Use of Musculoskeletal Ultrasound and Regenerative Therapies in Soccer

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Author Affiliation | Disclosures

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Take-Home Points

- Improvements in ultrasound technology have increased its use as a therapeutic and diagnostic modality.
- Ultrasound offers increased accuracy and efficacy with minimally invasive procedures.
- PRP is a safe and effective treatment for many musculoskeletal injuries, however return-to-play time frames limit its efficacy.
- While stem cell and amniotic products offer promising results, the paucity in data limits overall use.
- Care should be taken when discussing regenerative therapy as many products eclipse the concept of “minimal manipulation” and therefore require USFDA trials to establish safety data.

Ultrasound

Ultrasound (US) was first introduced for musculoskeletal (MSK) evaluation in 1957. Since then, US has gained increasing attention due to its ease of utilization in the clinical setting, repeatability, noninvasiveness, capability for contralateral comparison, lack of radiation exposure, and capability to provide real-time dynamic tissue assessment. Compared with magnetic resonance imaging or computed tomography, US presents limitations, including decreased resolution of certain tissues, limited field of view, limited penetration beyond osseous...
structures, incomplete evaluation of a joint or structure, and operator experience. However, advancements in technology, image resolution, and portability have improved the visualization of multiple anatomic structures and the accuracy of minimally invasive ultrasound-guided procedures at the point of care. The use of US for guided hip injections possibly decreases the cost relative to fluoroscopic guidance. Other studies have reported that US, as a result of its safety profile, has replaced fluoroscopy for certain procedures, such as barbotage of calcific tendinosis. US has been used for diagnostic purposes and guidance for therapeutic interventions, such as needle aspiration, diagnostic or therapeutic injection, needle tenotomy, tissue release, hydro-dissection, and biopsy. Given its expanding application, US has been increasingly used in the clinical setting, athletic training room, and sidelines of athletic events.

Diagnostic Ultrasound

An epidemiologic review of the National Collegiate Athletic Association (NCAA) men’s and women’s soccer injuries from 1988 to 2003 reported over 24,000 combined injuries. Over 70% of these injuries are MSK in nature and often affect the lower extremities. Ekstrand and colleagues also conducted an epidemiological review of muscle injuries among professional soccer players from 2001 to 2009. They found that 92% of all muscle injuries involved the lower extremities. The portability of US allows it to serve as an ideal modality for diagnostic evaluation of acute MSK injuries. Klauser and colleagues developed consensus based on the recommendations of the European Society of Musculoskeletal Radiology (ESSR) for the clinical indication of diagnostic ultrasound. A grading system was developed to describe the clinical utility of diagnostic US evaluation of MSK structures:

- Grade 0: Ultrasound is not indicated;
- Grade 1: Ultrasound is indicated if other imaging techniques are not appropriate;
- Grade 2: Ultrasound indication is equivalent to other imaging modalities;
- Grade 3: Ultrasound is the first-choice technique.

Henderson and colleagues conducted a review of 95 studies (12 systemic reviews and 83 diagnostic studies) that investigated the accuracy of diagnostic US imaging on soft tissue MSK injuries of the upper and lower extremities. They reported the sensitivity and specificity of the method for detection of over 40 hip, knee, ankle, and foot injuries and assigned corresponding grades based on diagnostic accuracy by using the same system developed by Klauser and colleagues. Common MSK injuries of the lower extremity and their corresponding ESSR grades are listed in the Table. This study demonstrated that diagnostic US is highly accurate for a number of soft tissue MSK injuries of the lower extremity and consistently matches the recommendation grades issued by Klauser and colleagues. In the hands of a skilled operator, US has become an increasingly popular and cost-effective modality for diagnosis and monitoring of acute muscle injuries and chronic tendinopathies among soccer athletes.

Ultrasound-Guided Therapeutic Procedures

The use of US at the point of care for needle guidance has led to its widespread application for therapeutic procedures, including injections and multiple regenerative therapies. Intra-articular US-guided injection and aspiration are common therapeutic interventions performed in the clinical setting. In a position statement of the American Medical Society for Sports Medicine, US-guided injections were found to be more accurate (SORT A evidence), effective (SORT B evidence), and cost effective (SORT B evidence) than landmark-guided injections. A
recent meta-analysis conducted by Daniels and colleagues\(^1\) demonstrated the improved accuracy and efficacy of US-guided injections at the knee, ankle, and foot. Injections may serve a diagnostic purpose when anesthetics, such as lidocaine, are used in isolation, a therapeutic purpose, or both.

**Regenerative Therapies for Musculoskeletal Conditions**

**Percutaneous Tenotomy**

Percutaneous tenotomy involves the introduction of a needle into damaged soft tissues, most often tendons (“needling”), in an effort to stimulate a healing response and resect the diseased tendon tissue. Although tenotomy was initially performed as an open or arthroscopic surgical technique, advances in US technology have led to improved sensitivity and specificity identifying areas of tendinous injury (hypervascularity, hypoechogenicity, and calcification); as such, the combination of these techniques has been used in the outpatient setting. New commercial models incorporate ultrasound guidance with needles or micro-resection probes for real-time débridement of damaged tissues. Percutaneous tenotomy has been described in the management of tendinopathy involving the rotator cuff, medial and lateral epicondyles, patellar and Achilles tendons, and plantar fascia.

Housner and colleagues\(^9\) evaluated the safety and short-term efficacy of US-guided needle tenotomy in 13 patients with chronic tendinosis of the patella, Achilles tendon, gluteus medius, iliotibial tract, hamstring, and rectus femoris. They reported no procedural complications and a significant decrease in pain scores at 4 and 12 weeks of follow-up.

Koh and colleagues\(^10\) conducted a prospective case series to evaluate the safety and efficacy of office-based, US-guided percutaneous tenotomy (using a commercial model) on 20 patients with chronic lateral epicondylitis. The authors reported no wound complications and significant improvement in pain scores at each follow-up period up to 1 year. Subsequent post-procedural US evaluation of injured tissues revealed evidence of healing (decreased tendon thickness, vascularity, and hypoechogenicity) in over half the cohort after 6 months compared with the baseline.\(^11\)

Lee and colleagues\(^12\) evaluated the efficacy of US-guided needle tenotomy combined with platelet-rich plasma (PRP) injection on chronic recalcitrant gluteus medius tendinopathy. In this case series, 21 patients underwent PRP and “needling” through the hypoechoic regions of the injured tendon under direct US guidance. After a period of rest, all patients completed the structured rehabilitation protocol. After an average follow-up of 10 months, all patients displayed significant improvements in all outcome questionnaires and did not report any significant adverse events. The authors concluded that tenotomy combined with PRP is a safe and effective method for treatment for recalcitrant gluteus medius tendinopathy.

These studies indicate that US-guided percutaneous tenotomy, alone or in combination with regenerative therapies, such as PRP, is a safe and effective treatment option for various tendinopathies. However, while tenotomy appears safe with promising results and no reported major adverse events, the level of evidence remains low.

**Orthobiologics**

Orthobiologics are substances composed of biological materials that can be used to aid or even hasten the healing of bones, muscles, tendons, and ligaments. Orthobiologics may contain growth factors, which initiate or stimulate
the body’s reparative process; matrix proteins, which serve as scaffolding for healing tissues; or stem cells, specifically adult stem cells, which are multipotent and can differentiate into several cell lines. Adult stem cells are categorized as hematopoietic, neural, epithelial, skin, and mesenchymal types. Mesenchymal stem cells (MSCs) are of particular interest in sports medicine applications because they secrete growth factors and cytokines with trophic, chemotactic, and immunosuppressive properties. MSCs are also multipotent and can differentiate into bones, muscles, cartilages, and tendons. MSCs are readily isolated from many sources, including bone marrow, adipose tissues, synovial tissues, peripheral blood, skeletal muscles, umbilical cord blood, and placenta. Several types of regenerative therapies used in orthopedic and sports medicine practice include PRP, stem cell therapy, and amniotic membrane/fluid preparations. While each therapy possesses the potential for promising results, the paucity of research and discrepancies among studies regarding the description of stem cell lines used limit the available evidence on the true clinical benefits of these regenerative therapies.

[Head 3] Platelet-Rich Plasma

PRP is an autologous product that has been used to stimulate biological factors and promote healing since the 1970s. Through the activation of platelets, PRP improves localized recruitment, proliferation, and differentiation of cells involved in tissue repair. Platelets, which are non-nucleated bodies located in peripheral blood, contain and release 3 groups of bioactive factors that enhance the healing process. Growth factors and cytokines released from alpha-granules play a role in cell proliferation, chemotaxis, cell differentiation, and angiogenesis. Bioactive factors, such as serotonin and histamine, released from dense granules, increase capillary permeability and improve cell recruitment and migration. Adhesion molecules also assist in cell migration and creation of an extracellular matrix, which acts as a scaffold for wound healing. Platelets are activated by mechanical trauma or contact with multiple activators, including Von Willebrand factor, collagen, thrombin, or calcium chloride. When activated, platelets release growth factors and cytokines, which create a pro-inflammatory environment that mediates the tissue repair process. After the procedure, the pro-inflammatory environment may result in patient discomfort, which can be managed with ice and acetaminophen. Use of nonsteroidal anti-inflammatory drugs may theoretically inhibit the inflammatory cascade induced by PRP, and they are avoided before and after the procedure, although evidence regarding necessary time frames is lacking.

PRP consists of the fractionated liquid component of autologous whole blood, which contains increased concentrations of platelets and cytokines. Different methods and commercial preparations are available for collecting and preparing PRP. Variations in the amount of blood drawn, use of anticoagulants, presence or absence of an activating agent, number of centrifuge spins, and overall platelet and white blood cell concentrations lead to difficulty in evaluating and interpreting the available evidence regarding PRP therapy. In vitro and animal studies demonstrated promising and safe results regarding the healing effect of PRP on injured soft tissues, such as tendons, ligaments, and muscles. In this regard, a number of studies have evaluated the effect of PRP on human MSK injuries. However, in addition to the above-mentioned variabilities in PRP, many of such studies lack standardization and randomization techniques and include a small number of patients only, thereby limiting the overall comparison and clinical application.

A landmark study conducted by Mishra and Pavelko concluded that PRP significantly reduced pain in patients with chronic elbow tendinosis. Similar findings were reported in high-level overhead athletes with ulnar collateral ligament insufficiency, which did not improve with conservative management. Fitzpatrick and colleagues found improvements in pain with the use of single PRP injection as treatment for chronic gluteal tendinopathy. PRP can effectively improve pain and recovery in chronic ligament and tendon injuries, such as lateral epicondylitis, patellar tendinopathy, and plantar fasciitis, when patients are unresponsive to traditional conservative
management. The application of PRP to treat acute MSK injuries has produced mixed results. Hamid and colleagues\(^{22}\) conducted a level II randomized controlled trial to evaluate the effect of PRP combined with a rehabilitation program for treatment of grade 2 hamstring injuries on return-to-play compared with rehabilitation alone. Fourteen athletes were randomized into the study and control groups. Hamid and colleagues\(^{22}\) reported improved return-to-play in the study group compared with that in the control (26.7 and 42.5 days, respectively). This study also reported lower pain scores in the PRP group over time, but the difference was not statistically significant. Zanon and colleagues\(^{23}\) conducted a prospective study to evaluate return-to-play in professional soccer players with acute hamstring strains treated with PRP and a rehabilitation program. This study determined that athletes treated with PRP were “match fit,” meaning they would be available for match selection in an average of 36.8 days. However, Zanon and colleagues\(^{23}\) did not include a control group for comparison. Other studies reported that PRP treatment of acutely injured muscles and medial collateral ligaments of soccer and basketball players decreased their return-to-play interval.\(^{18}\) Reviews by Hamilton and colleagues\(^{24}\) and Pas and colleagues\(^{25}\) concluded that PRP treatment of acutely injured tissues with good blood supply (eg, hamstring muscles) did not improve pain or return-to-play compared with standardized rehabilitation protocols. Similarly, in a double-blinded placebo controlled trial, Reurink and colleagues\(^{26}\) evaluated return-to-play in 80 athletes with acute hamstring injuries treated with a rehabilitation program and either PRP or placebo. Reurink and colleagues\(^{26}\) found no difference in return-to-play (42 days for both groups), but the difference was not statistically significant. PRP has also been used intraoperatively and shows promising results in total knee arthroplasty, anterior cruciate ligament reconstruction, acute Achilles tendon repair, rotator cuff repair, and cartilage repair. However, many of these intraoperative studies are limited to animal models.

In 2009, the World Anti-Doping Agency (WADA) prohibited the use of PRP because it contains autologous growth factors and IGF-1, which could produce an anabolic effect. Recent studies have failed to demonstrate any athletic advantages of using PRP. WADA has since removed PRP from its prohibited list. PRP is also not prohibited by the US Anti-Doping Agency (USADA) and many major professional sporting leagues in the United States. However, care must be taken in reviewing the components of PRP because many commercially available products differ in PRP formulation. Since 2010, many team physicians have increasingly used PRP to treat a wide range of athletic injuries. A recent anonymous survey conducted by a team of physicians on PRP use in elite athletes revealed minimal complications but significant variability among physicians with regard to timing, belief in evidence, and formulation and dosing of PRP treatments. Many physicians did implicate athlete desire as the main indication for treatment.\(^{27}\)

As an autologous treatment, PRP injection has no serious adverse effects beyond mild discomfort as a result of the procedure and pro-inflammatory state in the days following injection. Recent concerns regarding the potential of PRP treatment for heterotopic ossification have been reported, but published information is limited to case reports. PRP can improve pain and function in patients with chronic MSK injury. PRP appears to be a safe and effective alternative to surgery for patients with injury to poorly perfused tissue, which has not improved with conservative measures, such as rest, physical therapy, and anti-inflammatory medications. Care should be taken when treating athletes with PRP to establish regulations on doping by individual governing bodies.

**Stem Cell Therapy**

Use of stem cell therapy is based on the properties of the proliferation and differentiation of multipoint MSC lines. These stem cells can theoretically regenerate injured tissues and influence repair through immunomodulation; paracrine activity through the release of bioactive agents, such as cytokines, trophic, and chemotactic molecules; and cell differentiation into various cell lineages.\(^{15,16,13,17}\) Orthopedic surgeons have used microfracture to recruit MSCs during cartilage repair procedures for over 20 years. This procedure draws multipotent MSCs to the injured...
site to induce chondrogenic proliferation and fibrocartilage repair.\textsuperscript{28}

Adult MSCs provide a readily accessible autologous source of stem cells for regenerative therapies. MSCs can be isolated from a variety of tissues, including bone marrow, adipose tissues, synovia, human umbilical cord blood, and peripheral blood. The majority of stem cell therapies in the United States for sports medicine purposes are conducted using bone marrow aspirate concentrate (BMAC) and adipose tissues. The US Food and Drug Administration (FDA) allows the use of minimally manipulated autologous stem cells to be injected into the same patient on the same day. However, some studies reported that culturing stem cells or introducing products, such as collagenase to stem cells, can increase the stem cell concentration prior to injection. These processes constitute more than “minimal manipulation” and therefore would require drug trials prior to use in the United States.

Although MSCs can be readily obtained from a variety of tissue sources, the makeup of the cell concentrate differs. Bone marrow and adipose tissues are readily available sources of homogenous MSCs. Harvesting stem cells from adipose tissues provides a less invasive route of collection than from BMAC. Harvested BMAC and adipose tissues consist of heterogeneous cell populations that are composed of precursor and accessory cells, such as pericytes, endothelial cells, smooth muscle cells, fibroblasts, and macrophages in addition to MSCs.

Animal studies reported promising results when evaluating soft tissue lesions in small and large animal models.\textsuperscript{14,15} Although clinical and human evidence remains limited, the potential of MSCs for regenerative repair has led to a recent increase in the number of related clinical studies. Multiple systematic reviews have concluded that MSC therapy is safe for the treatment of osteoarthritis, cartilage lesions, and tendinopathies. Limited evidence is available regarding the safety of intramuscular use, and a theoretical concern arises on the development of heterotopic bone formation as a result of treatment.\textsuperscript{13,16} The efficacy of MSC therapy is difficult to determine due to the lack of standardization in stem cell populations, adjuvants (eg, PRP, hyaluronic acid, and scaffolding preparations), and delivery methods used.\textsuperscript{13,17}

Similar to PRP, the increased use of MSC therapy among high-profile athletes has led to the promotion of these therapies as safe and effective despite limited evidence.\textsuperscript{29} Although MSC therapy is a promising and safe treatment option for patients with soft tissue injuries, the paucity in data and human studies limit its clinical use. Moreover, data of MSC efficacy is complicated because of the disparity between clinical studies regarding MSC collection method (many of which eclipse the “minimal manipulation” standard), description of isolated cell concentrates, dosage, method of delivery, use of adjuvants, and lack of randomization. Further studies using [standardized] methods are needed before establishing a true consensus on the safety and efficacy of MSC therapy.

**Amniotic Membrane**

The placenta is a source of MSCs, a collagen-rich extracellular matrix, and bioactive growth and regulatory factors. The capacity of the placenta to modulate biological activities and tissue formation is thought to provide a means of tissue repair and healing. The placenta consists of amniotic fluid, amniotic membrane (AM), chorionic membrane, and umbilical cord blood and tissues. Although MSCs have been isolated from each component of placental tissues, amniotic and chorionic membranes and umbilical cord tissues yield the highest concentration.

The majority of regenerative studies involving the placenta used AM alone or in combination with other placental tissues. AM is a metabolically active tissue that consists of an epithelial layer, a basement membrane, and a mesenchymal tissue layer. In addition to being a source of stem cells, AM synthesizes many growth factors, vasoactive peptides, and cytokines, which are capable of tissue regeneration. AM was initially used as a biological
scaffold for the treatment of skin burns and wounds. Other intrinsic properties of AM include the provision of a matrix for cellular migration and proliferation, enhanced wound healing with reduced scar formation, antibacterial activity, and lastly, non-immunogenic and immunosuppressive properties. These inherent characteristics have spurred studies on the potential use of AM in sports medicine as a minimally invasive means to treat osteoarthritis and injuries of tendons, ligaments, muscles, fascia, and cartilages.

Animal studies reported positive results with the use of AM to treat osteoarthritis, cartilage defects, and tendon and ligament injuries. Few studies involving human participants also revealed favorable results with regard to the use of AM for the treatment of plantar fasciitis and osteoarthritis; however, these studies are industry-sponsored and employed small sample sizes. The unique mixture of a collagen-rich extracellular matrix, bioactive growth factors, and pluripotent stem cells may allow AM to become an effective treatment for MSK injuries. Although initial animal and human studies show promising results, variabilities regarding models (animal and human), pathologies, placental tissues, and methods of preparation, preservation, and delivery used limit the ability for comparison, analysis, and drawing of definitive conclusions. Thus far, no studies have evaluated the use of currently available AM products for the treatment of injuries sustained by soccer players.

Despite the current popularity of AM as regenerative therapy in academic research and potential use in clinical treatment in sports medicine, physicians should remain aware of the limited evidence available. Other barriers to research and use AM as a regenerative therapy include regulatory classifications based on the concept of “minimal manipulation” in biologic therapies. Minimally manipulated placental allografts are less regulated, less costly to study, and more easily commercialized. These products are not required to undergo FDA phase I to III trials prior to premarket approval. In 2000, the FDA position on all AM products falls into 2 categories. The first position states that AM that contains allogenic stem cells mixed with another drug that is micronized and/or cryopreserved is more than “minimally manipulated” and therefore categorized as “biologic” and would be subject to phase I to III trials. Dehydrated and decellularized AM, however, may meet the concept of minimal manipulation and is only approved by the FDA as a wound covering. Thus, any application of AM for the treatment of sports medicine pathology is not currently FDA-approved, considered off-label, not covered by insurance, and subject to out-of-pocket pay.

Conclusion

With improvements in technology and portability, US has become an effective imaging modality for point-of-care evaluation, diagnosis, and continuous monitoring of many MSK injuries. Additionally, as a dynamic imaging modality, US allows for increased accuracy and efficacy when combined with minimally invasive procedures, such as diagnostic and therapeutic guided injections and percutaneous tenotomy, in the clinical setting; thereby decreasing the overall healthcare costs. PRP is proven to be a safe treatment for several MSK conditions, such as lateral epicondylitis, patellar tendonitis, and plantar fasciitis. Although PRP has been included in the standard of care in some areas, this technique may be predominantly athlete driven. Conflicting evidence with regard to return-to-play timeframes following PRP treatment for muscular injuries and poor evidence in conditions, such as Achilles tendonitis, have led to inconsistent indications for use, dose, and timing of treatment. Although early evidence of MSC therapy is promising, high-level evidence for MSC therapy is insufficient, despite its increased use among athletes. Thus far, no data are available regarding the outcomes of the use of amniotic products for the treatment of injuries among athletes. Furthermore, the preparation of amniotic products has many regulatory concerns. The authors advocate for continuous high-level research on regenerative medicine therapies to establish clinical efficacy and safety data.
### Figures/Tables

**Table.** Clinical Indication Grades for Diagnostic Ultrasound Evaluation of Common Lower Extremity Injuries\(^8\)

<table>
<thead>
<tr>
<th>Hip</th>
<th>Knee</th>
<th>Foot/Ankle</th>
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</thead>
<tbody>
<tr>
<td>Synovitis/Effusion: 3</td>
<td>Quadriceps tendinosis/tear: 3</td>
<td>Anterior talofibular ligament injury: 3</td>
</tr>
<tr>
<td>Snapping hip (extra-articular): 3</td>
<td>Patella tendinopathy: 3</td>
<td>Calcaneofibular ligament injury: 3</td>
</tr>
<tr>
<td>Gluteal tendon tear: 3</td>
<td>Pes anserine bursitis: 3</td>
<td>Peroneal tendon tear/subluxation: 3</td>
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<td>Meralgia paresthetica: 3</td>
<td>Periarticular bursitis &amp; ganglion: 3</td>
<td>Posterior tibial tendinopathy: 3</td>
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<tr>
<td>Lateral femoral cutaneous nerve injury: 3</td>
<td>Osgood-Schlatter &amp; Sinding-Larsen: 3</td>
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<td>Retrocalcaneal bursitis: 3</td>
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<td>Muscle injury (high grade): 3</td>
<td>IT band friction: 2</td>
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<td>Ganglion cyst: 3</td>
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<td>Proximal hamstring injury: 2</td>
<td>Meniscal cyst: 2</td>
<td>Retinacula pathology: 3</td>
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<td>Common perineal neuropathy: 2</td>
<td>Achilles tendinopathy: 2</td>
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<tr>
<td>Psoas tendon pathology: 1</td>
<td>Intra-articular ganglion: 1</td>
<td>Deltoid ligament injury: 2</td>
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<td>Osteoarthritis: 0</td>
<td>Hoffa’s fat pad syndrome: 1</td>
<td>Plantar plate tear: 2</td>
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<td>Labral tear: 0</td>
<td>Loose bodies: 1</td>
<td>Syndesmotic injury: 2</td>
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<td></td>
<td>LCL injury: 0-1</td>
<td>Morton’s neuroma: 2</td>
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<td>Deltoid ligament injury: 1</td>
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<td>Plica syndrome: 0</td>
<td>Spring ligament injury: 1</td>
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<td>Anterolateral ankle impingement: 0</td>
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<td>Posterior talofibular ligament injury: 0</td>
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<td>Medial/lateral meniscus tear: 0</td>
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</tr>
<tr>
<td></td>
<td>Osteochondritis dissecans: 0</td>
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Abbreviations: ACL, anterior cruciate ligament; IT, iliotibial; LCL, lateral collateral ligament; MCL, medial collateral ligament; PCL, posterior cruciate ligament.
References


Multimedia

Product Guide

Product Guide

- STRATAFIX™ Symmetric PDS™ Plus Knotless Tissue Control Device
- STRATAFIX™ Spiral Knotless Tissue Control Device
- BioComposite SwiveLock Anchor
- BioComposite SwiveLock C, with White/Black TigerTape™ Loop

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