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Editorial

Vertebrogenic Pain: A Paradigm Shift in Diagnosis and Treatment of Axial Low Back Pain

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Background

In 1966, an article reported that the source of chronic low back pain (CLBP) could not be identified in 79% of male and 89% of female patients from a general practice population [1]. In the decades that followed many clinicians and researchers repeated this claim. Notably, the article's authors had no specialized training or education in diagnosing or treating painful spine disorders; and their study was conducted prior to the advent of advanced imaging such as magnetic resonance imaging (MRI) and even computerized topography (CT). Conclusions that seemed founded at that time are no longer accurate, as knowledge of spine biochemistry, biomechanics, and pathophysiology evolved to allow a more sophisticated approach to the diagnoses and treatment of CLBP.

Chronic low back pain is a common symptom of a heterogeneous group of causative conditions. Clinicians and researchers have long recognized that better subgrouping of individuals with CLBP is necessary for more targeted and effective treatments. Commonly described sources of CLBP include the zygapophyseal joints, sacroiliac joints, and intervertebral discs (often termed "discogenic" pain) [2]. Historically, the term "discogenic pain" has been associated with disc degeneration and internal disc disruption with the presence of fissures in the annulus fibrosus and associated nociception via branches of the sinuvertebral nerve [3–6]. Previously, it was thought that pathological neurovascular ingrowth penetrated into annular fissures, leading to increased sensitivity and nociception via the sinuvertebral nerve [7, 8]. However, more recent evidence appears to refute the occurrence of such neurovascular ingrowth in many cases [9]. In the late 1990s, a team of researchers led by Dr. Heggeness reported that vertebral bodies were richly vascularized by vertebral capillaries and innervated by nociceptors that traced back to a single source, the basivertebral nerve [10]. Subsequently, it was demonstrated that the BVN is a branch of the sinuvertebral nerve (SVN) that enters the vertebral body through the foramen in its posterior wall, then it arborizes caudal and

cephalad to densely innervate the vertebral endplates [11] (Figure 1). With progressive segmental degeneration or acute injury, altered force transfer and endplate stress can result in changes to endplate morphology and composition with concomitant impairment in permeability and transport [12, 13]. Histomorphology of human vertebral bodies demonstrated endplate nociceptor densification in areas of damage that were associated with increased disc degeneration. In addition, they found that only 30% of annular tears in degenerated discs had pathologic neural ingrowth, compared with 90% of adjacent endplates (which were twice as densely innervated) [9]. This distinction between annular and endplate innervation is likely due to differences in nerve ingrowth potential. For the annulus, nerve ingrowth is inhibited by physical pressure and proteoglycans [14, 15] and thus confined to proteoglycan-depleted annular fissures [16], whereas nerves can easily proliferate in fibrovascular bone marrow adjacent to sites of endplate damage [17]. Immunohistochemical studies of the BVN have demonstrated immunoreactivity to S-100, substance-P, and PGP 9.5 further supporting the BVN's role in nociceptive innervation [10, 11, 17, 18]. Accumulated damage to the discovertebral complex may result in chemical and mechanical sensitization of endplate nocioceptors [17, 19]. These histopathological findings led to exploration of an "endplate-driven" model of discovertebral pain, with nociception largely occurring via the basivertebral nerve to a greater extent than the sinuvertebral nerve [10, 20–22]. This research supports an "endplate-driven" model of anterior column degeneration and existence of a fourth distinct structural source of low back pain, popularly termed *vertebrogenic pain* [23].

Although the vertebral body endplates categorically possess the prerequisite features necessary to cause CLBP, the clinical and radiographic characteristics which distinguish vertebrogenic pain (transmitted via the basivertebral nerve) from discogenic pain (annulus fibrosis pain transmitted via the sinuvertebral nerve) and other sources of CLBP were poorly characterized previously. The following article describes advances in our understanding of the phenomenon of "vertebrogenic pain" and how new clinical science, based on the described neuroanatomical and histopathological findings, is changing the diagnostic and therapeutic paradigm of axial CLBP.

Clinical Presentation of Vertebrogenic Low Back Pain

To date, few studies have been published which describe the clinical presentation of vertebrogenic low back pain (LBP). In studies that use a treatment response to BVN RFA as a proxy for a "true" diagnosis of vertebrogenic pain (as a superior reference standard has yet to be established), vertebrogenic pain at the L3–S1 levels appears to present as mid-line low lumbar pain with minimal cephalad referral but potentially some referral to the paraspinal and/or gluteal regions [24]. This is in contrast to the lumbosacral facet joints or the sacroiliac joint (SIJ) complex, which typically present with lateralized paraspinal (facet) and posterior superior iliac spines (PSIS) region pain (SIJ complex), respectively [25, 26]. Lumbosacral facet joint pain is typically associated with paraspinal tenderness on examination [27]. SIJ pain is associated with a number of provocation maneuvers that produce sheer, rotational, and/or compressive forces on the SIJ [28]. The SIJ complex may also be associated with thigh pain depending on age [2, 25, 26, 29]. Analysis of pain patterns of those successfully treated with BVN RFA showed that no patients reported pain below the knee, suggesting that pain referral from endplates does not produce more distal radiation [24]. However, this pattern could also be artifactual since many candidates for BVN RFA might have been excluded if they had significant symptoms concerning for radicular pain. It is possible that patients with vertebrogenic pain experience referral into the lower leg, but this should only be entertained after exclusion of other potential sources such as lumbar spinal stenosis (LSS), lumbar radiculopathy, nerve entrapment syndromes, peripheral neuropathy, or non-musculoskeletal causes of lower leg pain. To be clear, this pain pattern mirrors what was previously described as axial "discogenic" back pain. Compared to CLBP controls, patients with CLBP and Modic type 1 changes (MC1) are more likely to report night pain, prolonged morning stiffness, and pain greatest in the morning [30]. Patients with presumed vertebrogenic LBP frequently report pain exacerbation with activity and absence of pain exacerbation during lumbar extension.

Although some patients experience relatively "pure" vertebrogenic pain due to pathologic degeneration of the discovertebral complex, others may experience pain transmitted via the BVN with concomitant pain related to annular pain transmitted via the sinuvertebral nerve, as well as pain from compression of neural elements within the spinal canal and/or neuroforamen. Coexisting facet joint-related pain, with nociception via the medial branch nerves is also possible, particularly given the frequency of disc height loss in patients with vertebrogenic pain, which results in greater facet joint loading at the spinal motion segment [31]. Indeed, it has been reported that Modic type 1 changes (MC1) and endplate defects commonly co-occur in patients with lumbar disc herniation and associated radiculopathy [32, 33], and these findings are associated with higher rates of conservative treatment failure prior to discectomy [34]. In patients with LSS, endplate defects are a stronger predictor of axial LBP intensity than the severity of the spinal stenosis [35]. However, multiple peer reviewed research papers have reported a low prevalence of multifactorial LBP [2, 36]. Nonetheless, it appears that the presence or absence of midline LBP can help differentiate between joint pain and anterior column

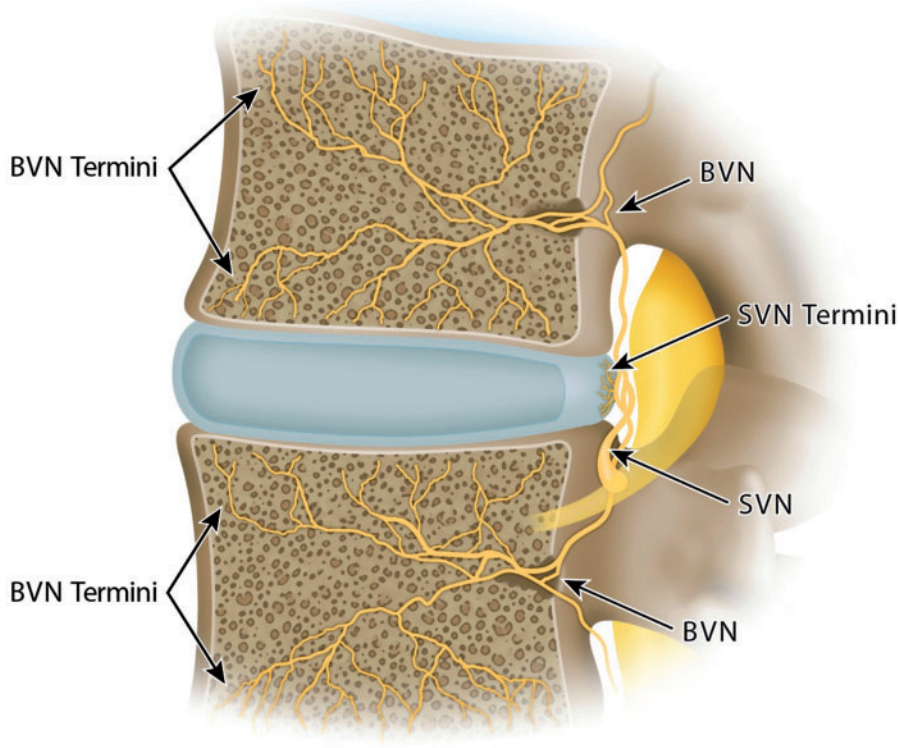

Figure 1. Neuroanatomy of the lumbar discovertebral complex. SVN = sinuvertebral nerve; BVN = basivertebral nerve.

component pain and can assist the evaluating clinician when examining LBP patients [24, 26, 29].

Imaging Characteristics of Vertebrogenic Pain: Endplate Defects and Modic Changes

A correlation between vertebral endplate pathology on MRI and LBP was first suggested in 1988 by Modic et al. who found intraosseous MRI changes adjacent to vertebral endplates defects in individuals with chronic LBP [37]. Inflammation and bone marrow changes surrounding endplate defects are visible as Modic changes (MC) on MRI [38]. Type 1 Modic changes are associated with bone marrow edema and hypervascularity of the vertebral body displayed as decreased signal intensity on T1-weighted images, and increased signal intensity on T2-weighted images. Type 2 Modic changes (MC2) are associated with fatty replacement of the red bone marrow in the vertebral body and display as increased signal intensity on T1-weighted images and on T2-weighted images.

An association has been established between the presence of MC1 and MC2 of the vertebral endplates and disabling CLBP [39]. Histopathologic studies corroborate the existence of both granulation and fibrotic tissue in areas of MC1 and MC2, indicating that MC are likely a consequence of cycles of inflammation and healing. Weishaupt et al. reported 88–100% specificity to CLBP in individuals depending on the extent of MC1 and MC2, and Kuisma et al. found a 2.28 odds ratio for the presence of Modic changes at L5-S1 in individuals with CLBP [40, 41]. Although MC lesions may be observed in up to 12.1% of asymptomatic individuals, there remains an overall strong association between their presence and CLBP [42]. This association is particularly strong for MC1; a meta-analysis found an odds ratio of 4.01 for the presence of MC1 and CLBP, while only 3% of asymptomatic subjects exhibited MC1 [42].

In addition to MC, other endplate defects observed on MRI also strongly correlate with CLBP. Either acute injury or chronic repetitive injury to the endplate is likely the inciting event that permits leakage of disc secreted factors into the vertebral body bone marrow, leading to inflammation and/or fatty infiltration, fibrosis, and increased bone turnover that may subsequently be visualized as MC1 and/or MC2 [8]. In this model, MC can be thought of as a "late stage" finding, whereas endplate injury(ies) may be considered the sentinel event(s). A systematic review including over 11,000 subjects concluded that "erosive" type endplate defects are strongly associated with low back pain (odds ratio [OR] 2.69) [43] and larger endplate defects have been associated with greater LBP related disability in some studies. However, in analysis of data from BVN RFA trials, endplate defect presence, size, and morphology were not found to influence treatment success or failure, possibly because all patients enrolled in these trials had already had MC1 or MC2 ("late stage" disease) [44]. Interestingly, patients with smaller volume MC, non-centrally located MC, and those with <25% involvement of the endplate respond similarly

as patients with large volume MC. Patients with MC1 vs MC2 experienced similar rates of success [44].

Spine specialists and musculoskeletal radiologists frequently encounter "degenerative spine syndrome" on MRI, where multilevel degeneration of the anterior and posterior columns coexist. Several studies examining how various degenerative findings impact the success of facet denervation procedures yielded mixed findings [45–49]. Until recently, there had been no description of how such findings impact treatment success of BVN RFA. Pooled analysis of multicenter trial data found that treatment success was not significantly impacted by degree of disc degeneration (Pfirrmann Grade), presence of high intensity zones, grade of facet joint arthropathy, or degree of foraminal, central canal, or lateral recess narrowing. The presence of facet joint fluid was associated with a lower probability of treatment success after BVN RFA (OR 0.578) but was considered a weak predictor of treatment outcome in the statistical model (area under the curve [AUC] 0.5609). It should be acknowledged that these observations were derived from strictly selected trial populations which excluded patients with clinical evidence of symptomatic spinal stenosis, radicular pain, lumbar facet joint pain or radiographic evidence of spondylolisthesis greater than 2 millimeters. In the presence of spondylolisthesis, facet joint effusions are strongly correlated with dynamic instability [50], however, population based cohort studies have shown that facet effusions alone are not significantly associated with the presence of LBP [51]. Considering this evidence, prior to considering BVN RFA, clinicians are encouraged to obtain standing flexion/extension lumbar radiographs in patients when there is clinical suspicion of segmental instability. Ruling out facet joint-mediated pain using medial branch nerve blocks (MBBs) should be considered when there is suspicion for facet joint pain, regardless of the presence of facet joint effusions [27].

Interventional Diagnosis of Vertebrogenic Low Back Pain

Given the complex and overlapping pain patterns of various structures within the lumbosacral region, clinicians have often utilized diagnostic/prognostic injections to test hypotheses formulated based upon the history, physical exam, and imaging. Examples of this include intra-articular SIJ anesthetic blocks, discography, and MBBs. While anesthetic administration to the proximal intraosseous portion of the BVN may initially appear attractive as a diagnostic test for vertebrogenic pain, there are several practical problems with this approach. Access without penetrating the vertebral bone would require an unacceptable transthecal needle path. As a result transpediclar access is required, which generally mandates conscious sedation and abundant opportunities for false positive or negative results. To access the pedicle, the territory of the traversing lumbar medial branch nerve would be encountered and anesthetized, which will further confuse assessment of the underlying source of pain. As a practical matter, additional invasive testing seems unjustified given the high rates of success and positive outcomes observed with BVN RFA when selection is based on clinical and radiographic criteria alone [52].

Lessons learned from decades of study related to spinal facet denervation procedures might also be applied to vertebrogenic pain. Although not a part of most standard practices, placebo-controlled triple blocks have been found to select patients with relatively "pure" zygapophyseal joint pain in the cervical and lumbar spine [53–55]. Patients selected by this type of paradigm are more likely to benefit from medial branch nerve RFA (compared to uncontrolled anesthetic blocks, which have a high false positive rate), but some have suggested that the practice of applying multiple blocks is expensive, and increases the rates of false negative responses, thus withholding treatment from some who could benefit [27, 56]. Even if a test to directly anesthetize the BVN were feasible, the costs and risks of such a practice would likely not be justified given that the current selection paradigm for BVN RFA results high rates of successful pain reduction, functional improvement, and reduction in healthcare utilization for 5 years or longer [57].

Provocation discography, while historically considered the gold standard for diagnosing "discogenic" pain [58], is of unclear value in differentiating pain arising from the disc annulus fibrosis vs the vertebral endplate. Although the probability of reproducing patient symptoms during provocation discography is significantly greater in patients with endplate damage [59], disc pressurization can potentially provoke nociception transmitted by both the annulus and the sinuvertebral nerve as well as the endplate and the basivertebral nerve, as pressurization results in stretch of annulus fibrosis fibers as well as endplate deflection [60, 61]. Endplate deflection of <1 mm occurs upon reaching intradiscal pressure of 75–100 psi in the absence of annular fissures [60, 62], but this deflection may be increased in the presence of endplate microdamage [63]. By definition, discs with internal derangement responsible for clinically meaningful CLBP produce such pain at <50 psi [59]. However, it is unknown how much endplate deflection can be evoked at low pressures in the presence of significant endplate damage. Furthermore, it is not known how much endplate deflection is necessary to provoke symptoms. It is sensible to presume that inflamed nerve endings in endplate are hypersensitive to any mechanical perturbation. The role of PLD to differentiate between painful annular fissures and painful VBE needs further study. Because of this, the role of provocation discography in identifying patients with vertebrogenic pain has yet to be clarified. Positive and negative responses to intradiscal anesthetic injection (i.e., functional anesthetic discography (FAD) or "discoblock") are strongly correlated with the

respective presence and absence of MC1 and MC2 [64, 65]. However, additional studies are needed to define the diagnostic characteristics of anesthetic discography in confirming or refuting vertebrogenic pain.

The diagnosis of vertebrogenic LBP should be strongly suspected when MRI demonstrates the presence of Modic 1 or 2 changes, with or without endplate defects. We encourage clinicians to apply evidenced based diagnostic tools to evaluate for alternative or comorbid spinal pain generators when suspected; this may include lumbar MBBs and/or intra-articular SIJ injections to evaluate for alternative causes of LBP depending on the clinical presentation [27, 58].

Treatment of Vertebrogenic Low Back Pain

The current evidence supporting intraosseous BVN RFA comes from two large RCTs comparing BVN RFA to sham and "standard care" and from four single group cohort studies [57, 66–76], all demonstrating similar benefits. Each study used transpedicular access and bipolar RFA to target the BVN terminus at motion segments from L3 to S1 with MC1 and/or MC2. Single-arm meta-analysis of outcomes after intraosseous BVN RFA demonstrates that 64% (95% confidence interval [CI] 43–82%) and 75% (95% CI 63–85%) of participants report ≥50% pain reduction and ≥15-point Oswestry Disability Index (ODI) improvement at 12 months [52]. These improvements appear durable in the two studies that reported outcomes at 2 years and 5 years [57, 71, 74]. Although changes in chronic opioid use were less robust, interventional/surgical healthcare utilization decreased substantially after BVN RFA. For example, 49% of patients in a cohort study by Macadaeg et al. had received epidural steroid injections (ESI) prior to BVN RFA, but only 2% of these same patients received an ESI in the 12 months following treatment [76], with similar single digit utilization rates observed following BVN RFA for fusion surgery in the two RCTs at 2 and 5 years [57, 74].

Other than intraosseous BVN RFA, vertebrogenic pain has been treated with extraosseous epiduroscopic BVN/SVN laser ablation or bipolar RFA [77–79], intraosseous plasma rich growth factor [80], intraosseous injection of bioresorbable cement [81], and full endoscopic disc debridement surgery [82]. Oral therapies for presumed low grade infection affecting the discovertebral complex remain controversial [83–87]; however, research interest remains as a large RCTs are planned to further determine subpopulations who might benefit from antibiotic treatment [88]. Multiple studies have shown an association with paraspinal muscle quality, MC, and presence of low back pain [89–93], but it remains unknown how treatments to address paraspinal muscle deficits might impact those with vertebrogenic low back pain. A retrospective study of bracing for those with CLBP and MC1 reported short term pain relief [94]; however, RCTs have questioned the effectiveness of this intervention in general LBP populations [95].

Summary

- Accumulated damage to the discovertebral complex may result in chemical and mechanical sensitization of endplate nociceptors resulting in chronic vertebrogenic LBP.
- Midline LBP, pain exacerbation by physical activity, sitting, and forward flexion are factors associated with treatment success after BVN RFA.
- In appropriately selected patients, BVN RFA results in substantial reduction in pain and disability in the majority of those treated at 12 months, with similar long term outcomes at 5 years.
- The presence of MC1 or MC2 is currently the best radiographic indicator of vertebrogenic pain. Outcomes after BVN RFA are not impacted by the volume of MC, location of MC, degree of disc degeneration, or presence/size of endplate defects. Patients with MC1 vs MC2 experience similar rates of success after BVN RFA.
- Clinicians are encouraged to select patients for BVN RFA based upon the clinical and radiographic criteria used in published studies to date.

Future Research

Exploration of clinical, imaging, or other characteristics associated with vertebrogenic LBP may enable further progress in patient selection for BVN RFA. Enhanced diagnostics to isolate the source(s) of pain and further differentiate annular pain from vertebrogenic pain, such as MR spectroscopy and novel MRI sequences such as IDEAL and UTE may also be of value [96–100]. Evidence suggests a correlation between MC and increased endplate metabolic activity as detected by Single Positron Emission Computed Tomography (SPECT/CT) or bone scintigraphy [101, 102], but further study is necessary to know whether or not such findings are suggestive of vertebrogenic pain. Early research in serum biomarkers linked to vertebrogenic pain appears promising [103–105]. Finally, objective monitoring of real-life physical performance using wearables recently demonstrated the ability to identify kinematic and behavioral markers of spine disease [106–108]. Ongoing investigation in these areas may lead to more accurate phenotypes of Vertebrogenic LBP and influence treatment paradigms.

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