. One study demonstrated up to 20% of patients without lower back pain had at least one positive level on discography [48]. This increased to 40% in patients who had history of prior lumbar fusion, but did not have low back pain postoperatively [49, 50] Discography should be reserved for patients undergoing surgical evaluation and planning without clear cut level associated with their symptoms. The risks and discomfort of the procedure do not change management otherwise [51].

Nonoperative Treatment

First-line treatment of cervical discogenic pain without radiculopathy or myelopathy should be treated with physical therapy and medications.

Acetaminophen, or Tylenol, is a weak anti-inflammatory with antipyretic and analgesic effects. Onset is within 30–60 min after ingestion. The incidence of adverse effects is low, and the drug is low cost. Risks include hepatotoxicity in accidental or intentional overdose. It is one of the first-line medications for the treatment of neck pain [52, 53].

NSAIDs are also first line for short-term treatment of neck pain and has the same efficacy as Tylenol [52, 54]. Select COX-2

inhibitors are not more efficacious than nonselective NSAIDs but are associated with lower incidence of gastrointestinal adverse effects [55].

Opioids are not first line due to increased risk of dependence, misuse, abuse, and diversion. Studies have shown opioids have no significant advantage in Tylenol or NSAIDs with regard to symptom relief or return to work [52, 56].

Steroids are potent anti-inflammatory medications that control biosynthesis of prostaglandins and leukotrienes. This class of medications is more advantageous for acute episodes of pain and should be prescribed for 5 days or fewer. The dosing options are Prednisolone 10 mg 3–4 times per day for 5 days or a Medrol dose pack, which is a blister pack titration of methylprednisolone. Diabetic patients should be warned about steroid-induced hyperglycemia [57].

Other medications used for cervical spondylosis and discogenic pain include anticonvulsants, muscle relaxants, tramadol, and tricyclic antidepressants. Anticonvulsants, such as gabapentin and pregabalin, may be indicated for neuropathic pain, as they suppress painful neural activity produced by nerve irritation. Cyclobenzaprine is a muscle relaxant used in patients with associated insomnia. Tizanidine can also be used for muscle spasms associated with back pain but may be more useful in spasticity [57]. Tricyclic antidepressants have conflicting evidence for use and are considered second or third line due to their adverse effects and slow onset [55, 58, 59]. Topical medications, such as Lidoderm patches or diclofenac gel, are not as beneficial for pain secondary to spondylosis.

The use of epidural injections have increased significantly [60]. These injections should be reserved for radicular back pain. Thirty six to forty three percent of patients with spondylosis associated with radiculopathy showed improvement in pain at 1 year evaluations [61, 62].

Gene therapy is also being pursued to promote proteoglycan synthesis in spondylosis. The goal of these treatments would be to increase water content, restore disc height, and its usual properties. In partial thickness tears, gene therapy is limited as the deficit is more commonly in the avascular area where growth factors

would not be usually associated with rupture of blood vessels, allowing for the growth factors to have a means to access damaged areas [63]. Further research needs to be completed [64].

Cell therapy is also being studied as a future treatment for degenerative disc disease. Targets of cell therapy would include growth factors, matrix components, such as type II collagen, transcription factors, signal transduction molecules, regulators like SonicHedgehog, anti-inflammatory mediators, inhibitors of apoptosis, and mesenchymal stem cells. The main limitation of this potential treatment is injected growth factors into cells of reduced viability may not be able to restore disc structure once the disc is already damaged. Their presence may also increase metabolic demand, risking further and expedited damage to the disc [65]. Additionally, restoration of the disc may not resolve the patient's symptoms. Further research is needed in this area of treatment as well [64].

Operative Treatment

Chronic degenerative disc changes of spondylosis may resolve spontaneously and usually are treated conservatively [66]. Due to anatomic proximity of the spinal cord and nerve roots to the IVD in the cervical spine, both types of disc herniation (acute and chronic) have potential to result in radiculopathy and myelopathy. Indications for surgery include profound or progressive myelopathy, herniation resulting in severe stenosis, MRI evidence of myelomalacia, progressive radiculopathy, and intractable symptoms that failed conservative management [67]. The primary goal of surgery in these cohorts is to decompress the neural elements to relieve pain, limit neurologic deficit, and improve quality of life [68]. The most optimal functional outcomes occur if the surgical intervention occurs within 6 months of symptom onset [69].

Surgical approach for cervical disc herniation can be both anterior and posterior. Posterior laminectomy and foraminotomy provides direct access to neural elements but limits access to more anterior structures. Currently, anterior discectomy and its variations are the most commonly performed [70].

Cervical total disc replacement (TDR) is indicated for degenerative disc disease at one level between C3 and C7. Cervical TDR allows for direct decompression and removal of the process causing symptoms. Additionally, cervical TDR has higher likelihood of preserving spine biomechanics versus anterior cervical fusion. It also avoids serious complications, such as esophageal injury, dural tear, dysphonia, dysphagia, neurovascular injury, and postoperative airway compromise from edema or hematoma formation [71]. The ideal patient for cervical TDR would have minimal spondylosis, single-level disc herniation, and associated radiculopathy that failed nonoperative management for 6 weeks or has a severe and progressive neurologic deficit. Contraindications for cervical TDR include severe spondylosis, multilevel involvement, bridging osteophytes or ossification of the posterior longitudinal ligament, spondylosis involving C1 or C2, disc height loss of greater than 50%, significant facet joint arthritis, significant spinal deformity, instability, tumor, infection, metabolic bone disease, and morbid obesity [72].

Nucleus pulposus replacement is another potential treatment for mild and moderate degenerative disease [73]. Similar to cervical TDR, NP replacement is best for patients with minimal disruption to other components of the joint, such as the annulus, end plate, and facet joints. The objective is to approximate the physiologic function of the nucleus and protect the integrity of intact components of the joint. The substitute nucleus can be either synthetic replacement or autologous cartilage implantation. Materials used include metals, ceramic, injectable fluid, hydrogels, inflatables, elastic coils. The most commonly used is hydrogels because it functions most similarly to the natural disc [65].

Two other operative alternatives to fusion are interspinous distraction and dynamic stabilization [73]. Interspinous distraction uses a posteriorly placed device to restrict lumbar extension. The result is decreased compression on nerve roots. These implants can be placed under local anesthesia, decreasing risks associated with anesthesia. Another major benefit of interspinous distraction is motion at other levels is spared, reducing postoperative compli-

cations, such as pseudoarthrosis, and this method does not contribute to the development of adult spinal deformity [74]. The crucial limitation to note for this approach is an extremity high failure rate demonstrated in one study [75]. Other studies have shown significant complications such as spinal process fracture, device loosening, wing breakage, and dura mater tears [76]. The patient and surgeon should have a conversation regarding risks and benefits to determine if this is the best option.

Dynamic stabilization is the insertion of flexible rods to connect one or more spinal segments. The outcome is stability by altering abnormal loads on the degenerated disc, while avoiding complete fusion. This method allows for controlled movements similar to external braces. It is useful in degenerative disc disease. Risks include loosening at the bone–implant interface, mechanical failure, insufficient stabilization requiring re-instrumentation and fusion, and auto-fusion. One major drawback is the lack of long-term studies and outcomes [12, 77, 78].

Conclusion

Spondylosis and degenerative disc disease may lead to discogenic pain, as the primary function of the IVD is to allow for spinal flexibility and dispersion of mechanical forces. Etiology is multifactorial, and further research is needed to understand, diagnose, and treat discogenic pain. Symptoms are vague and variable but can also be associated with radiculopathy and myelopathy. Additionally, patients with evidence of degenerative changes on imaging may be asymptomatic. Therefore, there is no one treatment for all patients with discogenic pain or spondylosis. Physicians should use physical therapy and medications to lessen symptoms and improve function. Surgical consultation should only be considered in patients with significant radiculopathy, myelopathy, or with intractable pain that failed conservative treatment. Future management may include gene and cell therapy as further research emerges.

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