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# The Effect of Stem Cells on Ankle Injuries

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## *Abstract*

*Ankle injuries lead to joint pain, limitation of movement, occasional effusion, and quality of life impairment. It is estimated that one injury occurs for every 10,000 people each day due to inversion of the ankle. 7-10% of all admissions to hospital emergency departments are a result of ankle injuries. It was found that 70% of acute ankle sprains and fractures display some osteochondral defects (OCD) of the talus. Twenty five percent of all injuries of the musculoskeletal system are related to inversion injuries. About 50% of these injuries are related to sports. Full thickness focal chondral defects in athletes have an overall prevalence of 36%. The ankle is the most injured area of the body for 24 of 70 sports that were studied. Basketball, soccer, football, volleyball, running, and dancing are the sports in which these athletic injuries are most common. Individuals under 35 years of age demonstrate majority of these ankle injuries. The most common age group is for those are between the ages of 15 and 19 years. Etiology of ankle OCDs can either be non-traumatic or traumatic. Seventy percent of acute ankle sprains and fractures occur in the OCD of talus. Potential side effects or medical complications may result from OCD surgeries. Animal and human subjects are commonly used by researchers to investigate the overall effectiveness of stem cells for OCD injuries. Mesenchymal stem cells (MSC) are often the source of preference for orthopedic procedures as they have the ability to differentiate into a variety of tissues. These tissues include bone, muscle, cartilage, and fat. Stem cell transplantation has shown improved tissue quality and rate of healing, sustained gains functionally, decreased pain, and enhanced clinical outcomes. Researchers believed the use of stem cells may offer choices for patients with orthopedic injuries including OCD to reduce recovery time and osteoarthritis as well as enhance function.*

**Keywords:** Ankle Injury, Stem Cells, Treatment, Mesenchymal Stem Cells, Musculoskeletal System, Osteochondral Defects

## Abbreviations

ACI :Autologous Chondrocyte Implantation; ADSC:Adipose Derived Stem Cells; AHFS:Ankle Hind Food Scale; AOFAS: American Orthopedic Food and Ankle Society; ATFL:Anterior Talofibular Ligament; BMA:Bone Marrow Adiposity; BMDCT:-Bone Marrow-Derived Cell Transplantation; BMC:Bone Marrow Concentrate; BM-MSC:Bone Marrow Mesenchymal Stem Cell; BMP:One Morphogenic Protein; BMS: Bone Marrow Stimulation; BMSC-EV:Bone Marrow Stem Cell Extracellular Vesicles; CFL:Calcaneofibular Ligament; CS:Coated Suture; CT:Computed Tomography; Dacm: Dehydrated Human Amnion Chorion Membranes; ECBMS:Excision, Curettage, and Bone Marrow Stimulation Techniques; ESC:Embryonic Stem Cell; FAOS:Foot Ankle Outcome Score; GF:Growth Factor; HA:Hyaluronic Acid; hESC:Human Embryonic Stem Cells; hAMUC:Human Amniotic Membrane And Umbilical Cord; ICRS: International Cartilage Repair Society; MAST:Matrix-Associated Stem Cell Transplantation; MOCART: Magnetic Resonance Observation of Cartilage Repair; MRI:Magnetic Resonance Imaging; MSC:Mesenchymal Stem Cell; NSAID:Non-Steroidal Anti-Inflammatory Drug; OATS:Osteochondral Autologous Transplantation Surgery; OCD:Osteochondral Defect; OCL:Osteochondral Lesion; OLT:Osteochondral Lesion Of Talus; PRF:Platelet Rich Fibrin; PRP: Platelet Rich Plasma; PTFL:Posterior Talofibular Ligament; RICE: Rest, Ice, Compression and Elevation; SI:Suture Plus Injection; SO:Substrate Only; SVF:Stromal Vascular Fraction; TERM:Tissue Engineering And Regenerative Medicine; VAS:Visual Analog Scale.

## Introduction

The foot and ankle are composed of more than 30 joints and many cartilaginous surfaces that are subject to articular cartilage injury [1]. Ten-thousand people per day are inferred to experience a single inversion injury of the ankle [2-5]. Ankle injuries constitute seven to ten percent of all hospital emergency departments admissions. [6]. Up to 70% of acute ankle fractures and sprains will experience osteochondral defects of the talus [7]. Twenty-five percent of all injuries of the musculoskeletal system are related to inversion injuries. About 50% of these injuries are related to sports [8]. There is a 36% overall prevalence of full thickness focal chondral defects seen in athletes [7]. Most of these ankle-related injuries occur in individuals that are younger than 35 years old. They are most common in those between the ages of 15-19 years [9-11].

Etiology of OCDs is often a single or repeated traumatic event but might also be idiopathic or non-traumatic [7]. Ankle injuries lead to joint pain, limitation of movement, occasional effusion, and quality of life impairment [12,13].

An osteochondral defect of the talus is a lesion involving the talus or distal tibia hyaline cartilage and its subchondral bone [7]. Osteochondral lesions are defects of the cartilaginous surface & underlying subchondral bone. Seventy percent of acute ankle sprains and fractures occur in the OCD of talus [7]. In the ankle, the majority of such lesions occur within the talar dome, with the tibial plafond more rarely involved. Talar dome lesions have been described as occurring predominantly in the posteromedial or anterolateral region of the talar dome [11]. Since articular cartilage has a poor reparative ability, the osteochondral lesion of talus (OLT) will heal spontaneously on rare occasions. More commonly, patients with OLT have chronic pain progressed at the ankle joint, with serious limits on sports activities and their daily life [13]. High energy intra-articular fractures are associated with the development of posttraumatic osteoarthritis, a consequence that results in an estimated annual economic burden of approximately $3 billion within the United States and constitutes approximately 12% of all patients with osteoarthritis of the hip, knee, or ankle [14].

## Anatomy & Physiological Function

Osteochondral lesions are flaws of the underlying subchondral bone and cartilaginous surface; the most intricate joints are knee and ankle. In the ankle, most lesions occur within the talar dome, with the tibial plafond less involved. Traditionally, talar dome lesions have been occurring mostly in the anterolateral and posteromedial area of the talar dome [10]. Most OCDs of the talus are found on the anterolateral or posteromedial talar dome. Lateral lesions are usually caused by a shear mechanism smaller and oval shaped. Usually derive from torsional impaction and axial loading medial lesions are frequently more cup-shaped and deeper [15].

One simple hinge joint that is more intricate due to its articular, tendinous, and ligamentous anatomy is the tibiotalar joint. The posterior talofibular ligament (PTFL) the calcaneofibular ligament (CFL), and the anterior talofibular ligament (ATFL) are three ligaments that compose of the lateral ankle ligament complex [16]. The ATFL runs from the lateral margin of the talus to the antero-inferior margin inserting close to the junction of the talar body and neck will blend with the ankle capsule of the fibula. Running underneath the peroneal tendons to insert on the lateral tubercle of the calcaneus, the CFL comes from the inferior margin of the fibula distal to the ATFL. The PTFL is a capsule that condenses from the posterior fibula to the lateral tubercle of the talus process posteriorly [16].

Two-thirds of all injuries are caused by damages of the ATFL ligament [17]. The stability of the ankle joint is maintained by these ligaments. One ligament cannot provide stability at all joint positions due to the talus rotating in the ankle mortise when ankle movement occurs. Brostrom found that 20% of cases combined ruptures of the CFL and ATFL and that isolated rupture of CFL was very infrequent [17]. In an inversion injury, The PTFL is usually not injured of the ankle because this ligament is lax when the ankle is plantar flexed and its maximal load to failure is three times that of the ATFL [17].

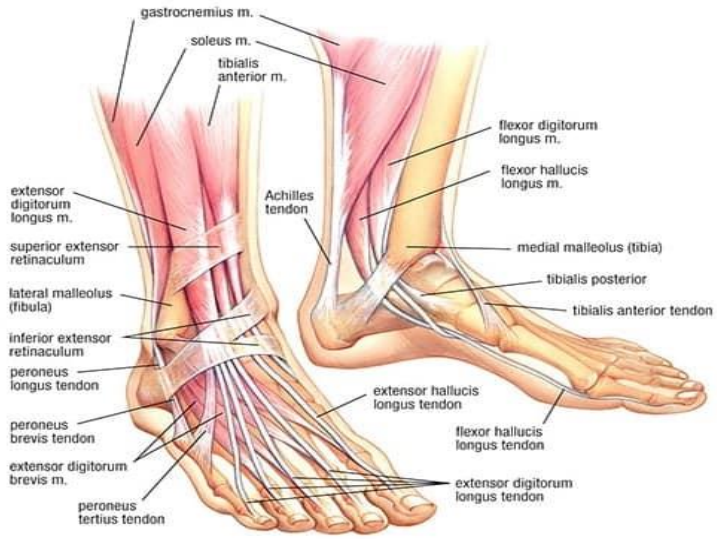


**Figure 1:** Outlines anatomy of the foot and ankle [18].

A thin layer of highly specialized tissue, the articular cartilage, functions to permit smooth, with limited friction movement and load-bearing force distribution throughout joints. This tissue is quite vulnerable to injury, these functional properties confer excellent durability to cartilage. Articular cartilage is alymphatic, avascular, aneural and contains a single cell type known as the chondrocyte. The chondrocyte is subject to damage from chronic or acute inflammatory conditions and events from impaction.

Because of its lack of vascularity, lack of progenitor cells, and high extracellular matrix to cell ration, cartilage has a very limited ability to heal after injury [1]. Chondral tissue will demonstrate limited regenerative capacity and poor healing capabilities; This can lead to the damage becoming irreversible and cause long-lasting disability status with repeated swelling, pain, early osteoarthritis, and function which is limited [19].

Articular cartilage defects that are partially thick cannot heal by themselves. A barrier between the bone marrow cells and the defect can be seen in this type of lesion due to the subchondral bone. Instead, in full-thickness cartilage defects, contact with the pluripotent MSCs are available. Filling the gap, spontaneous repair consists of the production of fibrocartilaginous tissue. This tissue is a weak substitute of hyaline cartilage that gradually degenerates with time. The goal for cartilage repair is to fill the cartilage defect with a tissue that has the same qualities mechanically as hyaline cartilage and the combination of this tissue with the original articular cartilage [20].

Being able to understand the injury mechanism is principal for optimizing injury prevention, treatment, and for research related objectives. An inversion of the foot and ankle is usually caused by a twisting injury or "going over on the ankle". The most usual trauma mechanism is adduction (inversion) or supination of the plantar-flexed foot. Sometimes, there is also a rotation externally of the lower leg in comparison to the joint of the ankle. As a result of the ligament being in this tight position, inversion injuries of the plantar-flexed foot result in ATFL injury [21].

Cartilage injuries are often a consequence of the respective and dynamic loading of the mechanical joint. Even though the cartilage is a poorly irrigated and innervated tissue, when the damage reaches the subchondral bone, complaints will increase swelling, catching, pain, and locking [22].

Without damage to the underlying subchondral plate, shearing forces may result in superficial cartilage lesions. After a high impact force or repeated trauma (chronic instability), the bone plate can also be damaged [23].

Chronic ankle instability or ankle sprains are an important causes of traumatic ankle OCDs. This seems to be the most frequent cause of these conditions. When the talus is inverted between the tibial plafond, lateral and medial malleoli linked by syndesmotic ligaments, the cartilage of the talus can be fractured and crushed leading to a separation in the layer superficially of the cartilage [24].

## Ankle Injury Classification

There are several staging and grading-related systems for ankle ligament injuries laterally based on symptoms clinically, anatomical injury, mechanism of trauma, severity, and stability of the ankle injury. Following International Cartilage Repair Society (ICRS) can be used to classify cartilage lesions as either partial or full thickness depending on their extension to the subchondral bone [11]. A unidimensional measure of pain intensity, the Visual Analog Scale (VAS), is utilized to report the pain progression of a patient or compare the severity of the pain between patients with similar conditions. The American Orthopedic Foot and Ankle Society (AOFAS) Ankle Hindfoot Scale will measure results of treatment in patients who continued a complex ankle or hindfoot injury. It combines both patient and clinician-reported data. The system first introduced by Hamilton and Kaikkonen comprises anatomical damage with symptoms of the patient through a standardized test for ankle injuries [25,26].

## International Cartilage Repair Society (ICRS)

| | |
|---|---|
| Grade 0 | normal cartilage |
| Grade I | cartilage softening and swelling |
| Grade II | partial thickness defect not extending to subchondral bone (<1.5 cm diameter) |
| Grade III | fissures up to subchondral bone level (>1.5 cm diameter) |
| Grade IV | OCD with exposed subchondral tissue |

**Table 1:** Outlines International Cartilage Repair Society Grading System for classifying lesions [11].

**Visual Analog Scale (VAS)**

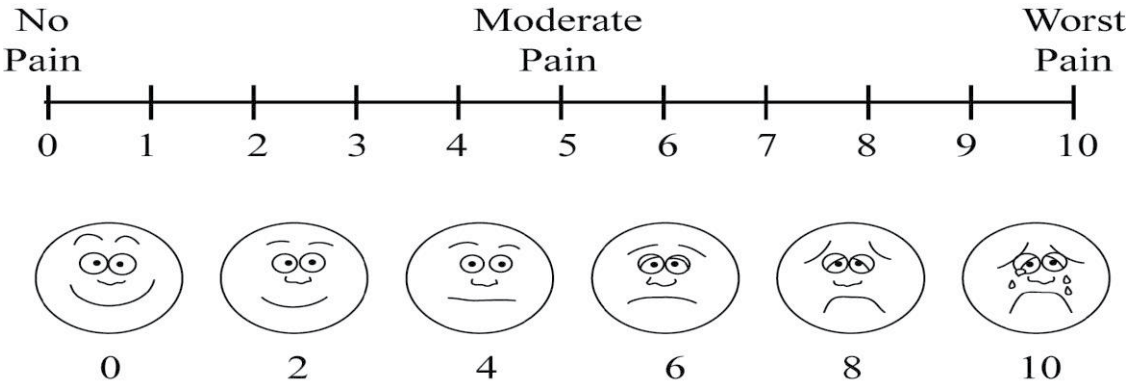


**Figure 2:** Describes pain outlined by Visual Analog Scale [11].

**American Orthopedic Foot and Ankle Society (AOFAS) Ankle Hindfoot Scale**

| Category | Criteria | Points |
|---|---|---|
| **Pain (40 points)** | | |
| | None | 40 |
| | Mild, occasional | 30 |
| | Moderate, daily | 20 |
| | Severe, almost always present | 0 |
| **Function (50 points)** | | |
| Activity limitations, support requirement | | |
| | No limitations, no support | 10 |
| | No limitation of daily activities, limitation of recreational activities, no support | 7 |
| | Limited daily and recreational activities, can | 4 |
| | Severe limitation of daily and recreational activities, walker, crutches, wheelchair, brace | 0 |
| Maximum walking distance, blocks | | |
| | Greater than 6 | 5 |
| | 4-6 | 4 |
| | 1-3 | 2 |
| | Less than 1 | 0 |
| Walking surfaces | | |
| | No difficulty on any surface | 5 |
| | Some difficulty on uneven terrain, stairs, inclines, ladders | 3 |
| | Severe difficulty on uneven terrain, stairs, inclines, ladders | 0 |
| Gait abnormality | | |
| | None, slight | 8 |
| | Obvious | 4 |
| | Marked | 0 |
| Sagittal motion (flexion plus extension) | | |
| | Normal or mild restriction (30° or more) | 8 |
| | Moderate restriction (15° - 29°) | 4 |
| | Severe restriction (less than 15°) | 0 |

| | | |
|---|---|---|
| Hindfoot motion (inversion plus eversion) | | |
| | Normal or mild restriction (75%-100% normal) | 6 |
| | Moderate restriction (25-74% normal) | 3 |
| | Marked restriction (less than 25% normal) | 0 |
| Ankle-hindfoot stability (anteroposterior, varus-valgus) | | |
| | Stable | 8 |
| | Definitely unstable | 0 |

AOFAS Ankle-Hindfoot Scale, Subjective Portion (90 points total)

**Table 2:** Outlines the American Orthopedic Foot and Ankle Society (AOFAS) Ankle Hindfoot Score that measures treatment outcomes [26].

### Hamilton & Kaikkonan Grading System

| | | |
|---|---|---|
| I. | Subjective assessment of the injured ankle | |
| | No mild symptoms of any kind | 15 |
| | Mild symptoms | 10 |
| | Moderate symptoms | 5 |
| | Severe symptoms | 0 |
| II. | Can you walk normally? | |
| | Yes | 15 |
| | No | 0 |
| III. | Can you run normally? | |
| | Yes | 10 |
| | No | 0 |
| IV. | Climbing down stairs | |
| | Under 18 seconds | 10 |
| | 18–20 seconds | 5 |
| | Over 20 seconds | 0 |
| V. | Rising on heels with injured leg | |
| | Over 40 times | 10 |
| | 30–39 times | 5 |
| | Under 30 times | 0 |
| VI. | Rising on toes with injured leg | |
| | Over 40 times | 10 |
| | 30–39 times | 5 |
| | Under 30 times | 0 |
| VII. | Single-limbed stance with injured leg | |
| | Over 55 seconds | 10 |
| | 50–55 seconds | 5 |
| | Under 50 seconds | 0 |
| VIII. | Laxity of the ankle joint (ADS) | |
| | Stable (≤5 mm) | 10 |
| | Moderate Instability (6–10 mm) | 5 |
| | Severe Instability (≥10 mm) | 0 |
| IX. | Dorsiflexion range of motion | |
| | Injured leg | |
| | ≥10° | 10 |
| | 5°–9° | 5 |
| | <5° | 0 |

**Table 3:** Outlines standardized test protocol for ankle injury designed by Hamilton and Kaikkonen [26].

### Diagnostic Procedures

Pre-operative planning is important and should always include weight-bearing x-rays for join assessment globally and evaluation of the alignment. The existence of a fracture must be excluded in acute lateral ankle ligament injury. A good prognosis is shown through the ability to walk again within 48 hours after trauma [20]. The delayed physical examination four to five days post trauma is the prime standard in diagnosis of acute ligament injury laterally [26]. Important features of physical examination are hematoma, swelling, pain on palpation that is localized, and a positive drawer test on the anterior side. A 90% chance that there is an acute lateral ligament rupture is due to localized pain on palpation in combination with hematoma discoloration [26]. Magnetic Resonance Imaging (MRI) and ultrasound can be helpful in identifying associated injury (bone, chondral, or tendon). The presence of joint effusion can be accurately identified using an

ultrasound. MRI is reliable in the evaluation of tendon disorders, diagnosis of acute ligamentous ankle injuries, occult fractures, and osteochondral lesions. Diagnosing osteochondral lesions are more reliable using computed tomography (CT) scans [26]. The size of the OCD can be overestimated using an MRI by the presence of bone edema surrounding the injury. Bony defect size and volume assessment is provided more reliably using a CT scan.

## Medical and Surgical Interventions for Ankle Injuries

Many non-surgical interventions can be used for the treatment of ankle injuries. During the inflammatory phase, the initial treatment is directed towards avoiding excess swelling and ongoing injury, thus optimizing the healing process. For the first four to five days, RICE (Rest, Ice, Compression and Elevation) therapy is the treatment that is chosen to lessen swelling and pain [27].

Enhanced function by improving proprioception and strengthening ankle dynamic stabilizers (calf, soleus, tibialis, etc.) can be caused by physical therapy and aerobic exercise. This approach can enhance the conservation of energy during walking and the optimization of work posture. Symptomatic relief can be improved through therapeutic modalities such as electrical stimulation and therapy, ultrasounds, and therapy through temperature (thermotherapy) [28].

A principal aspect of conservative treatment is the education of patients. It is important to explain to the risk factors for patients which are associated with ankle injuries and which of these risks can be altered. A risk factor for the onset and progression of varying musculoskeletal diseases is obesity. Walking/ running up and down slopes or stairs and impact sports are essential parts of someone's lifestyle that need to be modified [29].

Limiting the ankle mobility while walking and reducing pain by maintaining the alignment correctly of the talus are two goals of treatment orthodically of the ankle joint needed to achieve mechanical unloading of the joint [30].

Intra-articular corticosteroids and nonsteroidal anti-inflammatory drugs (NSAID) are pharmacological strategies that may be used. NSAIDs may be used to control inflammation. Efficacy of NSAIDs decreases over time and varies individually [31]. Corticosteroid injections are useful in the therapeutic and diagnostic measure as it will result in immediate pain relief. The mode of action is a result of its anti-inflammatory effect and reduction of lysosomal enzymes and leukocytes in the synovial fluid. Most studies have demonstrated a small duration effect, around four to eight weeks, although some patients showed benefits up to one year after just a single injection [32,33].

## Conservative Treatment of Ankle Injuries

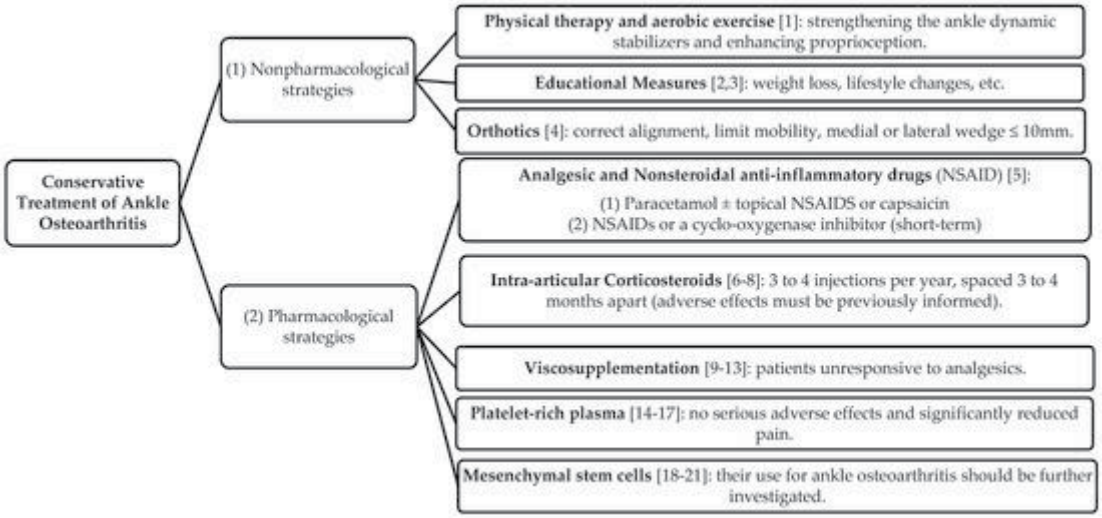


**Figure 3:** Outlines conservative treatments for ankle injuries [34].

## Types of Surgery

One major challenge for orthopedic surgeons has been returning the damaged articular cartilage back to normal state that is functional [11,35]. Multifactorial is the treatment surgically of osteochondral defects. The most frequently used surgical techniques for the treatment of osteochondral defects include fixation, microfractures, allogenic or autologous osteochondral transplantation or mosaicplasty autologous chondrocyte implantation, and autologous chondrocyte implantation that is matrix induced. So far, no method has been able to consistently attain repair of osteochondral defects close to the native tissue. Regenerative medicine and tissue engineering strategies promise new options for treatments in the future of osteochondral and cartilage defects [7].

The arthroscopic approach is currently the selected and most frequently used for both posterior and anterior compartments. Arthroscopy allows for simultaneous treatment of concomitant pathologies including instability when needed. Curettage, excision, and bone marrow stimulation techniques (ECBMS) aim to achieve formation of the fibrocartilaginous tissue. This approach is still the less invasive surgical method. ECBMS is considered in the majority of cases due to the outcome possibilities and lower cost and aggression

[7]. Arthroscopy provides the surgeon a minimally invasive treatment option for a wide range of indications in different joints. Recently, the enhancement of instrumentation and arthroscopic techniques allowed wider application of arthroscopy of the ankle [13]. According to the ICRS classification, the arthroscopic surgical treatment is indicated for focal osteochondral lesions of the tibial plafond or talar dome classified as grade 3-4 for the ankle (Area of lesion >1.0 cm2, depth of lesion <5 mm. [37]. For lesions of depth higher than 5 mm autologous bone grafting or demineralized bone matrix is required. Patients older than 60 years, patients with rheumatoid arthritis, and patients with kissing lesions or osteoarthritis of the ankle should not be treated using this technique [5,37].

Microfracture technique is a frequent and popular performed procedure for cartilage lesions. This technique uses micro penetration of the subchondral plate. This will lead to the filling of the cartilage defect with a blood clot that contains pluripotent mesenchymal stem cells derived from the marrow. This subsequently produces a mixed fibrocartilage repair tissue that contains inconsistent amounts of type II collagen [38]. Microfracture is beneficial because of its relatively short postoperative recovery time, low associated morbidity, restricted invasiveness, and overall cost effectiveness. Early surgical treatment of cartilage injury and younger age of the patient has been one of many factors that have contributed to the success of the treatment. This technique has been described many times is commonly used as the primary line of treatment of osteochondral lesions of the talus [39,40].

The enhanced microfracture technique takes the original microfracture technique and adds bone morphogenetic protein and growth factors such as transforming growth factor. These have been shown to cause chondrogenic marker gene expression for cartilage oligomeric matrix protein, type II and IX collagen, and aggrecan with both quantitative and qualitative improvement of the cartilage repair following microfracture [41,42]. Another microfracture based technique involved the use of scaffold guided in situ chondroinduction. This is a 3-dimensional scaffold that enhances the stability of the microfracture blood clot peripheral adhesion leading to the reduction of the risk associated with clot displacement [43].

The "lift, drill, fill, and fix" surgery should be preferred whenever possible since it provides protection for the majority of native tissue. The defect is lifted, drill by creating microfracture of bone marrow stimulation, use a bone graft to fill the defect, the fragment is fixed with bioabsorbable or metallic screws or pins. This can require open surgery in some cases or be done fully arthroscopically in others [44]. What is done to the knee joint is technically very similar to osteochondral autologous transplantation surgery (OATS). Harvesting osteochondral cylinders from the knee to fill an ankle defect will be required. This technique provides a hyaline cartilage repair through the harvest of cylindrical osteochondral grafts form areas with chondral surfaces that can be limited when weight bearing. Utilizing a press fit technique, these harvested osteochondral grafts are then transferred into chondral defects of the weight bearing cartilage. Promoters state this has a high rate of outcome to be successful, but a systematic review has shown this technique has a substantial amount of complications [45,46].

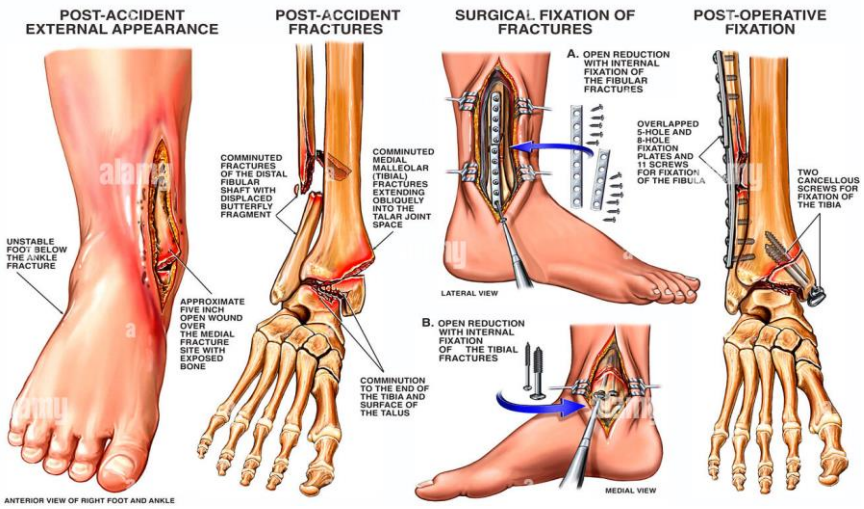


**Figure 4:** Outlines surgical approaches for ankle injuries [47].

Bioresorbable scaffolds have been created to avoid some of the potential complications associated with osteochondral autograft and allograft procedures and treat focal chondral and osteochondral lesions. Scaffolds can be used as an adjunct with micro fracturing techniques or be used individually. They are also designed to be osteoconductive, chondroconductive, or both. Scaffolds match the layers of the subchondral bone and adjacent cartilage to facilitate the ingrowth of osseous and cartilaginous cells into the bioresorbable implant. This will lead to a neomatrix that is layered. Created with the OATS procedure, the cylindrical scaffolds can also be used to backfill osteochondral autograft donor sites as well. The advantage of the scaffolds include that they are both time efficient and cost-effective, requiring only a single-stage procedure; scaffolds circumvent donor site morbidity, and they are

an alternative to allogenic tissues use and cell-based technology that can be expensive [47,60].

Tissue engineering and regenerative medicine (TERM) approaches promise a broader and better alternative for the future. However, scaffolds, cell-based therapies, and augmentation with hydrogels, despite very promising, have been unable to provide consistent results that are better. This is similar to what was observed in the knee. They are valid options for revision surgeries or large injuries that are not amenable by any of the previous techniques and without possibility for fixation and as an approach to primary ankle OCD. This research and technology are advised to be kept under controlled and research conditions before its extensive advertising [50].

Biomechanics remains a primary part of orthopedics. Enhancing the load distribution and joint alignment by means of osteotomy has demonstrated positive effects either isolated or paired with other procedures. The goal is to distribute forces to the most preserved part of the joint while unloading the most affected part. When dealing with symptomatic OCDs, ankle arthroplasty or fusion represents the last resource [12].

Using the cell, scaffold, and growth factor trilogy in the repair strategy has demonstrated the largest success repairing osteochondral lesions arthroscopically. Regenerative techniques are moving from traditional autologous chondrocyte implantation (ACI),that required two operations at high costs, to bone marrow-derived cell transplantation (BMDCT). This is a technique with the ability to provide a repair of the lesion by hyaline cartilage in a one stop procedure, in conjunction with engineered scaffolds and platelet gel able to support multipotent cells differentiation and growth. All of the bone marrow cellular pool is transplanted in this technique, instead of expanded and isolated mesenchymal stem cells, so MSCs are inserted with possible factors that are highly regenerative present in the bone marrow and all the mononuclear cells. Without the requirement for a laboratory phase, this technique will allow the cells to be directly processed in the operating room. The instrumentation used for ACI and a scaffold prior are utilized for a completely arthroscopic implantation, and the autologous platelet-rich fibrin (PRF) is added in order to provide a supplement of growth factors [37].

The day after surgery is when patients are usually discharged. Continuous pressure motion is instantly performed following the day of surgery and gradually increased as tolerated. This movement, through joint decompression and compression facilitates mesenchymal cells in their differentiation and proliferation in the sense of chondrocyte, stimulates the creation of molecules of the cartilage matrix and decreases the adhesion risk within the joint. Throughout the first six weeks following an operation, a person could walk with use of two crutches without the application of any load on the leg that was operated, followed by partial load. Eight to ten weeks is the time frame in which total weight bearing is allowed. Four months following a person's procedure, low-impact sports activities such as cycling and swimming are allowed, while it will take ten months to allow activities such as soccer, tennis, and running that are considered to be high-impact [11].

A device used to concentrate collagen powder and cells derived from the bone marrow or hyaluronic acid membrane as scaffolds for support of the cell and platelet gel has been investigated. The next step in osteochondral repair may become this arthroscopic technique [37].

## Ankle Injuries in Athletes

Athletes have significantly greater demand and load on the joints in their ankles than the average community and sports being performed at a competitive and high level are possibly an unfavorable prognostic factor for the progression of residual complaints [51,52]. Forty percent of all athletic injuries are ankle injuries. These injuries are most commonly seen in athletes playing in football, soccer, basketball, running, volleyball, and ballet or dancing [4,52-54]. Ninety five percent of ankle sprains during soccer were sustained during player contact except for goalkeepers in which seventy nine percent occurred during situations that were non-contact [55]. Ankle injuries can attribute up to 29% of soccer injuries, 53% of basketball injuries, and 12% of the time in football. [56,59]. When it came to volleyball-related injuries, there were 0.9 per 1,000 player hours with and 2.6% injuries during games and 0.7% during a practice [58]. The lateral ligamentous complex makes up three quarters of ankle injuries [59]. For commercial sports teams that compete at a high level, absence of important players due to injury may lead in economic loss and defeat.

## Discussion

### *Stem Cell Overview*

Orthopedic surgery has demonstrated great interest in platelet-rich plasma injections. It is a concentration of platelets taken from autologous blood. Autologous blood carries a high concentration of cytokines. These cytokines act by inducing cell differentiation and proliferation, as well as the promotion of wound healing [34,60]. A source of a cocktail of many autologous growth factors (GF), platelet rich plasma (PRP) cannot be all things to all tissues. PRP is acquired from a patient's own blood (autologous), and GFs from alpha granules of platelets become available following the procedure that platelets will become activated. Customizing the PRP for specific indications will be the next step. For an OCD, the primary purpose is to alter GFs and secretory proteins looking for both cartilage and bone restoration at the same time. Many questions remain to be answered including which method of preparation, the timing of therapy, volume, or dose, and frequency of treatment [61].

Bone morphogenic proteins (BMP) and PRP are the most widely used GFs. GFs can also be modified genetically to enhance its function or use gene therapy to increase expression of a specific GF if needed for the healing of tissues [62].

Mesenchymal stem cells are multipotent cell populations and

heterogeneous with the capability to differentiate into various other connective tissue cells such as chondral, muscular, bony, and tendon tissue. These cells respond to local microenvironmental stimuli such as growth factors and cytokines, which are released in response of tissue disease or injury. These cells can be induced and expanded, either in vivo or in vitro, to differentiate terminally into neural cells, osteoblasts, chondrocytes, myotubes, adipocytes, tenocytes, and supporting stroma that are hematopoietic [11,14,63]. MSCs secrete a wide range of bioactive molecules, which can include growth factors, chemokines, and cytokines which is thought to represent one of their most significant toles biologically under conditions. Research has suggested that regenerative repair is initiated through MSCs by influencing endogenous progenitor cells locally via paracrine communication [64].

In young adults, substitute cells are provided by MSCs for those cells that expire and can account for the support of turnover dynamics. When it comes to severe tissue damage, these cells function to assist the repair and regeneration process. The mobilization of MSCs could be due to the marrow or other depots or can be expanded culturally MSCs that are delivered to the site of damage either by injection directly or systemically. Inhibition factors are produced, once at the site of lesion, factors for apoptosis and scarring will encourage angiogenesis and stimulate host progenitors to differentiate and separate into regenerative units that are functional [63,65-68].

The immunomodulatory and anti-inflammatory capacity of MSC is very important in the recovery of localized or systemic conditions for regeneration of tissues and normal healing process. In several types of musculoskeletal trauma, inflammatory conditions located at the site of lesion, inhibit the natural repair procedure through local mature and progenitor cells. MSCs forbid function and proliferation of many cells in the immune system, including B cells, T cells, natural killer cells, macrophages, monocytes, and dendritic cells. In particular, MSCs re-establish balance in the types of helper T cells and macrophages: they indirectly promote the transition of the TH2 and TH1 cells, leading to the improvement of tissue regeneration in muscle and cartilage, and a change from macrophages M1, pro-inflammatory and inhibition of tissue growth, to M2, tissue and anti-inflammatory healing [69-71].

The first identified type of MSCs were the BMDCT, and the relatively high quantity of MSCs and facility of the collection still make bone marrow a source of mesenchymal stem cells that is used often. MSCs can be used as bone marrow concentrate or a cell suspension expanded by culture. MSCs, in addition to bone marrow have been found in many fetal and adult tissues, such as umbilical cord, dermis, synovial fluid, placenta, fat, blood, and amniotic fluid [71]. MSCs allow for transplantation without leading to a response of the immune system. MSCs show different performances. Treat chondral lesions and OCDs has been accomplished through the use of Bone marrow aspirates from the iliac crest [72]. MSCs might either be submitted to laboratory expansion within two to three weeks for later use or the aspirate itself after concentration can be instantly inserted. They might be combined with GFs, platelet-rich fibrin gel, collagen gel, fibrin glue, or collagen and hyaluronic acid (HA) scaffolds when it comes to TERM strategies [73].
Adipose derived MSCs acquired from lipoaspirates provide a great advantage as a cell source for the engineering of the cartilaginous tissue, due to their easy availability, abundance, and their potential to differentiate into tendons, cartilage, fate, bone, and skeletal muscle [74].

Synovial acquired stem cells have attracted significant attention as a source of stem cells for engineering of cartilage tissue due to their display of greater chondrogenic and less osteogenic potential than MSCs derived from the periosteum or bone marrow. However other studies are required to confirm this data [75,76].

The orthobiologics approach including, mesenchymal stem cells with or without hydrogels and anabolic proteins (growth factors) represents a step forward on minimally invasive or conservative therapy for OCDs [77,78]. GFs influence the capacity for tissue repair which have functions like chemotaxis, differentiation of cells, proliferation, and cellular responses, which could possibly enhance tissue healing. The use of recombinant autologous GFs is changing in several orthopedic fields [7].

Mesenchymal stem cell based treatment of OCDs and focal chondral lesions has demonstrated promising clinical outcomes in the joints of ankles [36,37,71]. Some reports of hyaline cartilage repair have been presented in recent times [79]. Human amniotic membrane and umbilical cord (hAMUC) fetal tissues and a cryopreserved form of human amniotic membrane has been introduced for osteochondral injuries. These tissues have unique growth factors and proteins in the extracellular matrix. They have also been shown to regulate inflammation, reducing scar formation and adhesion while encouraging healing through regeneration [80]. Hydrogels function by their own properties including anti-inflammatory, rheological, lubrication but they may also operate in combination of MSCs and/or GFs as well as promising scaffolds which may permit control of neovascularization process [81].

The primary purpose of any tissue repair is the combination of the TERM triad (cells, scaffolds, and GFs) even though this can be a challenge. The possibility of one-step procedures for full OCD repairs continues to be a primary goal to shorten the time for the recovery process and avoid costs and comorbidity. Some success has been viewed with this attempt [37,82-84].

Giannini et al combined PRP gel and bone marrow concentrate (BMC) with HA membrane or collagen powder in order to help treat talar OCDs with positive results that were short term. Hyaline-like cartilage have been shown through Histological biopsies. [19,84]. The enhancement in the regeneration of the native tissue with hyaline cartilage and subchondral bone can be seen through the use of multilayered scaffolds [71,79]. The development of an effective scaffold that is seeded with suitable growth factors and cells and matured in the laboratory with the use of bioreactors is one of the

final goals for TERM. It also hopes to accomplish a tissue that would be acceptable for clinical implantation with characteristics that are similar to the native one [7]. The introduction of the use of hydroxyapatite nanoparticles, which might enhance bone integration has observed through the development of a multilayered collagen-based scaffold [86].

Three dimensional (3D) bioprinting techniques are another encouraging possibility for TERM approaches, which enable to fabricate injury implants that are specific. This is useful in the difficult parts of joints geometrically. 3D bioprinting can be used to create regenerative constructs that are custom-made for tissue repair. The CT and/or MRI images of the lesion can help intake where to make the outer shape of the construct based on the patient's defects [87].

## Stem Cell Trials in Animals

Coban *et al*., in 2009 investigated the effects of membrane and human amniotic fluid in the treatment of ruptures of the Achilles tendon [88]. Throughout this study, 72 tendons of 36 Wistar rats had betamethasone sodium phosphate injected into them. By the end of fourth week, both tendons were tenotomized and restored. The samples were then divided into three groups. The rats in the first group were left untreated following suturing. The second group had human amniotic fluid injected into them, and the third group had amniotic fluid and membrane administered to them. There was found to be a substantial statistical difference only between Groups 2 and 3 for the histopathological results in the first week. Results of this study showed human amniotic fluid and membrane will not add anything in the early stage to the healing process of Achilles tendon ruptures [88].

The derivation of connective tissue progenitors from human embryonic stem cell (hESC) lines and fetal tissues was investigated by Cohen in 2010. The connective tissue progenitors were expanded significantly and induced to create tendon tissues in vitro, with biomechanical properties and ultrastructural qualities typical of mature tendons. They investigated a process for engineering tendon grafts that can repair injured Achilles tendons successfully and mend the extension movement of the ankle joint in mice. They also showed the connective tissue progenitor's ability to differentiate into cartilage, bone, and fat in rat models both in vivo and in vitro. This study showed evidence for the potential in the use of engineer grafts from stem cells in the replacement tissues that were missing and will set a basic platform for cell-based tissue engineering applications in the future for the medical specialties of reconstructive surgery and orthopedics [89].

Behfar *et al.*, in 2011 assessed the potential effects of tendon healing in relation to uncultured stromal vascular fraction obtained from adipose [90]. There were twenty-five white male adult rabbits from New Zealand that were used. Five of the rabbits were chosen to act as donors of adipose tissue. The remaining ones were divided into treatment and control groups. Unilateral tenotomy through the middle one-third of deep digital flexor tendon concluded the injury model. Immediately following suture repair, either fresh stromal vascular fraction as a result of digestion from enzymes of adipose tissue or placebo was inserted intratendinously at tendon stumps in both the control and treatment groups of rabbits. Two weeks following the surgery immobilization with cast was continued. Superior fibrillar linearity and continuity was indicated through histological evaluations, and decreased vascularity in treatment group demonstrated enhanced remodeling and organization of neotendons. In the treatment group, immunohistochemistry indicated a significant increase in the expression of collagen I. In comparison to the controls, energy absorption capacity and ultimate load were both significantly increased in cell-treated repairs. The results of this study showed that an improved mechanical and structural properties of tendon repairs could be due to intratendinous injection of uncultured adipose-derived stromal vascular fraction and it could be an effective modality for treating tendon injury [90].

Yao *et al*., in 2012 investigated effect of delivering both bioactive substrates and mesenchymal stem cells on a suture delivery vehicle in comparison with sutures that were coated with solely bioactive substrates [91]. Sprague-Dawley rat femurs were harvested for stem cells that were taken from the bone marrow. Precoated with cell adhesion intercellularly molecule 1 and poly-L-lysine, experimental substrate-coated and cell, coated suture (CS) group sutures were inserted with labeled derived stem cells from the bone marrow. The intercellular adhesion molecule 1 poly-L-lysine only coated Control (substrate-only [SO] coated) group sutures. Achilles tendons found within 105 Bilateral Sprague-Dawley rats were randomized and transected to SO and CS repairs. Results indicated the CS suture repairs exhibit higher levels of strength statistically compared to SO repairs at the seven and ten day mark. They were unable to observe a difference significantly between the overall strength of SO repairs compared with CS suture repairs at the 4, 14, and 28 day mark. The observation that bioactive CS sutures enhanced repair strength at 7 to 10 days were indicated by results of this study. There was effect was not noticeable in the later stages. Within the first 2 weeks after surgery, the strength nadir of a tendon repair will take place. A clinical advantage may be provided through bioactive suture repair by initializing the repair process throughout this strength nadir. Early strength enhancement may allow earlier mobilization that was unprotected [91].

Huang *et al*., in 2013 investigated if there was a relationship between rat MSCs cultured under hypoxic conditions and an increase in the tendon healing potential after transplantation into injured tendons in the Achilles [92]. Fifty Sprague-Dawley rats were utilized for these experiments. The rats were equally divided into 3 groups based on the cut Achilles tendons: normoxic MSC, hypoxic MSC, and nontreated (vehicle control). Outcome measures included histological analysis, mechanically testing 24 rats, and BrdU labeling/collagen immunohistochemistry in another 24 rats. At 2 and 4 weeks following the incision, the results indicated there was an ultimate failure load in the MSC hypoxic grouping that was substantially greater than that in the nontreated or normoxic MSC group. At both at 2 and 4 weeks, histological analysis disclosed that the hypoxic MSC group underwent an enhancement

significantly in Achilles tendon healing when compared with the MSC nontreated grouping. For Achilles tendon ruptures, this study revealed that transplantation of hypoxic MSCs may be a more readily available and better treatment than normoxic MSCs [92].

Adams et al., in 2014 investigated a rat model in order to determine whether the utilization of a stem cell-bearing suture will enhance the healing capabilities of the Achilles tendon [93]. 54 rats were chosen in which the Achilles tendon was transected in 108 bilateral hind limbs. Each of the limbs were randomized to repair with suture only (SO), suture loaded with MSCs (suture with stem cells, SCS), or suture plus injection (SI) of mesenchymal stem cells (MSCs) detected at the repair site. Results would demonstrate that both the SI and the SCS groups had significantly increased ultimate failure strength versus the SO group. At 28 days the strength was maintained in the SCS group, but it was not maintained in the SI group. The histology found the SCS group had significantly enhanced when compared to both of the other groups. Following Achilles repair, this study suggests the utilization of stem cells can improve healing and that embedding of stem cells straight into suture will provide sustained benefits early to tendon healing [93].

McQuilling in 2019 utilized a diabetic model with impaired hearing in order to evaluate the effect of dehydrated human amnion chorion membranes (dACMs) on tendon repair [94]. A full-thickness injury was created through the Achilles tendon and restored using an altered Kessler method. They wrapped repair tendons with dACMs or left them unwrapped as a control. Treatment of tendons with dACM resulted in increased cell migration, decreased failure rates, and improved mechanical qualities (compared with unwrapped controls). The dACM-treated tendons also showed alterations in the production of several significant biomarkers to tendon healing at both 14 and 28 days. The most notable one was Scleraxis which was found to be upregulated in the tendons treated with dACM. Results of this study highlight an encouraging treatment option for this challenging population clinically [94].

Grogan in 2019 orchestrated a study in which mesenchymal stem cell constructs derived from embryos were indicated to be press-fit into 3 mm subchondral defects in white rabbits found in New Zealand [95]. Following 8 weeks of being maintained they were assessed for early tissue repair, retention, and more mature cartilage regeneration. Infrapatellar fat pad mesenchymal stem cell neotissues integrated with the surrounding osteoarthritic host cartilage and demonstrated high levels of chondrogenic genes. As early as 2 weeks, embryonic-derived mesenchymal stem cell constructs generated chondrogenic neotissue in vivo and more mature tissue with higher glycosaminoglycan deposition following the 8 weeks [95].

## Stem Cell Trials in Human Ankles

In 2008, Hangody arranged a study evaluating autologous osteochondral mosaicplasties [45]. There were 1097 patients that would be included in the study. Of these patients, 98 of them had the procedure performed in the talus. The authors reported good to excellent clinical results in the talus for 93% of the patients based on assessment with the Hannover Scoring System [45].

Mei-Dan et al., in 2012 evaluated the efficacy short-term and safety of platelet-rich plasma (PRP) compared with hyaluronic acid (HA) in their ability to reduce pain and disability due to ankle osteochondral lesions (OCL) [96]. Thirty-two patients were assigned to a treatment through intra-articular injection of either HA (group 1) or PRP plasma rich in growth factors (PRGF) technique, group 2) for talus OCLs. 15 OCLs for each arm were administered as 3 intra-articular therapeutic injections consecutively. For the next 28 weeks, these people were followed and assessed. The injections' efficacy in enhanced functional ability and reduction in pain was analyzed and evaluated at each of the visits utilizing scales from the AOFAS; VAS for stiffness, pain, and functional ability; AHFS; and the subjective global function score. In groups 1 and 2 through the 28 week period, the AHFS score increased from 66 and 68 to 78 and 92. There was a reduction in groups 1 and 2 in mean VAS scores for pain, functional capability, and stiffness. By week 28, subjective global function scores increased for groups 1 and 2. Results of this study demonstrated that for at least 6 months osteochondral lesions of the ankle with the treatment of intra-articular injections of HA and PRP would cause a reduction in the pain scores and an improvement in functional capability. It would also result in minimal adverse events. Platelet-rich plasma treatment exhibited substantially improved outcome than HA [96].

In 2013, Giannini investigated the results after 4 years of a series of patients who underwent a one-step repair of talar dome osteochondral lesions, as well as the ability of MRI using a sequence that utilizes T2-mapping to foresee the clinical outcome [96]. A one-step repair of OLTs was performed on forty-nine patients with a mean of 28.08 and a standard deviation of 9. Patients were assessed clinically by AOFAS scores and radiographs and underwent MRI preoperatively and at predetermined times during postoperative follow-ups. In all patients, the cells were taken from the iliac crest, concentrated, and filled on a scaffold that was inserted arthroscopically. At 48 months, the overall AOFAS score increased preoperatively. The best results occurred at follow-up after the 24-month. The time between the surgery and occurrence of trauma was established to negatively affect the outcome clinically at the most recent follow-up. Results demonstrated one-step repair of OLTs had good clinical results that were remained over a period of time, even though there was a small reduction in AOFAS score at the latest follow-up. There was a direct correlation with the clinical results and the quality of the regenerated tissue detected by MRI T2 mapping [96].

Pierini et al., in 2013 investigated a comparison of the concentrate, total number of cells, and prevalence of colony-founding connective-tissue progenitors from the posterior and anterior iliac crest [97]. They also compared the multilineage differentiation potential and expansion kinetics of their culture-expanded progeny when processed to form mesenchymal stem cells. Marrow aspirate was accumulated from both the posterior and anterior iliac crest of twenty-two patients. The prevalence and concentration of colony-founding connective-tissue progenitors were estimated with the utilization of a colony formation assay. The multilineage differentiation potential was compared to the development kinetics of the culture-expanded mesenchymal stem cell populations obtained from these original samples. In

the posterior when compared with the iliac crest anteriorly, yield of colony-founding connective-tissue progenitors was found to increase by 1.6 times. No dissimilarities were discovered with respect to the expansion kinetics, phenotype, viability or potential multilineage differentiation of mesenchymal stem cell populations gathered from these two sites. Results of this study demonstrated obtaining bone marrow from the iliac crest posteriorly appears to be the preferred method, as it provided a modestly increased concentration of connective-tissue progenitors found in colonies than comparable aspirate from the iliac anteriorly crest [97].

In 2013, Kim assessed the outcomes clinically of the injection of MSC and stimulation arthroscopically of the marrow treatment with solely arthroscopic marrow stimulation treatment for the overall treatment of OLTs in patients that were older [98]. A total of 107 patients over the age of 50 with OLTs treated arthroscopically were incorporated throughout this study. Patients had separated into two groups: 35 patients solely treated with marrow stimulation treated arthroscopically (group A) and 30 patients who experienced arthroscopic marrow stimulation treatment along with MSC injection (group B). Outcomes clinically were assessed utilizing to the VAS, for pain, the AHFS provided by the AOFAS, and the scale from Roles and Maudsley. The average VAS score and AOFAS score notably showed signs of improvement in both groups. The Roles and Maudsley score demonstrated a substantially increased improvement post-surgery in group B in comparison to group A. The Tegner activity scale score had substantially improved in group B but not in group A. Results of this study indicated patients over the age of 50 were encouraged to inject MSCs with treatment via marrow simulation compared with patients that were treated with solely treatment involving marrow stimulation [98].

Kim et al., in 2014 assessed the magnetic resonance imaging (MRI) and clinical outcomes between injection of MSCs with stimulation of the marrow and solely- based patients who had OLTs and underwent marrow stimulation [99]. After arthroscopic treatment, there were 49 patients with OLTs who underwent a follow-up MRI. 26 of the total 49 patients underwent only marrow stimulation (conventional group), and 23 were injected with a stromal vascular fraction containing MSCs (marrow stimulation with MSC group). The clinical outcomes were assessed and analyzed in comparison to the VAS for pain, AOFAS AHFS, and Tegner activity scale. All clinical outcomes, including the scores from the AOFAS, VAS, and Tegner substantially improved when it came to the MSC group when compared alongside of the conventional group. Results demonstrated both clinical and MRI outcomes of a stromal vascular fraction injection containing MSCs with marrow stimulation were encouraging, compared with outcomes that involved solely the stimulation of marrow, for the OLTs related treatment [99].

Stein et al., in 2015 described the utilization of adipose derived stem cells (ADSC) in order to treat Achilles tendinopathy in comparison to the PRP injection [100]. There were a total of 44 patients were incorporated into the study. There were 21 in the ADSCs group and 23 in the PRP group, there was a sum of 28 tendons in each group that were treated. Patients were postoperatively and preoperatively assessed with the AOFAS AHFS and VAS pain scale. This study discovered that both groups had enhanced results from pre-op to post-op, but the ADSC group had significantly improved outcomes at both the 15 and 30 day post op in comparison to the PRP group. There was no noticeable difference that was recognized in later post-op time marks. This data proposes a positive effect on activities or early return to play for ADSCs group [100].

Anderson et al., in 2015 assess the utilization of amniotic membrane allograft throughout ankle arthroscopy/ microfracture for lesions of the talar dome less than 2 cm [101]. A sum of 101 patients who had gone through arthroscopy with micro-fracture technique for the treatment of a dome of the talar lesion less than 2 cm were incorporated in this study. There were 54 surgeries with human amniotic allograft that were completed; 47 were concluded without the human amniotic allograft (control group). Modified AOFAS scores that were taken prior to the operation of the ankle for the third, twelfth, and twenty-fourth months post-operatively. Visual analog pain scores were taken prior to the operation and 24 months following the operation. Following ankle arthroscopy with micro-fracture, there were notable enhancements in both scores of groups that were anticipated. However, when looking at the post-operative scores, the amniotic tissue group did substantially better when compared between the graft group and the control. For both 24 months following and early, pain scores comparing amniotic patient groups and control were notable with amniotic allograft patients demonstrating an increased improvement in an overall decrease in pain than the control. Findings of this study demonstrated that the combination of ankle arthroscopy/micro-fracture ankle technique involving lesions of the talar dome, less than 2 cm in length, which had a human amniotic allograft, substantially enhances the patients' AOFAS scores and pain [101]. McAlister et al., in 2015 arranged a study that revealed that the concentration of pluripotent cells was highest in the iliac crest [102]. A radiographic review and medical record was conducted to compare the overall effect of bone marrow adiposity (BMA) harvest site osteogenic progenitor cells on the fusion incidence. The radiographs were investigated further. There was a sum of 33 patients incorporated into the study. At 13 weeks, 32 of the 33 patients had a radiographic fusion (96.96%). A comparison of the fusion incidences with the utilization from 3 anatomic sites containing osteogenic progenitor cells demonstrated a lower-level incidence of complications and a higher level of fusion incidence. There was no association to be found between the fusion incidence and BMA concentration. This proposed a minimum concentration and biologic potential of pluripotent cells is required in order to achieve the effect of fusion clinically [102].

Hernigou et al., in 2015 orchestrated a study that would investigate the utilization of percutaneous technique in which bone marrow-derived, autologous, concentrated cells are inserted at the location of non-unions for patients who had diabetes with ankle and distal tibia fractures [103]. There were 86 ankle non-union patients with diabetes that were treated with bone marrow mesenchymal stem cells (BM-MSCs). These stem cells were delivered in bone marrow

concentrate (BMC) that was found to be autologous. The outcomes clinically of 86 BMC-treated diabetic non-union patients were compared with 86 complemented diabetically non-unions treated with an autograft from the bone iliac crest. Results demonstrated 70 out of the 86 patients with diabetes (82.1 %) had a decreased number of complications when treated with BMC promoted non-union healing. 53 (62.3 %) of the 86 diabetic individuals that were treated with iliac bone graft demonstrated healing. However, significant complications were observed: osteonecrosis of the fracture wound edge (11), amputations (5), and there were infections (17). This study demonstrated that in diabetic patients with ankle non-unions, the treatment of individuals with bone marrow concentrate-derived BM-MSCs might be the selected method as a result of the increased risks of major complications after iliac bone grafting and open surgery, and increased rates of healing compared with standardized autograft treatment of the iliac bone [103].

Hannon et al., in 2016 evaluated MRI and the functional outcomes following bone marrow stimulation (BMS) arthroscopically with and without concentrated bone marrow aspirate (cBMA) as an adjunct biologically to the osteochondral lesions (OCLs) surgical treatment of the talus [104]. There were 12 patients who underwent arthroscopic solely BMS for an OCL of the talus and twenty-two patients who had undergone BMS arthroscopically with cBMA (cBMA/BMS group) for an OCL of the talus were reviewed. The pain subscale from the Foot and Ankle Outcome Score (FAOS) and Short Form 12 questionnaire from general health physical component summary score (SF-12 PCS) produced a record of the patient's outcome scores both prior and after the operation. Scans from an MRI were evaluated following the operation utilizing the score from the magnetic resonance observation of cartilage repair tissue (MOCART). All patients had MRI performed following the operation at the 2-year visit postoperatively. The average SF-12 PCS and FAOS scores showed improvement substantially for the BMS/cBMA group. In the BMS/cBMA grouping, the score from the MOCART was significantly increased than that in the group with only BMS. Deep and superficial T2 relaxation values in BMS/cBMA individuals were increased in tissues that was repaired compared with adjacent native articular cartilage measurements. The results of this study demonstrate that good medium-term outcomes functionally can be due to BMS being an effective strategy for treatment of OCLs found in the talus. Arthroscopic BMS with cBMA also indicates functional outcomes similarly and enhanced repair tissue incorporation of the border, with less evidence of fibrillation and fissuring on MRI [104].

Usuelli et al., in 2018 evaluated the efficacy of stromal vascular fraction (SVF) and PRP injection for the treatment of non-insertional Achilles tendinopathy [105]. This study used forty-four patients; 23 of these patients were part of the PRP group while SVF group had 21 assigned to it, treated either bilaterally or unilaterally. After 15, 30, 60, 120 and 180 days all patients were assessed prior to operation clinically from treatment using the VAS pain scale, the VISA-A, the AOFAS AHFS and the SF-36 form. MRI and ultrasound were also used in order to evaluate the patients prior to treatment and following 4 and 6 months. The findings of this study demonstrated both treatments allowed for an enhancement in relation to the baseline. In comparison of the two groups, at fifteen and 30 days, VAS, AOFAS and VISA-A scored significantly better in the SVF when compared to the PRP group. The individuals treated with SVF acquired quicker results, thus indicating that this method of treatment should be considered for those individuals who need to resume daily activities or sports quicker [105].

For the management of OLT, Akpancar et al., in 2019 studied the use of PRP and prolotherapy injections [106]. Forty-nine patients who displayed OLT symptoms were evaluated in a cohort retrospective study. These symptoms had occurred for more than 6 months who were refractory to 3 months of treatment utilizing methods conservatively. These patients were separated into 2 groups. Twenty-two of the individuals in the first group were given PRP injections. Twenty-seven patients in the second group were given prolotherapy injections. Three 4 mL injections of solution were given to the patients that were administered into the intraarticular and periarticular ankle joint spaces. Post-treatment, patients were evaluated utilizing the VAS, Ankle Osteoarthritis Scale, and AOFAS. They were scored at their baseline and 21st, 90th, 180th, and 360th day periods at the follow-ups. Both the prolotherapy and PRP methods of treatment caused an increased improvement in ankle functionality and pain at one year follow-up periods. At follow-up periods, there was also no difference or abnormality observed between the groups for the results. The prolotherapy group demonstrated good/excellent outcomes in 88.8% of the individuals. The PRP group saw similar outcomes as 90.9% of individuals were reported as good or excellent. This study indicated both PRP and prolotherapy are safe and efficient treatment methods of OLT. Less cost and minimal invasiveness can be seen as advantages of prolotherapy [106].

Keene et al., in 2019 evaluated the effect of injections of platelet rich plasma following an acute tendon rupture of the Achilles [107]. Incorporated in this study were 230 adults aged over 18 years, with an acute tendon rupture of the Achilles. They were managed with non-surgical treatment and presented within 12 days following injury. Of the participants, 114 were given an injection of the platelet rich plasma while 116 were given a placebo injection. The individuals were randomly selected. All participants acquired standard rehabilitation care which incorporated ankle immobilization followed by physiotherapy. Primary outcome measurements included: heel rise endurance test, muscle tendon function at 24 weeks, quality of life questionnaire, Achilles tendon rupture score, visual analogue scale, functional scale that was patient specific, and adverse events. No difference was observed in muscle tendon functionality between participants were injected with the placebo and those receiving platelet rich plasma injections There is no evidence to suggest that injections of platelet rich plasma can enhance functionality of the objective muscle tendon/patient-reported or quality of life following a rupture of the acute tendon of the Achilles compared with placebo, or that they offer any benefits for the patient [107].

Richter et al., in 2019 analyzed the 5-year-follow-up following matrix-associated stem cell transplantation (MAST) in chondral lesions at the ankle as part of a complex approach surgically [108]. One hundred and twenty individuals with 124 chondral lesions were incorporated in the study. An assessment was performed on the location and size of the chondral lesions, method-associated problems, and the VAS during the follow-up and prior to the treatment. Blood containing many stem cells was taken from the bone marrow ipsilaterally of the pelvis. It was then fixed and centrifuged into the chondral lesion with glue containing fibrin. A five-year follow-up was then completed on one hundred patients (83%). VAS showed signs of improvement as it increased from 45.2 to 84.4. This study indicated that during the mid-term-follow-up, MAST as part of a surgical method led to overall enhancement and highly validated outcome scores [108]. Current evidence suggests that bone marrow aspirate has the ability to enhance cartilage in osteochondral lesions but continued clinical research trials are required for a better comparison of results with other biological adjuncts [11].

## Conclusion

Current treatment options for orthopedic procedures including ankle injuries offer surgical options as well as the utilization of MSC transplantation in subjects that are both human and animal. Ankle surgeries may lead to considerable medical complications, possible side effects and extended rehabilitation time. Researchers have found MSC transplantation displayed enhanced clinical and functional outcomes in animal models including improved healing response, regeneration of tissue, enhanced tensile strength and improved functional and activity level. Human trials have shown improved quality in tissue and rate of healing, sustained gains functionally, decreased pain, and enhanced outcomes clinically. Researchers believed the use of stem cells may offer options for patients with injuries related to orthopedics including OCD to reduce time of recovery, enhanced function, and reduced osteoarthritis. Additional research trials are required to investigate functional effects and the efficacy for transplantation of stem cells for human patients with ankle related injuries including outcomes that may be long-term.

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