Chapter 11
Regenerative Medicine for the Hip

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Introduction

The hip is a common source of pain not only in the adult and elderly population but also in our competitive athletes. Hip pathology can be found in newborns (developmental hip dysplasia), childhood (Legg-Calve-Perthes disease), adolescence (slipped femoral epiphysis), and adulthood (osteoarthritis, labral tears, tendinopathies, etc.). With adavancement in imaging studies and surgical techniques, we have gained insight into the incidence of labral tear pathologies, for example, and anatomical variants that can contribute to hip and groin pain. However, much work is still needed to search for new techniques that will improve our patient's clinical outcomes and quality of life. The goal of this chapter is to review the role of regenerative medicine techniques, including viscosupplementation, platelet-rich plasma, and stem cells in the management of hip pathologies. We will discuss the most common causes of hip pain, the current standard of care for management, and the evidence for the use of regenerative medicine in those pathologies.

Osteoarthritis (OA)

Hip osteoarthritis (OA), also known as degenerative joint disease, is the most common pathologic finding of the hip. The age-adjusted prevalence of radiographic and symptomatic hip osteoarthritis is 19.6% and 4.2%, respectively [1]. The etiology of hip OA is cartilage breakdown. The most common form is primary, due to the wear and tear occurring over time. Unlike rheumatoid arthritis, osteoarthritis is relatively

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noninflammatory during most stages of the disease process [2]. The treatment goals for hip OA are to decrease pain, improve function, and prevent subsequent joint damage. Current treatment options involve non-pharmacologic, pharmacologic, intra-articular injections, and surgery.

The American College of Rheumatology (ACR) 2012 guidelines for the management of hand, hip, and knee osteoarthritis strongly recommend that all patients with symptomatic hip osteoarthritis be enrolled in an exercise program that includes range of motion, muscle strengthening, and aerobic conditioning [3].

Pharmacologic therapy should be initiated when patients fail to respond to non-pharmacologic treatment. Pharmacologic recommendations for the initial treatment of symptomatic hip osteoarthritis include using one of the following: acetaminophen or paracetamol, oral nonsteroidal anti-inflammatory drugs (NSAIDs), and/or tramadol [3].

A detailed patient medical history and comorbidities should be addressed when prescribing pain medications. Acetaminophen or paracetamol is associated with hepatic side effects; NSAIDs are associated with gastrointestinal, renal, and cardiovascular side effects; and tramadol may cause sedation and dizziness.

The most common nonsurgical procedure for hip OA is an intra-articular injection. The most widely used among these are corticosteroids, and the ACR conditionally recommends their use for hip OA [3].

The evidence suggest that corticosteroid injections are effective improving range of motion, function, and pain at least short term. Studies have compared the effect of corticosteroid versus anesthetic injections [4] or simply normal saline [5] with sustained effects only seen for up to 3 months. Therefore, their utility for long-term relief has been questioned. There is also a wide variation in degree of response, and it has been difficult to identify specific characteristics such as age, BMI, gender, and even radiologic severity that will help select those who will respond to the intervention [6]. Nevertheless, due to their accessibility and cost-effectiveness, they are still a reasonable option, particularly for nonsurgical candidates.

Ultimately, there are concerns regarding their local as well as systemic side effects [7]. There is no clear consensus on the safe total number of injections, total volume, or frequency of corticosteroids that can be injected in a given timeframe. Therefore, the demand for other effective and safer therapies increased.

Hyaluronic acid, also known as viscosupplementation, was approved by the Food and Drug Administration (FDA) in 1997 for the treatment of knee OA. The regenerative effects are thought to be mediated by restoration of elastic and viscous properties of synovial fluid and hyaluronan synthesis by synoviocytes [8]. However, the medication is not currently approved for hip OA even when the evidence suggests that viscosupplementation for the hip is as effective as it has been shown for the knee [8]. In addition, it appears to be a safe and reasonable alternative to NSAIDs and intra-articular corticosteroids. In Mulvaney et al. literature review, they concluded that viscosupplementation of the hip may delay the need for hip replacement surgery and appears to work best in patients with fewer radiographic changes of osteoarthritis [8].

Among the emerging regenerative techniques, platelet-rich plasma (PRP) has been the one that has gained more popularity in part due to cost and ease of

preparation. In contrast to HA, it has been widely applied, not only for arthritis but also soft tissue pathologies (muscle, tendon, and ligaments). The proposed mechanism of action involves the stimulation of release of growth factors that are responsible for inducing tissue healing and interfering with catabolic processes [9].

Since the first randomized clinical trial of PRP in 2012, most of the studies have compared the effectiveness and safety of PRP to another intra-articular injection. Sanchez et al. in 2012 showed a significant benefit of PRP in patients with hip OA [10]. They studied 40 patients with unilateral severe osteoarthritis prospectively to assess the safety and effectiveness of intra-articular PRP [10]. They demonstrated a statistically significant reduction in hip pain at 7 weeks and 6 months and negligible side effects limited to a sensation of heaviness at the injection site. Notably, this study specifically used leukocyte-poor PRP preparation.

Recently, Ye et al. conducted a meta-analysis of randomized controlled trials comparing PRP versus HA in patients with hip osteoarthritis [11]. The authors concluded that PRP was associated with a significant reduction in pain at 2 months compared with HA. However, it did not show significantly better outcomes at 6 and 12 months. Again, no increased risk of adverse effects was observed.

The evidence suggests that intra-articular PRP injections for hip OA are safe and seem to be effective in pain reduction. In addition, studies have shown that PRP has a greater initial effect in pain reduction compared to HA. However, this effect is not sustained over time. An important aspect to consider when interpreting the available evidence is the inconsistency in preparation methods of PRP samples, particularly, leukocyte-rich versus leukocyte-poor, as it has been identified as a critical aspect for the outcomes among different pathologies. A call for standardization of regenerative medicine techniques has been advocated to minimize conflicting results [12].

The evidence for stem cell use and effectiveness in hip OA is lacking. To our knowledge there are no randomized clinical trials evaluating the use of stem cells in hip OA. However, there are randomized controlled trials evaluating stem cells in knee OA. Shapiro et al. [13] studied 25 patients with bilateral knee osteoarthritis who received bone marrow aspirate concentration (BMAC) plus PRP in one knee and saline placebo into the other knee. Pain scores in both knees decreased significantly from baseline at 1 week, 3 months, and 6 months; however there was no significant difference in pain reduction between the two groups. There were no serious adverse events from the BMAC procedure. There are cohort studies and case series demonstrating pain improvement. In 2017, Mardones et al. [14] investigated the safety and efficacy of the intra-articular infusion of bone marrow-derived mesenchymal stem cells (BM-MSC) in a cohort of ten patients with functional and radiological evidences of hip OA. Patients were evaluated, before and after completion of the cell infusion. Authors concluded that BM-MSC injections were safe and improved pain and function. Interestingly, the radiographic scores of the hip joint remained without variation in nine out of ten patients, therefore apparently halting the progression of hip OA. In 2018, Darrow et al. [15] reported a case series of four patients

treated with bone marrow concentrate (BMC) for hip OA, who underwent four BMC injections and experienced decreased pain at rest and when active when compared with baseline.

Also in 2018, Rodriguez-Fontan et al. [16] conducted a cohort study evaluating BMAC for early hip and knee OA. A total of 25 joints (10 knees, 15 hips) were treated with intra-articular BMAC. They concluded that intra-articular injections of BMAC for the treatment of early knee or hip osteoarthritis were safe and demonstrated satisfactory results in 63.2% of patients.

Currently, there is limited evidence to support the use of stem cells in the treatment of hip OA. Initial studies of stem cells have not reported significant side effects, suggesting that they might be safe. Further high-level quality studies are needed to evaluate its effectiveness and to continue evaluating their safety profile.

Tendinopathies

Tendon pathologies include tears (partial and complete) and acute and chronic tendinopathies. Tendonitis is often used to describe acute tendinopathies, whereas chronic tendinopathy refers to a chronic overload injury with possible tendon degeneration. Tendinopathies were initially described as tendonitis, as there was a belief that inflammation contributed to the pathology, but histopathological studies in the 1990s showed little to no evidence of inflammation. Tendon pathologies are considered to be a continuum, as described by Cook and Purdam model [17], where tendons that receive an excessive load and do not adapt properly are predisposed to have pathology, described in 3 stages: stage 1, reactive tendinopathy; stage 2, tendon disrepair; and stage 3, degenerative tendinopathy. This model served to establish targeted muscle therapies for tendon rehabilitation with the main goal to decrease pain, restore function, and improve tendon capacity with progressive loads. This model can be applied to the hip joint tendon rehabilitation as well.

Greater trochanteric pain syndrome (GTPS) is a common cause of lateral hip pain that affects 10–25% of people in developed countries [18]. Historically, it was thought that symptoms were caused by an isolated trochanteric bursitis. However, the underlying etiology for GTPS is most commonly a tendon tear or tendinopathy of the gluteus medius, minimus, or both at their insertion on the greater trochanter with or without a bursitis. Additionally, the greater trochanter serves as the insertion site for the piriformis and obturator internus muscles. The gluteus medius and minimus muscles are involved in stabilizing and externally rotating the hip. Similar to its counterparts at the shoulder rotator cuff, the hip rotator cuff concept has gained more attention in the last years.

The standard of care for GTPS includes activity modification, avoiding pressure over the lateral hip, ice, and physical therapy. Exercises focus on the core muscles, hip abductors, extensors, and external rotators. In addition, eccentric loading exercises of the gluteal muscles are recommended in cases of tendinopathy. Analgesic medications such as acetaminophen and NSAIDs can be used for pain management in the acute phase.

Patients not improving with conservative treatment may undergo a sono-guided corticosteroid injection into the bursa. Labrosse et al. [19] evaluated the effectiveness of these for the treatment GTPS associated with gluteus medius tendinopathy in 54 patients, with 72% of patients showing significant improvement in pain level at 1 month. However, the effect was only short term.

Regenerative interventions, mainly PRP, have been studied as treatment of GTPS. One of the first studies that included hip pathology was a collaborative multicentered retrospective study by Mautner and colleagues that evaluated the use of PRP to treat chronic tendinopathies [20]. From a total of 180 patients who received ultrasound-guided PRP injections, 16 were to the gluteus medius tendon. Of these, 13 (82%) of the patients reported moderate to complete resolution of symptoms postinjection at an average follow-up of 15 months. In 2018, Fitzpatrick et al. compared the effects of PRP versus corticosteroid injection for the treatment of chronic gluteal tendinopathy [21]. This was a double-blind randomized controlled trial that included 80 patients, with follow-up up to 12 weeks. No difference was observed within 2 or 6 weeks. However, significant clinical improvement in pain and function was observed at 12 weeks for 82% of the patients on the PRP arm when compared to 56.7% on the corticosteroid arm. In 2018, Ali et al. [22] performed a systematic literature review that included three randomized controlled trials and two case series for a total of 209 patients. It showed that PRP is an effective alternative for GTPS with improvements observed during the first 3 months and sustained up to 12 months.

While this evidence shows promising results for GTPS, controversy exists around the direct contribution of PRP among the different injection techniques. It is a common practice to perform tendon fenestration along with PRP injections. Some authors hypothesized that the tendon fenestration alone might be as effective as the PRP injections. This is highlighted by Jacobson et al. [23] where they compared PRP versus simple percutaneous tendon fenestration for treatment of GTPS. The study included a total of 30 patients; half were treated with fenestration and the other half were treated with PRP. While both groups showed significant pain score reduction, there was no difference between the two groups at 3 months. This suggests that tendon fenestration alone could be an effective treatment for GTPS. Further studies are needed to standardize these procedures along with PRP preparations.

Psoas tendinopathy, which may present as internal snapping hip syndrome, is a common cause of hip pain. It is usually caused by friction of the iliopsoas tendon sheath over the iliopectineal ridge or the iliacus tendon [24]. Iliopsoas tendinopathy typically responds within a few weeks of activity modification, physical therapy, acetaminophen, and/or NSAIDs. Patients unresponsive to initial treatment may undergo a sono-guided steroid injection into the bursa. However, there is limited evidence for its efficacy and long-term effect. Agten et al. [25] reported that fluoroscopic-guided injections into the iliopsoas bursa with corticosteroids were an effective treatment for suspected iliopsoas tendinopathy, with 49% reported clinically relevant improvement at 1 month. Additionally, Han et al. [26] showed that regardless of coexisting intra-articular hip pathology, corticosteroid injections are effective for iliopsoas tendinopathy, for at least 6 weeks. On the other hand, Garala et al. [24] carried out a 14-year retrospective case-control study showing that image-guided corticosteroid injection into both the iliopsoas tendon sheath and the bursa

was an effective treatment for reducing pain long term for only 8 out the 23 patients on the study. It is also suggested that in those patients who experienced temporary relief from the injection, psoas tenotomy might be a treatment with long-term efficacy [24].

Moreover, patients who remained symptomatic after a steroid injection may resort to surgical psoas release. To our knowledge, no study has evaluated the efficacy of regenerative medicine on iliopsoas tendinopathy.

The adductor muscles of the hip include sartorius, gracilis, pectineus, adductor longus, and adductor brevis. Groin pain over the adductor musculature is most commonly associated with the adductor longus muscle insertion site; therefore an entity that must be considered is athletic pubalgia, which will not be covered in this chapter. The standard of care is physical therapy, focused on Holmich's exercise protocol [27], which has showed its long-term effectiveness for adductor-related groin pain in athletes [28]. In patients not responding to physical therapy, injections can be considered. Lidocaine injections could help to confirm the diagnosis [29]. Corticosteroids has been used, however, due to the potential risk for tendon damage, has fallen in disuse. There is very limited evidence available to support the use of regenerative medicine techniques. Dallaudiere et al. [30] retrospectively evaluated the effectiveness of a single ultrasound-guided PRP injection for upper- and lower-extremity tendinopathies in 408 subjects that included 40 patients with adductor/hamstring tendinopathy. Those patients demonstrated significant functional and pain improvement at 6 weeks and at a mean of 20.2 months following injection. Like previously stated, standardized protocols need to be established in order to compare therapeutic interventions and reliably evaluate efficacy.

The hamstring muscles include the semimembranosus, semitendinosus, and biceps femoris. Hamstring tendinopathy can occur proximal at the ischial tuberosity or distally at the medial or lateral hamstring tendons. Imbalance between quadriceps and hamstring muscles predisposes injuries to the latter. Standard care consists of ice, NSAIDs, and physical therapy. Physical therapy should focus on hamstring stretching, strengthening with eccentric lengthening exercises, and correcting errors in the kinetic chain. In addition, there is evidence that shockwave therapy, another regenerative medicine modality not often discussed, is effective in the treatment of chronic proximal hamstring tendinopathy. Evidence comes from a randomized controlled clinical trial, consisting of 40 patients, which showed that the shockwave therapy group had significant difference in pain reduction compared to traditional exercise program for hamstring muscles [31]. Peritendinous injections with lidocaine and/or steroids can be effective short term. PRP injections have also been used in the treatment of hamstring tendinopathy. A study involving 17 patients, demonstrated that patients refractory to conservative treatment responded well to one PRP injection and returned to sport at average of 4.5 months [32]. Other studies with shorter follow-ups have not necessarily report benefits of PRP. Levy et al. [33] evaluated 29 patients up to 8 weeks postinjection and did not observe statistically significant difference of a single PRP injection for proximal hamstring tendinopathy. However, a level 1 systematic review by Miller et al. in 2017 suggested that PRP injections are superior to

other injections in patients with symptomatic tendinopathy [34]. They included a total of 16 randomized controlled trials of PRP versus control in different tendinopathies.

Stem cells theoretically have potential characteristics that may benefit injured multiple musculoskeletal structures, including tendon disorders. However, a systematic review in 2017 by Pas et al. concluded that there is no evidence to support the use of stem cells in tendinopathies [35].

Ligament Injuries

The main hip joint ligaments (iliofemoral, pubofemoral, and ischiofemoral ligament) are very strong and stable, therefore requiring a great amount of force to cause a ligament sprain or rupture. Typically, the mechanism of injury involves twisting and/or overstretching. The standard of care for any ligament injury involves protecting the injured area, rest, ice, compression, and elevation. Analgesics might be used as needed. In addition, clinical studies have also demonstrated that early mobilization improves ligament healing and strength. Temporary bracing might be needed; however, casting and prolonged brace should be avoided. Lastly, rehabilitation should focus in decreasing pain and swelling and improving range of motion and strength.

PRP in Ligament Injuries

To our knowledge there is no report of platelet-rich plasma on hip ligaments. The evidence in the knee suggests that PRP injections to the MCL in chronic injuries and the ACL intraoperative during reconstruction may accelerate healing and decrease pain post-reconstruction, respectively [36, 37].

Hip Labral Injury

The hip labrum is a fibrocartilaginous structure that attaches to the margin of the acetabulum and provides stability and support. Labral tears are the most common reasons to undergo a hip arthroscopy [38]. Hip labral tears are usually associated with traumatic injury such as a hip dislocation or bony abnormality like a hip dysplasia or femoroacetabular impingement (FAI). The standard of care for hip labral tears include activity modification, unloading the damaged labrum, gait retraining to minimize excessive hip extension, physical modalities, and analgesics as needed. Physical therapy is recommended focusing in core muscles, hip girdle, and proprioceptive exercises. Sono-guided corticosteroid hip injections seem to have limited therapeutic effect in patients with labral tears and FAI [39]. However, an anesthetic

only injection might be a good diagnostic tool for possible hip arthroscopy candidates [39].

PRP has been used intraoperatively in patients undergoing hip arthroscopy for labral treatment. However, *Redmond* et al. did not observe significant difference between groups receiving anesthetic versus PRP at a minimum of a 2-year follow-up [40]. There is no evidence to support platelet-rich plasma as an effective treatment of hip labral tears.

Conclusion

Hip pain is one of the most common complaints in a musculoskeletal practice. However, due to its intrinsic anatomic and functional complexity, pain can arise secondary to multiple etiologies. In many occasions the current standard of care does not improve the patient's symptoms. Therefore, there is increasing demand for new approaches that can effectively and safely target these pathologies. Among these, regenerative medicine techniques have become an attractive approach, especially with the widespread use of sports ultrasound to guide such procedures. We found evidence that among these, PRP is a reasonable alternative for hip tendinopathy. For hip osteoarthritis, PRP also appears to be superior to hyaluronic acid, at least for the first 2 months, however with similar effectiveness thereafter. Evidence for stem cells' role in hip pathology is still deficient, with available data not supporting its use for other tendinopathies. When making clinical decisions, we should evaluate the included patient population and specific pathology targeted in these studies, to establish their applicability to our specific patient population.

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