Current State for Clinical Use of Stem Cells and Platelet-Rich Plasma

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8.1 Introduction

Innovative biologic therapies continue to evolve for the treatment of orthopedic injuries. Platelet-rich plasma (PRP) and stem cells are at the forefront of these innovations designed to enhance the repair of tissues with high healing potential or augment the repair of tissues with limited healing potential and vascularity such as tendons, ligaments, and cartilage. The multipotency of these cells and their ability to modulate cellular signaling pathways provide promising therapeutic options, where traditional conservative or operative therapies have failed to achieve success. Basic science research has paved the way and affirmed proof of concept for utilizing these compounds as inflammatory regulators and biologic scaffolds for cellular maturation. But, initial clinical results, limited in number and power, have not been as convincing. Large-scale clinical trials with close follow-up are needed to clarify indications, dosing, cellular composition, safety, and overall efficacy.

8.1.1 Platelet-Rich Plasma

Platelet-rich plasma (PRP) is a supraphysiologic collection of platelets derived from centrifuged autologous blood that contains a heterogeneous milieu of growth factors, interleukins, and cytokines important for cell proliferation, differentiation, neovascularization, and signaling [1, 2]. Most notably, insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), vascular endothe-

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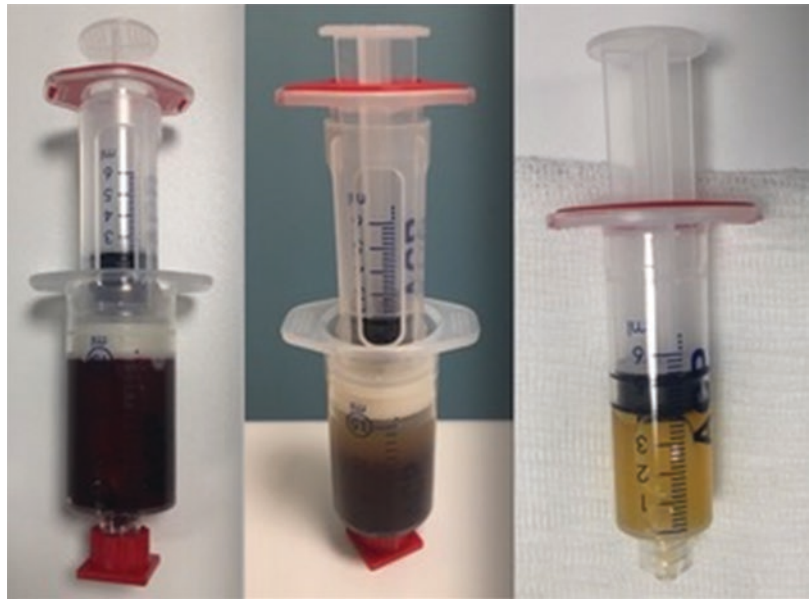

Fig. 8.1 Clinical images depicting the progression from peripheral blood draw to centrifuged specimen resulting in the extracted plasma product to be used for treatment. (From *Left* to *Right*) Peripheral blood draw. Centrifuged specimen. Extracted Plasma Product. Acknowledge Arthrex, The Double Syringe Autologous Conditioned Plasma (ACP) System

lial growth factor (VEGF), fibroblast growth factor (FGF), and transforming growth factor (TGF) all exist in differing concentrations within PRP [3]. These aforementioned growth factors have proven to be effective in maintaining cartilage integrity, increasing cell proliferation, promoting chondrocyte differentiation, and inducing angiogenesis [4]. Furthermore, the small molecule contents of PRP assist in recruiting mesenchymal stem cells and fibroblasts to the injury site [5]. Platelet-rich plasma is typically harvested from a peripheral blood draw, centrifuged down to separate components, and then extracted from the remaining fluid layers (Fig. 8.1).

Levels of leukocytes within PRP may positively or negatively affect the repair process [6]. The greater concentration of monocytes and neutrophils in "leukocyte-rich" PRP has been associated with increased levels of interleukin-1 and tumor necrosis factor-alpha, both of which are inflammatory cytokines. It is important to classify the leukocyte content of PRP because not all preparations are created equal. Depending on timing of collection and preparation method, leukocyte content varies significantly even within a single subject [7]. Clinical studies have demonstrated the advantage of "leukocyte poor" PRP compared to "leukocyte-rich" PRP for tendon healing and the treatment of osteoarthritis [6, 8]. Overall, the ideal concentrations of the numerous growth factors, cytokines, and interleukins within PRP have yet to be determined.

8.1.2 Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) were first described as a lineage of adult stem cells that have multipotent potential to differentiate into bone, cartilage, tendon, ligament, muscle, or other forms of connective tissue based on local environmental signaling and genetic potential [9, 10]. These stem cells differ from embryonic stem cells in that they are not pluripotent and cannot undergo transformation from one germ cell layer to another. Minimal criteria defined by the International Society for Cellular Therapy dictates that a MSC must (1) be plastic adherent; (2) express CD105, CD73, and CD90 while lacking CD45, CD34, CD14 or CD11b, CD79 alpha or CD19, and HLA-DR surface molecules; and (3) differentiate into osteoblasts, adipocytes, and chondroblasts in vitro [11]. Adult MSCs are typically harvested in one of two ways. The most common source with the highest yield is iliac crest bone marrow aspirate [12]. Harvest site pain and possibility for infection are potential complications. More recently, adipose-derived MSCs from liposuction tissue have been described as an alternative [13]. Furthermore, advancements in arthroscopic procedures of the shoulder and knee now allow for MSC harvest from muscle, tendon, ligaments, synovia, and bursa [14]. But, the exact cellular characteristics, differentiation potential, and variables with

regard to preparation of the aforementioned tissues limit clinical application without further investigation and randomized trials.

8.2 Application of PRP and Mesenchymal Stem Cells

There is a great deal of preclinical and clinical research focus concerning different techniques for delivery and location of delivery to optimize treatment protocols for various musculoskeletal conditions. The aim of many of these studies has focused on the treatment of rotator cuff pathology because it provides an excellent model to study the efficacy of biologics given the limited blood supply, intra-articular location of the rotator cuff, and tension often required to repair the tendon back down to the footprint. As such, augmentation of rotator cuff repairs with patches has evolved as a treatment option with improved clinical outcomes compared to non-augmented repairs [15, 16]. Patches act as scaffolds providing the structural framework for delivery of stem cells, matrix proteins, and growth factors. Current constructs are degradable and nondegradable, based on xenogeneic or allogeneic extracellular matrix (ECM).

At the current time, the most efficacious patch strategy and long-term safety profile have yet to be determined. Nondegradable scaffolds provide permanent mechanical support for healing; however, tissue compatibility can be of concern [17]. Material options include polycarbonate polyurethane, polytetrafluoroethylene, and polyester. To promote tissue ingrowth and incorporation with native tissue, these polymers are typically manufactured as a mesh-like material. Loss of mechanical integrity over time, chronic inflammation, and risk of infection must be considered despite favorable short-term outcomes in rotator cuff augmentation [18, 19]. ECM-based scaffolds, in contrast, provide temporary mechanical support to facilitate the healing response. These collagen-based constructs are extracted from porcine intestinal mucosa, porcine dermis, human fascia, or human dermis and are FDA approved and commercially available [17]. Concerns revolve around poor suture retention and limitations in mechanical properties in vivo, despite favorable results in animal models [20–22]. In addition, trace DNA and cellular content may lead to disease transmission and immune rejection [23]. Degradable synthetic scaffolds are also in development. These constructs also provide transient support for biologics, are less costly than ECM-based scaffolds, and carry no risk of disease transmission [24]. These scaffolds are derived from polyesters including poly-L-lactic acid, poly lactic-*co*-glycolic acid, polycaprolactone, and polydioxanone, which can be manufactured into sheets or patterned similar to collagen fibrils [25, 26]. Persistent degradation products and the hydrophobic nature of these materials impeding cell seeding have limited success during clinical application [25].

Clinical data supporting use for rotator cuff augmentation in humans is limited and industry-supported studies must be interpreted accordingly. Badhe et al. have highlighted significant functional improvements after augmented rotator cuff repair [15]. This prospective case series of 10 patients evaluated the clinical, ultrasound, and magnetic resonance imaging outcome 4.5 years after treatment of massive rotator cuff tears with porcine dermal collagen tendon augmentation grafting. Average constant scores improved from 41 preoperatively to 62 at final follow-up while pain and range of motion were significantly improved following surgery. Average graft patency on MRI was 80% at the final time point [15]. In contrast, Soler et al. demonstrated recurrent rotator cuff tear in all patients treated with porcine dermal collagen augmentation for massive tears. In their small cases series, graft failure was noted in all patients 3–6 months after repair [27]. Similarly, Iannotti et al. recommended against using porcine intestinal submucosa for augmentation of large and massive rotator cuff tears. In their randomized controlled trial of 30 patients, postoperative functional scores and rate of tendon-healing were not improved compared to tears repaired without augmentation [28].

Massive and irreparable rotator cuff tears are challenging because of the nature of the injured tissue and the inability to directly repair the tendon. New surgical techniques more effectively manage these injuries but improvements can still be made [29]. Scaffolds may play an important role in the treatment of these tears in the future. Despite mixed clinical results in the current literature, there is still concern over the potential adverse effects of synthetic breakdown products

[30]. Toxicities vary between polymers and data related to the shoulder at this time do not exist. Future studies aim to compare commercially available products in the long term in order to elucidate the true effect of breakdown products in humans.

8.3 Clinical Use of Platelet-Rich Plasma and Stem Cells

PRP and MSCs are widely used in both the operative and conservative treatment of soft tissue and cartilage pathology in orthopedic medicine. There is a growing body of literature detailing the basic science and cellular biology of PRPs and MSCs but the transition to clinical application has not been well defined. Multiple high-level studies evaluating the efficacy and recommendations for the clinical use of PRP and MSCs demonstrate polarized results with respect to patient functional outcomes, pain relief, and biologic regenerative augmentation. But, the current body of research does consistently demonstrate the safety profile and minimal side effects. PRP and MSCs have experienced the greatest utilization in the treatment of athletic injuries in sports medicine.

8.3.1 Treatment of Soft Tissue Injuries: Platelet-Rich Plasma

The possible indications for PRP as a therapeutic option for treating soft tissue injuries continue to expand. Injuries to the rotator cuff, ACL, meniscus, patellar tendon, Achilles tendon, and radial and ulnar epicondylitis are the most frequently documented applications of PRP in sports medicine. Less reported uses in sports medicine include the management of hamstring and turf-toe injuries [31, 32].

8.3.1.1 Rotator Cuff

PRP promotes healing on a cellular level in rotator cuff tissue by inhibiting the inflammatory response, protecting against oxidative stress that could lead to cellular apoptosis, and stimulating regenerative growth factor release leading to angiogenesis and tendon repair [33–35]. Clinically, PRP has been used in the rotator cuff as a nonoperative treatment modality and as an augmentation during operative management.

PRP has been used primarily as a subacromial injection in conservative management of rotator cuff pathology. Randomized controlled studies comparing PRP with placebo or corticosteroid injection show early improvement in pain relief and functional outcome scores that did not persist beyond 6-month follow-up [36, 37]. PRP injection may be of use in patients where corticosteroid injections have failed to provide pain relief.

Arthroscopic rotator cuff repair demonstrates good outcomes with smaller and more acute patterns. In massive rotator cuff tears known to have a high rate of failure of arthroscopic repair or those that exhibit limited healing potential, PRP has been employed as an augment to surgical intervention in an effort to promote soft tissue healing and improve patient outcomes. But, results from multiple Level 1 trials show limited effect on tissue healing, retear rates, and tear propagation with the addition of PRP to arthroscopic repair of rotator cuff injuries [38–47]. Inhomogeneous dosing, concentration, content, and site of application of PRP combined with lack of long-term follow-up limit the clinical applications of these studies. A recently performed meta-analysis did not show any differences in overall gain in outcome scores or retear rates between patients treated with and without PRP supplementation during arthroscopic rotator cuff repair [48].

8.3.1.2 ACL

In basic science and animal models, PRP stimulates release of growth factors that promote angiogenesis within the graft, graft maturation and remodeling, and ACL graft incorporation at the graft-bone interface [49–53].

There are no studies that have shown differences in patient reported outcomes, activity level, or complications after perioperative PRP administration regardless of graft type. Graft-bone interface healing and graft tunnel widening were not significantly different between patients that received supplemental PRP at the time of ACL reconstruction versus those who did not. One systematic review reported a possible beneficial effect on graft maturation and remodeling of up to 20–30% on average, but there was substantial variability between studies [54]. The most bene-

ficial effect of PRP with respect to ACL reconstruction is seen with application at the harvest site of a patellar tendon graft. Gapping of the patellar tendon harvest site was significantly lower, tissue regeneration was significantly higher, and patient outcome scores were significantly higher with PRP administration at the harvest site of a bone-tendon-bone graft [55–57].

8.3.1.3 Tendinopathy

Tendinopathy incorporates a range of injuries referring to a chronic and progressive degeneration of tendinous tissue marked by loss of normal tissue architecture, microtrauma, poor healing response without evidence of acute inflammation, and mucoid, lipoid, myxomatous, or hyaline degeneration [58]. Clinical presentations vary from asymptomatic patients to debilitating pain and disability that can lead to prolonged absences from athletic participation and competition. Basic science research suggests that PRP directly promotes tendon stem cell differentiation from irregularly shaped and disorganized cells (Fig. 8.2a) into more organized and elongated cells (Fig. 8.2b, C) that express less nucleostemin consistent with mature tenocytes (Fig. 8.2d–f). Furthermore, these cells were capable of further tenocyte proliferation and collagen deposition (Fig. 8.3) [59]. Clinical trials have studied the effects of PRP injection as a primary treatment or augmentation of current therapies for patellar tendinopathy, Achilles tendinosis, and lateral epicondylitis [60].

Patellar Tendon

Patellar tendinopathy affects athletes across a wide array of sports due to the high extension forces exerted on the knee during jumping, running, kicking, and cutting. Current first-line therapies for treating patellar tendinopathy are conservative in nature. More recently, PRP is being utilized in patients that have failed traditional conservative

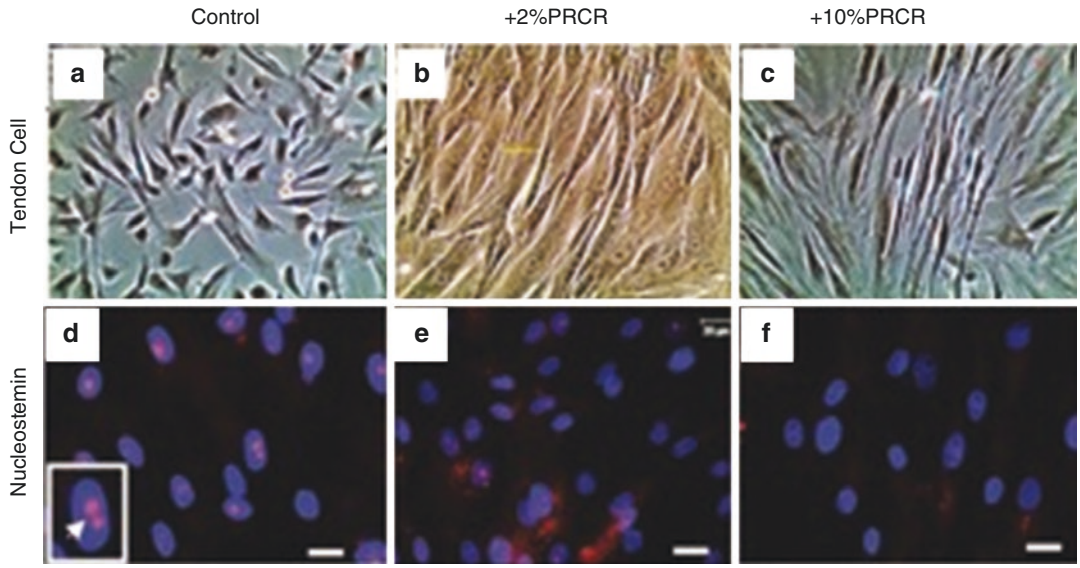

Fig. 8.2 The effect of platelet-rich plasma-clot releasate (PRCR) treatment on tendon stem/progenitor cells (TSCs). (**a**) TSCs in culture medium consisting of Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum (Control); (**b**) TSCs in culture medium with addition of 2% PRCR (2%PRCR); and (**c**) TSCs in culture medium with addition of 10% PRCR (10%PRCR). As seen, with increasing PRCR dosage, TSCs changed from an irregular shape to a well-spread and highly elongated shape. The cell size also markedly increased. (**d–f**) Expression of nucleostemin by TSCs in control culture, with 2% PRCR and 10% PRCR treatments, respectively. *Inset* in (**d**) shows an enlarged view of expressed nucleostemin in *pink* (*arrow*). With increasing PRCR dosage, fewer cells expressed nucleostemin, indicating that TSCs had undergone differentiation. Reproduced with permission of Zhang, J. & Wang, J. H. 2010. Platelet-rich plasma releasate promotes differentiation of tendon stem cells into active tenocytes. *Am J Sports Med,* 38, 2477-86

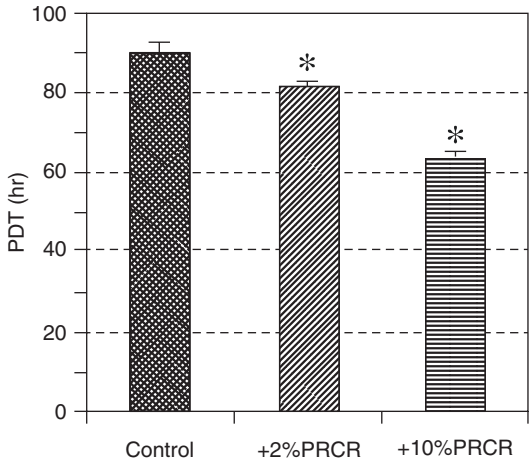

Fig. 8.3 The effect of platelet-rich plasma-clot releasate (PRCR) treatment on cell proliferation. With increasing PRCR dosage from 0 (i.e., control culture) to 2 to 10%, cellular population doubling time decreased, indicating that PRCR treatment stimulated tendon stem/progenitor cells to enhance proliferation rate in a dose-dependent manner (*P<0.05). Reproduced with permission of Zhang, J. & Wang, J. H. 2010. Platelet-rich plasma releasate promotes differentiation of tendon stem cells into active tenocytes. *Am J Sports Med,* 38, 2477-86

measures in an effort to dampen inflammation, alleviate pain, and instigate tendon regeneration and repair. A double-blind randomized clinical trial comparing eccentric strengthening exercises in combination with PRP or dry needling found an early improvement in clinical outcomes and pain relief with PRP injection that dissipated beyond 12 weeks [61]. A systematic review of eleven studies reported the beneficial effects of PRP injection for treating patellar tendinopathy to be inconclusive and inconsistent in comparative studies [62]. Overall, adverse outcomes or complications after PRP injection are rare [63] but the superiority of PRP injection for treating patellar tendinopathy has yet to be demonstrated in clinical trials.

Achilles Tendon

Achilles tendinosis is a chronic mucoid degeneration of the Achilles tendon most often due to overuse and repetitive injury. The abnormal cellular architecture and relatively poor vascularity greatly predispose affected individuals to acute tendon rupture. PRP injection is thought to promote tissue remodeling and angiogenesis in the degenerated Achilles tendon. But, in a double-blind randomized controlled trial of 54 patients with 1-year follow-up, no difference was found in functional outcome scores, pain relief, or neovascularization of tendon tissue with PRP compared to placebo injection with saline [64, 65]. Even after acute tendon rupture, PRP administration at the time of surgical repair has not been proven efficacious [66]. Again, the beneficial use of PRP for treating Achilles tendon pathology has not been verified in clinical trials and continues to be no more superior to placebo control.

Lateral Epicondylitis

Lateral epicondylitis is chronic tendinopathy of the common extensor tendon of the forearm, more specifically the extensor carpi radialis brevis (ECRB) that is more pronounced in the fourth and fifth decades of life due to an overuse scenario. Consistent with other tendinopathies, it is hallmarked by hyaline degeneration, abnormal vascularity, and tissue microtrauma without signs of acute inflammation. Treatment for lateral epicondylitis is primarily conservative with approximately 95% success rate. In refractory cases, surgical intervention to release the ECRB tendon can be utilized after failure of conservative treatment. In these refractory cases, clinicians have attempted treatment with PRP or autologous whole blood injections with some success and equivalent results between the two therapies after 6 weeks [67]. One multicenter, double-blinded, randomized controlled trial reported increased pain relief and diminished elbow tenderness at 24 weeks suggesting that PRP may have beneficial long-term effects for treating lateral epicondylitis compared to steroid [68].

There is ample basic science research supporting the use of PRP to modulate inflammation and stimulate tissue healing in the laboratory. But, randomized controlled clinical trials have not demonstrated significant results to justify regular clinical application. The optimal timing of administration, number of administrations, ideal concentrations, and leukocyte content has also not been delineated.

8.3.2 Treatment of Cartilage Defects and Osteoarthritis: Platelet-Rich Plasma

Osteoarthritis and superficial articular defects within the joints of the lower extremity continue to debilitate both the athletic and aging population as there are no proven therapies for completely restoring cartilage and congruity. Focal defects sustained during injury that measure greater than 15 mm in diameter may progress to global arthritis within the joint if left untreated. Traditionally, microfracture has been performed without biologic augmentation to treat these small focal cartilage defects measuring 2–4 cm by stimulating underlying bone marrow stem cells to regenerate cartilage within the lesion. But these mesenchymal marrow stem cells are unable to form physiologic hyaline cartilage within the defect and instead mature primarily into fibrocartilage. Newer biologic agents are being investigated as a potential therapy to stimulate hyaline cartilage regeneration that exhibits mechanical properties and longevity more similar to native physiology. Basic science research and animal studies have demonstrated promising initial results in the ability of PRP to upregulate chondrocyte proliferation, enhance chondrocyte differentiation, promote growth factor release, and increase molecular signaling pathways to limit inflammation and create an environment for cartilage healing [69–72].

8.3.2.1 Focal Articular Cartilage Defects

Treatment of isolated focal cartilage defects in the lower extremity solely with PRP is not well described. More frequently, PRP has been utilized intra-operatively as an adjunct to bone marrow stimulation techniques or in combination with bone marrow aspirates and cells. In vitro studies show PRP as a promising treatment and adjunct to traditional management of focal cartilage injuries due to its (1) anabolic effect on chondrocytes, mesenchymal stem cells, and synoviocytes; (2) action as a cellular scaffold for clot formation and cartilage regeneration [73]. Initial clinical research has shown a limited ability of PRP to decrease pain after surgical treatment of focal cartilage defects of the knee and ankle [74–80]. But, long-term follow-up and reported outcomes including functional scores, pain, and mechanical and radiographic properties of the repaired tissue have not been completed. Of note, no side effects or complications from PRP administration have been reported thus confirming the safety profile.

8.3.2.2 Osteoarthritis

Osteoarthritis affects an ever-increasing proportion of the population causing pain and debilitation that leads to increased medical care costs and financial burden on patients and the healthcare system at large. Conservative therapies such as physical therapy, NSAIDs, and lubricating injections have been prescribed to help slow the progression of the disease and limit pain. PRP is being investigated as a conservative treatment aimed at alleviating the symptoms of osteoarthritis and halting disease progression or possibly even reversing cartilage destruction. Basic science studies confirm PRP's ability to decrease inflammation, leading to increased function and better symptomatic management [81, 82]. High-level clinical trials comparing hyaluronic acid (HLA) injections, placebo (saline), and PRP document PRP's ability to decrease pain and increase functional outcome scores in patients suffering from arthritis [83, 84]. The beneficial effects of PRP are even more pronounced and longer lasting in younger patients and those suffering from more mild degenerative changes [85]. Systematic review of the published clinical trials, case reports, and cohort studies confirms superior results with intra-articular PRP injections compared to HLA and placebo for the treatment of osteoarthritis (Table 8.1) [73, 86–89]. Overall, PRP demonstrates significant improvement in pain and functional outcomes. Therapy appears to be well tolerated without side effects or complications. More research still needs to be performed regarding optimal timing of PRP administration, recommended number of injections, and ideal PRP content.

Table 8.1 Summary of clinical studies of platelet-rich plasma for treatment of degenerative cartilage lesions

Level of evidence	Patient number (age/range)	Intervention	Follow-up	Outcome	Adverse effects	References
Level IV	14 (18–87 years)	3 L-PRP injections every 4 weeks	12 m	Significant and linear improvement in KOOS.Pain reduced after movement and at rest	Modest pain persisting for days	[138]
Level IV	17 (30–70 years)	Single PRP injection	12 m	Pain decreased, whereas function improved. MRI showed no worsening in 12 of 15 knees	Unreported	[139]
Level IV	27 (18–81 years)	3 weekly L-PRP injections	6 m	Substantial pain reduction after 1st injection and further improved at 6 months. WOMAC improved	No	[140]
Level IV	40 (33–84 years)	3 weekly P-PRP injections	6 m	Pain and disability subscores were significantly reduced	Transient sensation of hip heaviness	[141]
Level IV	50 (32–60 years)	2 L-PRP injections every month	12 m	IKDC and KOOS improved; all returned to previous activities	Unreported	[142]
Level IV	91 (24–82 years)	3 injections of double-spun PRP activated by CaCl2 every 3 weeks	12 m, 24 m	Pain decreased and knee function improved, especially in younger patients at 12 months. The improvements decreased at 24 months, but still better than the basal evaluation	Mild pain persisting for days	[143], [144]
Level IV	261 (mean 48 years)	3 injections of CaCl2-activated P-PRP every 2 weeks	6 m	Significant differences in VAS, SF-36, WOMAC and Lequesne index	No	[145]
Level III	30 (36–76 years)	3 injections of double-spun PRP inactivated PRP or HA every 3 weeks	6 m	Both improved in IKDC, WOMAC and Lequesne index, but PRP exhibited better scores	Pain, swelling, but resolved in days	[146]
Level III	60 (61 years in HA, 64 years in PRP)	3 weekly injections of CaCl2-activated P-PRP or HA	5 w	33.4% patients in PRP group and 10% in HA achieved at least 40% pain reduction. Disability reduced more in PRP group than HA	Mild self-limiting pain and effusion in both groups	[147]
Level II	120 (19–77 years)	3 weekly L-PRP or HA injections	6 m	Better results in WOMAC and NRS in PRP than HA	Temporary mild worsening of pain	[148]

(*continued*)

Table 8.1 (continued)

Level of evidence	Patient number (age/range)	Intervention	Follow-up	Outcome	Adverse effects	References
Level II	150 (26–81 years)	3 injections double-spun PRP or HA every 2 weeks	6 m	Higher IKDC but lower VAS pain scores than HA, especially in younger patients	No	[84]
Level II	32 (18–60 years)	3 injections of CaCl2-activated P-PRP or HA every 2 weeks	7 m	Higher AOFAS but lower VAS pain scores than HA	Mild pain, but self-resolved	[149]
Level I	78 (33–80 years)	Single or twice leukocyte-filtered PRP injection, or single saline injection	6 m	WOMAC improved after PRP injection, whereas worsened after saline infiltration	Self-resolved nausea and dizziness	[150]
Level I	120 (31–90 years)	4 weekly injections of inactivated P-PRP or HA	6 m	Significantly better clinical outcome and lower WOMAC scores than HA	None observed	[83]
Level I	176 (41–74 years)	3 weekly injections of CaCl2-activated P-PRP or HA	6 m	14.1% more patients reduced pain at least 50% in PRP group, with a significant difference	Mild, evenly in 2 groups	[151]
Level I	96 (50–84 years)	3 injections of CaCl2-activated P-PRP every 2 weeks, or single HA injection	48 w	Significantly more efficient in reducing pain, stiffness and improving physical function than HA	Mild, evenly in 2 groups	[152]
Level I	109 (18–80 years)	3 weekly injections of double-spun PRP releasate after freezing or thawing and HA	12 m	No significant difference in all scores. Only a trend favoring PRP in patients with early OA	Mild pain and effusion	[153]

Reproduced with permission of Xie, X., Zhang, C. & Tuan, R. S. 2014. Biology of platelet-rich plasma and its clinical application in cartilage repair. *Arthritis Res Ther,* 16, 204

AOFAS American Orthopaedic Foot and Ankle Society, *HA* hyaluronic acid, *IKDC* International Knee Documentation Committee; Knee injury and Osteoarthritis Outcome Score, *L-PRP* leukocyte- and platelet-rich plasma, *m* months, *MRI* magnetic resonance imaging, *NRS* Numeric Scale, *P-PRP* pure platelet-rich plasma, *PRP* platelet-rich plasma, *SF* short form, *VAS* visual analogue scale, *w* weeks, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

8.3.3 Treatment of Soft Tissue Injuries: Mesenchymal Stem Cells

Human MSCs have been manipulated to differentiate into a tenogenic lineage and produce tendon and other soft tissues when exposed to the appropriate stimuli in culture [90]. The pluripotent potential of MSCs to repair damaged soft tissues by regenerating site-specific tissue based on local environmental exposure, mechanical loading, and cellular signaling makes them a strong candidate for biologic therapy.

8.3.3.1 Rotator Cuff

Research based on animal models comprises the majority of studies reporting on the use of MSCs for rotator cuff healing. Few clinical trials have been published and no Level I evidence exists examining the effects of MSCs on rotator cuff healing or repair augmentation. In a rabbit model, the application of MSCs to surgically created infraspinatus tears increased regeneration of more physiologic type I collagen fibers as opposed to type III collagen in the control and non-MSC groups. Increased fibrocartilage organization, Sharpey's fiber reconstitution, and deposition of type I collagen at the insertion of the infraspinatus tendons was also noted. These factors also coincided with higher mechanical strength of the regenerated rotator cuff tendon [91, 92]. Transduction of MSCs with certain additional growth or transcription factors, such as scleraxis and membrane type 1 matrix metalloproteinase, improves upon the ability of MSCs to augment the formation of fibrocartilage and increase mechanical properties of rotator cuff tendon tears at the tendon-bone interface [93, 94]. One clinical study reporting functional and radiographic outcomes of rotator cuff repair combined with application of MSCs has shown that MSCs are indeed safe but the true beneficial therapeutic effect remains to be clarified [95]. But this study was limited by lack of a control group for comparison. A case-control study reported that adjunctive injection of MSCs at the time of rotator cuff repair enhanced the healing rate and improved the quality of the repaired surface as determined by ultrasound and MRI at 10-year follow-up [96]. Preclinical studies regarding the role of MSCs in treating rotator cuff tendon injury is promising but the paucity of randomized controlled trials limits clinical indications for use.

8.3.3.2 Tendinopathy

Excessive mechanical stimuli during tendon overuse have been proposed as the leading mechanism of tendinopathy because it induces the production of cytokines, inflammatory prostaglandins, and matrix metalloproteinases as well as tendon cell apoptosis and chondroid metaplasia [58]. Equine veterinary literature serves as a well-established source for basic science and preclinical studies reporting efficacy of MSC application in tendinopathy [97]. Although autologous MSC treatment in thoroughbred racehorses for flexor digitorum superficialis tendinopathy has shown success, the successful translation to human clinical settings for the treatment of common tendinopathies, such as in the patellar tendon and Achilles tendon, has not been demonstrated.

8.3.3.3 Meniscus

Meniscal tears continue to plague both clinicians and patients alike due to a limited healing potential stemming from tenuous vascularity and nutrient supply. Inventive biomimetic materials demonstrate comparable mechanical properties to native meniscal tissue when combined with standard surgical repair techniques for meniscal tears [98]. The possibility of combining these constructs with stem cells could theoretically improve durability and integration of these scaffolds. MSCs offer a hopeful intervention for tissue healing and regeneration in the setting of acute tears and chronic pathology after failed conservative treatment. Preclinical research examining the effects of bone marrow-derived MSCs on meniscal injury in a rabbit model showed a higher proportion of healing with meniscus-like fibrocartilage as opposed to scarce fibrous tissue present in the control group [99]. More randomized controlled clinical trials are needed before widespread utilization can be recommended.

8.3.4 Treatment of Cartilage Defects and Osteoarthritis: Mesenchymal Stem Cells

Biologic therapy continues to evolve beyond the first marrow stimulation techniques to treat articular cartilage injuries and degeneration. But, completely effective and definitive restorative therapies for articular cartilage still elude physicians. Mesenchymal stem cells exhibit plausible possibilities to fill this therapeutic gap in the

management of both focal cartilage defects and global osteoarthritis.

8.3.4.1 Focal Articular Cartilage Defects

Microfracture remains as a standard surgical procedure for the treatment of focal articular cartilage defects by promoting the release of subchondral bone marrow stem cells into the lesion of interest. But, this reparative tissue histologically mirrors fibrocartilage as opposed to physiologic hyaline cartilage across joint surfaces. Updated MSC-based treatments beyond microfracture for focal cartilage defects gain interest as the potential for restoring native cartilage is favorable in preclinical studies. Animal models validate proof of concept for the application of MSCs for treating focal cartilage defects. In rabbit, porcine, and equine studies, not only was reparative tissue of MSC-treated defects more histologically similar to native articular cartilage, but some specimens demonstrated complete subchondral bony regeneration in larger defects [100–104]. Human application to the knee, patellofemoral joint, and talus prove to be safe and effective in terms of improving histologic quality of repaired tissues, subjective assessment of cartilage repair, and patient outcome scores [76, 77, 104–115]. Cultured MSCs and unmodified aspirate, used alone or in conjunction with other cartilage procedures (microfracture, autologous chondrocyte implantation, osteochondral autograft transfer) have emerged as a therapy with good chondrogenic and osteogenic potential [116]. As with most contemporary biologic agents, randomized controlled human clinical trials are needed to substantiate widespread usage.

8.3.4.2 Osteoarthritis

Inherently, focal cartilage defects entail a localized injury that can be addressed surgically with focused treatment within the lesion. Generalized joint osteoarthritis is challenging because the cartilage loss is frequently too excessive to address without arthroplasty. With the advent of injectable therapies, such as viscosupplementation, to help postpone surgery, research has attempted to evaluate the efficacy of injectable MSCs to address cartilage damage. Injectable MSCs for the treatment of cartilage defects in a porcine model demonstrated improved histologic and morphologic characteristics of the reparative tissue compared to saline and hyaluronic acid [117]. In a sample of 18 patients, injected MSCs for the treatment of knee osteoarthritis resulted in no complications, decreased pain, increased functional outcome scores, decreased lesion size, increased articular cartilage volume within the defect, and more hyaline-like regeneration on histologic examination [118]. Similar results have been reported in several other case series [119–122]. Even more encouraging is that these results have been confirmed at 24-month follow-up during second-look arthroscopy [123]. Although these studies report promising data, more research must be conducted to determine ideal cellular composition and patient-specific algorithms for treatment of osteoarthritis with MSCs.

8.4 Regulatory Challenges

There are numerous regulatory hurdles that challenge the widespread implementation and adoption of new advancements in the field of biologics [124]. In the United States, the U.S. Food and Drug Administration (FDA) is the regulatory body that oversees implementation of new medical technologies, including MSCs and PRP [124–127]. In Europe, the European Union (EU) and the European Medicines Agency (EMA), in addition to individual national agencies, oversee regulations governing biologic therapeutics [128, 129]. Medical progress dictates that the healthcare community strikes a delicate balance between the risk of stringent regulations that may stifle innovation and a lack of regulations that may jeopardize patient safety. However, it seems that the current state of stem cell and PRP regulation is inclined towards regulation [130].

In Europe, all stem cell-derived products and biologics can be subject to a dizzying array of regulations, including guidelines on marketing, production, and good clinical practice.

Furthermore, each nation must approve these therapies and the policies and procedures are not homogeneous across countries [128]. In fact, European Commission survey results indicated that clinicians and researchers perceived the European regulatory environment as extremely burdensome [128]. Academic institutions without the support of large pharmaceutical companies often have difficulty moving a potential biologic therapy through the numerous phases of regulatory approval. Much of the language in the varying regulations is ambiguous, and new product marketing authorizations have been somewhat stagnant. This has led to a call for more streamlined pathways to allow a more rapid and robust movement from the laboratory to the clinic.

Similarly, the US regulatory environment is complex. It is telling that large corporations have shied from entering the healthcare field in the United States due to the complex regulatory environment [131]. In terms of orthopedic therapies, biologic therapeutic products are divided into either low-risk (Section 361) or high-risk (Section 351) categories according to the Public Health Service Act. Many MSCs that could potentially be utilized for orthopedic use must follow the 351 pathway, subjecting them to additional inspection. Section 351 requires preclinical development including animal trials, phased clinical studies, and premarket FDA review. Ultimately, a Biologic License Application may be approved after animal, Phase I, Phase II, and Phase III studies. Currently, stem cells that are cultures, allograft cells, and cells obtained from adipose or placental cells are restricted under Section 351 guidelines [130].

Therapies classified under Section 361 are not required to undergo preclinical development testing and instead required to follow less stringent standards that are mostly aimed at preventing the spread or transmission of communicable disease. Examples of therapies that are currently regulated under Section 361 (low-risk) are bone marrow aspirate cells and PRP [130]. For therapies to meet criteria for the 361 pathway (low-risk, and therefore more easily employed in clinical practice), they must (1) require minimal manipulation during preparation, (2) be used homologously (same patient, similar site or purpose as its original origin), (3) must not be combined with other products, and (4) must show a lack of systemic effects. Perhaps the most profound effect of this tiered pathway in orthopedics relates to FDA regulations that prevent stem cells obtained in the operating room from being cultured, augmented, or further manipulated prior to re-implantation, in order to fall under Section 361 guidelines. They also cannot be extracted from one site and placed into another (e.g., adipose cells into the knee joint). Therefore, this limits intra-operative use to those cells that are collected intra-operatively, minimally manipulated, and injected back into the same type of tissue.

Similarly, the amount of analysis performed on the cells collected intra-operatively is limited, as the cells cannot be removed from the operating room prior to re-implantation [132]. As such, the resulting re-injections or re-implantations are inconsistent and the exact concentrations and types of cells and biologic factors are not usually known [9, 124]. This is important because the number of stem cells harvested can be technique dependent, age dependent, and affects clinical outcomes. Clinical results are therefore variable, and it is unknown how different concentrations and combinations of cells may affect outcomes, resulting in an unknown dose–response curve [124, 130, 132]. The regulatory burden is so high that many researchers and clinicians have ceased attempts to develop new technology and instead focus on working within their current confines. In fact, there have been few major advances in biologics and stem cells in musculoskeletal treatment since the approval of autologous chondrocyte implantation (ACI) two decades ago [124].

8.5 Future Directions

Fortunately, the use of bone marrow-derived MSCs and PRP hold significant promise in the future. The key will be to perform high-quality clinical and laboratory studies to further elucidate and define the most appropriate indications for treatment and to further understand the mech-

anisms by which MSCs are activated and directed into the desired pathway. In addition, the regulatory bodies that control these therapies will need to evolve so that fast-changing technology can be adopted more readily. For instance, Japan has created a new class of therapies termed "regenerative medicine products" by which new stem cell therapies can progress through an expedited approval system. South Korea and England have made similar changes [130].

Future research will need to determine the ideal method of preparation that will allow tissue-specific and injury-specific solutions. There is significant variability in the current body of literature on PRP, with limited adoption of PRP classification systems and poor reporting of PRP composition used. If determination of optimal PRP characteristics (growth factors, platelet concentration, leukocytes) is to occur, clinical studies will need to standardize the reporting of PRP contents so that clear and consistent comparisons can be made across trials. In fact, the results of clinical studies that do not control for platelet concentration and leukocyte presence should be interpreted with caution. Similarly, future studies will need to identify the ideal dosing, timing, and frequency of application for varying injuries, tissue types, and operative procedures, and all should report the PRP volume, composition, and platelet concentration utilized [132].

Similarly, there is significant potential for advancement in our understanding of bone marrow-derived MSCs. In particular, the optimal tissue environment for MSC implantation needs to be further studied. The mechanism of action is poorly understood, and future research will need to determine whether MSCs produce their effects through a paracrine mechanism, immunomodulation, or direct engraftment [124, 132, 133]. Additionally, research is being performed to improve recruitment of tissue-specific stem cells, develop serum-free media for MSC culture and expansion, allow identification of novel genetic markers and subsets of MSCs that may be specialized according to tissue types, and advance methods to obtain purified autograft perivascular MSCs. In addition to implantation of MSCs, it may be possible to identify factors that stimulate the release, recruitment, and activation of native stem cells [132, 134, 135]. Further unanswered questions include the presence of any sex-related differences, optimal method of administration, and how to minimize any immunogenicity-related problems such as graft-versus-host disease [136].

MSCs hold promise in the use of tendinopathy [60]. As ongoing and future research advances our understanding of tendinopathy basic science, the role of angiogenesis in tendon healing, and the link between histology and clinical findings, the use of MSCs will likely continue to play an increasing role in treatment of this common yet often recalcitrant pathology. Research has shown that areas with pathologic tendon have lower MSC concentrations, [133] and tendon usually has less healing potential than other tissues [137]. However, it is unknown whether this is due to a lower baseline MSC concentration in this patient population or whether it represents a depletion of the tissue's supply of MSCs. Regardless, augmenting these injured tissue beds could potentially improve the healing response. It remains to be seen what the optimal concentration of cells is, and what the optimal source of MSCs is in this type of setting (i.e., bone marrow-derived, adipose-derived, or tendon-derived) [132, 135]. As we further our understanding of the mechanism of effect, these details should also become more apparent. These questions underscore the importance of well-designed clinical studies with standardized reporting of MSC composition, harvesting technique, culturing technique, and final volume that is implanted, as well as the need for standardized clinical outcome reporting [124]. Tendon-specific imaging may allow for better outcomes tracking in the future. Studies have described the use of both MRI and ultrasound to quantify the healing throughout various stages of tendinopathy. It is possible that this technology would allow for improved tracking and assessment of tendinopathy after MSC treatment [132].

However, furthering the use of MSCs is not without significant challenges. For example, there is a relatively limited availability of MSCs available for harvest in host tissues. In most cases, they will need expansion prior to implantation.

Furthermore, the complexity of the regulatory system provides a significant barrier to new research and innovation. In the future, it may be possible to utilize other sources of stem cells such as induced pluripotent cells, embryonic stem cells, or other recently identified adult stem cell populations.

Conclusions

In summary, the use of PRP and MSCs in orthopedic surgery undoubtedly has a bright future. It is imperative that clinicians and scientists identify barriers to success and address them head on. The regulatory environment must improve and adapt to modern science if innovation is to continue. This will require the involvement and collaboration of practitioners across the world in their local and national regulatory bodies. Research should also focus on the utility of adjuncts such as scaffolds, which may improve the efficacy of the administered stem cells [137]. Furthermore, consistent reporting of the composition of biologic therapies used, the method of preparation and administration, timing, dosing, as well as the use of standardized protocols and collection and reporting of quantifiable objective and subjective outcomes is paramount to success and advancement of these potentially life-altering therapeutics. Similar to the development of modern arthroscopy, the use of PRP and MSCs have the potential to revolutionize the treatment of sports medicine injuries.

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