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Narrative Review

Functional Spinal Unit Approach for Orthobiologic Injections for Low Back Pain

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Background: Low back pain (LBP) is a common and complex health issue with a multifactorial origin, involving structures such as the lumbar intervertebral discs (IVDs), facet joints, muscles, ligaments, and nerve roots. Typically, traditional pain management approaches target isolated pain generators. However, recent advancements, particularly regenerative injection techniques, have shifted the focus toward a more comprehensive treatment model that addresses the entire functional spinal unit (FSU), providing a disease-modifying approach.

Objectives: The purpose of this narrative review is to provide a scoping overview of the concept of the FSU and evaluate the potential role of orthobiologics, such as platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs), in treating back pain associated with various spinal conditions.

Study Design: Narrative literature review.

Methods: Relevant peer-reviewed manuscripts were identified through a comprehensive search of electronic databases, such as PubMed, Embase, and Google Scholar. Studies focusing on the anatomy, biomechanics, and pathology of the FSU, as well as those concerning the application of PRP and MSCs in spinal disorders, were included.

Results: The FSU, the smallest structural unit of the spine, consists of 2 vertebrae, an IVD, facet joints, and associated supporting ligaments. The FSU is crucial for absorbing shock, distributing mechanical loads, protecting the spinal cord and nerve roots, and maintaining spinal stability and mobility. Orthobiologic therapies, including PRP and MSCs, have shown promise in modulating disease processes and promoting tissue repair in spinal conditions. Emerging evidence supports the efficacy of these therapies in reducing pain and improving functional outcomes by targeting multiple components of the FSU. A thorough understanding of the biomechanical processes and the dynamic distribution of mechanical load across its various structures is essential to recognizing that chronic LBP often arises from multiple pain generators rather than a single source. Therefore, an integrated treatment approach that addresses these multiple pain generators collectively, considering the FSU and the entire spine, is critical for optimizing patient outcomes.

Limitations: Rather than being systematic, this narrative review is focused on providing an overview of the effects of orthobiologics in the treatment of chronic LBP using an FSU approach. The heterogeneity of study designs, variability in treatment protocols, and limited long-term data pose challenges in establishing standardized guidelines for orthobiologic therapies in LBP management.

Conclusions: Orthobiologic treatments offer a promising disease-modifying approach by addressing the entire FSU rather than isolated pain generators. Future research should focus on optimizing multitarget injection strategies, thereby standardizing treatment protocols.

Key words: Low back pain, orthobiologics, platelet-rich plasma, functional spinal unit, mesenchymal stem cells

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Low back pain (LBP) is a prevalent health issue and a leading cause of activity limitations and work absences across all age groups and socioeconomic strata. Research indicates that up to 23% of adults globally suffer from chronic LBP, with annual recurrence rates ranging from 24% to 80% (1). The global burden of LBP continues to rise, with an estimated 619 million people—nearly 10% of the world's population—affected in 2020, and projections suggest this number will increase to 843 million by 2050 (2).

The lumbar intervertebral discs (IVDs), facet joints, sacroiliac joints, ligaments, fascia, muscles, and nerve root dura are all potential sources of pain in the low back and lower extremities (3). Recognizing warning signs of the condition and determining the most appropriate treatment are critical components of managing LBP. While most cases thereof are amenable to conservative management, the presence of nerve dysfunction and other alarming symptoms necessitates comprehensive evaluation and a multidisciplinary approach (4). The effective management of spinal pain and musculoskeletal disorders hinges on precise diagnosis and the implementation of evidence-based, cost-effective therapeutic interventions. Traditional interventional pain management has been predominantly guided by a narrow "pain generator" model, targeting a limited range of structures as temporary measures rather than adopting a disease-modifying approach (5,6). The introduction of regenerative injection techniques has expanded this paradigm, moving beyond the singular focus on isolated pain sources to encompass the entire osteoligamentous complex, referred to as the functional spinal unit (FSU).

Over 5 decades ago, White and Punjabi introduced the concept of the FSU, proposing that each of the 24 levels of the spine—comprising the cervical, thoracic, and lumbar regions—functioned as an integrated mechanism designed to provide a stable support base for the body (7). The FSU, or spinal motion segment, is defined as the smallest structural unit that embodies the functional characteristics of the entire spinal column. This unit consists of 2 vertebrae, the IVD, zygapophyseal (facet) joints, and supporting ligaments, including the ligamentum flavum, supraspinous, interspinous, anterior longitudinal, and posterior longitudinal ligaments (Fig. 1) (8). At each spinal level, the IVD and paired facet joints form a 3-joint complex that facilitates load transmission and permits motion among adjacent vertebrae (9). In this model, various tissue types—such as fascia, muscles, synovial joints, and ligaments—are considered and treated.

Segmental instability, often due to ligamentous laxity or degenerative disc height loss, frequently precedes pain and predisposes individuals to injury over time as increased stress and inflammation affect related structures (11,12). Spinal ligaments, which act as passive stabilizers, are uniaxial structures that connect adjacent vertebrae, enabling the spine to move within safe limits to protect surrounding neurological structures. These ligaments, composed of a high percentage of collagen along with varying amounts of elastin, proteoglycans, and water, contribute to spinal stability. Additionally, the paraspinal muscles—such as the multifidus, erector spinae, and psoas major—play a crucial role in the stability of the lumbar spine. Muscle atrophy and fatty degeneration are commonly observed in patients with chronic LBP, highlighting the importance of the emerging role of these dynamic stabilizers in the treatment of degenerative spinal conditions (13).

Understanding the basic principles of spinal biomechanics is essential to grasping the etiology of spinal diseases and understanding how each bony and soft tissue component contributes individually and collectively to overall spinal stability. A study investigating the influence of posterior elements on the mechanical properties of the human L4-5 FSU found that these elements contributed 24-30% to compressive stiffness and 42-54% to torsional stiffness. Moreover, the apophyseal joints had a statistically significant effect on both compressive and torsional stiffness of the L4-5 FSU (14). Ligaments function primarily to stabilize the spine by restricting excessive motion, while facet joints guide spinal movement and limit excessive intervertebral shear and torsion. Ligament stiffness and motion response have been shown to correlate with age, disc level, and the stage of disc degeneration. Additionally, disc degeneration alters the geometry of the vertebrae, facet joints, and IVD, leading to modified segmental motion behaviour (15). A study employing a combination of the finite element method and response surface methodology investigated the influence of patients' gender, age, weight, and height on the movements of the FSU. The findings indicated that being overweight or obese could exert a significant impact on the behavior of the FSU, with those effects being more pronounced in men than in women as well as in older individuals, potentially affecting patients' quality of life (16).

Therefore, the main functions of an FSU can be summarized as follows:

1. Stability: The FSU provides stability to the spine, helping maintain the structural integrity of the

vertebral column while supporting the body's weight.
2. Mobility: The unit allows for a range of movements, including flexion (bending forward), extension (bending backward), lateral bending (side bending), and rotation. The IVD and facet joints facilitate these movements while maintaining control and preventing excessive motion.
3. Load-bearing: The FSU distributes loads and stresses applied to the spine during activities such as walking, lifting, or twisting. The IVD plays a key role in absorbing shock and minimizing stress on the vertebrae.
4. Protection of neural structures: The unit protects the spinal cord and nerve roots from injury. The vertebral bodies, discs, and ligaments provide a stable environment to prevent compression or damage to these neural structures.

This paper aims to elucidate the concept of the FSU and explore the potential of orthobiologics, such as platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs), in treating back pain associated with various spinal conditions. The focus will be on reviewing the literature and highlighting future directions for multi-target injection strategies.

Orthobiologics

The field of regenerative medicine has expanded the horizon of the management of musculoskeletal and spinal pain. Regenerative medicine is focused on human cells and encompasses biological therapies that reduce inflammation and provide symptomatic relief in the short term, alongside addressing the root cause of the pain, repairing and restoring the damaged tissues, and delaying the degenerative process to aid in their long-term regeneration (17).

The concept of regenerative medicine can be traced back to the eighth century BC, symbolized by the myth of the Titan Prometheus, whose liver regenerated daily. However, it was not until the late nineteenth century that regenerative medicine began to be understood in the form recognized today (18). Over the last several decades, prolotherapy has been considered a promising therapeutic technique for treating instability related to lax spinal ligaments (19). Prolotherapy is often regarded as the precursor to modern orthobiologics. Though its roots go back nearly a century, prolotherapy's modern evolution began in the 1950s, when Dr. George Hackett, a U.S. general surgeon, formalized

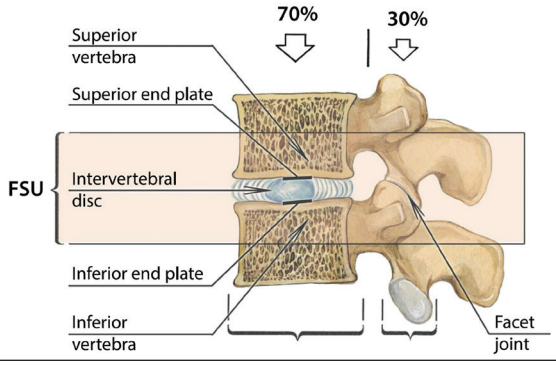

Fig. 1. *Functional spinal unit embodies the 2 vertebrae, intervertebral disc, paired facet joints, and the adjacent ligaments (10).*

injection protocols based on over 30 years of clinical experience. This technique involves injecting a small volume of an irritant or sclerosing solution into painful ligament and tendon attachments and nearby joint spaces. These injections, tailored to each condition's severity and the practitioner's approach, are typically administered over several sessions to stimulate healing and strengthen weakened areas (20). In the present day, PRP and MSCs are the 2 main pillars of orthobiologics used for the management of spinal pain in the United States.

PRP is an orthobiologic agent that has been studied extensively in clinical settings for nearly 4 decades. Derived from whole blood through differential centrifugation, PRP contains growth factors that play a crucial role in the healing process. The orthobiologic properties of PRP make it nonimmunogenic and free from the risk of disease transmission, distinguishing the use of the agent from xenobiologic and allobiologic treatments. Although the methods for preparing PRP may vary, they aim consistently to concentrate the platelet count within the patient's plasma sample before the agent is applied at the site of tissue regeneration. A substantial body of preclinical and clinical research has explored the efficacy of PRP in managing spinal pain, given its long history and relatively noninvasive preparation process (21,22).

The term "mesenchymal stem cells" (MSCs) was introduced in the 1990s to describe a class of cells with the in vitro potential to differentiate into bone, cartilage, fat, and other tissues via the mesengenic process. In 2006, the International Society for Cellular Therapy established a set of criteria for MSCs, stipulating that those cells must adhere to plastic under standard

culture conditions, have surfaces that express specific cluster of differentiation (CD) glycoprotein antigens, and possess the ability to differentiate into osteoblasts, chondroblasts, and adipocytes in vitro (23). MSCs can be sourced from various tissues, both autologous and allogeneic, including bone marrow, adipose tissue, and amniotic-derived tissues such as Wharton's jelly and the umbilical cord. Among these, bone marrow and adipose tissue are the most commonly utilized sources for treating spinal pain (24). Stem cells derived from bone marrow can differentiate into multiple cell types, including osteoblasts, adipocytes, chondroblasts, and neurogenic cells (25). In the context of cartilage regeneration, which is a key focus of regenerative medicine for spinal diseases, bone marrow is recognized as a valuable source for inducible chondrogenic differentiation (26).

Components of the FSU

Facet Joints

The lumbar facet joints are the only true synovial joints in the spine, formed by the articulation between the medially oriented superior articular process of the lower vertebra and the smaller, laterally oriented inferior articular process of the superior vertebra. These diarthrodial joints comprise an aneural hyaline articular cartilage that covers the surfaces of the superior and inferior subchondral bone (Fig. 2) (27). The lumbar facet joint is surrounded by a capsular ligament consisting of 2 layers: an outer one made of densely packed parallel bundles of collagen fibers and an inner one made of irregularly oriented wavy elastic fibers (28-30). This capsular ligament plays an important role in maintaining the stability of lumbar facet joints. The presence of collagen and elastin administrates substantial mechanical support against shear and tensile forces developed during motion and vertebral loading (31). The subchondral bone, synovium, synovial folds, and joint capsule are innervated extensively. These nerve endings, which form part of the medial branch emanating from the dorsal ramus, are involved in pain sensation and proprioception (30). The facet joints may refer pain to the lower back, lateral hip, posterolateral thigh, groin, and, occasionally, to the leg and foot.

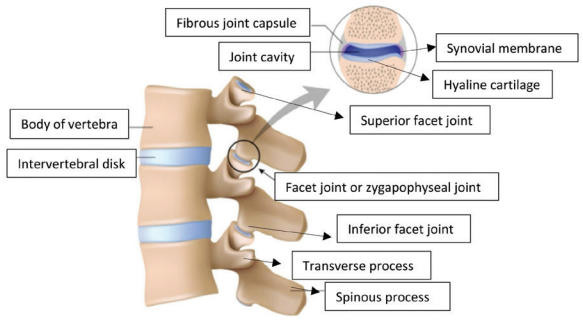

Fig. 2. *Lateral view of the lumbar spine showing vertebral bodies, intervertebral disc, and facet joints. A closer look (top right) at the facet joint anatomy displaying the joint cavity along with the joint capsule, hyaline cartilage, and synovial membrane (27).*

These joints regulate the direction and amplitude of spinal movement, bearing up to 25% of the load transmitted through the 3-joint complex. Proper spatial symmetry of the facet joints is crucial for optimal function; any asymmetry predisposes the spine to instability and accelerates degeneration of the facets and IVDs. In degenerative conditions, load sharing across the facet joints can nearly double, contributing to further deterioration (32). Chronic remodeling and destabilization of the facet joints, coupled with degenerative changes in the posterior ligaments, are major factors in the development of degenerative spondylolisthesis (9). Lumbar facet joints are implicated in an estimated 15-40% of chronic LBP cases, primarily due to mechanical stress and deformation of the joint capsule, which activates nociceptors (33).

The 2 primary modes of treating facet pain include intra-articular injections or medial branch denervation. The facet joint injection is usually accomplished via an intraarticular approach using fluoroscopy or ultrasound (Fig. 3). Peri-facet joint blocks have also been described when the needle tip is placed and injectant delivered adjacent to but not inside the facet joint. Inkelbarger and colleagues injected triamcinolone acetonide and lidocaine into 19 patients who had chronic LBP with or without leg symptoms but with mild to severe lower lumbar facet joint arthrosis confirmed by magnetic resonance imaging (MRI). Ultrasound-guided lumbar peri-facet joint blocks were performed on 19 patients (4 men and 15 women, mean age 55) at the L4/5 and/or L5/S1 segments at paraspinal points of palpable focal pain. One patient was lost to follow-up, and telephone reviews with the remaining 18 patients over a period of 2-6 months noted that 59.73% experienced significant and sustained pain relief (36).

Over the past decade, multiple studies have supported the use of PRP for treating facet joint pain. An

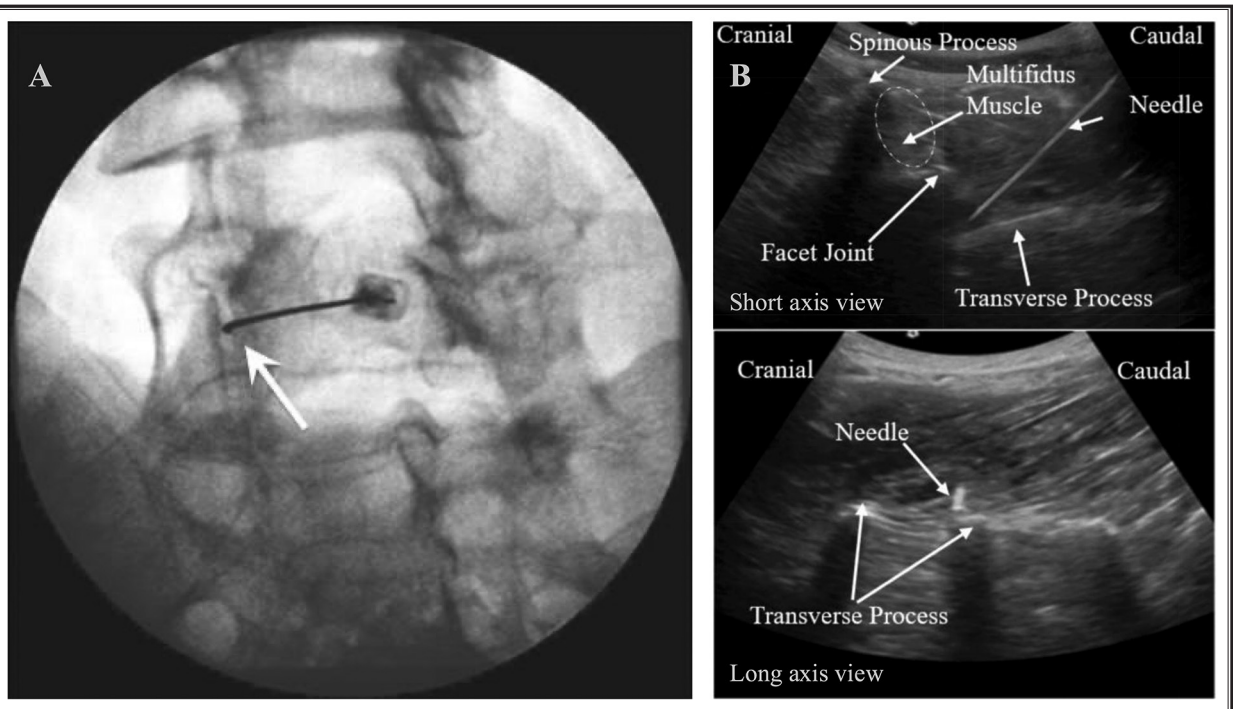

Fig. 3. *A. (34) demonstrates intra-articular facet joint injection under fluoroscopic guidance. B. (35) shows 2 views of facet joint injection under ultrasound guidance with needle entry. On the left, the injection appears in the short-axis view and is directed to the junction between the facet joint (superior articular process) and transverse process. On the right, the injection appears in the long-axis view to confirm the needle position at the superior border of the transverse process.*

early case series from 2015 involving 5 patients reported that PRP injections into facet joints and surrounding ligaments led to improvements in visual analog scale (VAS) and functional scores during a 6–12-month follow-up period (37). Subsequent prospective trials in 2016 and 2017 compared PRP to corticosteroid injections as a treatment for lumbar facet pain syndrome (38,39). A recent randomized prospective study that included 30 patients with lumbar facet joint disease demonstrated comparable improvements in clinical parameters, such as scores in pain and functional disability levels, after 3 months of treatment with either PRP or corticosteroids. However, MRI findings revealed that the PRP injections were associated with a greater reduction in facet joint synovitis, suggesting that that form of treatment held potential for a longer duration of efficacy (40). Despite these promising outcomes, the existing literature is limited by small sample sizes, lack of controls, and the absence of high-quality randomized controlled trials (RCTs), systematic reviews, or meta-analyses.

Additionally, a pilot study evaluated the safety of injecting an advanced investigational product consisting of an extracellular vesicle of bone marrow–derived MSC from into 20 patients' lumbar facet joint space to treat their chronic LBP. The study reported improved pain and disability scores with no complications at the 3-month follow-up (41). There are currently no studies demonstrating the efficacy of MSCs specifically in the treatment of facet joint pain syndrome. There is a paucity of literature supporting the use of soft tissue injections on patients with facet-mediated pain.

Intervertebral Disc

The intervertebral disc (IVD) is a complex, avascular structure consisting of the nucleus pulposus at its core, surrounded by the concentric lamellar fibers of the annulus fibrosus (Fig. 4). Positioned between the cartilaginous endplates, which facilitate the metabolic processes within the IVD, the disc operates in a hypoxic environment (43). This acidic, anaerobic, and acellular milieu creates a challenging condition for cellular repair and regeneration. The IVD is a dynamic entity with a microenvironment dependent on a delicate balance between anabolic and catabolic factors, which is essential for normal disc cell turnover (44). Anabolic factors

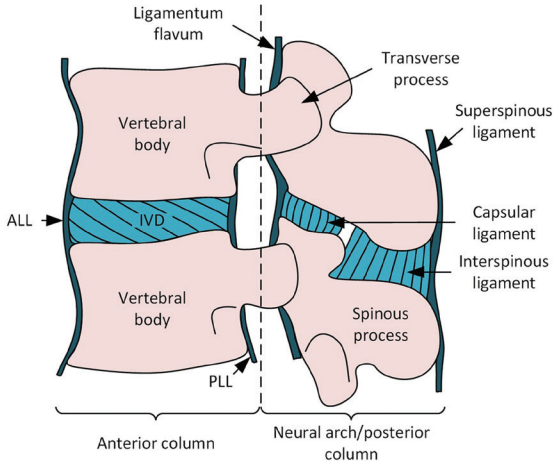

Fig. 4. *Graphical representation of a motion segment; sagittal view. ALL and PLL refer to the anterior and posterior longitudinal ligaments, respectively. The capsular ligament encloses the zygapophysial joint (42).*

include growth factors such as TGF-α, BMP, GDF5, and IL-GF, while catabolic processes are driven by enzymes, inflammatory cytokines, and proteinases, including IL-1 and TNF-α. IVD degeneration is a chronic, irreversible process characterized by increased matrix degradation, loss of nucleus pulposus proteoglycan, and decreased hydration, leading to the respective disruption and reduction of the disc's structure and disc height. Degenerative disc disease is marked by nuclear dehydration and fibrosis, resulting in the narrowing of the disc space. This alteration redistributes the axial mechanical forces exerted on the disc, vertebral body, and facet joints.

Degenerated discs exhibit reduced height under compressive loading, which in turn alleviates stress on the ligamentum flavum. This load redistribution to the posterior elements increases the pressure on the facet joints and spinal ligaments. Multilevel disc degeneration imposes greater stress on ligaments and pedicles than does single-level disc degeneration. In addition, multilevel disc degeneration increases facet joint contact forces. Furthermore, the presence of noncontiguous degenerated discs has been associated with a reduction in stresses and forces exerted on the surrounding ligaments, facet joints, and pedicles. These biomechanical patterns provide a plausible explanation for the variability observed in clinical correlations between symptomatic and asymptomatic disc degeneration (45).

The rationale for utilizing biological agents in the unique milieu of IVD stems from the critical roles that various biocellular activities play in the repair processes within disc structures. Orthobiologic therapeutic strategies aim to harness biological processes for the purpose of addressing IVD degeneration by administering molecules that modulate the metabolism of disc cells. These strategies seek to biologically enhance extracellular matrix (ECM) accumulation by promoting IVD matrix synthesis and inhibiting abnormal ECM catabolism. Clinical evidence supporting the use of PRP for treating IVD degeneration in humans has been reported since 2011 (46). Several observational studies demonstrate the efficacy of intradiscal PRP injections (47,48). A prospective, double-blinded, randomized controlled study by Tokouli-Wosornu et al (49) demonstrated significant improvements in pain and function among 47 patients who received a single intradiscal injection of PRP. A subsequent meta-analysis comprising 3 studies on intradiscal PRP treatment reported promising outcomes, including reductions in discogenic LBP and improvements in disability scores (50). The evidence supporting the use of intradiscal MSCs for the treatment of discogenic LBP includes several clinical studies and a few systematic reviews (51-54). One example of the latter was conducted by Wu et al (55), who analyzed 6 studies and found that cell-based therapies were associated with improvements in pain and disability scores among patients with discogenic back pain. In the post-intervention MRI data that Wu and colleagues also evaluated, one study reported an improvement in disc height, and another showed increased fluid content within the disc.

A recent multicenter randomized controlled trial by Navani et al (43) compared the effects of a placebo, intradiscal PRP, and bone marrow concentrate (BMC) on 40 patients. The study found that a single intradiscal injection of either biologic agent was equally effective in alleviating discogenic low back and leg pain. At the 12-month follow-up, patients experienced significant improvements in both pain and functional outcomes and reported enhanced satisfaction scores (43). While stem cell therapy presents a promising approach for IVD regeneration, further evidence from larger randomized controlled trials is needed to assess the long-term efficacy, safety, adverse events, and cost-effectiveness of this therapy before it can be established as a standard treatment for patients unresponsive to conservative management.

Vertebral Endplate

A promising target for biologic therapy in the treatment of LBP is the vertebral endplate, which plays a

crucial role in mediating IVDs and vertebral health. The endplates' structural porosity facilitates the transport of nutrients and chemicals, while the mechanical strength of these layers prevents the collapse of the disc-vertebra interface. The vertebral endplate is a key determinant of nutrient diffusion into the IVDs (56). Degeneration and calcification of the endplate cartilage, however, compromise this nutrient supply. With aging, the cartilage endplate undergoes changes in proteoglycan and collagen content, leading to a gradual thinning and calcification. The most compelling evidence for the role of the vertebral endplate in chronic LBP is the correlation between discography-confirmed discogenic pain and vertebral bone marrow abnormalities, as indicated by Modic changes seen on MRI scans.

Kirchner et al developed a novel technique involving the intraosseous injection of plasma rich in growth factors (PRGF) into the vertebral body via a transpedicular approach (57). The procedure resulted in significant improvement in patients' Oswestry Disability Index scores and a reduction in the diameters of Schmorl's nodes, suggesting that the localized delivery of growth factors might have exerted a direct influence on vertebral bone metabolism. Similarly, Cesar Amescua-Garcia et al retrospectively reviewed 57 cases of complex chronic LBP with a neuropathic component treated with PRP. Among these patients, 33.3% had had prior lumbar surgery, 56.7% exhibited Modic changes revealed by MRI scans, and 84.2% reported severe pain (VAS 8-10). The researchers concluded that 96.5% patients experienced significant improvement after PRP treatment (58).

Sacroiliac Joint

The sacroiliac joint, the largest axial joint in the body, is situated between the sacrum and the ilium, connecting the spine to the pelvis and facilitating load transfer from the lumbar spine to the lower extremities. The sacroiliac joint consists of an anterior synovial joint and a posterior syndesmosis, which is reinforced by the interosseous and posterior ligaments (Fig. 5). The sacrotuberous ligament extends from the sacrum to the ischial tuberosity at the infero-posterior aspect of the pelvis. Positioned posterior to the sacrotuberous ligament, the sacrospinous ligament attaches to the outer edge of the sacrum and coccyx, connecting them to the ischial spine (59). The articular surfaces of the sacrum and ilium form an elongated L shape, with hyaline cartilage covering the sacral surface and fibrocartilage covering the ilial surface. The joint allows

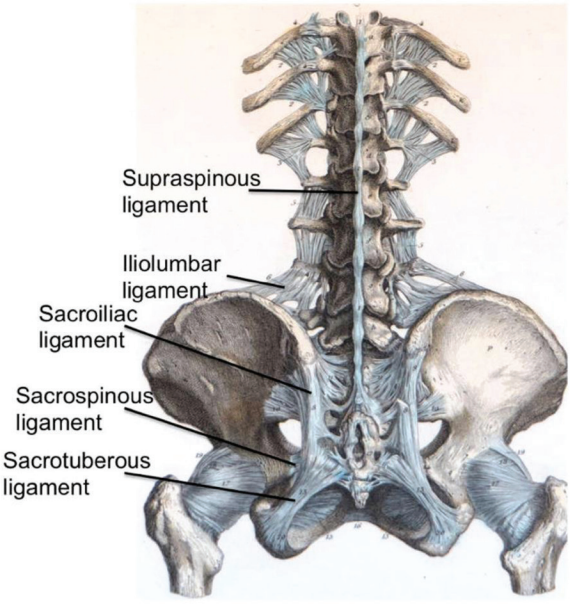

Fig. 5. *Posterior view of the ligaments surrounding the sacroiliac joint (62).*

for minimal motion, rotating across 3 planes—flexion-extension, rotation, and translation—by approximately 2 degrees, with movement occurring in multiple planes simultaneously rather than linearly (60,61).

The current evidence on the use of PRP for sacroiliac joint pain has shown positive results but has been limited by moderate-quality RCT and observational studies with small sample sizes (63-65). Therefore, the support for PRP in this context has been assessed as Level III evidence. No studies have yet assessed the role of MSCs in patients with sacroiliac joint pathology, and this remains an area of future research (66).

Spinal Muscles and Ligaments

Spinal stability is derived from the IVDs, surrounding ligaments, and muscles (Fig. 6). While the discs and ligaments provide intrinsic stability, the muscles offer extrinsic support. The main ligamentous structures supporting the spine can be categorized into 4 groups:

1. The anterior and posterior longitudinal ligaments, which are attached to the vertebral bodies, extend along the entire length of the spine, and, respectively, primarily prevent hyperextension and hyperflexion.
2. The interspinous and supraspinous ligaments,

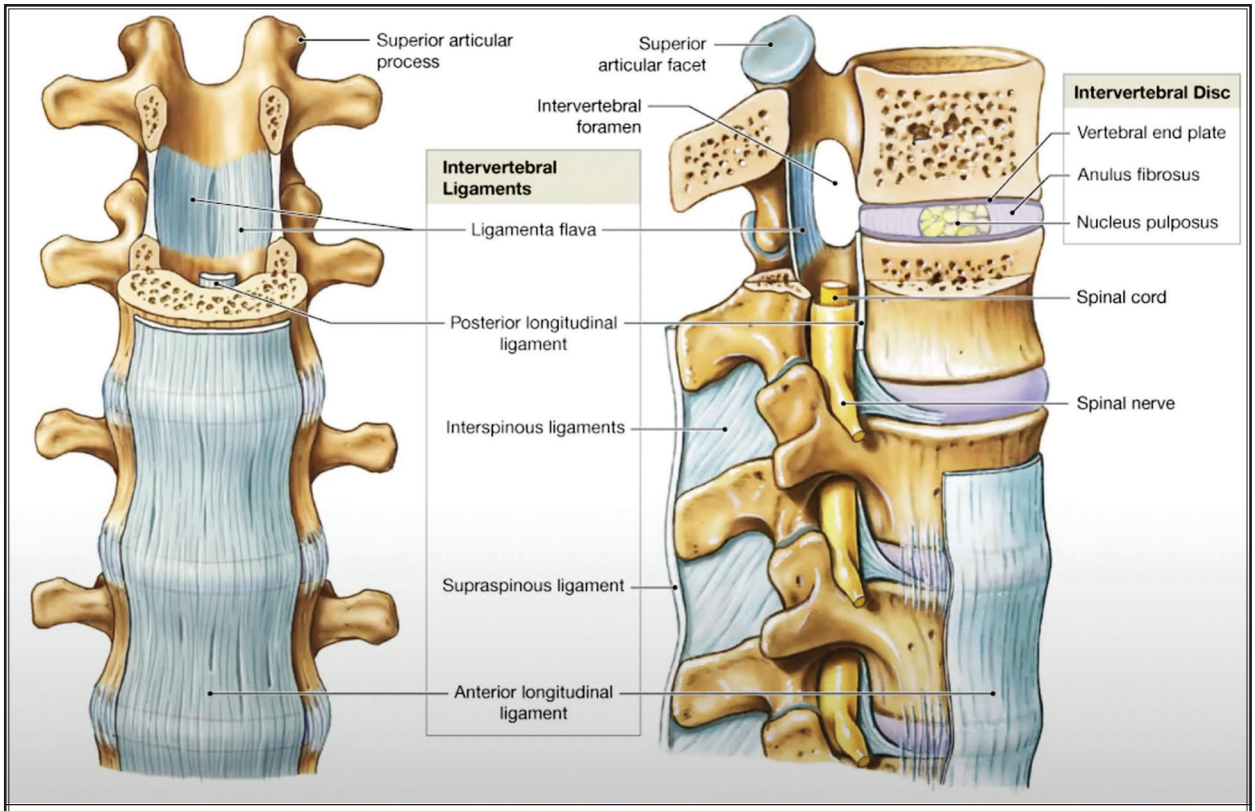

Fig. 6. *Anterior view (left) and lateral view (right) of the vertebral ligaments stabilizing the lumbar spine (67).*

which connect between the spinous processes and their tips, respectively.

3. The intertransverse ligaments, which link the transverse processes of adjacent vertebrae, contributing to lateral stability.
4. The ligamenta flava (singular: ligamentum flavum), commonly referred to as the yellow ligaments, which connect the ventral surfaces of the laminae of adjacent vertebrae, supporting spinal flexibility and alignment.

Atrophy of the paravertebral muscles has been linked to LBP, with both animal studies and human MRI findings revealing a causal relationship between fatty infiltration of these muscles and discogenic pain (69,70). The frequent observation of muscle atrophy and fatty degeneration in chronic LBP highlights the critical role of paraspinal muscles in maintaining lumbar spine stability. This atrophy can increase stress on the facets and discs, perpetuating a cycle of pain and degeneration. In one study, 115 patients who received weekly PRP injections combined with physiotherapy and walking, 71% of these patients had significant improvement in pain and disability scores sustained through to the 24-month follow-up. Post-procedure MRIs showed improvements in preexisting multifidus muscle atrophy, with patient satisfaction reaching 87.8% (71). In another study, PRP injections were administered to the lumbar ligaments, muscles, and fasciae of 30 patients with chronic nonspecific LBP. After 6 months, all pain and disability assessments favored PRP (72). The study also highlighted the synergistic effect of PRP and prolotherapy in strengthening the lumbosacral fascia and ligaments. However, the absence of ultrasound guidance during injections was a limitation, since ultrasound imaging could enhance the effectiveness of the procedure by ensuring precise delivery of the treatment to the targeted tissues.

In a study, 67 patients with chronic non-specific LBP were injected with one or more PRP injections in the ligaments, muscles, and fascia of the lumbar spine, including the quadratus lumborum, thoracodorsal fascia, iliac crest, interspinous and supraspinous ligaments, and/or sacroiliac ligaments. Patients reported decreased pain and improved functional scores compared to the baseline (73).

Multiple Injection Targets

The evaluation of chronic LBP is inherently complex due to the involvement of various anatomical structures and the multifactorial nature of the condition. A long-term study assessing outcomes in a large prospective observational cohort of older adults with back pain revealed that only 16% of the patients experienced complete resolution of their pain and disability after 2 years, despite undergoing multiple spinal interventions (74). A more comprehensive approach that aims at the FSU through biologic injections, including ones made into the facet joints, epidural space, interspinal ligaments, and other structures contributing to spinal stability may result in improved functional outcomes over those associated with treatment focused solely on the IVD.

In a retrospective pilot study of 86 patients with LBP, Kirchner and Anitua injected PRGF into multiple structures in the lumbar spine. To each patient, intradiscal, intra-articular facet joint, and transforaminal epidural injections were administered under fluoroscopic guidance, and the researchers observed statistically significant pain reduction that lasted for up to 6 months (75). A prospective nonrandomized trial was conducted by Atluri et al to evaluate the effectiveness of autologous bone marrow MSCs for the treatment of chronic LBP associated with lumbar spinal degeneration and involving multiple anatomical structures. Forty patients in the treatment group received autologous BMC into the discs, facet joints, and sacroiliac joints and around the spinal nerves. Pain location served as the principal determinant in selecting the target pain generator for BMC administration. Specifically, midline axial pain was managed with intradiscal injections, paracentral pain with facet joint injections, and radicular pain with epidural injections. At the 12-month follow-up, 67% of patients in the treatment group demonstrated significant improvements in pain and functional outcomes, along with a reduction in opioid use. This study is the first of its kind to illustrate the benefits of administering bone marrow–derived MSC injections across multiple structures in a single setting for chronic spinal degeneration (76). In another prospective case series, 46 patients with chronic LBP were injected with PRP into the facet joints, IVDs, epidural space, and/or paravertebral muscles. A reduction of approximately 35% in mean VAS score was seen across the cohort while the disability score decreased by about 40% at the one-year follow-up. In this study, more than 80% of the patients showed radiographic evidence of more than one abnormality on their MRI scans, including facet joint arthropathy, spinal canal stenosis, IVD disease, and paravertebral muscle atrophy. This was a pilot study investigating multitarget PRP injections in addressing multiple pain generators (77).

Most published studies on the use of orthobiologics in the spine focus primarily on the treatment of degenerative disc disease. A deeper understanding of the biomechanical processes of the spine and the dynamic distribution of this burden among its various structures is necessary to comprehend that in most patients with chronic LBP, pain comes from multiple generators rather than a single source. Consequently, a comprehensive treatment strategy that simultaneously targets these pain generators and addresses the FSU along with the entire spine instead of isolating individual components is crucial for enhancing patient outcomes.

A recent case series by William et al demonstrated the safety and efficacy of autologous concentrated platelet product injections and prolotherapy in 14 patients with neck pain after an FSU treatment protocol. In this study, patients who had axial neck pain with or without radiculopathy underwent multiple injections targeting the cervical facet joint, including cervical facet capsule, cervical supraspinous and interspinous ligaments, and cervical epidural injections. The results indicated clinically significant improved pain scores and functional outcomes at the 24-month follow-up. These findings support the FSU treatment paradigm, suggesting its potential application in managing spinal pain by addressing ligamentous laxity, intraarticular facet arthritis, and nerve root irritation (78).

Conclusion

Over the past 2 decades, there has been a significant increase in research focused on spine biomechanics and the application of orthobiologics for spinal pain. This review aims to contextualize the novel findings related to the fundamentals of spine biomechanics and its application for the comprehensive management of spinal pain. While the pursuit of new research is essential, it is equally important to recognize and build upon the contributions of earlier investigators. Only through this approach can we achieve genuine and meaningful advancements in the field. Future research should focus on validating the therapeutic potential of orthobiologics, optimizing their combinations and application methods, and leveraging advanced study designs centered on the FSU approach. Such efforts are essential to achieving transformative breakthroughs in the treatment of chronic spinal pain and improving patient outcomes.

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