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Review Article

The Effects of Stem Cell Therapy on Recovery of the Anterior Cruciate Ligament and in its Repair Following Surgical and Non-Surgical Intervention

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Abstract

Currently, the Anterior Cruciate Ligament (ACL) is one of the most injured ligamentous structures in the human body. Through unyielding technological advancements in surgical procedures and increased knowledge in physiotherapeutic methods, recovering from an ACL tear is currently easier than ever. However, even with such advancements and increased knowledge, the period of recovery following an ACL injury is still extensive, with or without surgical intervention. Not to mention, the risks associated with either option or increased susceptibility of retear following an injury. It is evident that progress through unwavering efforts must continue to be made to improve the current state of treatments used for ACL ruptures. This literature review intends to present evidence to advocate for the use of Stem Cell Therapy (SCT) simultaneously with surgical or non-surgical methods to improve overall recovery and reduce the possibility of re-injury following an ACL tear. After presentation of this evidence, optimistically a better understanding of the current state of SCT for use in ACL injuries will be formed, stimulating further research and increasing financial interest from potential investors.

Keywords: Stem Cells; Anterior Cruciate Ligament (ACL) Repair; Therapy

Abbreviations

SCT: Stem Cell Therapy; ACL: Anterior Cruciate Ligament; ESCs: Embryonic Stem Cells; ASCs: Adult Stem Cells; iPS: Induced Pluripotent Stem Cells; HSCs: Hematopoietic Stem Cells; MSCs: Mesenchymal Stem Cells; ATT: Anterior Tibial Translation; PCL: Posterior Cruciate Ligament; MCL: Medial Cruciate Ligament; LCL: Lateral Collateral Ligament; IN: Intercondylar Notch; AMB: Anteromedial Bundle; PLB: Posterolateral Bundle; ALB: Anterolateral Bundle; PMB: Posteromedial Bundle; sMCL: Superficial Medial Collateral Ligament; dMCL: Deep Medial Collateral Ligament; MFL: Meniscofemoral Ligament; MTL: Meniscotibial Ligament; PTT: Posterior Tibial Translation; MRI: Magnetic Resonance Imaging; BMC: Bone Marrow Concentrate; BMAC: Bone Marrow Aspirate Concentrate; SF-MSCs: Synovial Fluid Mesenchymal Stem Cells; , BM-SCs: Bone Marrow Stem Cells; HUC-MSCs: Human Umbilical Cord Mesenchymal Stem Cells; PSCs: Periosteum Stem Cells; SMSCs: Skeletal Muscle Stem Cells; AT-MSCs: Adipose Tissue Mesenchymal Stem Cells; PRP: Platelet Rich Plasma; PL: Platelet Lysate; BTB: Bone Patellar Tendon Bone; IKDC: International Knee Documentation Committee

Introduction

Stem Cell Therapy

Stem Cell Therapy (SCT) is a form of regenerative medicine that has the potential to treat innumerable health conditions. Additionally, Stem Cell Therapy is a potent tool that aims to restore the structure and function of damaged tissues at the cellular level that otherwise would be impossible with standard operative or allopathic methods. Stem Cell Therapies use stem cells, which are unspecialized cells that have the unique ability to self-renew or differentiate into specialized cells [1,2].

Stem cells can be classified as Embryonic Stem Cells (ESCs), Adult Stem Cells (ASCs) or induced Pluripotent Stem Cells (iPS). Stem cells are further categorized by their specific abilities and limitations [2]. Totipotent stem cells have the ability to differentiate into all cell types including embryonic membranes. Pluripotent stem cells can differentiate into all types of cells but unlike totipotent stem cells, are limited in their ability to differentiate into embryonic membranes. Multipotent stem cells can differentiate into multiple mature cells.

ESCs are totipotent stem cells that are harvested from blastocysts, which are embryos that are 2-11 days of age [3]. ASCs often referred to as postnatal stem cells or somatic stem cells are multipotent stem cells that can be further classified as Hematopoietic Stem Cells (HSCs) or Mesenchymal Stem Cells (MSCs) [2]. ASCs that can be harvested from blood tissue, including cord blood and bone marrow fall under the classification of HSCs. MSCs are found in tissue that was originally formed by the mesoderm layer. Bone marrow, umbilical cord tissue, limbic tissue, adipose tissue and dental tissue are some examples of mesoderm tissues used to harvest stem cells classified as MSCs. iPS or induced pluripotent stem cells are stem cells derived from MSC's that have been genetically reprogrammed to behave like embryonic stem cells through manipulation of genes [2,4]. Stem cell therapy can stimulate the natural process of healing an organism possesses and even extend that healing to treat diseases, conditions or injuries that are otherwise too complex to be treated using only allopathic methods.

Musculoskeletal System

Osseous tissue, fibrous tissue, cartilage tissue and muscle tissue all come together to form the musculoskeletal system, which provides stability, support and locomotion. The musculoskeletal system facilitates upright movement, daily activity, physical activity and basic strength. Arguably the most integral component of the musculoskeletal system is the osseous tissue that makes bones. Bones make up the basic framework of the body, permit locomotion, protect vital organs, provide electrolyte homeostasis, mineral storage and synthesize new cells. Skeletal muscle tissue forms muscle which provides additional rigidity, strength and facilitates locomotion, homeostatic temperature and storage of glycogen. Fibrous tissue makes the tendons and ligaments which together make the anchoring points of muscle to bone and bone to bone interactions. Cartilage tissue resists bone wasting and provides shock absorption for the compressive forces withstood by the musculoskeletal system. Osseous tissue, fibrous tissue, skeletal muscle and cartilage tissue are the constituents of the musculoskeletal system and provide a basis for locomotion and homeostasis [5,6]. Therefore, due to the nature, importance and complexity of the musculoskeletal system it is crucial to be conscious and aware about precautionary actions that can reduce risk of ACL injuries such as maintaining health through exercise and adequate nutrition.

ACL Injuries

ACL injuries are common injuries that occur in the lower extremities of the musculoskeletal system and can occur in a variety of ways but typically occur while participating in the high demand activities seen throughout a multitude of sports. ACL injuries can present after an individual experiences a non-contact injury, direct trauma and indirect trauma. Commonly, ACL injuries occur following rapid deceleration, rapid directional change, jumping or after landing in a position that would be contrary to that of normal anatomical movement [7,8]. Many other factors may contribute to risk of ACL tears including sex and genetics.

Incidence and Epidemiology of ACL Ruptures

One of the most frequently torn ligaments in the human body is the ACL [9]. In a study it was found that approximately 1 in 3500 people in the United States tear their ACL's and an approximate 400,000 ACL's are reconstructed in the US yearly [10]. Recent studies reveal that females are at an increased risk of ACL tears when compared to their male counterparts. Weaker hamstrings or dominance of the quadricep is thought to be a factor that increases likelihood of females tearing an ACL, which employs greater tensile forces on the ACL during deceleration [10]. Females tend to position their knees in a way that increases knee valgus angulation when changing directions, which decreases hip and knee flexion and places enormous loads on an ACL. Increased flexibility, smaller ACL's, increased body mass index and small femoral notches are also factors that contribute to increased ACL tear risk in females [10]. Additional factors are suspected to increase risk in females, but are mostly theories and otherwise controversial.

Other risk factors surrounding the nature of different sports are evident. Sports referred to as high demand sports, such as skiing, football, soccer and basketball may expose athletes to a multitude of strenuous movements or even trauma, which obviously increases the risk of rupturing an ACL. Like other health issues, having a family history of ACL injury increases the probability of injuring an ACL [11]. Higher risk of ACL tears can additionally be attributed to the age of a person. Between the ages of 19 and 25, males are predisposed to have ACL tears, while females are more predisposed between the ages of 14 and 18 [12]. Anyone that is interested in maintaining a healthy lifestyle and being a productive athlete should be aware of the risks and patterns that can lead to ACL tears and how to minimize them.

Etiology of an ACL Rupture

Non-contact, direct trauma and indirect trauma are several ways an ACL can be damaged. Anterior Tibial Translation (ATT) and valgus angulation from trauma, rapid change in direction and jumping can easily provoke an ACL rupture. Football players are the athletes at highest risk of tearing an ACL due to trauma, while soccer player, basketball players and skiers usually risk tearing an ACL through non-contact. It is common for imaging or arthroscopy to reveal damage to neighboring tissues such as the Posterior Cruciate Ligament (PCL), Medical Collateral Ligament (MCL), Lateral Collateral Ligament (LCL) and menisci following an injury to an ACL [10].

Anatomy and Physiology of the Knee

Anatomy

The knee is a synovial hinge joint that is comprised of the femur, tibia, fibula, cruciate ligaments, collateral ligaments, menisci and articular cartilage. The Anterior Cruciate Ligament (ACL) and the Posterior Cruciate Ligament (PCL) make up the cruciate ligaments. The cruciate ligaments sit within the intercondylar fossa often referred to as the Intercondylar Notch (IN) [10].

The ACL sits parallel to Blumensaat's line and originates at the posteromedial aspect of the lateral femoral condyle and inserts at the anteromedial aspect of the intercondylar area of the tibial plateau [13]. The ACL is divided into two major fiber bundles named the Anteromedial Bundle (AMB) and the Posterolateral Bundle (PLB). The AMB is tightest with knee flexion, while the PLB is tightest with knee extension [10, 13, 14]. The PCL originates from the anterolateral aspect of the medial femoral condyle and inserts along the posterior aspect of the tibial plateau [15]. Like the ACL, the PCL is also divided into two major fiber bundles named the Anterolateral Bundle (ALB) and the Posteromedial Bundle (PMB). The ALB and PMB function synergistically, with the ALB being tight while the PMB is lax with knee flexion, whereas the ALB is lax and the PLB is tight with knee extension [15,16].

The collateral ligaments are comprised of the Medial Collateral Ligament (MCL) and the Lateral Collateral Ligament (LCL), which as hinted by their name, sit on the medial and lateral aspects of the knee respectively. The MCL is a flat band composed of the superficial Medial Collateral Ligament (sMCL) and the deep Medial Collateral Ligament (dMCL). The sMCL originates proximally at the medial femoral epicondyle and inserts distally at the posteromedial tibial surface [17]. As the name suggests, the dMCL rests underneath the sMCL and is made up of the Meniscofemoral Ligament (MFL) and the Meniscotibial Ligament (MTL) [18]. The MFL originates slightly distal to the sMCL's proximal origin, but instead anchors distally at the medial meniscus [17]. The MTL originates distally at the articular cartilage of the medial tibial plateau and anchors at the medial meniscus, where it converges with the MFL to form a complete dMCL [17-19]. The LCL is a cord-like ligament that originates at the lateral femoral epicondyle and inserts distal to the fibular styloid tip [20].

The menisci are two crescent-shaped structures made of fibrocartilage that rest on the tibial plateau. One crescent is called the medial meniscus and the other is called the lateral meniscus. The medial meniscus is the larger of the two and is divided into five anteroposterior zones [21,22]. Zone 1 is called the anterior root attachment and zones 2A and 2B are the anteromedial portion between the posterior border of the anterior root and the anterior border of the sMCL. Zone 3 is adjacent to the sMCL, zone 4 is the posterior horn and finally zone 5 is the posterior root. While the medial meniscus is large, the lateral meniscus is relatively uniform in thickness. The lateral meniscus is divided into six anteroposterior zones [22]. Zone 1 is the anterior root and zones 2A and 2B make up the anterolateral zone between the anterior root and anterior border of the popliteal hiatus. Zone 3 is called the popliteal hiatus, zone 4 is the posteroinferior popliteomeniscal fascicle, zone 5 is called the ligamentous zone and zone 6 is called the posterior root. Together the femur, tibia, fibula, cruciate ligaments, collateral ligaments, menisci and articular cartilage form the basic structure of the knee.

Physiology
All components of the knee work together to provide the stability and strength that characterizes a functional knee. The most important knee stabilizers are the cruciate ligaments. The ACL functions by preventing Anterior Tibial Translation (ATT) and by being a secondary restraint to internal rotation and varus-valgus angulation [24]. The PCL prevents Posterior Tibial Translation (PTT) and act as a secondary stabilizer to varus, valgus and external rotation about the knee [15].

The MCL's superficial and deep portions, have unique functions. The proximal sMCL resists valgus forces, whereas the distal sMCL stabilizes external rotation of the knee specifically when the knee is flexed at 30-degrees. The dMCL stabilizes internal knee rotation from 90-degrees of flexion through full extension. The MCL additionally resists tensile loads, prevents hyperextension and functions as a secondary restraint to PTT [17]. The LCL primarily resists varus stress and provides posterolateral knee stabilization. When the knee exhibits 0-degrees to 30-degrees of flexion the LCL resists external tibial rotation. If the cruciate ligaments happen to tear, the LCL will minimally prevent ATT and PTT [20].

The knee menisci function by deepening the tibial plateau, transmitting joint load, providing shock absorption and increasing knee stability [21-23]. Due to the flat nature of the tibial plateau, the menisci create a concave superior surface that precisely molds to and surrounds the shape of both femoral condyles. The triangular cross-sectional shape of the menisci provides exceptional transmission of joint loads that function by improving the joint interaction between the tibial plateau and the femoral condyles and in turn minimize contact pressure on articular cartilage. The elastic nature of the menisci help it function as a shock absorber when the knee experiences usual daily movements. Lastly, the articular knee cartilage provides a smooth surface with firm consistency that distributes loads with little frictional resistance, ensuring the knee exhibits true synovial joint characteristics.

Discussion

Causes and Types of Injuries
ACL tears typically occur in people who play high-demand sports such as football, soccer, basketball, gymnastics and skiing. ACL injuries commonly arise in varying fashion including non-contact injuries, direct trauma and indirect trauma. Most ACL injuries are non-contact and occur with rapid deceleration, directional change, stopping, pivoting, jumping, pivoting or landing awkwardly after a jump. In other scenarios, patients may experience an ACL rupture after direct trauma to the legs, commonly after impact to the anterior tibial aspect. ACL injuries are classified by severity, with Grade I, II or III sprains [25]. Grade I tears display ATT of approximately 3-5 mm and are indicative of an ACL sprain or less commonly a tear that is less than one third of the ligament. Grade II tears are rare with approximately 5-10 mm of ATT and usually indicate a partial rupture of the ACL. Grade III tears are the most common ACL injuries characterized by ATT that is 10 mm or greater. Grade III tears are used to classify a completely torn ACL that is incapable of stabilizing a knee. Depending on the nature of the injury and the mechanism by which the injury occurred, ACL injuries can also be accompanied by damage to neighboring tissues, primarily the MCL and menisci.

Symptoms and Diagnosis
Patients with torn ACL's generally present with severe pain, edema, hemarthrosis, restricted range of motion and instability after experiencing a popping sensation during the incident. If a patient with a Grade I tear decides to return to activity without seeking appropriate medical attention, symptoms may be exacerbated and a Grade III tear can occur. To diagnose a torn ACL a physician performs a physical examination that involves inspecting, palpating, moving and implementing provocative maneuvers to the injured knee. Through inspection physicians can determine if a patient demonstrates quadriceps avoidance gait [10]. Palpation can indicate signs of tenderness that may be associated with the ACL or accompanying injured tissue and also aids a physician in determining how severe edema may be. Aside from palpation, movement may show signs of damage to surrounding ligaments besides the ACL. During a physical exam, provocative movements are the best method to assess an ACL injury. Provocative movements include the Lachman test, anterior drawer test, pivot shift test, lever sign test and the KT-1000 test [10]. The Lachman test is by far the most effective at evaluating an ACL rupture. A physician can perform the test with a patient in the supine position and the knee flexed at approximately 30-degrees. The physician will then stabilize the distal femur with one hand and pull the tibia forward with the other hand. Increased ATT will be a good indicator of a ruptured ACL. The anterior drawer test can be done while a patient is in the supine position with the foot planted and 90-degrees of knee flexion. A

physician can stabilize the patients foot by sitting on it before gripping the proximal tibia with both hands and pulling it forward. Presence of abnormal ATT provides strong evidence of a torn ACL. The pivot shift test is performed by applying valgus stress to the knee while simultaneously providing internal rotation of the tibia and shifting the knee between extension and flexion. To perform a lever sign test, a patient will lie in a supine position and the physician will place his fist under the patient's tibia while applying downward force to the distal femur. If pushing on the distal femur results in extension, it is a good indication of an intact ACL. However, if a physician pushes on the distal femur and the patient's heel remains on the examination table, the ACL may be ruptured. The KT-1000 test is performed using a KT-1000 arthrometer which slightly flexes the knee and puts it between 10 to 30-degrees of external rotation, helping a physician quantify anterior laxity. After experiencing an ACL rupture, a patient may display guarding due to pain, making it difficult for a physician to perform a physical exam. Additionally, a physician might have difficulty assessing the severity of the injury or determining if accompanying ligamentous structures are damaged. With imaging, a physician can more accurately diagnose an ACL injury without causing significant amounts of pain to the patient. Magnetic Resonance Imaging (MRI) and radiographs are generally used to diagnose ACL ruptures [10]. Primary signs of an ACL tear in an MRI include edema, increased signal on T2 or proton density images, discontinuity or absence of fibers, abnormal orientation relative to Blumensaat's line, empty notch sign or a flat appearance of ACL fibers. Secondary signs are lateral femoral condyle and posterolateral tibial plateau edema, ATT greater than 7 mm, displacement of the posterior horn of the lateral menisci, MCL or LCL injury, Segond fracture, PCL bowing, PCL line sign and tibial spine avulsion fractures [10,20,26,27]. Radiographs are not used to diagnose ACL injuries but rather help rule out fractures and non-specific features like the Segond fracture, Arcuate fracture, deep sulcus terminalis sign, joint effusion and deep lateral sulcus sign.

Traditional Treatment Options

When an Orthopedic surgeon approaches the treatment of an ACL rupture, there are currently two main methods to care for a patient. One method takes a non-surgical approach, while the second method uses surgery to treat an ACL. To decide which of these two methods meet the demands of a patient, a surgeon must consider the patient's age and health status, their daily activity level, whether the patient participates in sports and the condition of neighboring ligamentous tissues [10].

A non-surgical approach is common in patients with Grade I tears. It is also typical in the elderly population where the health benefit post-operation does not outweigh the damages that may be done through anesthesia or the recovery process. Non-surgical approaches require lifestyle modifications, including regularly attending physiotherapy appointments in effort to regain knee function. If a patient with good health is unable to regain function or reports increased weakness after attempting a non-surgical approach, surgery should be considered due to concerns with regressing or compromised knee health.

Surgical approaches are generally common compared to non-surgical approaches. If patients have Grade II or III tears, desire a return to a normal lifestyle or are athletes, a surgeon may recommend a surgical approach. Two surgical options are ACL reconstruction and ACL repair. ACL reconstruction is the more popular method due to its higher success rate amongst patients, particularly those participating in high demand activities post-operatively [10,29]. ACL reconstruction utilizes an autograft or an allograft in place of the original ACL ligament, with autografts generally being more popular [28]. ACL reconstruction's higher success rate can be attributed to its reliability in restoring knee stability with use of a graft, which minimizes probability of secondary ligamentous injuries or chondral knee injuries [10,29].

Contrary to ACL reconstruction, ACL repair aims to restore the pre-ruptured state of the original ACL ligament without use of a graft, with proximal ACL tears being most suitable for repair. ACL repair more closely replicates the native anatomy of the ACL, particularly the insertion sites, bundle morphology, innervations, biological integration and intrinsic cell populations [30]. Additionally, ACL repair eliminates the risk of disease transmission and immunological rejection that accompanies grafts, particularly allografts.

Reasons Traditional Treatment Options are Ineffective

ACL reconstruction is currently the most effective treatments for a torn ACL. Reconstruction leads to a desired outcome in approximately 80-90% of patients [31]. However, even with the positive reputation of ACL reconstruction surgery, it is still important to note that 10-20% of patients still experience some sort of graft failure and necessitate an ACL revision operation. In a separate publication, risk of failure ranged from 1.8-11.1% at mid-term follow-up and as high as 10.4-16.7% at long-term follow-up [28]. There are various intraoperative and postoperative complications which contribute to ACL reconstruction failure.

Inadequate healing and postoperative trauma are factors that certainly contribute to ACL revision incidence [32]. Nonetheless, surgical techniques still contribute significantly to incidence of ACL revisions. Examples of complications relevant to this study are technical errors, missed diagnosis and the stiffness that can be associated following a surgery [28,32,33].

Although trauma is the single greatest contributor to graft failure, accounting for nearly 29-70% of revisions, it is evident that technical errors contribute significantly. Nearly 22-79% of graft failures occur because of technical errors [28]. Tunnel malpositioning is a technical error that is one of the leading causes of graft failure. Mitchell, et al., found that 52% of ACL revision cases can be attributed to tunnel malpositioning, while Ozbek, et al., found that more than 80% of graft failures are caused by tunnel malpositioning [32,34]. Tunnel malpositioning during an ACL surgery can obviously occur on both the femoral and tibial side, with the most often misplaced side being the femoral side [32]. Side effects of tunnel malpositioning are graft strain, instability, graft impingement and meniscal lesions [28,32,35]. A femoral tunnel placed in an increased vertical and anterior position can result in rotational instability, increased tightness with flexion and abnormal laxity with extension [10]. Anterior malpositioning causes ligamentous failure when controlling rotary laxity, resulting in residual pivot shift [35]. On the contrary, when a femoral tunnel is misplaced in a decreased vertical and posterior position, there will be laxity with flexion and tightness with extension [10]. Positioning a femoral tunnel in a distal position also yields an increase in ATT during stress [35]. As far as the tibial side, anterior misplacement results in tightness with knee flexion with accompanied roof impingement during extension [10]. Tibial tunnel posterior misplacement yields a reconstructed ACL in an increased vertical position that impinges on the PCL and affects anteroposterior and rotary knee stability [10]. Surgical tunnel malpositioning contributes significantly to intraoperative complications resulting in postoperative graft failure. An additional but uncommon form of technical failure is a fixation failure. Fixation failure cases account for 2-5% of graft failures and can also be placed in the category of hardware failures [35]. Inadequate fixation like graft screw divergence greater than 30 degrees can lead to a decrease in the tensile loads an ACL can withstand during high-demand activity [10].

Additionally, graft failure can result from missed diagnosis of surrounding tissue structures and improper graft diameter. Missed tears affecting surrounding knee tissues can negatively impact native knee kinematics even after an ACL reconstruction has been performed [34]. For example, if an MCL is damaged, ACL strain and ATT can be seen when a knee is under stress, which raises risk of graft failures [28]. Although it is generally less accepted, damaged menisci that are left untreated during an ACL reconstruction have been linked to potential cause of ACL revisions. It is important to realize that the menisci serve as secondary restraints to unnatural forces experienced by a knee during activity, making them anatomically relevant during an ACL reconstruction. Another possible complication during ACL reconstruction is a posterior wall blowout. Posterior wall blowouts occur when a surgeon mistakenly perforates the posterior femoral cortex during an intraoperative procedure. If posterior wall blowout occurs, there are several methods to complete a successful ACL reconstruction, but such complication is undesired because it can lead to the loss of appropriate graft fixation as well as premature graft failure [32]. A posterior wall blowout requires careful postoperative following of a patient.

A consequence of receiving nearly any surgery is increased stiffness and arthrofibrosis. Following a deep tissue laceration, it is the body's innate response to heal and form a scar with thickened fibrous tissue through a process called fibrosis [36]. Even though fibrosis is an innate response of the body to heal itself, it can severely reduce mobility and cause pain, specifically in areas where movement happens such as joints [37]. Fibrosis is a process that is sometimes unavoidable after a surgery if proper pre-operative precautionary measures and preparation are not taken, ultimately leading to a potentially devasting complication. It is critically important to control fibrosis, most importantly arthrofibrosis which occurs in joints, in this case the knee. To control arthrofibrosis of the knee following a surgery, it is important for patients to do physical therapy preoperatively [10,37]. It is even more important to properly rehabilitate following a surgery for obvious reasons. However, even with rehabilitation efforts, it is difficult to achieve perfectly native knee kinematics.

Most patients who undergo ACL reconstruction return to activity. But quite often, life is not as comfortable as it was prior to a rupture. This is especially true for athletes. Many athletes who had an ACL reconstruction return to activity, but only two-thirds of said injured players can truly compete at the level which they competed at prior to their ACL rupture 3 years after a surgery [31]. Decrease in performance is an unwanted result of ACL reconstruction because it may force athletes into retirement or worse, a re-rupture of the same ACL. A re-rupture requires an ACL revision which prolongs recovery periods and ability to carry out a healthy lifestyle. In the case of re-rupture requiring an ACL revision surgery, several studies have reported that approximately

60-80% of patients regain the athletic capability they had prior to injury, leaving 20-40% of patients with an undesirable outcome [38].

An additional undesirable outcome that isn't discussed enough following ACL reconstruction is the predisposal to osteoarthritis. In a long-term follow-up study, Barenius, et al., found that there was a 3-fold increase in prevalence of osteoarthritis after an ACL reconstruction compared to the contralateral healthy knee [39]. A separate study revealed a positive correlation between the development of osteoarthritis and increasing follow-up time after ACL surgery [40]. Both studies demonstrated that incidence of osteoarthritis was higher when there were associated chondral and meniscal injuries. Ultimately, long term follow-up of patients with ACL reconstruction often reveals that osteoarthritis is a prevalent and unwanted side effect, leaving patients with functional knee impairment, pain, stiffness and reduced quality of life.

Another issue that deserves significant attention is the inefficacy of non-surgical approaches. Often, a non-surgical approach will still leave a patient with significant limitations and daily discomfort. Furthermore, non-surgical management can lead to exacerbation of injury and damage of surrounding tissues [10,24]. If surrounding structures are significantly damaged, knee functionality can be largely decreased.

Evidently, there are limitations to both non-surgical and surgical approaches. With the limitations set forth by current treatments and methods, it is clear that other methods must be considered or used in conjunction to offer an increase of desired outcomes. Stem cell therapies could be a method that can offer improved results post-operation or even increase the regenerative capability of poorly healing ligaments like the ACL.

Stem Cell Therapy for ACL Injuries

The wide range of available stem cells, their specific capabilities and where they are sourced from indicate that there are a multitude of factors to consider when deciding which category of stem cells should be used. Adult Stem Cells (ASCs), Embryonic Stem Cells (ESCs) and induced pluripotent stem cells (iPS) are the different stem cells that can be considered when it comes to using SCT. The most effective, accepted and sensible stem cells to use in the application of Stem-Cell Therapy (SCT) are ASCs. While using ESCs for SCT can be effective, harvesting ESCs from human blastocysts is an extremely unethical process as it is considered the destruction of innocent human life. Aside from the unethical nature of harvesting stem cells from embryos, ESCs increase the possibility of SCT patients developing tumors due to development of mutations while in culture [41,42]. Like ESCs, iPS are another type of stem cell that are ineffective and mainly used for disease modeling [41,42]. Not only do iPS require a reprogramming process that may be time consuming, inefficient and impractical, but certain methods of reprogramming use retroviruses, which can be carcinogenic [42,43]. Although certain techniques to reduce tumorgenicity in iPS reprogramming continue to be researched and improved, they are currently impractical for large scale use of SCT. With ESCs and iPS yielding undesired side effects, ASCs are the most realistic option for SCT.

Unlike ESCs, ASCs can be directly harvested from a patient which means ethical concerns are eliminated. The category of ASCs most applicable for use following an ACL surgery are MSCs. Compared with both iPS and ESCs, MSCs are comparably proliferative, have easy accessibility as well as genomic stability and are not plagued by ethical issues [42]. Additionally, MSCs can be sourced from multiple types of tissues including Synovial Fluid Mesenchymal Stem Cells (SF-MSCs), Bone Marrow Stem Cells (BM-SCs), the Human Umbilical Cord Mesenchymal Stem Cells (HUC-MSCs), periosteum stem cells (PSCs), skeletal muscle stem cells (SMSCs) and adipose tissue mesenchymal stem cells (AT-MSCs) [45,46]. Of these types of MSCs, both BM-SCs and HUC-MSCs have demonstrated the highest potential when used for SCT [44,47-50].

A handful of studies have demonstrated that Bone Marrow Concentrate (BMC) or Bone Marrow Aspirate Concentrate (BMAC), which contains BM-SCs, provided significant improvement of ACL injuries following BMAC introduction to the site, with both surgical and non-surgical approaches [51-53]. Additionally, one recent study demonstrated the unprecedented healing capability of HUC-MSCs in a male athlete with an acute ACL tear [54]. With the evidence in these studies, the regenerative and clinical applications of SCT, particularly using MSCs are extremely important and relevant to the future of the medical field. Further research on MSCs will help us tap the true potential of SCT. Furthermore, larger clinical trials with long term follow-up have the potential to provide vast amounts of evidence about the regenerative capabilities of SCT using MSCs.

Animal Studies Trial Results

Sun, et al., investigated the effect of BM-SCs on graft bone integration and midsubstance ligamentization in a rat model that had ACL reconstruction. In this study, human bone marrow MSCs were harvested from a 35-year-old male. The stem cells were then prepared extensively to obtain an MSC conditioned medium that could be used for SCT. Following ACL repair rat groups that received a weekly MSC conditioned medium injection had narrower femoral and tibial bone tunnels, increased bone formation and bone-graft integration at 4 and 8 weeks compared to the control group [55]. Additionally, rats that were injected with the stem cell conditioned medium performed better on biomechanical tests, showed increased myofibroblast proliferation and increased collagen synthesis [55].

Kanaya et al. investigated whether injecting MSCs from BMAC into rats accelerated healing in partially torn ACLs. Bone marrow aspirations were done on the tibial bone of Green Fluorescent Protein (GFP) transgenic rats. This aspirate was then prepared into a desired SCT solution and was injected into Sprague-Dawley rats that had their right ACLs partially transected. A control group (no SCT) and experimental group (SCT) of rats then had their ACLs biomechanically and histologically tested. The experimental group of rats showed significantly higher ultimate failure load of the femur-ACL-tibia complex 4 weeks after surgery compared to the control group [56]. 4 weeks after the transection procedure, the control group showed severe retraction and no evidence of healing tissues in all specimens, whereas in the experimental group none of the specimens showed retraction, 5/6 specimens had a gap covered by healing tissues, 4/6 of the specimens had increased fibroblast presence and 3/6 specimens had evidence of collagen fiber formation [56].

Another study conducted by Jang, et al., investigated the effect of transplantation of HUC-MSCs during ACL reconstruction in a rabbit model. HUC-MSCs were sourced and then adequately prepared. ACL reconstruction was then performed in rabbits that had a prior ACL transection with (experiment) and without (control) the introduction of HUC-MSCs to the site. Both groups then underwent histological and biomechanical testing. The treatment revealed an absence of immune rejection, enhanced tendon-bone healing and narrower tibial and femoral tunnels compared to the control group [57]. These 3 studies clearly demonstrate positive evidence after using MSCs for SCT in animals with ACL injuries. The promising results offered by these experiments underscore the extensive potential of SCT when used simultaneously with or without surgery.

Human Clinical Trial Results

In a study by Centeno, et al., a group of 29 patients with all 3 categories of ACL tears and less than 1 cm retraction were enrolled to investigate the effects of BMAC along with platelet products on ACL injury. Bone marrow aspirations were done on each patient’s posterior superior iliac crest using ultrasound or fluoroscopic guidance. Additionally, blood was drawn and used to isolate and prepare Platelet-Rich-Plasma (PRP) and Platelet Lysate (PL). After proper preparation of the aspirate, a solution consisting of BMAC, PRP and PL was then injected percutaneously into each patient’s ACL bundles using fluoroscopic guidance. 77% of the patients involved in the study showed and reported a significant improvement in ACL integrity after an average of 8.8 months [51]. Follow-ups, imaging and programs dedicated for ACL assessment were provided to keep track of patient progress and results.

An additional double blinded study by Forsythe, et al., explored the effects of BMAC augmentation on ACL reconstruction with Bone-Patellar Tendon-Bone (BTB) allografts using MRI and clinical outcome results. 80 patients were randomized into one group that received BMAC injections and another group that did not receive the injections. In the experimental group, bone aspirate was harvested from each patient’s iliac crest, concentrated and then injected into the BTB allograft site during ACL repair. In the control group, a small sham incision was made near the iliac crest, making it appear as if bone marrow aspiration was collected to ensure proper blinding. One patient asked to be withdrawn from the study, another patient was excluded after becoming pregnant, one other patient was excluded from the study following a re-tear after experiencing a traumatic injury and 4 patients were lost to follow-up. Consequently, 73 patients were successfully included in the study, 36 having BMAC injections and 37 being in the control group. 9 months post-op patients with BMAC injections had significantly greater International Knee Documentation Committee (IKDC) scores compared to the control group [53]. MRI’s done 3 months post-operatively revealed greater signal intensity ratio in the BMAC group, indicating an increase in metabolic activity, bone remodeling and ligamentization [53].

Another study conducted by Javvaji, et al., used HUC-MSCs on a 55-year-old male competitive tennis player presenting with an acute left knee ACL tear after failed conservative treatment. Using ultrasound guidance, a needle containing a solution of 50 million HUC-MSCs was inserted into the posterior knee and injected into the proximal ACL at the site of the tear. This same process was repeated 2 additional times, each one month apart. The patient simultaneously performed physical therapy, which included proprioception exercises and treadmill walking. A year following completion of the stem cell treatment, a KT-1000 machine recorded a 67% decrease in left knee displacement and an MRI revealed 80% ACL reattachment proximally [54]. The patient also reported a significant reduction in pain and a notable improvement in knee biomechanics and functionality [54]. Additionally, the patient denied episodes of morning stiffness, swelling, knee locking or knee catching. Not only do favorable outcomes by 3 separate studies provide strong support toward the use of MSC based SCT, but they provide an optimistic outlook toward the true untapped potential of SCT in the field of orthopedics.

Future Directions

Ethical Concerns

It is without question that stem cells therapies are plagued by ethical concern. Major ethical concerns arise particularly from the way stem cells are harvested. Destroying human embryos to harvest ESCs is undoubtedly unethical and seen as the destruction of human life [41,42]. Furthermore, the carcinogenic side-effects that occur by implanting iPS into patients is cause for more ethical concern [42,43]. Such ethical concerns are one of the main reasons as to why there is limited research about SCT. Nonetheless, based on the positive outcomes discussed in this paper, it is important to continue research based on SCTs. A stem cell breakthrough in the near future could be a considerable contributor to the advancement of the medical field.

Costs

While ethical concerns are certainly a huge barrier to overcome, the cost of SCT is yet another hurdle. One study investigating the effect of BMAC on patients with hip osteoarthrosis used BMAC injections that had an average out of pocket cost of $2300 [58]. Another study seeking to improve production methods and costs of MSCs using bioreactor expansion rather than the conventional manually created flask MSCs, listed the price of the manual flask method to be $2,056.85 per 100 million cells [59]. Using the bioreactor not only nearly halved the price of stem cell production to $1077.43, but it also reduced hands on production time and overall production time [59]. However, even with such advancements and cost reduction, SCT is still relatively costly and is not covered by insurance due to experimental classification, making it inaccessible to most patients [60]. It is apparent that with new technological advancements, time and better understanding of stem cells, SCT will become increasingly accessible.

Importance of Continued Research

As of now, surgical treatments and conservative management are options that considerably improve quality of life in patients who have suffered an ACL injury. However, the use of stem cell therapies in conjunction with surgical treatment or conservative management has the potential to provide significantly better results for patients. With research showing evidence of significant improvement in cases where SCT is used with and without surgery, it is vital to acknowledge the relevance SCT has as a viable treatment option for patients that have suffered an ACL injury. Despite positive results demonstrated in recent studies of SCT, ethical concerns, cost and lack of research are 3 crucial challenges that SCT must overcome before it can be considered a proper treatment for not only ACL injuries, but other health conditions as well. Through continued research and unwavering efforts, it is only a matter of time before SCT becomes a common option for treating ACL injuries.

Conclusion

After treatment with BMAC and HUC-MSC's based stem cell therapy, subjects showed improved ACL biomechanics, functionality, integrity and increased bone formation as well as bone-graft integration. Additionally, SCT subjects had narrower femoral and tibial tunnels, increased failure load postoperatively, higher IKDC scores, increased ligamentization, reduced pain and decreased discomfort. Based on these results, it is difficult to ignore the clinical significance of SCT. SCT has the potential to offer revolutionary and relevant medical benefits to athletes, patients seeking an active lifestyle or even patients that can have detrimental side-effects following surgical intervention. Although recent studies suggest SCT has the capability to improve surgical and non-surgical outcomes of ACL injuries, further research, clinical trials with long term follow-up and a larger randomized controlled trial are all warranted to fully understand its use in clinical settings and to make it a more available treatment.

Conflict of Interest
The authors declare no conflicts of interest.

Ethics Approval and Consent to Participate
Not applicable.

Declaration
We hereby declare that no artificial intelligence technology or software was used in the creation, drafting or editing of this literature review and that all the information contained in this literature review was created using information from credible sources in my own words, without deliberately plagiarizing information from said sources.

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