Chapter 12
Regenerative Medicine for the Knee

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Knee Osteoarthritis

The two joints within the knee that are susceptible to osteoarthritis (OA) are the tibiofemoral joint and the patellofemoral joint. The tibiofemoral joint consisting of the femur proximally and the tibia distally is the major weight-bearing joint of the two. The patellofemoral joint consists of the patella and the femur, more specifically the patellar groove of which the patella would glide through.

Knee osteoarthritis is the most common OA in the lower extremities. The severity of knee OA ranges from mild to severe and usually classified using X-rays. For this reason, many approaches to treating this major joint have been described. The American College of Rheumatology (ACR) recommends several non-pharmacological interventions like aerobic and resistance exercise, aquatic therapy, weight loss for those overweight, psychosocial intervention, lateral or medial wedged insoles for medial or lateral compartment OA, respectively, walking aids, thermal agents, Tai chi programs, acupuncture, and transcutaneous electrical stimulation [1]. Pharmacological treatment can also be recommended. The ACR strongly recommended in 2012 the use acetaminophen or paracetamol, oral or topical nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, and intra-articular glucocorticoids injections [1]. In one meta-analysis, Gregori et al. looked at several classes of medications that are now used to treat the condition which included a long list consisting of analgesics, antioxidants, bone-acting agents, NSAIDs, intra-articular injection medications such as hyaluronic acid (HA) and corticosteroids, symptomatic slow-acting drugs in osteoarthritis, and putative disease-modifying agents [2]. In the advent of systemic medication control and individuals wanting

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G. Cooper et al. (eds.), *Regenerative Medicine for Spine and Joint Pain*,
https://doi.org/10.1007/978-3-030-42771-9_12

to remain active and avoid surgery, regenerative medicine has been proven to be an option worth exploring.

The use of regenerative medicine in the knee has certainly been described in the literature, but strong evidence is still lacking. Though first described in 2008 to be used in the treatment of knee osteoarthritis, platelet-rich plasma (PRP) continues to have contradicting literature on its efficacy as a treatment modality. In 2017, Bennell et al. published a paper reviewing randomized control trials done between the years 2012 through 2017 [3]. Though, ultimately, the paper concludes that, due to methodological variability, much research have to be done before a true conclusion is to be made, it does report that there is evidence, though not strong, that PRP is promising in the treatment of knee osteoarthritis [3]. The evidence of the PRP being efficacious seems to be more promising in younger participants with less structural changes and also when put head to head with HA injections. In a meta-analysis done by Laudy et al., 10 RCTs which included 1069 subjects concluded that at 6-month follow-up, pain relief and improvement in function in subjects injected with PRP and those injected with HA were comparable. However, at 12-month follow-up, it appears that those who received PRP did significantly better than those who received HA [4]. Importantly, this paper concluded that there was no noted increase in adverse events with PRP when compared to HA and saline injections. In a systematic review, Xing et al. looked even closer at risks associated with PRP injections and also concluded that there was no increased risk with the proposed procedure [5].

Another regenerative medicine modality with "therapeutic potential" is stem cell therapy. Mesenchymal stem cells possess the theoretical potential to promote tissue growth and regeneration. In one prospective, single-blinded, placebo-controlled trial, individuals with bilateral knee OA were injected with bone marrow aspirate concentrate (BMAC) in one knee and saline in the other knee. There was significant pain relief with BMAC; however, there was no statistical significance in the difference of symptoms between the BMAC knee and placebo control knee [6]. A promising study done by Gobbi and Whyte showed significant improvement in pain and function in subjects who had HA injection + BMAC versus microfracture procedure [7]. Significant improvements in outcome scores were achieved in both treatment groups at 2 years ($P < 0.001$). In the microfracture group, 64% were classified as normal or nearly normal according to the International Knee Documentation Committee (IKDC) objective score at 2 years, compared with 100% of those treated with HA + BMAC ($P < 0.001$). Normal or nearly normal objective assessments in the microfracture group declined significantly after 5 years to 28% of patients ($P = 0.004$). All patients treated with HA + BMAC maintained improvement at 5 years according to IKDC subjective scores. Lysholm and IKDC subjective scores were similar between treatment groups at 5 years [7]. Several other similar studies were done with similar results; however, it is hard to give definitive recommendations as there is no standardized approach to BMAC preparation and injection technique, therefore making the evidence harder to correlate and apply. Another study that looked at the effect of peripheral blood stem cells (PBSC) and their effect on cartilage growth investigated histological effect of using them postoperatively

after arthroscopic subchondral drilling. Results showed that after arthroscopic subchondral drilling into grade 3 and 4 chondral lesions, postoperative intra-articular injections of autologous PBSC in combination with HA resulted in an improvement of the quality of articular cartilage repair over the same treatment without PBSC, as shown by histologic and MRI evaluation [8].

Prolotherapy is another modality with potential benefit in treating knee OA. A meta-analysis looked at the role of prolotherapy in knee pain, and it showed promising results in the treatment of knee osteoarthritis [9]. Studies used subjective scales such as the WOMAC that were used to assess posttreatment pain. Results showed that prolotherapy yielded higher score difference (decrease in pain and symptoms) when compared to the control group who performed exercise alone. Another study discussed in this meta-analysis showed that prolotherapy with exercise yielded a greater decrease in WOMAC score than placebo saline injection with exercise [9].

Tendinopathies

Bony structures in the knee serve as attachment sites for several tendons. These tendons include the quadriceps, patellar, popliteus, as well as distal hamstrings. Tendons are susceptible to multiple modes of injuries from acute or chronic tendinopathies to partial and complete ruptures. These injuries are quite often seen in not only the athletic setting, with an estimated 40–50% of athletes getting tendon injuries, but also in the aging population and in some occupational settings [10].

Similar to degenerative disease in the knee, different modalities for treating tendinopathies have been studied and include both interventional procedures and physical therapy and modalities. A focus on eccentric strengthening of the muscles to promote healing has been the standard of care when treating tendinopathies with physical therapy and exercise. Treating pain is accomplished by the use of oral analgesics, topicals to the area (more effective for superficial tendons), and more recently described interventional regenerative techniques.

The evidence for use of regenerative medicine in soft tissue injuries was found to be insufficient by a large Cochrane review performed by Moraes et al. [11]. The main reason is the lack of standardization of PRP and aspirate preparation. There has been literature on the composition of the injectate, most popularly stating that leukocyte-rich PRP is recommended for tendons, while leukocyte poor for intra-articular applications. The key components of leukocytes are neutrophils and monocytes, which may also release many bioactive factors and proteins. Neutrophils mainly release myeloperoxidase, bactericidal phagocytins, collagenase, gelatinase, and proteases. Monocytes secrete platelet-activating factor, TGF-β, VEGF, FGF, and EGF. Many of these factors have been shown to influence tendon healing [12]. One double-blinded randomized control trial looking at patellar tendinopathy compared concomitant ultrasound-guided dry needling with the injection of leukocyte-rich PRP (PRP group) versus dry needling alone (DN group), both groups receiving physical therapy adjunctively. Exercises consisted of eccentric strengthening routines

which are currently widely accepted for the treatment of tendinopathy. The Victorian Institute of Sports Assessment (VISA) score for patellar tendinopathy improved at 12 weeks significantly more in the PRP group, but this difference was not significant at 26 weeks. Of note, no adverse events were reported on either group [13].

Though the literature remains promising, there is a lot in the way of standardizing preparation and administration of PRP into the tendons of the knee. The majority of the literature looks at the patellar tendon, presented mostly in case series and smaller randomized control trials [14]. Further investigation is needed before definitive recommendations are given concerning PRP in musculoskeletal soft tissue, especially the surrounding knee tendons not mentioned in many studies. On the opposite side of the coin, it appears that knowing the proposed mechanism of leukocyte-rich PRP and the evidence strongly against any adverse events, it is a safe and reasonable option to use in the treatment of tendinopathy. Of the regenerative medicine modalities, PRP seems to be the most described in treating tendon injuries in the knee. Prolotherapy has been described in treating tendons in the ankle, such as the Achilles, and also in the shoulder, such as the rotator cuff. The literature on prolotherapy for the knee is more for treating intra-articular pathologies, namely, knee OA, as previously discussed.

Ligamentous Injuries

Common injuries that can cause significant pain and instability in the knees are ligamentous injuries. The more commonly discussed ligaments of the knee include the cruciate ligaments (ACL and PCL), medial collateral and lateral (fibular) collateral ligaments (MCL and LCL), as well as the medial patellofemoral ligament (MPFL). Injury to these structures includes sprains and complete or partial tears and can cause significant mechanical symptoms and subsequently pain. Treatment of such pathology includes both surgical and nonsurgical management. Most cases with severe instability, intractable pain, and failed conservative measures become surgical. However, in a clinically stable knee and also in a patient without intricate demand on the knee, nonoperative management is preferred. To date, the most common management would be physical rehabilitation to strengthen the secondary stabilizers of the knees which are dynamic muscles to compensate for the loss of the static ligament stabilization. Pain is managed similarly to the above pathologies with the use of oral analgesics and intra-articular injections of corticosteroids to reduce the local inflammatory effects of injury.

As previously mentioned, evidence is still lacking when it comes to the application of regenerative techniques with soft tissue injuries. Several studies observed the use of regenerative medicine (PRP, stem cells) as an adjunct to ACL reconstructive surgery. The earlier studies investigated the effect in animal models (rabbits) using adipose-derived regenerative cells (ADRC). Rabbits were divided into two groups, both receiving allograft ACLs; one group had the tissue coated with ADRC while the other group did not. Though histological patterns were improved and appeared to be more favorable

toward healing, the failure load was higher in the treated group. However, this was not statistically significant. It seemed that local administration of ADRCs promoted the early healing process at the tendon-bone junction, both histologically and mechanically, in a rabbit ACL reconstruction model [15]. With promising results in these animal model studies, further investigation was done on treating ACL injuries nonsurgical or surgical with allografts to determine whether it would enhance biological healing [16].

Though the literature is stronger for prolotherapy in knee OA and tendons involved in other joints, there is case study-level evidence for the use of prolotherapy in ACL injury. In one case study, an 18-year-old female skier suffered a complete rupture of her ACL and deferred surgical management. At 21 weeks post-injury, she was having pain with ambulation and was unable to negotiate stairs and had a 1 cm positive anterior drawer test. She agreed to and had seven prolotherapy sessions over 15 weeks and exercise program that started after her third injection. The patient showed improvement with walking on flat ground, which improved 4 weeks after initiation of prolotherapy. She was also able to ride a stationary bicycle for 30 minutes by week 12. By 15 weeks, the patient had no reported instability climbing and descending stairs, the anterior drawer test was negative, and MRI showed an intact ACL with fibrosis. Subsequently, she returned to full sport activity [17].

References

1. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 2012;64(4):465–74.
2. Gregori D, Rovati LC, Giacovelli G, Barbetta B, Azzolina D, Gualtieri F, et al. Association of pharmacological treatments with long-term pain control in patients with knee osteoarthritis. JAMA. 2018;320(24):2564–79.
3. Bennell KL, Hunter DJ, Paterson KL. Platelet-rich plasma for the management of hip and knee osteoarthritis. Curr Rheumatol Rep. 2017;19(5):24.
4. Laudy ABM, Bakker EWP, Rekers M, Moen MH. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. Br J Sports Med. 2015;49(10):657–72.
5. Xing D, Wang B, Zhang W, Yang Z, Hou Y, Chen Y, et al. Intra-articular platelet-rich plasma injections for knee osteoarthritis: an overview of systematic reviews and risk of bias considerations. Int J Rheum Dis. 2017;20(11):1612–30.
6. Shapiro SA, Kazmerchak SE, Heckman MG, Zubair AC, O'Connor MI. A prospective, single-blind, placebo-controlled trial of bone marrow aspirate concentrate for knee osteoarthritis. Am J Sports Med. 2017;45(1):82–90.
7. Gobbi A, Whyte GP. One-stage cartilage repair using a hyaluronic acid-based scaffold with activated bone marrow-derived mesenchymal stem cells compared with microfracture. Am J Sports Med. 2016;44(11):2846–54.
8. Saw KY, Anz A, Siew-Yoke Jee C, Merican S, Ching-Soong Ng R, Roohi SA, et al. Articular cartilage regeneration with autologous peripheral blood stem cells versus hyaluronic acid: a randomized controlled trial. Arthrosc – J Arthrosc Relat Surg. 2013;29(4):684–94.
9. Rabago D, Nourani B. Prolotherapy for osteoarthritis and tendinopathy: a descriptive review. Curr Rheumatol Rep. 2017;19(6):34.

10. Ulasli A. Ultrasound imaging and guidance in the management of knee osteoarthritis in regenerative medicine field. J Clin Orthop Trauma. 2019;10(1):24–31.
11. Moraes VY, Lenza M, Tamaoki MJ, Faloppa F, Belloti JC. Platelet-rich therapies for musculoskeletal soft tissue injuries. Cochrane Database Syst Rev. 2014;4:CD010071.
12. Zhou Y, Wang JH-C. PRP treatment efficacy for tendinopathy: a review of basic science studies. Biomed Res Int. 2016;2016:9103792.
13. Dragoo JL, Wasterlain AS, Braun HJ, Nead KT. Platelet-rich plasma as a treatment for patellar tendinopathy: a double-blind, randomized controlled trial. Am J Sports Med. 2014;42(3):610–8.
14. Andia I, Maffulli N. Use of platelet-rich plasma for patellar tendon and medial collateral ligament injuries: best current clinical practice. J Knee Surg. 2015;28(1):11–8.
15. Kosaka M, Nakase J, Hayashi K, Tsuchiya H. Adipose-derived regenerative cells promote tendon-bone healing in a rabbit model. Arthrosc – J Arthrosc Relat Surg. 2016;32(5):851–9.
16. Hirzinger C, Tauber M, Korntner S, Quirchmayr M, Bauer HC, Traweger A, et al. ACL injuries and stem cell therapy. Arch Orthop Trauma Surg. 2014;134(11):1573–8.
17. Grote W, Delucia R, Waxman R, Zgierska A, Wilson J, Rabago D. Repair of a complete anterior cruciate tear using prolotherapy: a case report. Int Musculoskelet Med. 2009;31(4):159–65.