Chapter 7
Regenerative Medicine for the Spine

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Introduction

The spine consists of 33 vertebrae comprising the cervical, thoracic, lumbar, sacral, and coccygeal segments. Each vertebra unit has attachments to muscles and ligaments, as well as sites of articulation with adjacent vertebrae. The typical vertebra has six joints. Due to this complex network, there are several targets where regenerative medicine can prove to be an effective treatment. This chapter will highlight the current evidence for regenerative medicine to treat common spine pathology.

Epidemiology

Back pain is among the most common patient complaints. In the adult general population, the point prevalence for low back pain is believed to be approximately 12%, the one-month prevalence 23%, the one-year prevalence 38%, and the lifetime prevalence approximately 40% [1]. In regard to neck pain, it is estimated that 20% of the adult population experiences neck pain over a one-year period and around 66% experience neck pain at one point in their lives [2]. In the United States (US), low back pain is the number one cause of years lived with disability and neck pain is ranked sixth [3]. Between 2008 and 2012, a study of the Medicare database illustrated 6,206,578 patients were diagnosed with lumbar and 3,156,215 patients were diagnosed with cervical degenerative conditions [4]. It has been estimated that 10–15% of back pain becomes chronic and, in this subset,

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can lead to long-lasting disability. Around 80–90% of health care and social costs stemming from back pain result from this small cohort who develops chronic low back pain and disability. Just over 1% of adults in the US are permanently disabled by back pain, and another 1% are on temporary disability [5]. Those with chronic low back pain also have higher odds of unemployment [6]. With an aging population, preventative measures or treatments with the capability to reverse or halt progression are needed.

Most current treatments for back pain focus on targeting the overactive nerves responsible for the pain sensations. The most common are steroid injections and nerve ablations. In the short term many of these treatments provide significant relief; however, if the initial aggravating factors are not improved, the pain will often relapse. This leads to a population with chronic back pain. Furthermore, before the opioid crisis, many of these patients were routinely started on narcotic medications. Opioid use disorders have moved from the 11th leading cause of disability-adjusted life years in 1990 to the 7th leading cause in 2016, representing a 74.5% (95% UI, 42.8–93.9%) increase. Opioid use disorder from 1990 to 2016 went from 52nd place to 15th place on years of life lost due to premature mortality [3]. Back pain and opioid use are often linked; from one population-based survey more than 50% of opioid users reported back pain [7]. Today, the negative effects of chronic opioid use are better understood. Thus, newer treatment methods including regenerative medicine have the opportunity to provide significant relief while also proving to be safer than historical treatments. To understand the targets of regenerative medicine we will discuss the spine anatomy.

Anatomy

The spine consists of 7 cervical vertebrae, 12 thoracic vertebrae, 5 lumbar vertebrae, the sacrum (5 fused sacral vertebrae), and the coccyx (3–4 fused coccygeal vertebrae). Each vertebra unit has attachments to muscles and ligaments, as well as sites of articulation with adjacent vertebrae. The typical vertebra has two symphysis joints and four synovial joints. Each symphysis includes an intervertebral disc: one above connecting the superior vertebra and one below connecting the inferior vertebra. The synovial joints are located posteriorly and are between the articular processes. Connecting the sacrum to the lower body and distributing weight to both lower extremities is the pair of sacroiliac synovial joints. The intervertebral disc (IVD) consists of an outer annulus fibrosus and an inner nucleus pulposus. The annulus fibrosus consists of an outer ring of collagen surrounding a wider zone made of fibrocartilage and configured in a lamellar fashion. This fiber arrangement limits rotation among vertebrae. The nucleus pulposus (NP) is the center of the disc and is a gelatinous substance. It is responsible for absorbing compression forces. Between adjacent vertebra lies the intervertebral foramen through where the spinal nerve emerges from the spinal column [8].

The joints between vertebrae are supported by numerous ligaments. These ligaments reinforce the joints as they pass between vertebral bodies and interconnect structures of the vertebral arches. Along the anterior and posterior vertebral bodies lie the anterior and posterior longitudinal ligaments. The ligamenta flava connect the lamina of adjacent vertebrae. Passing along the posterior tips of the vertebra spinous processes from C7 to the sacrum is the supraspinous ligament. From C7 to the skull the ligament is known as the ligamentum nuchae as it has distinct features responsible for supporting the head. Interspinous ligaments pass between adjacent spinous processes [8].

The sacroiliac (SI) joints act to transmit forces from the lower limbs to the vertebral column. These joints are synovial joints; they lie between the L-shaped articular facets on the lateral surfaces of the sacrum and similar facets on the iliac. The joint is designed with irregular contour and interlocks to resist movement. With age the joint can become fibrous and may become completely ossified. The joint is stabilized by surrounding ligaments: the anterior sacroiliac ligament, interosseous sacroiliac ligament, and posterior sacroiliac ligament. Because this joint is weight-bearing, it is prone to degenerative changes [8].

The back musculature can be divided into the superficial group that aid in movements of the limbs, the intermediate group that may serve in respiration, and the deep group that are related to movements of the vertebral column. This deep group becomes essential for the health of the spine. Thoracolumbar fascia covers these deep muscles. The largest group of these intrinsic back muscles are the erector spinae muscles: the iliocostalis, longissimus, and spinalis. Deep to these muscles are the transversospinalis muscles which include the semispinalis, multifidus, and small rotatores muscles. The deepest group of muscles include the segmental muscles which pass between adjacent spinous processes and transverse processes. All the muscles above provide some form of stabilization or movement to the spine itself. Any derangements in these muscles, or the abdominal muscles that counteract them, can lead to abnormal function of the spine that may progress to pathology that manifests as back pain [8].

In understanding spinal pain, it is important to identify the innervated structures. These include: the vertebrae bony body (by the sinuvertebral nerve anteriorly), the zygapophyseal joint (by the medial branch of the dorsal primary ramus), the external annulus of a healthy disc (posteriorly by the sinuvertebral nerve), the anterior longitudinal ligament and anterior external annulus (by the recurrent branches of rami communicantes), posterior longitudinal ligament (by the sinuvertebral nerve), interspinous ligament (medial branch of the dorsal primary ramus), muscles (specifically the multifidus by the medial branch of the dorsal primary ramus and the paraspinal musculature by small branches of the dorsal primary ramus) and fascia (by small branches of the dorsal primary ramus), and the nerve roots themselves. The ligamentum flavum and a healthy disc's internal annulus fibrosus and nucleus pulposus are not innervated and therefore do not transmit pain signals. The posterior longitudinal ligament is often thought to be the cause of pain perception in disc herniation [9].

Overview of Back Pain Pathology and Treatment

As discussed above, the spine is composed of bones that are further supported by a network of ligaments and muscles. The spine's main role is to protect the sensitive spinal canal and support the upper body. Its secondary function is to provide mobility and movement, which is allowed by the various joint spaces along each vertebra. These include the two zygapophyseal joints (facet joints) and the intervertebral disc itself with each vertebral end plates. The spine has a natural opposing curvature pattern to soften loading forces and disperse force throughout each vertebra. Any abnormality at each of the above structures can lead to inefficient working of this spine complex that often presents as pain. As instability or increased forces target one particular location of the spine, this area often begins to generate pain.

Pain from the spine is traditionally divided into axial or radicular. Axial pain is located primarily at the spine level, where radicular pain is mostly experienced in the extremities. Radicular pain results from irritation or pinching of a spinal nerve as it exits the spinal cord. Axial back pain can be further divided into discogenic, facet mediated, or stenotic. Pain located below L5 can also be caused by the sacroiliac joint. Furthermore, fractures can occur at any boney location, most commonly at the pars interarticularis [9].

Treating back pain proves to be a challenge particularly because there is often no concrete single diagnosis and there is rarely one physical exam, laboratory, or imaging test that gives a precise answer. One study looking at MRIs of asymptomatic, pain-free individuals found that 37% of those 20 years of age showed disc degeneration and >90% of those over 60 years of age had degenerative spine changes on MRI. Similarly, 4% of the asymptomatic patients 20 years of age showed facet degeneration, while 50% of those aged 60 years old did [10]. In another MRI study, disc herniations were strongly associated with low back pain; however, annular fissures, high-intensity zone lesions, Modic changes, and spondylotic defects were all not associated with low back pain severity [11]. Thus, the pain generator often may not correlate with specific findings on imaging or other studies.

Prior to trialing a regenerative intervention, it is essential to first categorize the likely etiology of the pain. While nerve blocks and ablations target the nerves causing pain directly, regenerative medicine has the additional opportunity to target the precipitating cause of the pain. By targeting the reason why the patient has pain in the first place, it is hopeful some form of regenerative medicine will eventually be able to provide a cure, or at least halt the disease progression, rather than temporarily masking the pain.

Back pain is often multifaceted and results from a combination of pathologies. To provide a theoretical framework to highlight the effectiveness of regenerative medicine, we will group similar mechanical pain and pathology into common categories. It is important to keep in mind that the patient may suffer from multiple individual pathologies which when combined together are now the cause of presentation. Similarly, once one element of the vertebral unit is affected this often

places abnormal stress on the rest further causing pathology at distinct locations. In chronic low back pain, around 42% are related to the discs, 31% related to SI joint, and 18% related to zygapophyseal joint [12].

Pain Generators of the Spine

Intervertebral Disc Pain

The intervertebral disc itself is crucial to the health of the spine. Several pathologies of the disc itself, including internal disc disruption, tears in the disc, degeneration of the disc, and loss of disc height, can predispose patients to discogenic back pain. The disc acts as a shock absorber. Degeneration often correlates with loss of disc height that can lead to excess motion and unstableness throughout the other joints of the spine. While we will focus on pain related to the disc itself, damage to the disc may lead to excess forces and damage throughout the spine. In order to illustrate the action of regenerative medicine on the disc it is important to understand the disc's histological makeup.

The disc is a central part to the complex biomechanical system of the spine, which allows for mobility and the spreading of stress. The disc is divided into four separate regions. The outer annulus is highly organized with mostly type 1 collagenous lamellae running in an alternating pattern to assist in strength. The inner annulus is larger and more fibrocartilaginous, with less collagen and lacking the lamellar structure; this collagen is mostly type II. The cells here are both fibroblasts and chondrocytes. The third layer is the transition zone made up of a thin acellular fibrous layer. The final layer, the central nucleus pulposus, is an amorphous matrix of highly hydrated proteoglycans that are embedded in now a loose network of collagen [13].

The disc itself is a sensitive environment as it is avascular at baseline. Thus, it depends on diffusion for nutrients and waste movement. This diffusion capacity is relatively poor and worsens with both age and pathology. In normal discs, nerve endings are limited to the outer one-third of the disc and are not found in the inner annulus or nucleus pulposus region [14]. In degenerated IVDs, nociceptive nerve fibers along with vasculature migrate into the central disc regions [15]. It is theorized that neurotransmitters together with changes within the extracellular matrix itself and the release of cytokines regulate this nerve ingrowth to the IVD. In addition, pain-related peptides and proinflammatory cytokines are increased.

Disc failure can be a result of overloading. Forces may lead to desiccation of the disc and annular tears. The disc itself has a limited capacity for compression and this capacity decreases with decreasing water content—as fluid is not compressible. To improve disc failure, the treatment goal is to regain disc height to reduce the axial nerve compression and to restore the tissue dynamics (fluid content) of the annulus. Secondly, the goal is to reconstitute the central nucleus with a matrix environment

that can hold water and improve nutritional flow. A prosthetic disc nucleus has been designed to restore the disc height. However, it fails to fully simulate the compressibility and plasticity of the original disc. Furthermore, this implantation requires a fairly invasive procedure. Using regenerative medicine techniques, the hopes are to "regenerate" the nucleus and disc by injecting the nucleus with a complement of its original cells. In theory, these cells will reconstitute a matrix that will have the capacity to change the damaged internal environment of the disc and eventually reorganize to improve and return disc function [16].

As discussed, the IVD is composed of an interconnected unit of tissues that work together: the nucleus pulposus, annulus fibrosus supporting the nucleus pulposus, and the cartilaginous end plates that connect these tissues to the vertebral bodies providing nutrients. Thus, either of these can be targeted for potential regenerative medicine. Depending on degree of degeneration, different strategies are proposed. In early degeneration, biomolecular treatment strategies (including platelet-rich plasma (PRP), prolotherapy, and hyaluronic acid) are often considered to best support the viable cells remaining in hopes of reverting or halting progression of disease. In intermediate degeneration, cell-based therapies (articular chondrocytes, nucleus pulposus, disc chondrocytes, and stem cells) are required as the numbers of viable cells are decreased. At advanced degeneration, tissue engineering may be required as there is now structural damage and the number of viable cells is severely limited. The literature review by Moriguchi et al. suggests that protein injections are limited due to their relatively short life span. Gene therapy, which involves delivering certain genes through viral or nonviral vectors, has a promising future as it is able to induce modification of the intradiscal expression of genes for a long-term effect. Furthermore, tissue engineering advancements allow for the development of biocompatible and biomimetic scaffolding material to recover extensive loss of matrix cells and structural environment [17]. A meta-analysis by Wu et al. suggests that mesenchymal stem cell (MSC) and chondrocyte therapy for discogenic low back pain correlates with improved pain relief and function metrics. Currently, the authors conclude that there lacks an optimal cell therapy protocol. At this time, cell therapy is not considered a standard treatment; however, it has the potential to be a consideration especially in patients that have not adequately responded to nonoperative management [18].

Much of regenerative medicine studies regarding the spine focus on the intervertebral disc itself. An ex vivo experiment by Pirvu et al. on bovine annular fibrosus cells shows that platelet-rich preparations increased the matrix production and cell number after their injection into an annular fibrosus defect [19]. Another ex vivo study by Kim et al. looked at nucleus pulposus cells from human discs that were cultured in a collagen matrix. PRP administration markedly suppressed cytokine-induced pro-inflammatory degrading enzymes and mediators in the NP cell. As per the authors, it stabilized NP cell differentiation through rescued gene expression concerning matrix synthesis [20]. An additional study by Akeda et al. looked at in vitro porcine IVD cells post-PRP exposure. They concluded PRP had a mild stimulatory effect on cell proliferation. There was a significant upregulation of proteoglycans and collagen synthesis and proteoglycan accumulation compared to

platelet-poor plasma [21]. These studies provide data that suggests PRP supports a regenerative-like environment at the cellular level.

One animal study by Wang et al. looked at rabbits that underwent annular needle puncture to simulate early degenerative discs. The rabbits were then injected with BMSCs and PRP, just PRP, and a control group of phosphate-buffered saline. At 8 weeks postinjection, PRP-containing bone marrow-derived mesenchymal stem cells (BMSCs) were more effective than PRP alone as evidenced by an increase in signal intensity over time, and under histological staining the extracellular matrix and cell density as well as type II collagen staining were preserved. Several other animal studies show promising results [22]. A study on platelets and BMSCs by Xu et al. demonstrated effective repair of annulus defects [23]. Another study by Hou et al. on PRP intradiscal injections post needle puncture demonstrated significant recovery of MRI signal intensity. They suggest PRP can enhance the nucleus pulposus cell's proliferation and anabolic pathway while slowing IVD degeneration in rabbits [24]. A randomized controlled trial (RCT) by Gui et al. investigated intradiscal PRP in rabbits post annulus fibrosus puncture. In the control groups, there were significant IVD height changes compared to the slight decrease in the PRP-treated group [25]. Gullung et al. looked at six rats each in a control, sham, PRP immediately post disc injury with needle, and PRP 2 weeks after disc injury. The PRP groups had fibers that were damaged with empty spaces and inflammatory cells; however overall there was maintenance of the ring structure and the nucleus appeared to keep a healthy central portion. They conclude that immediate injection has a more pronounced effect as the disc height and fluid content on MRI was significantly better in the immediate injection group compared to the sham group at 4 weeks. This study suggests that there may be a time component to treatment effects with regenerative medicine. As most patients often receive injections years after initial injury, this beneficial effect may have limited value in the clinical population [26].

While several of these above studies were RCTs and there seems to be some scientific agreement in favor of regenerative medicine, it is difficult to adopt these animal study results into clinical practice. It is important to highlight that these animals do not reflect the same stressors and pathology that is evident in patients with chronic degenerative disc disease (DDD). Often, the animals are relatively healthy and undergo a single acute stressor event to create disc pathology. Hence the environment of the disc may be more salvageable compared to that of a classic patient presenting with chronic degenerative disc disease.

Focusing on selected human trials, Miller et al. analyzed 76 consecutive patients that received intradiscal prolotherapy who suffered from internal lumbar disc derangements. These patients had undergone two epidural steroid injections (ESIs) 2 weeks apart and had initial good relief followed with later a return of symptoms. Post prolotherapy, 43.4% of patients had at least 20% reduction in pain scores and pain relief was maintained at an average of 18 months. This study provides some support in favor of intradiscal prolotherapy to treat internal disc disease [27].

Focusing on PRP, Akeda et al. led a prospective clinical study evaluating intradiscal PRP releasate in 14 patients who had positive diagnostic discography. More

than 50% reduction in low back pain was seen in 71% of patients within 4 weeks of injection, and this relief was generally maintained throughout the 48-week study period. Furthermore, the authors conclude there was no change in T2 imaging and disc height which suggests no negative effects on the disc matrix [28]. In a similar prospective trial, Levi et al. injected 22 subjects intradiscally with PRP and at 2 months 41% had a successful outcome of greater than 50% decrease in visual analogue scale (VAS). At 6 months, 63% had a VAS improvement at least 20 mm [29]. An RCT by Tuakli-Wosornu et al. randomized 29 patients to intradiscal PRP and 18 to the control group receiving intradiscal contrast only. Over 8-week follow-up there were statistically significant improvements in patients who received the intradiscal PRP in pain scale, function, and patient satisfaction compared to controls. Furthermore, those who received PRP were able to maintain significant improvements in the Functional Rating Index (FRI) for at least 1-year follow-up [30].

Other studies examined PRP in patients undergoing spine surgery. Sys et al. randomized 18 patients to undergo spinal fusion with PRP-soaked autologous bone to fill the cages and 18 patients to serve as a control without the PRP soaking. The added PRP in posterior lumbar interbody fusion did not lead to a substantial improvement or deterioration when compared with autologous bone only. The PRP and autologous group trended toward improvements in VAS and Oswestry Disability Index (ODI). This study points out that there may be little improvement in using PRP during spinal fusions and it can be justified from a clinical and radiological point of view; however it may not be efficient from an economical perspective [31].

Overall PRP is generally safe and has few documented adverse effects besides from local pain temporarily post procedure. Furthermore, as patient's own blood is used this limits risks of infection and rejection. One downside to PRP is that it only provides the IVD with certain factors that may aid repair. However, if the disc cells are already severely damaged, some suggest that no amount of PRP may make a difference [32]. Thus, PRP may be more efficient when applied at an earlier stage of degeneration, in a patient that has relatively a healthy amount of functioning cells. This is where stem cells theoretically may have the advantage as they may act to replace severely degenerated cells.

Investigating stem cells, Orozco et al. reported on a case series of ten patients with chronic discogenic back pain that were treated with autologous culture-expanded bone marrow MSCs injected into the nucleus pulposus area. This study showed strong safety and feasibility. Patients exhibited improvements in both pain and disability measures. Disc height was not recovered, but water content was significantly improved on MRI [33]. Similarly, Elahd et al. studied five patients with DDD post intradiscal injection of autologous, hypoxic cultured, BMSCs. Post 4–6 years, no adverse events were reported. All patients self-reported overall improvement [34]. Pettine et al. analyzed 26 patients that were candidates for spinal fusion or total disc replacement surgery. Instead, they underwent autologous bone marrow concentrate intradiscal injection into the nucleus pulposus. After 36 months, only six patients progressed to surgery. The remaining 20 other patients reported improvements in ODI and VAS. One year MRI showed that 40% of the subjects improved one modified Pfirrmann grade and no patients worsened. Those with greater concentration of

stem cells had better outcomes [35]. Furthermore, Centeno et al. studied autologous MSCs in 37 patients with DDD with secondary radicular pain. The treatments in this study included a preinjection 2 weeks before MSC injection that included a platelet lysate transforaminal epidural injection. Then, MSCs that had been cultured in platelet lysate were injected intradiscal. Two weeks later a second transforaminal epidural with platelet lysate injection was performed. At all-time points from 3 months to 24 months there was significant improvement in pain scores. FRI was statistically improved at all-time points except at 12 months. Twenty patients underwent posttreatment MRI and 85% showed reduction in disc bulge size. Due to a lack of control group, this study is limited in determining the efficacy of these interventions as it is well known that patients often improve with time regardless of treatment [36]. Although the above studies are promising, further RCTs are needed before recommendations can be made.

In an RCT by Noriega et al. 24 patients were randomized so that 12 patients received intradiscal allogeneic (from someone else) MSCs and 12 patients received sham paravertebral musculature local anesthetic treatment. This study demonstrated stem cell-treated subjects had significant improvements in algofunctional indices. However, the improvement seemed to be restricted to a group of responders representing 40% of the cohort. Degeneration graded by MRI and Pfirrmann grading improved in those treated with stem cells and worsened in the controls. This study supports the utilization of allogeneic stem cells which are more convenient than the autologous MSC treatment that must be harvested from the patient [37]. A second RCT by Bae et al. randomized a total of 100 patients to intradiscal injection treatment: 20 patients received hyaluronic acid, 30 patients received allogeneic mesenchymal precursor cells (MPCs) at 6 million dose, 30 patients received allogeneic MPCs at 18 million dose, and 20 received saline to serve as a control. The authors concluded that allogeneic MPCs showed improvements in pain and function and reduced interventions compared to the control group. However, when comparing the stem cell group to the hyaluronic acid group, the results did not reach statistical significance [38].

Secondary to the myriad of components and mixtures that can be utilized in regenerative medicine, studies comparing different mixtures or recipes of injectate present a challenge. Mochida et al. studied mixing autologous NP cells with BMSCs. Nine patients scheduled for fusion underwent harvesting of NP cells. Viable NP cells were co-cultured in direct contact with autologous BMSCs. At 1-week post fusion they underwent transplantation at adjacent levels to the fusion of the now activated NP cells. Imaging revealed improvement in one case, and functional improvement overall was minimal [39]. Studies are needed to determine the best dosage, combination, and type of injectate.

It has been shown that stem cells can also be derived from adipose cells. Kumar et al. looked at adipose tissue-derived mesenchymal stem cells combined with hyaluronic acid in ten patients who had discogenic pain with positive discography. There were no serious adverse effects at 1 year and these patients had significant improvements in VAS, ODI, and Short Form-36 (SF-36). Three of the ten patients were determined to have increased water content in their discs as determined by

MRI [40]. Similarly, Comella et al. analyzed 15 patients that underwent adipose tissue-derived stromal vascular fraction (SVF) injection directly into the nucleus pulposus. At 6 months there were no serious adverse effects, and patients improved in flexion and VAS and SF-12. ODI and Dallas pain questionnaire only showed positive trends [41].

Others have utilized stem cells from the umbilical cord. Pang et al. looked at two patients with chronic discogenic pain that were treated with human umbilical cord tissue-derived MSCs. In the two patients, pain and function improved and was maintained for a 2-year follow-up. Furthermore, the water content in the degenerative disc of one patient was found to have significant improvement. This method avoids the invasive procedures required in harvesting stem cells [42]. A separate class of stem cells include hematopoietic stem cells that have the capability to give rise to other blood cells. Huafe et al. looked at ten patients with positive discograms that received intradiscal injection of hematopoietic precursor stem cells obtained from their pelvic bone marrow. Zero patients reported improvement. This study suggests that while there may be benefit for MSCs, HSCs do not appear to have similar efficacy. The authors suggest that perhaps the HSCs are unable to survive the oxygen-poor environment of the inner disc [43]. More studies are necessary to determine which types of stem cells, if any, have the best efficacy for each diagnosis.

Fibrin is another injectate that has been trialed to help those with discogenic pain. Yin et al. reported on 15 adults with confirmed discogenic pain that underwent intradiscal injection of a fibrin sealant. Eighty-seven percent of the subjects achieved at least a 30% reduction in low back VAS compared with baseline at the 26-week primary end point. Although this was not an RCT and only evaluated 15 patients, fibrin may provide benefits in certain patients. Fibrin is composed of purified prothrombin and fibrinogen and reconstituted with aprotinin and calcium. When injected into the annular tears, it has the ability to form a matrix sealant protecting the nucleus pulposus [44].

Intradiscal methylene blue (MB) has also been trialed for patients with discogenic pain. Peng et al. looked at 72 subjects equally randomized to either the MB injection or the control group that received isotonic saline instead. In the MB group, there was a mean reduction in the numeric rating scale (NRS) of 52.4 and ODI by 35.58 and 91.6% patient satisfaction at 24 months. This was a significant improvement over the control group [45]. Once again further studies are needed to replicate these strong findings.

Others have suggested that regeneration of the disc should not be the primary goal when treating these patients with back pain. Adams et al. suggest that we should separate our focus among healing a painful disc and reversing disc degeneration, as these may be two distinct pathways. Discs are often the cause of pain as nerves in the peripheral annulus or vertebral endplate become affected by inflammation and/or radial tears. Adams et al. conclude we should primarily focus on this peripheral region which has the cell density and metabolite transport to improve, rather than the more difficult notion of regenerating the nucleus pulposus. Regardless of the degenerative changes in the nucleus, promoting healing at the periphery can provide significant pain relief. Physical therapy, which employs mechanical loading, can act

as a healing stimulus in the peripheral disc. For radial fissure, the authors recommend initial controlled mobilization toward the direction that decreases pain; then after scar formation, stretching should be directed toward the painful direction in hopes of promoting remodeling. In the case of an endplate fracture, initial therapy would include unloading followed by progressive loading and if needed intermittent traction [46].

Although the above studies (Table 7.1) are promising treatments for IVD pain, there is a general lack of comparable RCTs leading to poor overall evidence level. In examining these studies, it is crucial to acknowledge the diagnosis being treated and the precise injectate utilized. Before recommendations for treatment can be more RCTs are needed to support evidenced-based medicine.

Radiculopathy

Moving from pain resulting from the disc itself, a second generator of pain is caused by irritation or pressure on the nerve root creating a radiculopathy. This can be caused by a bulging disc, herniated disc, and/or stenosis. The classic pain felt is in the distribution of the sensory nerve root. For instance, in the lower back this shooting, electrical type of pain will be reported to be traveling down the lower extremities. Depending on which nerve root is involved, the pain often localizes to a certain extremity or dermatome. Affected cervical nerve roots often will transmit pain down the ipsilateral arm, while affected lumbar nerve roots will have symptoms from the waist down.

For acute radicular pain the routine care is commonly epidural or transforaminal steroid injection. However, although they show some short-term pain relief, they have increasingly been criticized for failure to provide lasting benefit while exposing the patient to potential risks and side effects. To better improve outcomes several clinicians have investigated the efficacy of PRP, dextrose or prolotherapy, and stem cells.

In a pilot study by Bhatia et al. ten patients with prolapsed IVD were injected with 5 ml of PRP with an interlaminar approach into the area of affected nerve root. A significant number of patients showed relief and sustained relief at 3 months. The authors conclude that PRP can be used in replace of steroids; however, a randomly controlled trial comparing the two is needed [47]. In 2017, Cameron et al. reported on PRP injections in 88 total subjects: 38 for cervical, 38 for lumbar, and 12 for both cervical and lumbar disc herniation. PRP was injected in a circumferential manner of the affected area into the lateral masses, facet joints, lateral gutters, and inter- and supraspinatus ligaments, Kambin's triangle, and spinous process. This prospective nonrandomized clinical study suggested each group of patients showed a significant improvement in pain scores [48].

Similarly, Centeno et al. analyzed a case series of 470 patients who were treated with platelet lysate and nanogram dose hydrocortisone. As per the authors, the nanogram amount of steroid used in the formation of platelet lysate is one million

Table 7.1 Regenerative medicine for intervertebral disk pain studies reviewed

Author, date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis	Injectate preparation and route	Results	Authors' conclusion	Study analysis and notes
Miller et al. [27] [prolotherapy]	Prospective consecutive patient series $n = 76$ Intradiscal dextrose inj. biweekly, responders received injs. up to five times biweekly	P-NRS biweekly before inj. and at 2, 6, and 18 mos. F/u (f/u) 6–41; mean of 18 mos.	Internal lumbar disc derangement who underwent two ESIs 2 wks. apart w/ initial relief followed by return of symptoms. Confirmed w/ discography	Biweekly disc space inj. 3 mL w/ final concentration of 25% dextrose and 0.125% bupivacaine. Solution 50% dextrose and 0.25% bupivacaine	43.4% (33/76) of pts. showed a sustained treatment response (≥20% reduction in pain). For responders, the avg. improvement in the PNRS was 71%	Reductions in P-NRS were maintained in pts. w/ uniformly moderate to severe disc desiccation at an avg. of 18 mos. Those pts. who experienced no appreciable improvement from the treatment were not worse in any sustained way	Level IV
Akeda et al. [28] [PRP releasate]	Prospective clinical feasibility study, primarily a safety assessment $n = 14$ PRP intradiscal inj. Post positive diagnostic discography	VAS and RMDQ F/u 4, 8, 16, 24, 32, 40, and 48 wks. X-ray and MRI analysis	Discogenic LBP w/o leg pain for more than 3 mos. ≥ At 1 lumbar disc w/ evidence of degenerative changes per MRI and ≥50% of normal disc height	Autologous PRP releasate, 2 mL at center of targeted disc Mean platelet count of PRP was ≈3.7 times > than whole blood. Mean WBC count of PRP was about 1/230 of whole blood. Avg. level of PDGF-BB was ≈2.1 times > autologous serum	>50% reduction of LBP was observed in 71% (10/14) of pts. within 4 wks.; generally maintained through 48 wks. Improvement in RMDQ was relatively better than that in VAS. Particularly, 79% of pts. (11/14) showed a significant reduction (>50%) in RDQ scores 4 wks. after PRP releasate inj. This was maintained for 48 wks.	Lumbar radiographs no significant change in disc height. No change in T2 imaging of AF and NP. No negative affect on the matrix of degenerated IVDs No persistent neurologic deficits	Level IV

Levi et al. [29] [PRP]	Prospective trial $n = 22$ PRP inj. directly into the disc nucleus	VAS and ODI scores F/u 1, 2, and 6 mos. Successful outcome = 50% VAS improvement and a 30% ODI improvement	Discogenic pain w/o moderate to severe lumbar radiculopathy. If agreed SI and facet joint blocks were done to rule out other sources of pain	Contrast with gentamicin 16 mg injected for discitis prophylaxis Lidocaine 4%, 0.5 mL. Then, 1.5 mL of autologous WBC-rich PRP was injected intradiscal	At 2 mos. 32% and at 6 mos. 47% of pts. had a successful outcome. At 2 mos. 4 % of pts. had a >50% decrease in VAS. At 6 mos. 63% had a VAS improvement ≥20 mm	Encouraging preliminary 6-month findings, using strict categorical success criteria, for intradiscal PRP as a treatment for presumed discogenic low back pain. Randomized placebo-controlled trials are needed to further evaluate the efficacy of this treatment	Level IV Negative discography was exclusion criteria; however only presumptive discogenic pain was inclusion criteria
Tuakli-Wosornu et al. [30] [PRP]	Prospective, double-blind, randomized controlled $n = 47$ w/ a positive provocative discography 29 received PRP 18 received only contrast (control group)	FRI; P-NRS, SF-36; NASS Outcome Questionnaire 1, 4, and 8 wks., 6 mos., and 1 yr.	Adults w/ chronic (6 mos.), moderate-to-severe lumbar discogenic pain unresponsive to conservative treatment	1–2 ml contrast into midportion of suspected disc Only disc levels that elicited concordant pain w/ evidence of incomplete annular disruption (<2 mL) were then injected additionally w/ either 1–2 mL of PRP or contrast	Over 8 wks. of f/u, there were statistically significant improvements in participants who received intradiscal PRP w/ regard to pain (P-NRS Best Pain), function (FRI), and patient satisfaction (NASS Outcome Questionnaire) compared w/ controls	Those who received PRP maintained significant improvements in FRI scores through at least 1 year of f/u	Level II No cell counts of PRP collected. Longer f/u needed

(continued)

Table 7.1 (continued)

Author, date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis	Injectate preparation and route	Results	Authors' conclusion	Study analysis and notes
Sys et al. [31] [PRP]	Prospective randomized controlled trial $n = 36$ pts. 18 underwent spinal fusion w/ PRP-soaked autologous bone to fill the cages 18 underwent spinal fusion w/ autologous bone added w/o being soaked in PRP	VAS, ODI, SF-36. F/u at 3, 6, 12, and 24 mos.CT scans of the lumbar spine at 3, 6, and 12 mos.	Pts. scheduled for posterior lumbar interbody fusion surgery w/ single-level disc disease	PRP-soaked autograph bone used to fill the cages during spinal fusion	More pronounced improvements in VAS and the physical component summary score in pts. who received autograft w/ PRP. However, improvement was not substantial and did not reach statistical significance. CT scans showed uneventful osseous healing in all but one patient w/ no difference between groups	From a clinical and radiological point of view, the use of PRP seems to be justified in posterior lumbar interbody fusion surgery. From an economical point of view, the expense of using PRP cannot be justified until statistical significance can be reached in a larger study	Level II Showed little improvement of surgery w/ added PRP. Study limited to specific criteria and use

Orozco et al. [33] [autologous bone marrow MSC]	Case series pilot phase 1 $n = 10$ 10 pts. w/ chronic back pain treated w/ autologous expanded bone marrow MSC injected into the nucleus pulposus area	VAS, ODI, and SF-36. Clinical evolution was followed for 1 year. MRI measurements of disc height and fluid content	DDD w/ preserved external annulus fibrous and persistent LBP failing 6 mos. of conservative treatment	Inj. into IVD Autologous culture-expanded bone marrow MSCs $10 \pm 5 \times 10^6$ cells per disc from a suspension containing 10^7 cells/mL	Rapid improvement of pain and disability (85% of maximum in 3 mos.) ≈ 71% of optimal efficacy. Feasibility and safety were confirmed and strong indications of clinical efficacy identified. Although disc height was not recovered, water content was significantly elevated at 12 mos. No improvement in disc height, some increase in T2 signal	MSC therapy may be a valid alternative treatment for chronic back pain caused by DDD. Advantages over current gold standards include simpler and more conservative intervention w/o surgery, preservation of normal biomechanics, and same or better pain relief. This outcome compares favorably w/ spinal fusion or total disc replacement	Level IV

(continued)

Table 7.1 (continued)

Author, date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis	Injectate preparation and route	Results	Authors' conclusion	Study analysis and notes
Elabd et al. [34] [bone marrow-derived MSC]	Long-term f/u study $n = 5$ 5 pts. diagnosed w/ DDD received an intradiscal inj. of autologous, hypoxic cultured, bone marrow-derived mesenchymal stem cells as part of a previous study. These pts. were re-consented and followed for 4–6 years	Physical examination, low back MRI, and quality of life questionnaire	Lumbar degenerative disc disease associated w/ protruding discs. Pts. previously treated as per prior study	Previous inj. of 15.1–51.6 million autologous, hypoxic cultured, bone marrow-derived mesenchymal stem cells	Lower back MRI showed absence of neoplasms or abnormalities surrounding the treated region. No adverse events were reported due to the procedure or to the stem cell treatment 4–6 years post procedure. All pts. self-reported overall improvement, as well as improvement in strength, post stem cell treatment, and 4/5 pts. reported improvement in mobility	This early human clinical data suggests the safety and feasibility of the clinical use of hypoxic cultured bone marrow-derived MSCs for the treatment of LBP due to DDD and support further studies. A larger double-blind, controlled, randomized clinical study w/ significant number of pts. and implementation of validated end point measurements are next steps in order to demonstrate efficacy of this biologic	Level IV

Pettine et al. [35] [autologous BMC]	Prospective, open-label, nonrandomized, single-arm study using the data from four FDA IDE studies as a comparative baseline *n* = 26 Pts. injected w/ intradiscal BMC in lumbar discs and followed for 3 years	ODI and VAS F/u at 3, 6, 12, 24, and 36 mos. 12-month MRI. All compared to patient demographics and BMC cellularity	DDD and candidates for spinal fusion or total disc replacement surgery	2 ml of autologous bone marrow concentrate intradiscal inj. into nucleus pulposus Cellular analysis showed an avg. of 121 million total nucleated cells per ml. Avg. CFU-F of 2713 per ml and avg. CD34+ of 1.82 million per ml in the BMC	At 36 mos., six pts. progressed to surgery. The remaining 20 pts. reported avg. ODI and VAS improvements from 56.7 ± 3.6 to 82.1 ± 2.6 at baseline to 17.5 ± 3.2 and 21.9 ± 4.4 after 36 mos., respectively. 1-year MRI: 40% of pts. improved 1 modified Pfirrmann grade. Pts. w/ greater concentrations of CFU-F (>2000/ ml) and CD34+ cells (>2 million/ml) tended to have better clinical improvement	There were no adverse events related to marrow aspiration or inj., and this study provides evidence of safety and feasibility of intradiscal BMC therapy. No radiologic evidence of worsening. Pt. improvement and satisfaction w/ this surgical alternative supports further study of the therapy	Level III

(continued)

Table 7.1 (continued)

Author, date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis	Injectate preparation and route	Results	Authors' conclusion	Study analysis and notes
Centeno et al. [36] [autologous MSCs]	Pilot study on safety and efficacy $n = 33$ Treated w/ culture-expanded, autologous, bone marrow-derived MSCs	P-NRS, SANE, FRI, measurement of the intervertebral disc posterior dimension, and adverse events F/u at 1, 3, 6, 12, 18, and 24 mos. and annually up to 6 yrs.	DDD and LBP w/ a posterior disc bulge diagnosed on MRI	Pre-inj. 2 wks. prior to MSC, transforaminal epidural using 3–5 cc of PL only at target Then, once MSCs had been subcultured and suspended in 10–20% PL, they were injected into disc annulus Post-inj. 2 wks. after the IVD re-inj. of MSCs, another transforaminal epidural using 3–5 cc of PL at same target	P-NRS changes relative to baseline were significant at 3, 36, 48, 60, and 72 mos. posttreatment. Avg. improvement was 2.3. The avg. SANE ratings showed a mean improvement of 60% at 3 yrs. FRI posttreatment change score avgs. exceeded the minimal clinically important difference at all-time points except 12 mos. 20 pts. treated underwent posttreatment MRI and 85% had a reduction in disc bulge size, w/ an avg. reduction size of 23% posttreatment	Pts. treated w/ autologous cultured MSCs for lower back pain w/ radicular symptoms in the setting of DDD reported minor adverse events and significant improvements in pain, function, and overall subjective improvement through 6 years of f/u. Three pts. reported pain related to procedure that resolved. No serious adverse events (i.e., death, infection, or tumor) w/the procedure	Level IV

Noriega et al. [37] [allogeneic MSCs]	Phase I–II prospective randomized controlled clinical trial $n = 24$ 12 received intradiscal allogeneic MSCs 12 received sham paravertebral musculature local anesthetic treatment	VAS, ODI F/u 3,6,12 mos. Disc quality was followed up by magnetic resonance imaging	Lumbar LBP w/ Pfirrmann grade II–IV DDD, unresponsive to conventional treatments (physical and medical) for at least 6 mos. before recruitment	Allogeneic MSCs (25×10^6 MSC in 2 mL of saline per disc) under local anesthesia intradiscal Or sham infiltration of paravertebral musculature close to the affected disc(s) w/ 2 mL of 1% mepivacaine	MSC-treated pts. displayed a quick and significant improvement in algofunctional indices versus the controls. This improvement seemed restricted to a group of responders that included 40% of the cohort. Degeneration, quantified by Pfirrmann grading, improved in the MSC-treated pts. and worsened in the controls	Feasibility and safety were confirmed and indications of clinical efficacy were identified. Allogeneic MSC therapy may be a valid alternative for the treatment of DDD that is more logistically convenient than the autologous MSC treatment. The intervention is simple, does not require surgery, provides pain relief, and significantly improves disc quality	Level II

(continued)

Table 7.1 (continued)

Author, date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis	Injectate preparation and route	Results	Authors' conclusion	Study analysis and notes
Bae et al. [38] [allogeneic MPCs]	Prospective, multicenter, randomized, double-blind, controlled study $n = 100$ 20 pts. injected w/ saline. 20 pts. inj. w/ HA MPC inj. groups: 30 pts. w/ 6×10^6 MPCs 30 pts. w/ 1.8×10^7 MPCs	VAS and ODI F/u at 1, 3, 6, 12, 24, and 36 mos. Success = 30% improvement in VAS, 10-point improvement in ODI. MRI and X-ray for stability	Moderate to severe chronic LBP due to moderately degenerated discs after exhausting conservative treatment options	Two control groups intradiscal inj. w/ either saline or HA MPC treatment group intradiscal injs.: 30 pts. w/ six million MPCs. 30 pts. w/ 18 million MPCs	At 12 mos., 6 million MPC group w/ 69.2% and 18 million MPC group w/ 61.5% of pts. achieving ≥50% reduction in VAS, while the saline group w/ only 31.3% and the HA group w/ 35.3% successes Three times increase in the number of MPC-treated pts. that achieved concordant pain and function treatment success at both 6 and 12 mos. relative to saline controls	Allogeneic MPCs were well tolerated, showed improvements in pain and functional improvement, and reduced interventions compared to controls. Needs randomized phase 3 studies. When compared to HA results did not reach statistical significance	Level II

Mochida et al. [39] [NP cells and autologous MSCs]	Three-yr. result of prospective clinical phase I study, to assess the safety and efficacy of activated NP cell transplantation in the degenerate lumbar IVD $n = 9$ 1 wk. post fusion w/ NP tissue transplantation at adjacent levels to fusion	JOA back pain score 1, 2, and 4 wks., 3 and 6 mos., as well as 1, 2, and 3 yrs. X-ray and MRI	Pts. aged 20–29 yrs. who had Pfirrmann grade III disc degeneration at the level adjacent to the level scheduled for posterior lumbar intervertebral fusion. Two pts. had disc herniation and seven pts. had discopathy	Viable NP cells from the fused disc were co-cultured in direct contact w/ autologous bone marrow-derived MSCs. One million activated NP cells were transplanted into the degenerated disc adjacent to the fused level at 7 days after the first fusion surgery	No adverse effects were observed during the 3-yr. f/u period. MRI did not show any detrimental effects to the transplanted discs and revealed a mild improvement in one case. No cases reported any LBP. There was minimal functional improvement and some MRI changes	This clinical study confirmed the safety of activated NP cell transplantation, and the findings suggest the minimal efficacy of this treatment to slow the further degeneration of human intervertebral discs	Level IV

(continued)

Table 7.1 (continued)

Author, date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis	Injectate preparation and route	Results	Authors' conclusion	Study analysis and notes
Kumar et al. [40] [AT-MSCs and HA]	Single-arm, open-label, phase I clinical trial $n = 10$ Underwent a single intradiscal inj. of combined HA derivative and AT-MSCs	VAS, ODI, SF-36 F/u 1 week and 1, 3, 6, 9, and 12 mos. Lumbar spine X-ray imaging and MRI	Chronic LBP for more than 3 mos. w/ a minimum intensity of 4/10 on VAS and disability level ≥30% on ODI. Post positive discography	Adipose tissue-derived mesenchymal stem cells at a dose of 2×10^7 cells/disc ($n = 5$) or 4×10^7 cells/disc ($n = 5$) both combine with HA	VAS, ODI, and SF-36 scores significantly improved in both groups receiving both low and high cell doses and did not differ significantly between the two groups. Among six pts. who achieved significant improvement in VAS, ODI, and SF-36, three pts. were determined to have increased water content based on an increased apparent diffusion coefficient on diffusion MRI	Combined implantation of AT-MSCs and HA derivative in chronic discogenic LBP is safe and tolerable. However, the efficacy of combined AT-MSCs and HA should be investigated in a randomized controlled trial in a larger population No procedure or stem cell-related adverse events or serious adverse events during the 1-year f/u period	Level IV

Comella et al. [41] [SVF, fat stem cells]	Open-label study. $n = 15$ SVF injected directly into the nucleus pulposus	VAS, PPI, ODI, BDI, DPQ, and SF-12 F/u 2 and 6 mos.	DDD of two or three lumbar discs w/ predominant back pain after conservative treatment for at least 6 mos.	60 ml fat aspirated, buffered in saline, and digested using collagenase and centrifuged to collect SVF pellet. Pellet then resuspended in ≈1 ccs of autologous PRP. 20–60 million cells in 1–3 cc PRP	Improvement in VAS scores from avg. of 5.6 at baseline to 3.6 at 6 mos. No severe adverse events reported. Statistically significant improvements in flexion, pain ratings, VAS, PPI, and short form questionnaires. ODI and Dallas pain questionnaire only showed positive trends	SVF proved promising; however a true evaluation of efficacy and safety would require larger phase II/III studies	Level IV
Pang et al. [42] [HUC-MSCs]	Clinical trial $n = 2$ Two pts. w/ chronic discogenic LBP were treated w/ HUC-MSC transplantation	VAS and ODI F/u at 6, 12, and 24 mos.	Pts. w/ positive discography with discogenic LBP	Human umbilical cord tissue-derived mesenchymal stem cells (HUC-MSCs) The suspension of 1 mL HUC-MSCs containing $\approx 1 \times 10^7$ cells	After transplantation, the pain and function improved immediately in the two pts. The VAS and ODI scores decreased during a 2-year f/u period. The water content in the degenerative painful disc in 1 out of 2 pts. was significantly increased at 2 years posttransplantation	The clinical outcomes indicated that HUC-MSC transplantation is a favorable alternative method for treating chronic discogenic LBP. This method avoids the invasive harvesting of stem cells. The shortcoming of this study is that it is a preliminary study w/ only two pts.	Level IV

(continued)

Table 7.1 (continued)

Author, date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis	Injectate preparation and route	Results	Authors' conclusion	Study analysis and notes
Huafe et al. [43] [HSCs]	Prospective case report $n = 10$ Intradiscal inj. of HSCs followed by a 2-week course of hyperbaric oxygen therapy	VAS F/u at 6 and 12 mos.	Discogenic pain Attempted endoscopic discectomy w/o relief for 3 mos. w/ positive provocative discograms	Hematopoietic precursor stem cells (HSCs) obtained from pts.' pelvic bone marrow in an attempt to rejuvenate the disc. 1 cc injected into each painful disc	Of the ten pts., none reported a VAS reduction in their pain at 1-yr. post inj. After 1 year, seven of the original ten pts. underwent fusion surgery and one underwent artificial disc replacement surgery. Two continued conservative therapy	Even though MSCs have been suggested as a possible treatment for degenerative discs, this study reveals that HSCs, which are similar precursor cells, are of no benefit in living human subjects. Possibly the HSCs cannot survive in the oxygen-poor environment of the disc, even w/ hyperbaric oxygen therapy	Level IV

Yin et al. [44] [fibrin]	Prospective multicenter pilot study $n = 15$ Fibrin intradiscal inj.	VAS, RMDQ, F/u at 72 hours, and 1, 4, 13, 26, 52, and 104 wks. MRI and neurological status to evaluate for potential adverse events	Discogenic lumbar pain w/ chronic, single, or contiguous two-level lumbar discogenic pain confirmed through meticulous provocation discography	BIOSTAT BIOLOGX Fibrin Sealant w/ the Biostat Delivery Device intradiscal until sustained pressure above 100 psi, entire volume of 4 ml fibrin sealant delivered, or until pt. could not tolerate continued inj.	87% achieved ≥30% reduction in VAS score compared w/ baseline at the 26-wk. primary end point. Mean LBP VAS decreased from 72.4 at baseline to 31.7, 35.4, and 33.0; mean RMDQ score improved from 15.2 at baseline to 8.9, 6.2, and 5.6 at 26, 52, and 104 wks., respectively. Safety neurological assessments, X-ray, and MRI showed no significant changes	Intradiscal inj. of fibrin appears safe and may improve pain and function in selected pts. w/ discogenic pain There was two instances of low back muscle spasm and one case of discitis was considered related to the procedure or product	Level IV
Peng et al. [45] [intradiscal methylene blue]	Randomized placebo-controlled trial $n = 72$ 72 subjects became eligible after discography. 36 w/ intradiscal inj. MB and 36 w/ placebo treatment	P-NRS, ODI F/u at 6, 12, and 24 mos.	Discogenic low back pain w/o radiculopathy lasting longer than 6 mos., w/ no comorbidity	1 ml of 1% MB (10 mg) inj. into the discogram-proven diseased disc, followed by inj. of 1 ml of 2% lidocaine for anesthetic The placebo group: inj. of 1 ml of isotonic saline and 1 ml of 2% lidocaine into the painful disc	At 24 mos., the pts. in MB inj. group showed a mean reduction in P-NRS of 52.50, a mean reduction in ODI of 35.58, and satisfaction rates of 91.6%, compared w/ 6.91, 1.68, and 14.3%, respectively, in placebo treatment group, all statistically significant. No adverse effects or complications were found in the group of pts. treated w/ intradiscal MB inj.	The current clinical trial indicates that the inj. of methylene blue into the painful disc is a safe, effective, and minimally invasive method for the treatment of intractable and incapacitating discogenic low back pain	Level II

(continued)

Table 7.1 (continued)

Author, date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis	Injectate preparation and route	Results	Authors' conclusion	Study analysis and notes

Abbreviations: *pt.* patient, *inj.* injection, *P-NRS* Pain Numerical Rating Scale, *mos.* months, *f/u* follow-up, *ESI* epidural steroid injection, *w/* with, *wk.* week, *avg.* average, *VAS* visual analogue scale, *RMDQ* Roland-Morris Disability Questionnaire, (x-ray); *MRI* magnetic resonance imaging, *LBP* low back pain, *ODI* Oswestry Disability Index, *yr.* year, *FRI* Functional Rating Index, *SF-36* pain and physical function domains of the 36-item Short Form Health Survey, *NASS* the modified North American Spine Society, *DDD* degenerative disc disease, *FDA* Food and Drug Administration, *IDE* investigational device exemption, *SANE* modified single assessment numeric evaluation, *PL* platelet lysate, *HA* hyaluronic acid, *NP* nucleus pulposus, *JOA* Japanese Orthopaedic Association, *SVF* stromal vascular fraction obtained from a mini-lipoaspirate procedure of fat tissue, *PPI* present pain intensity, *BDI* Beck Depression Inventory, *DPQ* Dallas Pain Questionnaire, *(SF)*-12 short form, *HUC-MSCs* human umbilical cord tissue-derived mesenchymal stem cells, *MB* methylene blue

times less than those used in regular epidural steroid injections. At this low level, the steroid provides an anti-inflammatory effect similar to that of endogenous glucocorticoids. The patients showed significant improvements in both their numerical and functional scores. At 24 months posttreatment, patients had a 49.7% rating for their own improvement. Although this was a large study, it lacks both randomization and a control group [49].

In terms of prolotherapy and dextrose injections, Maniquis-Smigel et al. conducted an RCT that looked at 19 patients who received epidural injections of 5% dextrose and 16 who received normal saline into the caudal epidural space. Subjects who received the dextrose reported greater significant pain relief at 15 minutes and up to 48 hours, but not at 2 weeks. Although demonstrating short-term efficacy, this study suggests that dextrose may have positive results and a long-term study should investigate the effects of serial dextrose epidural injections and prolotherapy [50].

Focusing on stem cells, one RCT trial, by Bertagnoli et al., investigated the use of autologous disc-derived chondrocyte transplant in patients undergoing sequestrectomy. Only the interim analysis has been published which looked at 26 patients in each the treated and control group. The results are promising as the control group showed decreases in disc height, while the treated group did not have any cases of disc height loss. Furthermore, the discs treated with chondrocyte cells had adjacent intervertebral discs segments that appeared to retain hydration when compared to the control group. This study suggests that the autologous chondrocyte cells seem to improve disc structure and may even have beneficial effects on neighboring discs. Because the population of this study was only those undergoing discectomy, it is difficult to generalize these findings to the general patient with radicular back pain [51].

While regenerative therapy targeting herniated discs and radiculopathy seem to show promising results (Table 7.2), more long-term RCTs are needed before a general recommendation can be formulated.

Zygapophyseal Joint (Facet) Arthropathy

The current standard of care for facet-mediated pain includes directly targeting the medial branch nerve that is responsible for the innervation of this joint. This can be done with local anesthetic, steroids, and/or ablation. For each of these above procedures, often the pain returns as the medication wears off or the nerve heals. Furthermore, the root cause of the pain is not addressed. As these facet joints are synovial joints, therapies that have had success in other joints in the extremities have been further investigated. Treatments trialed include PRP, prolotherapy, and viscosupplementation.

In 2016, Wu et al. published on a new technique to treat lumbar facet pain using intra-articular injection with autologous PRP. Nineteen patients had good pain relief outcomes up to 3 months postinjection [52]. Wu later reported a prospective, randomized, controlled study of 46 subjects diagnosed with facet joint arthropathy through positive successful lidocaine blocks. Twenty three subjects underwent PRP injection

Table 7.2 Regenerative medicine for radiculopathy studies reviewed

Author, date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis	Injectate preparation and route	Results and author	Conclusions	Study analysis
Bhatia et al. [47] [PRP]	Pilot study $n = 10$ Efficacy of PRP via interlaminar epidural route in treatment of pain in pts. w/ prolapsed IVD	VAS, SLRT, and MODQ F/u at 3 wks. and 3 mos.	Lumber disc herniation / prolapse in MRI, < 65 yrs. old, w/ complaints of backache w/ or w/o radiculopathy for >4 wks. w/ a + SLRT and not responding to the conventional treatment	5 ml of autologous PRP under fluoroscopic guidance via interlaminar lumbar epidural inj. into area of affected nerve root	Pts. showed improvements in VAS and MODQ sustained during the 3-mo. study period. Apart from one pt. w/ VAS of 5, the rest showed improvement and their VAS was ≤4 at 3 mos. For most of the pts. MODQ score was <30% and SLRT improved to >70 at 3 mos. PRP was not associated with complications	Autologous PRP can be considered as a good alternative to epidural steroids and surgery in management of pts. w/ chronic prolapsed intervertebral disc. Possible alternative for steroids	Level IV
Cameron et al. [48] [PRP]	Prospective, nonrandomized, single center $n = 88$ 38 treated for cervical disc herniation. 38 for lumbar disc herniation, 12 w/ both cervical and lumbar	4 wks. to 6 wks., at 6 mos. to 12 mos., and up to 8 yrs. VAS were annually up to 8 yrs. ODI assessed in 36 pts. at least 1 yr. post procedure	Neck and/or low back pain caused by spinal disc herniation w/ or w/o radiation symptoms and failed conservative treatment for 3–6 mos. Pts. 18 to 65 yrs. old	Autologous PRP using a standardized protocol. Inj. in a circumferential manner subfascially into the lateral masses, facet joints and lateral gutters, and the inter- and supraspinatus ligaments, Kambin's triangle, and spinous processes	The duration of f/u ranged from 4 mos. to 8 yrs. (mean of 5 yrs.). 87% of pts. reported a successful outcome. Within the cervical group, the preoperative VAS showed 81% improvement. For the lumbar pts., the preoperative VAS improved by 77%. Both statically significant No complications were reported	Autologous PRP is a safe and effective treatment for neck and back pain secondary to disc herniation. Results were durable up to 8 yrs. Limitations include the multiple different time points for surveys and lack of ODI baseline scores	Level IV

Centeno et al. [49] [platelet lysate]	Case Series $n = 470$ Treated w/ PL epidural injs. presenting w/ symptoms of lumbar radicular pain	P-NRS; FRI; modified SANE; F/u 1, 3, 6, 12, 18, and 24 mos.; and annually thereafter	Diagnosed w/ lumbar radicular pain based on history, physical exams, and MRI findings	Either a transforaminal or interlaminar epidural 3–5 cc of PL 50% by volume, 4% lidocaine at 25% by volume, and compounded preservative-free 100–200 ng/ml hydrocortisone at 25% by volume	NPS change in score ranged from 1.6 to 2.4 Pts. treated w/ PL epidurals reported significantly lower ($p < 0.0001$) NPS and FRI change scores at all-time points compared to baseline. Avg. modified SANE ratings showed 49.7% improvement at 24 mos. posttreatment. 29 (6.3%) pts. reported mild adverse events related to treatment	PL inj. had significant improvements in pain compared to baseline, exceeded the minimal clinically important difference for FRI, and reported subjective improvement through 2-year f/u	Level IV
Maniquis-Smigel et al. [50] [prolotherapy]	Randomized double-blind (injector, participant) controlled clinical trial $n = 37$ 19 received epidural inj. of 5% dextrose 16 received normal saline inj. into the caudal epidural space	P-NRS, F/u at 15 minutes; and 2, 4, and 48 hours and 2 wks. post-inj. 50% or more pain reduction at 4 hours	Adults w/ moderate-to-severe nonsurgical LBP w/ radiation to gluteal or leg areas for at least 6 mos.	S single 10 mL of 5% dextrose or 0.9% saline over 1 minute using a published vertical caudal inj. technique w/ pressure sensation being rate-limiting factor	Dextrose participants reported greater P-NRS change at 15 minutes (4.4 ± 1.7 vs 2.4 ± 2.8 points), 2 hours (4.6 ± 1.9 vs 1.8 ± 2.8 points), 4 hours (4.6 ± 2.0 vs 1.4 ± 2.3 points), and 48 hours (3.0 ± 2.3 vs 1.0 ± 2.1 points), but not statistically significant at 2 wks. (2.1 ± 2.9 vs 1.2 ± 2.4 points) 84% (16/19) of dextrose recipients and 19% (3/16) of saline recipients reported ≥50% pain reduction at 4 hours	These findings suggest a neurogenic effect of 5% dextrose on pain at the dorsal root level; waning pain control at 2 wks. suggests the need to assess the effect of serial dextrose epidural injs. in a long-term study w/ robust outcome assessment	Level II

(continued)

Table 7.2 (continued)

Author, date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis	Injectate preparation and route	Results and author	Conclusions	Study analysis
Bertagnoli et al. [51] [autologous disc-derived chondrocyte (ADCT)	A multicenter, prospective, randomized, assessment-blinded, controlled clinical trial, EuroDISC study $n = 53$ 27 pts. within the ADCT-treated group 26 pts. control group All pts. were treated w/ a sequestrectomy	ODI, QBPD, VAS F/u 2 yrs. Disc height was assessed by MRI	Chronic back pain post lumbar disc herniation. Pts. 18–60 yrs. of age requiring surgical intervention at one level between L3 and S1	ADCT-treated group, the sequestrated disc tissue was used for disc chondrocyte isolation and their autologous propagation. 3 mos. later the disc-derived chondrocyte transplants were transplanted back into the operated discs nucleus region	During the f/u of 2 yrs., significant differences for ODI, QBPD, and VAS were found for the autologous disc-derived chondrocyte transplantation Decreases in disc height over time were only found in the control group, and of potential significance, intervertebral discs in adjacent segments appeared to retain hydration when compared to those adjacent to levels that had undergone discectomy w/o cell intervention	The interims results give strong evidence for the safety and efficiency of the disc-derived chondrocyte transplantation applied following sequestrectomy to delay or inhibit ongoing processes of disc degeneration	Level II

Abbreviations: *SLRT* straight leg raising test, *MODQ* Modified Oswestry Disability Questionnaire, *QBPD* Quebec Back Pain Disability, *VAS* visual analogue scale

and 23 underwent standard of care lidocaine with steroid. At 1 week and 1 month the steroid group outperformed the PRP group. However, as time progressed the PRP group began to outperform the steroid group with significantly improved VAS scores from 2 months on. The steroid group peaked around 1 month and relief diminished to 6 months. The PRP group seemed to improve up to 3 months and then plateaued [53]. There seems to be promising evidence for the use of PRP to treat facet-mediated pain.

Prolotherapy has also been studied to treat facet pain. Hooper et al. reported a retrospective case review of 15 patients (three patients treated bilaterally to make 18 total facet joint sides) who were treated with intra-articular prolotherapy after confirmation of cervical facet pain post whiplash injury. This procedure significantly improved the mean neck disability index at months 2, 6, and 12. These results are promising; however this study lacks a control and furthermore may have been confounded as 13 of the patients' pain was caused by motor vehicle accidents in which they were in litigation. Furthermore, patients had concurrent physiotherapy which may have supported better outcomes [54]. Hooper et al. later reported a retrospective series on 177 patients with chronic spinal pain who each received prolotherapy to the facet capsules of the cervical, thoracic, and lumbar spine in regions that correlated with pain (in addition, the iliolumbar and dorsal sacroiliac ligaments were injected in patients with low back pain). Ninety-one percent of these patients reported reduction in pain. Lumbar and thoracic patients proved to have greater significant relief than compared to cervical [55]. These studies are in favor of prolotherapy for facet-mediated pain.

In terms of viscosupplementation, a pilot prospective study by Cleary et al. recruited 13 patients with symptomatic lumbar-facet joint pain who were treated with injection of hyaluronic acid: 18 facets of the 13 patients were injected. At 6 weeks there was no significant improvement in pain scoring. This study was limited as there was no definitive diagnostic testing for facet arthropathy [56]. A more promising study by DePalma et al. followed 15 patients with identified facet joint pain through successful trial of comparison local blocks. In this prospective uncontrolled pilot study, patients had positive results with significant improvements in VAS and ODI up to 6 months; however results were not sustained at 12 months. However, this study is flawed by its lack of control and blinding [57]. Fuchs et al. followed two groups with axial back pain: one received intra-articular sodium hyaluronate and the control received intra-articular glucocorticoids targeting the facet joints. In this observer-blinded RCT, both groups had positive results, with the hyaluronate group showing prolonged benefits in the long term at 3 and 6 months [58]. An RCT, by Annaswamy et al. investigated 30 subjects with facet pain and injected them either with hyaluronate or with steroid. While the steroid group only providing short-term functional improvement, the hyaluronate group outperformed by providing both short-term and long-term functional improvement, as well as short-term pain relief [59].

In conclusion, for PRP we identified one RCT that suggests it outperforms steroids with its longevity lasting up to 6 months. For prolotherapy, the studies seem to show improvements in pain; however an RCT is lacking. Lastly, the two viscosupplementation RCTs show hyaluronic acid to improve pain up to 6 months. The two other studies showed mixed results, with one trial confirming the positive results

and the other showing no significant improvement in pain scoring. Further studies are needed that include a control group and stricter inclusion criteria confirming facet-mediated pain. Each study had a strong safety profile, suggesting these interventions (Table 7.3) can be trialed when evidence-based medicine fails to provide appropriate relief.

Sacroiliac Joint Dysfunction

Another common cause of chronic low back pain stems from the sacroiliac joints and ligaments. The SI joint acts to transmit forces from the lower limbs to the vertebral column. These synovial joints are prone to degeneration and instability. In addition, other joints of the pelvis including the sacrococcygeal joint can be a source of pain.

One case series investigated the efficacy of viscosupplementation. Srejic et al. reported on four patients treated with viscosupplementation to the SI joint. At 12–16 weeks postinjection pain was reported as 40–67% improved. The authors conclude further studies are needed to look at long-term duration and overall outcomes [60].

Others have examined the effects of prolotherapy theorized to provide stabilization of the painful instable SI joint. In a retrospective cohort study by Hoffman et al. 103 patients received prolotherapy aiming at the SI joint for a total of three injections at approximately 1 month intervals. At an average of 117 day follow-up, 23% of these patients showed a minimum clinically important improvement in ODI. Many of the responders had a median of 2 years of back pain. This suggests prolotherapy could be beneficial in a subset of patients [61]. Similarly, Mitchell et al. reported on prolotherapy in 131 patients injected around the SI joint into the deep interosseous ligament. Over 70% of patients were satisfied with the procedure. The majority of patients demonstrated at least 50% improvement in pelvic/lumbar strength. Two-thirds of patients demonstrated some pain relief with a mean of 51.6% reduction at 12 months [62]. Kim et al. investigated the current routine treatment of steroid injection and compared that to prolotherapy injection to the SI joint. Both groups (23 patients received prolotherapy and 25 patients received steroid) showed similar significant pain relief results at the 2-week follow-up. However, at 15 months the cumulative incidence of greater than 50% pain relief was 58.7% in the prolotherapy group while just 10.2% in the steroid group. This study suggests prolotherapy may have more long-term efficacy compared to steroids [63].

Examining other joints of the pelvis, Khan et al. studied patients with chronic coccygodynia and performed two injections of prolotherapy 15 days apart to the sacrococcygeal joints. Due to the good relief obtained, this prospective observational study recommends that dextrose prolotherapy should be trialed in patients with chronic, recalcitrant coccygodynia prior to undergoing coccygectomy [64].

Focusing on PRP, a case series by Ko et al. reported on four patients who had two sessions of PRP injections to the SI Joint at the three Hackett's points at the ligament-bone interface. Each of these patients showed significant reduction in pain

Table 7.3 Regenerative medicine for zygapophyseal joint (facet) arthropathy studies reviewed

Author and date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Disease type	Injectate and route	Results	Author conclusions	Study analysis
Wu et al. [52] [PRP]	A prospective clinic evaluation $n = 19$ 19 pts. received lumbar facet joint inj. w/ autologous PRP	VAS at rest and flexion, RMDQ, ODI, and modified MacNab criteria F/u 1 wk., 1 mo., 2 mos., and 3 mos.	Lumbar facet joint syndrome	Intra-articular lumbar facet joint inj. w/ 0.5 ml autologous PRP PRP tested to ensure concentration 4–5 times than in native peripheral blood	1 wk. after treatment, LBP reduced significantly compared w/ baseline pain both at rest and during flexion. The outcomes were assessed as "good" or "excellent" for 9 pts. (47%) immediately after treatment, 14 pts. (74%) at 1 wk., and 15 pts. (79%) at 1, 2, and 3 mos.	In short-term period of 3 months, PRP lumbar facet joint injections are effective and safe. Future studies would benefit from control group and longer f/u	Level IV

(continued)

Table 7.3 (continued)

Author and date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Disease type	Injectate and route	Results	Author conclusions	Study analysis
Wu et al. [53] [PRP]	Prospective, randomized, controlled study $n = 46$ 23 w/ PRP 23 w/ lidocaine and steroid	VAS, RMQ, ODI, modified MacNab at 1 week, 1, 2, 3, and 6 mos.	Lumbar facet joint syndrome with continued pain 1 mo. post conservative treatment and post successful lidocaine block	Steroid group: 0.5% lidocaine and 5 mg/mL betamethasone total of 0.5 mL inj. per joint PRP group: 5–10 ml of venous blood. Centrifuged to 1–2 ml. Platelet concentration was almost 4–5 times greater than native peripheral blood 0.5 mL inj. at each joint level	Both steroid and PRP improved in VAS, RMQ, and ODI. Both groups showed improvements in VAS throughout. However, steroid group showed more significant decrease in VAS at wk. 1 and mo. 1. However, by 3 mos. after inj. and at 6 mos. pain relief, satisfaction, and functional capacity were significantly better in the PRP group	At 2 mos. the PRP group began to outperform the steroid group in terms of VAS as the steroid group peaked around 1 mo. and worsened to 6 mos. The PRP group seemed to improve to 3 mos. and then plateaued. PRP proved superior for longer duration efficacy	Level II

Hooper et al. [54] [prolotherapy]	Retrospective case series. Consecutive pts. *n* = 177 Prolotherapy inj. done on a weekly basis for up to 3 wks. A set of three injs. was repeated in 1 mo. time if needed	Improvement in activities of daily living, level of pain, and ability to work F/u 2 mos. to 2.5 yrs.	Chronic low back pain not responding to conventional therapy and manual assessment demonstrating laxity	Pts. were treated w/ a proliferant solution containing 20% dextrose and 0.75% xylocaine. 0.5 mL of proliferant inj. into the facet capsules of the cervical, thoracic, and lumbar spine or combination. The iliolumbar and dorsal SI ligaments if LBP	91.0% of pts. reported reduction in level of pain; 84.8% of pts. reported improvement in activities of daily living, and 84.3% reported an improvement in ability to work. Women required on avg. three more injs. than men. Cervical spine response rates were lower than thoracic or lumbar spine. No complications from treatment were noted	Dextrose prolotherapy appears to be a safe and effective method for treating chronic spinal pain that merits further investigation. Future studies need to consider differences in gender response rates	Level IV Limited by lack of definitive diagnosis of facet arthropathy by positive blocks

(continued)

Table 7.3 (continued)

Author and date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Disease type	Injectate and route	Results	Author conclusions	Study analysis
Hooper et al. [55] [prolotherapy]	Retrospective case review of prospective data *n* =15 Intra-articular prolotherapy Three pts. had bilateral treatment, leaving 18 sides to analysis. Injs. repeated every 1–2 mos. if manual physiotherapy identified ongoing laxity	Mean NDI. F/u at 2, 6, and 12 mos.	Chronic whiplash-related neck pain that failed conservative and interventional procedures. Facet joint pain confirmed by diagnostic block	Intra-articular zygapophyseal joint prolotherapy by placing 0.5–1 mL of 20% dextrose solution into each zygapophyseal joint, after confirmation of intra-articular location w/ radiographic contrast. Solution was prepared by diluting D50W w/ 1% lidocaine. Treated C2-C7	Mean NDI pre-treatment was 24.7 and decreased posttreatment to 14.2 (2 mos.), 13.4 (6 mos.), and 10.9 (12 mos.). Avg. change NDI = 13.77 baseline versus 12 mos. Symptoms for 14 pts. were from motor vehicle accident, of which 13 were in litigation. Pts. attending physiotherapy over the course of treatment had better outcomes than those w/o physiotherapy. Women needed more injs. (5.4) than men (3.2)	Intra-articular prolotherapy improved pain and function. The procedure appears safe, more effective than periarticular inj., and lasted as long, or longer, than those pts. w/ previous radiofrequency neurotomy. Concurrent physiotherapy helped reduce post-inj. neck stiffness. Future trials should consider gender when deciding how many treatments to administer. Litigation was not a barrier to recovery	Level IV

Cleary et al. [56] [viscosupplementation]	Pilot study to test the potential effectiveness of HA inj. therapy in the treatment of lumbar facet joint arthritis *n* = 13 18 facets in 13 pts. were injected w/ HA	VAS, ODI, F/u at 6 wks.	40–75 yrs. old w/ symptomatic lumbar facet joint arthritis as defined by diagnostic criteria and MRI evidence	A single inj. of HA (Suplasyn 2 mL, 10 mg) into affected facet joint was performed, w/ correct placement confirmed on fluoroscopy	At 6-wk. f/u, there was no significant improvement in pain when measured on the VAS. There was also no significant improvement in the ODI	Preliminary results from this pilot study do not demonstrate any benefit of viscosupplementation in the management of symptomatic lumbar facet arthropathy	Level IV Limited by lack of definitive diagnosis of facet arthropathy by positive blocks

(continued)

Table 7.3 (continued)

Author and date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Disease type	Injectate and route	Results	Author conclusions	Study analysis
DePalma et al. [57] [viscosupplementation]	Prospective, uncontrolled, pilot study $n = 15$ 15 pts. underwent intra-articular Hylan G-F 20 injs, 10 days apart, into the painful facet joint. A third Hylan G-F 20 inj. was offered as needed	VAS, ODI, SF-36, FTF, tolerance (standing, sitting, walking), and analgesic usage F/u. 7–10 days and at 1, 3, 6, and 12 mos.	Facet joint pain diagnosed by positive local comparative blocks	1.0VmL intra-articular Hylan G-F 20 injs. performed twice 10 days apart, into the painful facet joint. A third Hylan G-F 20 inj. was offered to pts. dissatisfied w/ the results obtained w/ the first two injs.	Repeated measure mixed models indicated that VAS (avg., standing, walking), ODI, SF-36, FTF, and sitting tolerance all showed significant changes from baseline up to 6 mos. but were not sustained at 12 mos.; w/ the exception of the baseline to 12-month difference for FTF. There was no evidence of changes over time in standing ($P = 0.085$) or walking ($P = 0.084$) tolerance. Satisfaction initially increased from baseline (0%) to 7–10 days (64%) but declined over time (36% at 12 mos.)	Viscosupplementation for lumbar facet joint arthropathy w/ Hylan G-F 20 is associated w/ modest efficacy that predominately lasts up to 6 mos. As compared w/ baseline (80%), analgesic usage decreased over time showing significant decreases at 6 mos. (33%) and increased slightly at 12 mos. (45%). Limitations include a small sample size and lack of both a control and blinding. Larger RCTs are indicated to clarify its clinical safety, efficacy, and utility	Level IV

Fuchs et al. [58] [viscosupplementation]	Randomized, controlled, blind-observer clinical study *n* = 60 30 received 10 mg sodium hyaluronate (SH) 30 received 10 mg triamcinolone acetonide (TA) per facet joint	VAS, RMQ, ODI, LBOS, SF-36 F/u immediate effects, 3 and 6 mos.	Chronic nonradicular lumbar pain for at least 3 mos. Radiologic confirmation of facet osteoarthritis	The facet joints on both sides at levels S1-L5, L5-L4, and L4-L3 were treated once per wk. Each patient ultimately received six injs. of the assigned test product 10 mg/ml sodium hyaluronate or 10 mg/ml steroid (triamcinolone acetonide), max of 1 ml per facet joint	Pts. reported lasting pain relief, better function, and improved quality of life w/ both treatments. Mann-Whitney analyses of RMQ, ODQ, and LBOS very consistently showed that SH is not inferior to TA. In addition, the efficacy of SH was largely comparable w/ that of TA on the VAS and SF-36	Intra-articular SH is a very promising new option for the treatment of pts. w/ chronic nonradicular lumbar symptoms with evidence of facet osteoarthritis. No adverse effects were reported after administration of the test products. SH-treated pts. showed greater benefits in the long term at 3- and 6-month f/u	Level IV Limited by lack of confirmation testing by facet blocks

(continued)

Table 7.3 (continued)

Author and date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Disease type	Injectate and route	Results	Author conclusions	Study analysis
Annaswamy et al. [59] [viscosupplementation]	Prospective double-blind randomized controlled trial $n = 25$ 13 pts. in steroid group 12 subjects in the HA group all received intra-articular facet injs.	VAS, PDQ, overall percent improvement at 6 mos. F/u at 1, 3, and 6 mos.	Symptomatic lumbar facet arthritis w/ axial chronic LBP w/o radiculopathy. Met criteria for facetogenic back pain	After randomization, bilateral L3–4, L4–5, and L5–S1 facet joints were injected. Each joint received either 1 ml of triamcinolone (10 mg/ml Kenalog) or 1 ml of Synvisc-One® (8 mg of Hylan G-F 20 per vial)	For pain, Synvisc group showed significant difference at 1 mo. (69.60 ± 19.68 to 45.15 ± 25.23). For PDQ, Kenalog group showed significant difference at 1 mo. (100.2 ± 22.93 to 77.42 ± 29.89) and Synvisc group showed significant differences at all-time points (101.93 ± 27.83 to 74.08 ± 33.90 to 74 ± 35.58 to 79 (median, 52–99.5))	Hyaluronate injs. provided statistically significant short- and long-term functional benefits and short-term pain improvement but triamcinolone injs. only provided statistically significant short-term functional benefit and no significant short- or long-term pain improvement compared to within-group baseline levels. Triamcinolone and hyaluronate injs. into facets provide similar pain and functional benefits in pts. w/ symptomatic lumbar zygapophyseal joint arthropathy causing chronic LBP	Level IV Limited by lack of facet diagnostic block and sham control. No intergroup differences were observed when comparing overall satisfaction at 6 mos.

Abbreviations: *NDI* neck disability index, *HA* hyaluronic acid, *FTF* finger to floor distance, *RMQ* Range of motion questionnaire, *ODQ* Oswestry Disability Questionnaire, *LBOS* Low Back Outcome Score and the Short Form 36 (SF-36) questionnaire, *PDQ* Pain Disability Questionnaire

and improvements in quality of life [65]. A prospective randomized study by Singla et al. treated 20 patients with steroid and 20 patients with PRP to the SI joint. At 6 weeks and 3 months the PRP group had significantly better intensity of pain. The efficacy of steroid injection was reduced to only 25% at 3 months, while efficacy remained at 90% in the PRP group [66]. This study, similar to the prolotherapy study, demonstrates a longer efficacy of the regenerative medicine (PRP group) compared to steroids.

To examine the efficacy of PRP versus prolotherapy, Saunders et al. compared his prospective trial of 45 patients with PRP injection into and around the dorsal interosseous ligament to a control of a prior separate study using prolotherapy to treat presumed SI joint pain. At 3 months the PRP group had good pain and functional improvement without further improvement at 12 months. When this trial was statistically compared to a prior prolotherapy study, the PRP group had better outcomes in pain scores and function and required on average 1.6 injections compared to the three injections of the prolotherapy control group [67].

Viscosupplementation, prolotherapy, and PRP have an excellent safety profile and have shown promising results in treating SI joint pain (Table 7.4). Patient selection, injection target, and injection schedule remain significant variables lacking a gold standard. As previously noted, more well-designed comparative studies are necessary.

Back Musculature Atrophy

Pain in the back can also be related to musculature dysfunction. There are several muscles of the back that attach to the spine and act to add strength and support, often stabilizing the spine joints through various movements. When there is a misbalance, pain can result from poor mechanics and additional destructive forces. Furthermore, the general physiological response to back pain is for the muscles to disengage as they inactivate. This leads to atrophy of muscles over time, which further promotes a negative cycle.

A study by Hussein et al. analyzed 104 patients with chronic nonspecific back pain and confirmed muscle atrophy on MRI. These patients were treated with platelet leukocyte-rich plasma (PLRP) into the lumbar multifidus (LMF) muscle weekly for 6 weeks. Patients improved in pain and function as reported on questionnaires. Furthermore, 12-month MRI follow-up showed increased cross-sectional area and decreased fatty degeneration of LMF muscle. This study suggests that PLRP may better pain and function outcomes by improving LMF atrophy. One limitation includes the lack of a control group and the fact the patients were advised to remain active and walk 30 minutes per day. Thus, physical therapy targeting these muscle groups may play an important part in relieving back pain, whether in conjunction with regenerative therapy or on its own. Although this technique had promising outcomes (Table 7.5), again there is a need for RCTs [68].

Table 7.4 Regenerative medicine for sacroiliac joint dysfunction studies reviewed

Author and date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Disease type	Injectate and route	Results	Author conclusions	Study analysis
Srejic et al. [60] [viscosupplementation]	Case series $n = 4$ Pts. received three injs. of Hylan G-F 20 in the sacroiliac joints 2 wks. apart	VAS. F/u at 12–16 wks. post inj.	SI joint syndrome by means of pt. history, physical examination, and intra-articular local anesthetic inj. Preceded by SI arthrogram	Three injs. of Hylan G-F 20 in the SI joints 2 wks. apart 1 cc (8 mg) of Hylan G-F 20 (Synvisc) into each joint	12 to 16 wks. after the injs., the pain was reported to be 40–67% better when measured on the VAS. The duration of the beneficial effect of Hylan on arthralgia and joint function was undetermined	Viscosupplementation of the SI joint induced a significant degree of analgesia in all four patients. This treatment modality could represent an option in the management of SI joint pain and dysfunction	Level IV

Hoffman et al. [61] [prolotherapy]	Retrospective cohort study *n* = 103 All pts. received prolotherapy for SIJ	ODI, f/u immediately preceding each prolotherapy inj. and at 3–4 mos.	SI joint pain and instability When diagnosis uncertain, pt. underwent diagnostic inj. or positive initial prolotherapy response	Mixture of 7 ml of 1% lidocaine and 3 ml of 50% dextrose (15% dextrose solution), w/ the solution being injected aiming at the SI joint Series of three injs. at about 1 month intervals	At a median of 117 days, 24 pts. (23%) showed a minimum clinically important improvement despite an avg. of 2 years w/ LBP and a mean pre-inj. ODI of 54. Much of the improvement was seen after the first prolotherapy inj., and a 15-point improvement in ODI prior to the second inj. had a sensitivity of 92% and specificity of 80% for determining which pts. would improve	A satisfactory proportion of pts. w/ symptomatic SI joint instability as an etiology of LBP can have clinically meaningful functional gains w/ prolotherapy treatment. Those w/ abrupt onset of low back pain were unlikely to have relief	Level IV Limited by lack of pain scores and most injs. w/o imaging guidance

(continued)

Table 7.4 (continued)

Author and date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Disease type	Injectate and route	Results	Author conclusions	Study analysis
Mitchell et al. [62] [prolotherapy]	Prospective, observational study n = 131 Consecutive pts. undergoing prolotherapy treatment around the SIJ	Back/hip/pelvic strength, pain relief ODI, patient satisfaction and analgesic use F/u at 6 and 12 mos. post-inj.	Diagnostically confirmed SIJ instability and pain	The deep interosseous ligament injected w/ 1.5 ml Naropin 0.75% and 10 ml 50% glucose over multiple sites Injs. were repeated, on avg. three times, at 6 weekly intervals	At 12 mos., 66% of pts. reported improvements in pelvic/lumbar strength. Mean strengthening was 59.4%; 71.1% of pts. achieved ≥50% improvement. 66% also experienced at least some pain relief (mean 51.6% reduction) at 12 mos., while 80% reported they had ≥50% improved stability. Clinically meaningful mean ODI score reductions (6.58 points at 6 mos. and 8.27 points at 12 mos.) were observed	Almost half the cohort reduced their use of analgesia posttreatment and 70% of pts. were satisfied w/ the outcomes from the prolotherapy procedure. Pain relief was dependent on improved strength and correlated w/ reductions in disability score	Level IV

Kim et al. [63] [prolotherapy]	Prospective, randomized, controlled trial $n = 48$ 23 in prolotherapy group 25 in steroid group	Pain and disability scores F/u at 2 wks. and monthly for 12 mos.	SI joint pain lasting 3 mos. or longer, confirmed by ≥50% improvement in response to local anesthetic block and who failed medical treatment	Prolotherapy group, inj. 2.5 mL of 25% dextrose solution into the SIJ every other wk. up to three times. The dextrose solution 50% dextrose water w/ 0.25% levobupivacaine. Steroid inj. group 2.5 mL of triamcinolone acetonide 40 mg in 0.125% levobupivacaine	The pain and disability scores were significantly improved from baseline in both groups at the 2-week f/u, w/ no significant difference between them. The cumulative incidence of ≥50% pain relief at 15 mos. was 58.7% in the prolotherapy group and 10.2% in the steroid group. There was a statistically significant difference between the groups	Intra-articular prolotherapy provided significant relief of sacroiliac joint pain, and its effects lasted longer than those of steroid injs. Further studies are needed to confirm the safety of the procedure and to validate an appropriate inj. protocol	Level IV

(continued)

Table 7.4 (continued)

Author and date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Disease type	Injectate and route	Results	Author conclusions	Study analysis
Khan et al. [64] [prolotherapy]	Prospective observational study $n = 37$ Pts. received two injs. of prolotherapy 15 days apart. A third inj. given 4 wks. later to eight pts. w/ pain scores >4	VAS F/u 15 days and 4 wks.	Chronic coccygodynia not responding to conservative treatment for more than 6 mos. 27 of the pts. had received local steroid injs. elsewhere	8 ml of 25% dextrose and 2 ml of 2% lignocaine into the coccyx Inj. over the most tender spot of the coccyx, using an image intensifier to locate the sacrococcygeal joint	The mean VAS before prolotherapy was 8.5. It was 3.4 after the first inj. and 2.5 after the second inj. Minimal or no improvement was noted in seven pts.; the remaining 30 pts. had good pain relief	Dextrose prolotherapy is an effective treatment option in pts. w/ chronic, recalcitrant coccygodynia and should be used before undergoing coccygectomy. Randomized studies are needed to compare prolotherapy w/ local steroid injs. or coccygectomies	Level IV Limited by lack of functional outcome studies

Ko et al. [65] [PRP]	Case series $n = 4$ Pts. inj. w/ PRP to SI joint for two sessions	SFM, P-NRS, ODI, f/u at 12 mos. and 48 mos.	SI joint instability diagnosed by combination of pt. history, provocative tests, or suggestive imaging	Inj. to SI joint at Hackett's points A, B (medial to PSIS), and C (inferior to the PSIS). 0.5 ml of PRP w/ each needle contact of the ligament-bone interface. Two sessions total. PRP platelet concentration was 5–6 times baseline blood	At f/u 12-mo. posttreatment, pooled data from all pts. reported a marked improvement in joint stability, a statistically significant reduction in pain, and improvement in quality of life. The clinical benefits of PRP were still significant at 4-year posttreatment	PRP therapy exhibits clinical usefulness in both pain reduction and for functional improvement in pts. with chronic SI joint pain	Level IV

(continued)

Table 7.4 (continued)

Author and date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Disease type	Injectate and route	Results	Author conclusions	Study analysis
Singla et al. [66] [PRP]	Prospective randomized open blinded end point (PROBE) study $n = 40$ 20 in group S received steroid inj. 20 in group P received PRP inj.	VAS, modified ODI, SF-12, and complications F/u at 2 wks., 4 wks., 6 wks., and 3 mos.	SI joint area LBP. Unilateral SIJ seen on either x-ray, MRI, or nuclear scan w/ three or more positive provocative tests	Group S received 1.5 mL of methylprednisolone (40 mg/mL) and 1.5 mL of 2% lidocaine w/ 0.5 mL of saline Group P received 3 mL of leukocyte-free PRP w/ 0.5 mL of calcium chloride into ultrasound-guided SIJ inj.	Intensity of pain was significantly lower in group PRP at 6 wks. as compared to group steroids. The efficacy of steroid inj. was reduced to only 25% at 3 mos. in group steroids, while it was 90% in group platelets. There were no serious adverse events	The intra-articular PRP inj. is an effective treatment modality in LBP involving SIJ. PRP group exhibited greater pain and functional improvements which lasted longer compared to steroid group	Level II Limited by lack of pt. blinding

Saunders et al. [67] [PRP vs prolotherapy]	Prospective open label $n = 45$ 45 pts. received PRP inj. The results were then compared to a matched control group who had received hypertonic glucose injs. following tertiary referral from specialized sports medicine physicians	VAS, RMDQ, and QBPD. As well as clinical tests of SIJ incompetence F/u at 3 and 12 mos.	Pain in the lumbosacral region w/ 3 of 4 positive validated clinical signs. Confirmed by the fused single photon emission computed tomography and low-dose x-ray computed tomography	Inj. into and around the dorsal interosseous ligament rather than the synovial portion of the sacroiliac joint On avg. 1.6 injs. per pt. The system used concentrate platelets 1.6 times baseline	At 3 mos. the PRP group had good pain and functional improvement w/o further improvement at 12 mos. The outcome measures of change in pain scores; improvement in function between the groups was superior for the PRP group. All PRP pts. experienced significant improvement in pain score and function. The number of injs. required was less for the PRP group (mean of 1.6) than the controls (mean 3.0)	PRP is a viable alternative to prolotherapy into the dorsal interosseous ligament in patients who have failed physiotherapy for SIJ incompetence	Level III Limited by lack of documented amount of PRP or prolotherapy injected and matched control group comparison

Abbreviations: *Inj.* injection, *SFM* short-form McGill Pain Questionnaire

Table 7.5 Regenerative medicine for back musculature atrophy studies reviewed

Author and date	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis type	Injectate and route	Results and author conclusion	Conclusion	Study analysis
Huessein et al. [68] [PLRP]	Prospective trial $n = 104$ pts. w Pts. treated w/ weekly PLRP injs. into lumbar multifidus muscle (LMF) for six wks. and followed up for 24 mos.	NRS, ODI, patient satisfaction index, and modified MacNab criteria F/u at 1 day, 6 mos., 12 mos., and 24 mos. Lumbar MRI at 12 mos.	Chronic non-specified LBP, atrophy of multifidus muscle seen in MRI scan and at least one level of degenerative disc disease	Needle targeted the deep fibers of the LMF muscle at the degenerated lumbar motion segment. Needle was withdrawn 1–2 mm from lamina and 2.5 mL of PLRP injected per side Weekly PLRP inj. for 6 wks. into the LMF muscle Platelet count ranged from 0.8 to 1.2 million/mL or 4–6 times baseline blood values	NRS significantly improved gradually from a mean of 8.8 ± 8 pre-inj. to 3.45 ± 2.9 by 12 mos. and ODI significantly improved gradually from a mean of 36.7 ± 3.9 to 14.6 ± 12.8 by 12 mos. After reaching maximum improvement between 12 and 18 mos., all outcome measures remained stable till the end of the 24 mos. 87.8% (65/74) of the satisfied pts. showed increased cross-sectional area and decreased fatty degeneration of LMF muscle on MRI at 12-mo. f/u	PLRP injs. into atrophied LMF muscle represents a safe, effective method for relieving chronic LBP and disability w/ long-term patient satisfaction and success rate of 71.2%. We recommend the use of the lumbar PLRP injs. of LMF muscle to refine the inclusion criteria of lumbar fusion to avoid failed back syndrome	Level IV Limited by lack of control group and all pts. encouraged to walk 30 minutes a day and remain active

Abbreviations: *LMF* lumbar multifidus muscle, *LBP* lower back pain

Back Ligament Dysfunction

Similar to the muscles of the back, the ligaments act to support the spine and its joints. Ligaments can be visualized as guy wires providing strength, reinforcement, and stability. Due to this important role, ligaments can be another target for regenerative therapy. Historically, prolotherapy has been used in theory to strengthen ligaments.

Dechow et al. reported a randomized, double-blind, placebo-controlled trial of 74 mechanical back pain patients, with 36 undergoing three once weekly dextrose injections and 38 in the control group receiving normal saline. Sites injected included the tip of the spinous process of L4 and L5 and associated supraspinous and interspinous ligaments, apophyseal joint capsules at L4–5 and L5–S1, attachment of the iliolumbar ligaments at the transverse processes of L5, attachment of the iliolumbar and dorsolumbar fascia to the iliac crest, and attachments of the long and short fibers of the posterior sacroiliac ligaments and the sacral and iliac attachments of the interosseous sacroiliac ligaments. The authors' findings showed no statistically significant differences between the control and the prolotherapy group. The authors acknowledge that their inclusion criteria did not evaluate for instability and hence the treatment sample group may not have been the ideal patient cohort that could potentially benefit from prolotherapy [69]. A retrospective case study published by Hauser et al. analyzed 140 patients that received prolotherapy to sites that included the sacroiliac, iliolumbar, sacrotuberous, lumbosacral, supraspinous and interspinous, sacrococcygeal, and sacrospinous ligaments, as well as the gluteal and pyriformis muscle attachments on the iliac crest. On an average of 12-month follow-up, 89% of these patients demonstrated more than 50% pain relief with prolotherapy. Again, this study lacks both a control and blinding [70].

Klein et al. randomized 39 chronic low back pain patients to a xylocaine/proliferant group and 40 to a xylocaine/saline (control group) that received injections into the posterior sacroiliac and interosseous ligaments, iliolumbar ligaments, and dorsolumbar fascia. Although both groups improved, the proliferant (prolotherapy) group showed a statistically significant improvement in number of patients that achieved a 50% or greater diminution in pain or disability scores at 6-month follow-up [71]. Similarly, an RCT by Yelland et al. treated 110 patients with either prolotherapy or normal saline injections into tender lumbo-pelvic ligaments and was then randomized to either flexion/extension exercises or normal activity over 6 months. Although each ligament injection group showed improvement and sustained reductions in pain and disability, no significant attributable difference was seen among the prolotherapy group. This suggests that any needling of these ligaments may provide relief; a different control group that did not receive injectate could better identify these findings [72].

These studies (Table 7.6) show promise that prolotherapy can help in cases of ligament dysfunction. Furthermore, they highlight the importance of identifying

Table 7.6 Regenerative medicine for back ligament dysfunction studies reviewed

Author, date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis	Injectate preparation and route	Results and author	Conclusions	Study analysis
Dechow et al. [69] [prolotherapy]	Randomized, double-blind, placebo-controlled trial $n = 74$ 36 underwent three once weekly injs. of dextrose-glycerine-phenol w/ lignocaine 38 in the control group received three once weekly injs. of saline plus lignocaine	McGill Pain, the modified Somatic Pain Questionnaire, the Zung Depression Inventory, the ODI, and modified Schober to measure spinal flexion F/u at 1, 3, and 6 mos.	Mechanical back pain of more than 6 mos. duration	Treatment group: 5 ml of dextrose 25%, glycerine 25%, and phenol 2.4% made up to 100 ml w/ sterile water combined w/ 5 ml of 1% lignocaine Control group: 5 ml of the normal saline solution combined w/ 5 ml of 1% lignocaine Inj. sites: included the tip of the spinous process of L4 and L5 and associated supraspinous and interspinous ligaments, apophyseal joint capsules at L4–5 and L5–S1, attachment of the iliolumbar ligaments at the transverse processes of L5, attachment of the iliolumbar and dorsolumbar fascia to the iliac crest, and attachments of long and short fibers of the posterior sacroiliac ligaments and the sacral and iliac attachments of interosseous SI ligaments	There were no statistically significant differences in patient characteristics between the placebo and treatment groups at baseline or for any measure at f/u	Three weekly sclerosant injs. alone may not be effective treatment in many pts. w/ undifferentiated chronic back pain. Patient selection and combination w/ other treatment modalities may be factors in determining treatment success	Level II Limited by undifferentiated LBP without clear diagnosis. No clinical measures of instability were tested

Hauser et al. [70] [prolotherapy]	Retrospective case studies *n* = 145 Each treated quarterly w/ Hackett-Hemwall dextrose prolotherapy An avg. of four lower back treatments, given every three mos., per pt.	Pain level, physical and psychological symptoms, and activities of daily living F/u at an avg. of 12 mos., at end of treatment	Unresolved chronic low back pain for an avg. of 4 years	Each site was injected w/ 0.5–1 cc of solution of 15% dextrose, 0.2% lidocaine solution w/ a total of 60 to 90 cc of solution per lower back treatment Inj. sites included the sacroiliac, iliolumbar, sacrotuberous, lumbosacral, supraspinous and interspinous, sacrococcygeal, and sacrospinous ligaments, as well as the gluteal and pyriformis muscle attachments on the iliac crest	In the 145 pts., pain levels decreased from 5.6 to 2.7 after prolotherapy; 89% experienced more than 50% pain relief w/ prolotherapy; more than 80% showed improvements in walking and exercise ability, anxiety, depression, and overall disability; 75% were able to completely stop taking pain medications	The decrease in pain reached statistical significance including the subset of (55) pts. who were told there were no other options for their pain and those (26) who were told surgery was their only treatment option. Prolotherapy should be considered in those with unresolved LBP	Level IV

(continued)

Table 7.6 (continued)

Author, date [injectate]	Methodology, patients, and comparison group	Follow-up and outcome measures	Diagnosis	Injectate preparation and route	Results and author	Conclusions	Study analysis
Klein et al. [71] [prolotherapy]	Randomized, double-blinded clinical trial $n = 79$ 39 in Xylocaine/ proliferant group 40 in control Xylocaine/saline solution group	VAS, disability, and pain grid scores and w/ objective computerized triaxial tests of lumbar function F/u at 6 mos.	Chronic LBP that had failed to respond to previous conservative care	Proliferant solution consisted of dextrose 25%, glycerine 25%, and phenol 2.4%. 15 ml w/ 15 ml of 0.5% lidocaine. Max of 30 ml at each inj. section Control group 30 ml of solution, 15 ml of 0.5% lidocaine w/ 15 ml of sterile normal saline Inj. sites: included posterior sacroiliac and interosseous ligaments, iliolumbar ligaments, and dorsolumbar fascia	30 of the 39 pts. randomly assigned to the proliferant group achieved a ≥50% diminution in pain or disability scores at 6 mos. compared to 21 of 40 in the group receiving lidocaine. Improvements in VAS, disability, and pain grid scores were greater in the proliferant group and reached statistical significance. The MRI and CT scans showed significant abnormalities in both groups, but these did not correlate w/ subjective complaints and were not predictive of response to treatment	Objective testing of range of motion, isometric strength, and velocity of movement showed significant improvements in both groups posttreatment but did not favor either group. LBP may in part be related to injury of the fibrous posterior supporting structures of the lumbar motion segments and posterior SI ligaments. Proliferant inj. known to induce collagen proliferation appears to be a useful treatment in appropriately selects pts.	Level II

Yelland et al. [72] [prolotherapy]	RCT w/ two-by-two factorial design, triple blinded for inj. status, and single blinded for exercise status $n = 110$ 28 had repeated prolotherapy and exercise 26 had prolotherapy and normal activity 27 had saline and exercise 29 had saline and normal activity Injs. into tender lumbo-pelvic ligaments and randomized to perform either flexion/extension exercises or normal activity over 6 mos.	VAS and RMDQ. F/u at 2.5, 4, 6, 12, and 24 mos.	Chronic nonspecific low back pain	The primary guide for inj. sites was tenderness in ligaments and broad tendinous attachments (entheses) of the lumbosacral spine and pelvic girdle, w/ consideration of the patterns of local and referred pain. Injs. were performed through an anesthetized wheal of skin over each tender site Approximately 3 ml solution was infiltrated at each site (mean 7.3) and a maximum of ten sites treated at each visit If no improvement was noted by the fifth session, the deeper interosseous sacroiliac ligaments on the affected side or sides were also treated Injs. occurred every 2 wks. until six treatments. At 4 and 6 mos. were repeated if partial response. Injs. repeated from 6 to 12 mos. as needed. Mean of 7.1 treatments total Prolotherapy composition: 20% glucose/0.2% lignocaine	Ligament injs., w/ exercises and w/ normal activity, resulted in significant and sustained reductions in pain and disability throughout the trial, but no attributable effect was found for prolotherapy injs. over saline injs. or for exercises over normal activity At 12 mos., the proportions achieving >50% reduction in pain from baseline by inj. group were glucose-lignocaine (0.46) versus saline (0.36). By activity group these proportions were exercise (0.41) versus normal activity (0.39). Corresponding proportions for >50% reduction in disability were glucose-lignocaine (0.42) versus saline (0.36) and exercise (0.36) versus normal activity (0.38)	There were no between group differences in any of the above measures In chronic nonspecific low back pain, significant and sustained reductions in pain and disability occur w/ ligament injs., irrespective of the solution injected or the concurrent use of exercises	Level II Limited by lack of significant differences found among groups and lack of control group

Abbreviations: *RCT* randomized controlled trial

the disease pathology one is attempting to treat. For instance, a treatment might fail in an individual patient and have success in another based on the pathology of the patient and the target of the injectate. More RCTs would hopefully define both the optimal patient selection criteria and the ideal injectate target.

Overall Levels of Evidence

When reviewing the available literature, it is important to objectively determine the evidence level that can be drawn from the authors' conclusions. It is crucial to define this evidence level prior to adopting the study outcomes into clinical practice. In order to systematically grade the evidence, Manchikanti et al. have developed an interventional specific pain management instrument used in assessing the methodological quality of trials. Randomized controlled trials are often considered the gold standard and superior evidence compared to studies without randomization and/or without controls. Case reports and observational clinical experiences or reports of expert committees are determined to be the lowest level of evidence. This qualified modified approach (Table 7.7) to grading allows us to define the level of evidence for a specific treatment [73]. However, it remains important to remember the specific patient population treated, the exact injectate utilized, and the overall magnitude of results achieved by each study. By utilizing this qualified modified approach to grading, we are better able to categorize the evidence.

Table 7.7 The qualified modified instrument developed by Manchikanti et al. in assessing the methodological quality of trials and grading the overall scientific evidence in interventional specific pain management [73]

Level I	*Strong*	Two or more relevant high-quality RCTs for effectiveness or four or more relevant high-quality observational studies or large case series for assessment of preventive measures, adverse, consequences, and effectiveness of other measures
Level II	*Moderate*	At least one relevant high-quality RCT or multiple relevant moderate- or low-quality RCTs or at least two high-quality relevant observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures
Level III	*Fair*	At least one relevant high-quality nonrandomized trial or observational study with multiple moderate- or low-quality observation studies or at least one high-quality relevant observation study or large case series for assessment of preventative measures, adverse consequences, and effectiveness of other measures
Level IV	*Limited*	Multiple moderate- or low-quality relevant observational studies or moderate-quality observation studies or large case series for assessment of preventative measures, adverse consequences, and effectiveness of other measures
Level V	*Consensus based*	Opinion or consensus of a large group of clinicians for effectiveness as well as to assess preventive measures, adverse consequences, effectiveness of other measures, or single case reports

Limitations of Current Studies and Future Implications

There are several common pitfalls when analyzing regenerative medicine trials. In terms of injectate (whether stem cells, PRP, viscosupplementation, or prolotherapy), there is often not a defined common mixture or recipe. With each injectate the exact effective dose is vital, and each clinician should strive to achieve what is considered the gold standard formula. Further studies should strictly define and list the active dose of the injectate utilized. Although in certain cases the injectate cannot be standardized, for instance, where the injectate is partially derived from the patient (PRP, stem cells), a dose-response relationship should be developed. Furthermore, a combination of regenerative medicine substances should be trialed for greatest benefit. With many pain trials, a control group is essential as often seen some pain may heal with time independent of treatment. In addition, the construct of a control or sham is significant as any injectate or needling may provide some hidden benefit on its own.

The selection criteria in spine pain studies are essential to ensure that the patient has the pathology the clinician is attempting to treat. Poor selection can lead to poor results, as some patients may not have the specific disease that the intervention was designed to treat. Furthermore, injection technique is crucial to ensure the injectate reaches the precise target. Attention must be placed on the scales used to measure a positive result. Regarding pain, function, and quality of life scales it is important that a statistically significant difference makes for a clinical impact on the patient. Lastly, most studies focus on the lumbar spine likely secondary to a lower perceived risk. Although these results have the possibility to be generalized, more data and controlled studies are needed for the thoracic and cervical spine to demonstrate efficacy as well as define a risk profile.

Overall regenerative medicine for the spine appears relatively safe with few side effects or adverse reactions reported from the injectate alone. Prolotherapy, viscosupplementation, and PRP can be used with few risks. Compared to current routine treatments of local anesthetics and steroids, these regenerative treatments may have a superior safety profile with most adverse events coming from the injection technique itself. For stem cells, the safety data is also strong, but longer time frame studies are needed. Most clinical studies have not followed patients for enough time to evaluate long-term safety prognosis. One case report describes a 66-year-old male that, in hopes of curing his deficits from an ischemic stroke, traveled to three separate countries for infusions of mesenchymal, embryonic, and fetal neural stem cells into his spine. He was later found to have a spinal tumor that resulted from the intrathecally introduced exogenous stem cells [74]. Although the pluripotent stem cells this patient received are of a different cell type than those used primarily in regenerative medicine for joint and spine pain, this exceptionally rare and unfortunate case serves as a cautionary tale for possible unforeseen risks.

Regulation Concerns

Currently much of the field of regenerative medicine is regulated in the United States under section 361 by the Federal Drug Administration (FDA). Section 361 of the Public Health Service Act gives the FDA authority to make and enforce regulations

if the substance meets certain specifications, is minimally manipulated, is intended for homologous use, is for autologous use, and does not involve combination of the cells or tissues with another article except for water, crystalloids, or a sterilizing, preserving, or storage. Products that do not meet these criteria fall under Section 351 and these products are to be regulated as biologicals. This includes any virus, serum, antitoxin, vaccine, blood component or derivative, allergenic product, or analogous product that is used in the medical care of patients. 351 products are either more than minimally manipulated or used in a nonhomologous manner (different from original function). To summarize, 351 products are defined as a biologic drug and require complete FDA review, including premarket approval and clearance before the biologic drug can be legally marketed. Thus, the average time to market for substances labeled under Section 351 is around 10 years costing millions of dollars similar to the requirements of more traditional chemical drug products. Substances labeled as 351 products fall under the higher regulation and therefore may currently be unattainable for routine clinical use. To the contrary, most of the regenerative medicine substances discussed fall under Section 361 making them easily accessible. One of the substances in a gray area is adipose stem cells. After harvesting the adipose stem cells, preparation requires enzymatic dissociation of the tissue. This would suggest more than minimal manipulation and classify these adipose stem cells as a biologic drug under Section 351 [75]. With advancements in regenerative medicine, it is crucial to understand and follow the evolving regulations set forth.

Future Directions

New technology and advances should allow for better efficacy of regenerative medicine. Currently 3D printing utilizing bio-ink materials creates the ability to provide an optimal artificial extracellular environment to cells which allows for ideal adhesion, proliferation, and differentiation. Cells can now be encapsulated with this 3D printed structure with high viability. Important cell building blocks can be incorporated into this matrix [76]. Furthermore, studies have analyzed the use of exosomes which are extracellular vesicles that carry microRNA, proteins, and other molecules that work to mediate biologic function through gene regulation and intercellular communication. MSC exosomes have in theory the ability to mediate functional recovery by upregulating and promoting repair utilizing the patient's own intact cells [77].

Conclusion

Traditional pain management treatments target individual pain generators with the main goal of eliminating or masking pain through interrupting the transmission of painful signals. In this approach it is essential to isolate the activated nerves. Similarly, due to this complex network of possible pain generators, there are several

targets where regenerative medicine can prove to be an effective treatment. With regenerative medicine, the goal is to create a favorable environment in which the body can jumpstart the healing cascade, promote repair, and hence revitalize itself. Consequently, it may be important to view the entire spine in a holistic approach. Individually deactivating painful nerves may control pain signals, but will not improve the original cause of the pain. Idealistically, through regenerative medicine, the etiology of the pain can be corrected, and pain relief will naturally follow and sustain.

Furthermore, we must use caution with the term regenerative medicine, as the term "regenerative" may not apply to all treatments and may not accurately portray the actual science on a cellular level. While pain and function may improve, this does not necessarily prove that anything has indeed been physically "regenerated." The pain signal may resolve, but the fundamental pathology itself may remain.

As many of these interventions remain at the investigational level, more quality long-term, randomized, controlled human trials are required if these promising treatments are to become evidence-based medicine and the standard of care in everyday clinical practice. While there is a substantial amount of data on lumbar spine utilization, there is a paucity of studies analyzing intervention at the thoracic and cervical level. As regenerative medicine is a relatively new field with constantly developing technology and biologics, clinicians must continue to judiciously evaluate the evidence. With new evolving therapies, it is vital to remember the first priority remains to do no harm. Overall, due to an increase in promising evidence (Table 7.8) and a relatively good safety profile, regenerative medicine remains an important tool in the physician's armamentarium to trial on a case-by-case basis: especially (even more so) when routine medical care fails to provide acceptable results. However, at this point regenerative medicine for spinal pain remains a hopefully optimistic treatment to be perfected in the future.

Table 7.8 A summary of the overall level of evidence for the listed regenerative medicine treatments and each specific pain syndrome targeted

Evidence level for regenerative medicine based on reviewed studies				
	Prolotherapy	PRP	Hyaluronic acid	Stem cells
IVD-mediated pain	Level IV	Level II	Level V	Level III
Radicular pain	Level IV Level II (at 2 weeks)	Level IV	x	Level II (in discectomy patients)
Facet joint pain	Level IV	Level II	Level II	x
SI joint pain	Level II	Level II	Level IV	x
Musculature mediated	x	Level IV	x	x
Ligament mediated	Level II	x	x	x

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