

Review Article

Stem Cell Therapy for Rotator Cuff Injuries

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Abstract

Rotator cuff injuries are a common issue among athletes and the aging population that have significant impacts on athlete's performance and individuals' quality of life. Traditional treatment options for rotator cuff injuries include physical therapy, surgery, medication and rest. Unfortunately, these traditional treatments options provide limited success in tissue regeneration and restoring function in the injured rotator cuff. Stem cell therapy has emerged as a potential treatment for rotator cuff injuries, offering the promise of enhanced healing and functional recovery. This literature review aims to synthesize the current state of research on stem cell therapy for rotator cuff injuries. The review encompasses a range of studies, including clinical trials and animal case studies. The potential of Mesenchymal Stem Cells (MSCs) derived from adipose tissue and other sources to promote tendon repair and mitigate muscle atrophy and fatty infiltration is a central focus. Studies have explored various approaches, such as intratendinous injection of bone marrow derived MSCs, adipose-derived stem cells loaded with fibrin gel and bone marrow stimulation. Overall, this literature review provides a comprehensive overview of the current landscape of stem cell therapy for rotator cuff injuries, highlighting both the progress made and the areas that require further exploration, as well as the ethical and safety concerns.

Keywords: Stem Cells; Rotor Cuff Injuries; Embryonic Stem Cells; Mesenchymal Stem Cells

Introduction

Stem Cell Therapy

Stem Cell Therapy is a rapidly evolving field that is showing promising results for the treatment of a variety of medical conditions [1]. Stem cells are unspecialized cells that have the ability to differentiate or renew themselves [2]. They can differentiate into specialized cells or create new stem cells [2]. If they differentiate, they become specialized cells with specific functions [3]. Stem cell therapy is extremely popular in regenerative medicine due to the cells ability to be guided into specific cell types and its potential to repair or replace damaged tissues [1].

Stem cells come from a variety of different sources, including embryonic tissue, bone marrow, adipose tissue, etc [2]. Embryonic stem cells are derived from embryos that are developed from eggs in an IV clinic [2]. Adult stem cells are found in a multitude of organs and tissues throughout the body, such as the brain, bone marrow, cord blood, blood vessels, fat, skeletal muscle, skin, teeth, heart, gut, liver, hair follicles, urine and amniotic fluid [2]. Induced Stem cells or iPCs, are adult stem cells that have been reprogrammed to act like embryonic stem cells [2]. There are also different classifications of stem cells based on their ability to differentiate. They can be classified as totipotent, pluripotent, multipotent, oligopotent and unipotent. Totipotent stem cells have the ability to differentiate into any cell type and unipotent stem cells can only produce cells of their own type [2]. Pluripotent stem cells can differentiate into almost any cell type, multipotent stem cells can differentiate into related cell types and oligopotent stem cells can differentiate into a select few cell types [2].

Stem cell therapy is designed to repair or replace damaged cells by using stem cells to promote the body's natural healing process [1]. It is thought to involve the release of growth factors and cytokines to promote tissue regeneration and repair [1]. Stem cell therapy is currently being studied as a potential treatment for a multitude of medical conditions, including osteoarthritis, heart disease, neurological disorders, sports-related injuries, etc. Stem cell therapy is showing great promise in regenerative medicine and has the potential to treat a wide range of medical conditions.

Musculoskeletal System

The musculoskeletal system is composed of a network of muscles, tendons, ligaments and bones [4]. This complex network provides support, stability and movement in the human body [5]. The musculoskeletal system allows people to perform daily activities, participate in sports, physical activity and other recreational activities. The bones in the musculoskeletal system provide support for body weight and also help keep the body in an upright position [5]. The muscles in the musculoskeletal system, along with the bones, provide strength, stability and flexibility, enabling people to be able to move and maintain posture [5]. Additionally, the cartilage, ligaments and tendons in the musculoskeletal system provide shock absorption and cushioning that protect the joints and prevent injury [5].

The musculoskeletal system also provides essential functions in movement and mobility. Muscles contract and relax to produce movement, allowing people to walk, run, jump, lift and perform other physical activities [5]. A joint is where two bones meet and they allow for flexibility and range of motion for movement [5]. Overall, the musculoskeletal system is vital for overall physical well-being. Exercise or physical activity helps to strengthen the muscles, bones and joints [5]. Strength in the musculoskeletal system allows individuals to maintain balance and prevent falls, which is vital for older adults who are at higher risk for injury [6]. Therefore, it is important to maintain the health and wellness of the musculoskeletal system through exercise, physical activity and proper nutrition to prevent injury and maintain mobility throughout an individual's life [5].

Rotator Cuff Injuries

Injuries to the rotator cuff can occur in many ways but the most common are repetitive overhead movements, degeneration of tendon due to wear and tear and falls or accidents [7]. Rotator cuff injuries are extremely common and become even more prevalent with age [7]. In individuals with injuries at younger ages, it typically occurs from ball-throwing sports or repetitive overhead motions in jobs [7]. Rotator cuff injuries can range from tendonitis to partial or full thickness tears [8]. There are partial, complete, acute and degenerative tears that can occur in the rotator cuff [9]. A partial tear is classified when the tendon is damaged but not completely torn, a complete tear on the other hand is where the attachment is completely severed and the tendon is no longer attached to the humerus [9]. Acute tears occur due to trauma to the tendon from heavy lifting, falling or an accident [9]. Degenerative tears are where the tendon has been worn down over time and is more likely as individuals age [9]. Rotator cuff tendonitis is the swelling or inflammation of the rotator cuff tendons and can be acute or chronic [10]. Acute tendonitis typically occurs in athletes from direct hits to the shoulder, poor throwing technique or falls on the shoulder [10]. Chronic tendinopathy can be due to repetitive injury, vascular changes, age, sex, genetics and tensile forces [10]. Overall, the injuries to the rotator cuff can range from mild to severe but without proper treatment can worsen.

Incidence and Epidemiology of Rotator Cuff Injuries in US

Injuries to the rotator cuff are common in the United States, especially in athletes and the elderly. Due to age-related changes and tendon degeneration, rotator cuff injuries are highly common in the aged population [11-14]. Research has indicated that the aging population is more susceptible to rotator cuff injuries because of weakening cuff tendons brought on by age-related degeneration [12]. Furthermore, it is anticipated that as people age and become more active, the occurrence of rotator cuff injuries would increase [14]. Additionally, the underlying causes of the high incidence of tendon-to-bone injuries caused by rotator cuff strains in the older population remain a mystery [11].

When it comes to sports-related injuries, overhead athletes are particularly susceptible to rotator cuff tears, which can cause chronic discomfort, joint dysfunction and impairments that limit their ability to participate in sports and frequently force them to retire early [15]. Furthermore, research has indicated that muscle stiffness and weakness are associated with an increased risk of developing rotator cuff tendinopathy in athletes who perform overhead [16]. In addition, rotator cuff injuries-which occur in the articular part of the tendon and at the intersection of the supraspinatus and infraspinatus tendons-are common among

athletes who play ball-throwing sports [17]. Moreover, strains have been reported in studies of sports athletes, particularly in the recreational skiing and snowboarding community and rotator cuff injuries are known to come from falls [18]. The frequency and epidemiology of rotator cuff injuries in the United States are impacted by age-related changes, tendon degradation and the sports and activities that people participate in. Understanding the prevalence and risk factors associated with rotator cuff injuries is crucial for developing effective prevention and treatment strategies for both the elderly population and athletes.

Etiology and Pathology of Rotator Cuff Injuries

Both extrinsic and intrinsic variables have a role in the complex genesis and pathophysiology of rotator cuff problems. Subacromial and internal impingement, tensile overload and repeated stress are examples of extrinsic causes; poor vascularity, changes in material characteristics, matrix composition and aging are examples of intrinsic factors [19]. The mechanical theory has been put forth as the main explanation for rotator cuff tendinopathy, highlighting the part that mechanical elements play in the condition's development [20]. Furthermore, rotator cuff tendinopathy in overhead sportsmen has been linked to muscle stiffness and weakness, underscoring the significance of muscular strength in averting these injuries [16].

The distinct anatomical and biomechanical properties of the rotator cuff contribute to its pathology and injury and biomechanical variables are also important in the etiology of rotator cuff pathology [21]. Moreover, a variety of external stressors can cause the rotator cuff tendon to be overworked and overstretched, which can lead to traumatic tears. This multifaceted etiology of chronic rotator cuff tears includes both extrinsic and intrinsic components [22]. Furthermore, genetic predisposition has been linked to the development of rotator cuff tears, emphasizing the involvement of genetics in the pathophysiology of the rotator cuff [23]. The pathology of rotator cuff injuries is often related to specific activities, such as overhead sports, where overload and internal momentum can cause injuries to the supraspinatus muscles and injuries to the anterior and posterior labrum of the anterior and posterior humerus [24]. In addition, rotator cuff injuries are known to occur as a result of falls, particularly in recreational skiing and snowboarding, highlighting the impact of traumatic events on the development of these injuries [18]. A combination of external and internal factors influences the etiology and pathology of rotator cuff injuries, including mechanical stress, muscle weakness, genetic predisposition and specific activities.

Anatomy and Physiology of Rotator Cuff

Anatomy

The rotator cuff is made up of four different muscles, the subscapularis, supraspinatus, infraspinatus and teres minor [25]. These four muscles work together to stabilize the shoulder joint and facilitate various movements. The supraspinatus muscle originates from the supraspinous fossa of the scapula and attaches to the top portion of the humerus, also known as the greater tuberosity [26]. The infraspinatus muscle and teres minor originate from the infraspinous fossa and attach to the middle and back of the greater tuberosity [26]. Finally, the subscapularis muscle originates from the subscapular fossa and attaches to the lesser tuberosity of the humerus [26]. All of these muscles contain tendons, with the subscapularis tendon being the largest of the four and they all four attach to form the rotator cuff tendon and attach to the top of the humerus [26].

Physiology

The shoulder is a ball and socket joint [5]. The rotator cuff muscles work together to stabilize the glenohumeral joint and allow rotation of the arm [26]. The supraspinatus muscle and deltoid muscle work in conjunction to allow the arm to be lifted away from the body (abduction) [26]. The infraspinatus and teres minor muscles allow for the arm to rotate laterally [27]. Lastly, the subscapularis muscle is responsible for the medial rotation of the arm and helps keep the humerus in place in the glenohumeral joint [27].

Stem Cell Therapy in Rotator Cuff Injuries Overview

Stem cell therapy can be used to help regenerate tissue or replace damaged tissues. Stem cell therapy is a promising treatment option for rotator cuff injuries. The goal is to generate the body's natural healing response by introducing stem cells to the injured area. This can be very beneficial for athletes who are eager to return to play because the healing process has been found to be shorter than in standard treatment options. In just a single clinical trial, the implantation of mesenchymal stem cells after the repair of rotator cuff tears displayed significant improvements in healing rates [28]. In rotator cuff tears, stem cell therapy has been shown to improve healing at advanced rates and improve the quality of healing after surgery, allowing patients to return

to normal activities sooner [28]. It has also prevented retears for up to ten years after the repair [28]. While there is a lot of potential in stem cell therapy for rotator cuff injuries, there is still a need for more research.

Summary of Objectives

The major goal of this paper is to investigate current literature on stem cell therapy in rotator cuff injuries and its use of them to treat them. The objective is to provide an overview of the potential benefits of stem cell therapy for treatment of rotator cuff injuries and to also explore the limitations and risks associated with this treatment. This paper aims to provide a better understanding of the current state of literature on stem cell therapy for rotator cuff injuries in hope of stimulating further research.

Discussion

Causes and Types of Injuries

A rotator cuff injury is typically caused by overuse, trauma or degeneration [29]. This can occur in sports or everyday activities. It can be torn by repetitive overhead movements that are common in sports like tennis, baseball or swimming [29]. It can also be caused by people who tend to lift heavy objects or reach overhead a lot [29]. There are two types of rotator cuff injuries, including tendonitis and tears [30]. There are acute tears and degenerative tears, acute tears typically happen due to a sudden event and can occur in conjunction with other injuries, such as a broken collarbone or dislocated shoulder and degenerative tears often occur due to wear and tear with age and repetitive stress [31]. The rotator cuff can be partially or completely torn. A partial tear is one where the tear has not extended all the way through the tendon [32]. A complete tear is one where the rotator cuff is entirely detached from the humerus [31].

Symptoms and Diagnosis

Rotator cuff injuries can present with a variety of symptoms, including shoulder pain during rest and movement, limited range of motion due to joint and muscle stiffness and arm weakness [31]. Night pain, although not exclusive to rotator cuff tears, is commonly associated with shoulder impingement symptoms [33]. Athletes may face significant challenges in returning to sports after rotator cuff injuries, but some cases have reported successful outcomes following rotator cuff repair [34]. These injuries can manifest as a range of lesions, from tendinopathy to partial- or full-thickness tears [35].

Diagnosing rotator cuff injuries typically involves a combination of clinical evaluation and imaging studies. Clinical tests like the empty and full can tests are commonly used for the initial assessment of rotator cuff tears [36]. Researchers have also explored the predictive value of individual anatomical measurements of the scapula in diagnosing rotator cuff injuries [37]. Imaging modalities such as ultrasound and Magnetic Resonance Imaging (MRI) are crucial for diagnosis, with ultrasound showing promise in assessing muscle injuries and acromioclavicular joint pathology [38]. MRI, extensively utilized for evaluating rotator cuff tears, has been subject to studies examining its diagnostic accuracy and comparing it to the added value of ultrasonography [39]. Comparisons between ultrasonography and MRI underscore the significance of accurate imaging for making diagnostic and management decisions. Nevertheless, diagnosing rotator cuff tears remains challenging based on patient characteristics, symptoms and physical examination findings, largely due to a lack of sufficient data.

Traditional Treatment Options

Rotator cuff injuries can be treated non-surgically and surgically. Typical initial treatment is non-surgical and involves rest, activity modification, non-steroidal anti-inflammatory medication, physical therapy and injections [31]. Injections can range from cortisone injections, platelet-rich plasma and prolotherapy [40]. Cortisone injections are typically just used for pain management, while platelet-rich plasma and prolotherapy are used to promote healing [40]. Platelet-rich plasma injections try to promote healing in the injured tendon [40]. Prolotherapy involves several injections that contain irritants to stimulate inflammation and, in the hope, stimulate healing [40]. Platelet-rich plasma injections and prolotherapy do require several injections to promote healing, but platelet-rich plasma is still being researched [40]. Physical therapy is also used to help restore function in the shoulder with tendonitis or partial thickness tears [40]. Rotator Cuff tendonitis can be treated through surgery if symptoms persist through an arthroscopy [41]. There are multiple surgeries for rotator cuff tear repairs depending on the severity of the tear [40]. There is an arthroscopic repair where the surgeon inserts an arthroscope through small incisions in the shoulder and sews the torn tendon back together [41]. An open repair is typically performed when the tear is large and complex; the surgeon will make a large

incision and part the deltoid muscle to get a better visual and then perform the repair by reattaching the tendon to the bone [41]. There is also a mini-open repair procedure where the surgeon will make a smaller open incision and use arthroscopy to determine the extent of the damage and then the surgeon will repair the damage to the tendon through the small incision instead of using the arthroscopy to repair the damage [41]. After surgery of either a tear of tendonitis, the patient will go through physical therapy and be given medication to help relieve pain [41].

Reasons Traditional Treatment Options are Ineffective

Traditional treatment options for rotator cuff injuries, including non-surgical and surgical approaches, have limitations that contribute to their ineffectiveness. Non-surgical treatments, such as NSAIDs, injections and physical therapy may provide symptomatic relief but often do not address the underlying pathology of the rotator cuff. The rotator cuff has limited regenerative capacity due to the poor vascularization of the tendon tissue, which can hinder the effectiveness of non-surgical treatments [42]. Additionally single injections of platelet-rich plasma may not have sufficient therapeutic effect on rotator cuff lesions, limiting the efficacy of this treatment modality [43].

Surgical options, including open or arthroscopic repair, have shown good clinical outcomes in terms of pain relief, range of motion and strength. However, surgical repair does not fully address the underlying degenerative changes in the rotator cuff, such as fatty infiltration and muscle atrophy, which can progress despite treatment [44]. The development of fatty infiltration and atrophy after rotator cuff injury may limit the effectiveness of traditional treatment options, as these pathologies are challenging to reverse [45].

In addition, after rotator cuff repairs there is a 13-94% occurrence of retears and are extremely common following repair [46]. The degenerative changes of the rotator cuff were seen to influence the effectiveness of rotator cuff repairs which contributes to the poor functional outcomes and the occurrence of reruptures [47]. Moreover, the unique response of the rotator cuff to injury, as well as the progression of fatty degeneration after rotator cuff injury, may explain the poor outcomes of rotator cuff tears compared to other muscle-tendon injuries, highlighting the challenges in effectively managing these injuries [48].

The limitations of traditional treatment options for rotator cuff injuries underscore the need for more effective therapeutic modalities that can address the underlying degenerative changes, promote tissue regeneration and improve long-term functional outcomes. Stem-cell based therapies and tissue engineering may offer promising alternatives to traditional treatments by targeting the regenerative capacity of the rotator cuff and addressing the complex pathophysiology of these injuries.

Stem Cell Therapy in Rotator Cuff Injuries

Stem cell therapy, particularly using mesenchymal stem cells (MSCs), has emerged as a promising approach for treating rotator cuff tears. Clinical trials have predominantly utilized bone marrow derived MSCs, which have demonstrated anti-inflammatory potential when differentiating into mesodermal tissue [49]. In these trials, MSCs were delivered to the site of the rotator cuff tear through injections, showing significant promise in enhancing tendon healing and preventing retearing.

One clinical trial involving 14 patients with rotator cuff tears investigated the efficacy of bone marrow aspirate concentrate injected into the tendon and bone following acromioplasty and tendon repair [50]. Postoperatively, patients showed substantial improvements, with 13 out of 14 patients experiencing no re-tear after a year, a significant outcome given that retears typically occur within the first year after surgery [50]. Another trial involving 90 patients receiving bone marrow derived MSCs at the time of arthroscopy for rotator cuff repair demonstrated remarkable results [28]. At the ten-year follow-up, 87% of patients injected with MSCs had intact rotator cuffs, compared to only 44% of the control group, highlighting the potential of MSC injection in enhancing rotator cuff healing and preventing retearing [28].

In contrast, traditional treatment options for rotator cuff tears, such as rest, physical therapy and surgery, have shown limited long-term recovery and high re-tear rates [28]. Stem cell therapy, particularly MSC injection, has demonstrated effectiveness in preventing retearing and enhancing the healing rate for patients with rotator cuff tears [28]. While further research is needed, the promising outcomes of MSC injection in enhancing rotator cuff healing underscore the potential of stem cell therapy as a valuable treatment option for these injuries.

Most Effective Type of SCT of Rotator Cuff Injuries

Based on the provided references, Mesenchymal Stem Cells (MSCs) emerge as the most effective type of stem cell for the treatment of rotator cuff injuries. MSCs have been widely studied and utilized in clinical trials for their regenerative potential and therapeutic properties. MSCs are known for their accessibility from multiple tissues, anti-inflammatory characteristics, secretion of trophic factors and differentiation abilities [51]. Bone marrow derived MSCs have been particularly prominent in studies aimed at improving the treatment of rotator cuff tears with stem cell therapy. These cells have demonstrated the ability to differentiate into multiple mesenchymal tissues, making them a promising candidate for regenerative medicine [51].

Clinical trials have provided compelling evidence of effectiveness of MSCs in enhancing the healing of rotator cuff injuries [28]. Studies have shown that patients injected with bone marrow derived MSCs experienced significant improvements, with a high percentage of patients showing complete healing and intact rotator cuffs at follow-up assessments [28]. Furthermore, the injection of MSCs has been associated with enhanced tendon healing and prevention of retearing in patients with rotator cuff injuries [28]. The regenerative potential of MSCs has been demonstrated in animal models, where bone marrow derived MSCs were injected and increased muscle mass in the supraspinatus muscle of the rotator cuff [52]. Additionally, the use of MSCs has shown promise in enhancing the healing of the rotator cuff and preventing retearing, offering a potential alternative to traditional treatment options [28].

In conclusion, based on the available evidence, mesenchymal stem cells, particularly bone marrow derived MSCs, have demonstrated significant promise in the treatment of rotator cuff injuries. Their regenerative potential, anti-inflammatory properties and ability to enhance tendon healing make them the most effective type of stem cell for addressing rotator cuff injuries. Further research and larger clinical trials are needed to fully understand the effects of MSC therapy in rotator cuff healing, but the current evidence suggests that MSCs hold significant potential as a therapeutic tool in regenerative medicine.

Animal Studies

Animal studies conducted using stem cell therapy in rotator cuff injuries have provided valuable insights into the regenerative potential of various stem cell types. MSCs have been the primary focus in these studies, demonstrating promising outcomes in enhancing tendon healing and preventing retearing. In a rodent animal model, bone marrow derived mesenchymal stem cells were delivered in a fibrin glue carrier to enhance regeneration of the supraspinatus tendon [53]. At around 4 weeks there was more fibrocartilage present at the insertion site as well as improved biomechanical strength [53].

Another study investigated an engineered tendon-fibrocartilage-bone composite revitalized through a cell sheet full of bone marrow derived MSCs to repair the rotator cuff in canines [54]. At around 6 weeks there was seen to be enhanced structure of the rotator cuff, collagen organization, fibrocartilage and biomechanical strength [54]. In a rabbit animal study, polyglycolic acid sheets embedded with MSCs were used to reconstruct tears in the infraspinatus tendon of the rotator cuff [55]. The bone marrow derived mesenchymal stem cells were able to promote enhanced healing of the regenerated tendon and able to regenerate the tendon belly and tendon-bone insertion with better tensile strength than the control group [55]. In another study conducted, rats with rotator cuff tears underwent repairs and fibrin glue with human MSCs was applied at the repair site [56]. Within the first two weeks there was enhanced biomechanical strength, improved collagen organization and increased fibrocartilage formation [56]. Overall, animal studies have provided valuable insights into the regenerative potential of MSCs in the context of rotator cuff injuries. These studies have demonstrated the ability of MSCs to promote healing, prevent retearing and accelerate the restoration of tensile strength in animal models, highlighting the potential of MSC therapy as a promising treatment modality for rotator cuff injuries.

Human Clinical Trials

One clinical trial had 14 patients with rotator cuff tears; these patients underwent an acromioplasty to allow for more subacromial space, then the tendon was repaired and the bone marrow aspirate concentrate was injected into the tendon and bone [50]. After the repair and injection, patients had to wear a sling for four weeks and then physical therapy began after the four weeks [50]. Preoperatively the patient's UCLA scores were at a mean of twelve and postoperatively they were at a mean of 31 showing great improvements [50]. 13 out of the 14 patients did not experience re-tear after a year, which typically occurs in the first year after surgery [50].

A clinical trial with 182 patients studied the effects of an injection of adipose-derived MSCs in fibrin glue during arthroscopic repair of the rotator cuff [57]. Of the 182 patients 35 received the injection [57]. The patients were evaluated based off pain scales, range of motion, UCLA shoulder rating scale and MRI assessments a year or more after surgery [57]. There were no significant differences in the pain scales, range of motions or UCLA assessments, but there in MRI assessments was a lower occurrence of retears in the injection group versus the control group [57].

One clinical trial of 111 patients with chronic full-thickness rotator cuff tears investigated bone marrow stimulation during arthroscopic repair [4]. Forty-four patients underwent the arthroscopic surface holding procedure with Bone Marrow Stimulation (BMS) where 4-6 holes were drilled into the humerus footprint while the other 67 patients only underwent the arthroscopic surface holding procedure [4]. The goal of the bone marrow stimulation was to stimulate migration of the bone marrow derived MSCs [4]. Postoperatively patients had to use abduction pillows for 6-8 weeks, they went through a rehabilitation program starting two weeks after their surgery and active elevation was permitted after 8-10 weeks [4]. After 6 months or more the patients were allowed to resume heavy work or sports after an assessment of their muscle strength and range of motion [4]. They found that retears were less common in those treated with BMS than those without [4]. In a similar trial of 124 patients with full-thickness rotator cuff tears, 57 patients had an arthroscopic repair with multiple channeling and 67 just had the repair [58]. This clinical displayed similar results as the prior one, the patients with multiple channeling showed a lesser chance of retears than the control group [58].

Another clinical trial had 90 patients, 45 in the control group and 45 receiving the bone marrow-derived mesenchymal stem cells at the time of arthroscopy for rotator cuff repair [28]. The tears in the patient's tendons ranged from 1.5 to 3.5cm, the patient's tear could not extend to other tendons and the tear had to be repaired with an arthroscopy to be included in the trial [28]. The MSCs were injected into the tendon (4mL) and into the bone (8mL), with each patient receiving a total of 12mL of the bone marrow concentrate [28]. The patients received, on average, 51,000 stem cells in their injection [28]. At one-week post-op, patients had to wear an arm sling; at six weeks, active range of motion exercises began; at eight weeks, patients started active resistance muscle strengthening exercises; from two to three months, patients could perform light daily activities and manual labor or sports activity were reintroduced after six months [28]. The patients had follow-ups every month for 24 months with ultrasound and MRI at 3 and 6 months, one and two years and ten years [28]. Injection of bone marrow-derived mesenchymal stem cells to enhance healing in the rotator cuff does show significant promise in tendon healing, but further research is needed [28]. Larger clinical trials are needed to fully understand the effects of stem cell therapy in rotator cuff healing. However, there was enhanced healing in the rotator cuff after the injection of MSCs [28].

Clinical Trial Results

The first clinical trial revealed through the preclinical trial that there was potential for using MSCs to promote healing and repair of the rotator cuff, because 13 out of the 14 participants did not experience a re-tear after injection of the bone marrow mononuclear cells [50]. Another clinical trial displayed similar results in a much larger clinical trial where patients who were injected with adipose derived mesenchymal stem cells also saw a decrease in re-tear rates compared to those who did not receive the injection [57]. In these two clinical trials [4][58], there was a different approach to stem cell therapy because they were not directly injected, but instead stimulated by drilling into the humerus to stimulate migration of bone marrow derived MSCs to promote healing from the rotator cuff repair. These two trials both saw lower occurrences in retears in the patients who had BMS. In the clinical trial performed by Hernigou et al 2014, there were significant results yielded that could potentially influence larger more influential clinical trials. 100% of the patients that were injected with MSCs were healed by six months [28]. At the ten-year follow-up, 87% of patients injected with the MSCs had intact rotator cuffs and only 44% of the control group had intact rotator cuffs after the ten-year follow-up [28]. They found that when patients were injected with more than 30,000 MSCs, they had healed more than 2 cm over the footprint at three months; if the patient received less than 30,000 MSCs, they needed four months or more to achieve the same degree of healing and patients who did not receive the MSC injection did not reach 2 cm of healing for at least six months [28]. There were significant improvements in the rate of tendon healing and prevention of re-tearing [28].

Future Directions

Stem cell therapy is so versatile and can be used in treating various medical conditions. More research can be done to improve our understanding of how stem cells differentiate and interact with other cells in the body. Also, more research can be done to

develop new stem cell sources to see which one is most effective in clinical applications. Stem cell delivery and administration can be further researched to better understand the best way to administer stem cells that proves most effective. Also, combination therapies, where stem cells are combined with other treatments, can be further researched to see if they enhance the regenerative potential of stem cells. Stem cell therapy has the potential to be applied in a wide range of clinical settings, including sports medicine, orthopedics, neurology, cardiology and more. As research continues, stem cell therapy could become a standard treatment option for many injuries and diseases.

While stem cell therapy does hold great promise, there are also challenges that must be addressed, such as safety concerns, regulatory issues, cost and ethical concerns. There is still a lot that is unknown about the safety of stem cell therapy in the long term. As stem cell therapies become more widely used, clear regulations will be needed to ensure that they are being used safely and effectively. Since stem cell therapy is known to be expensive, it may limit access to some patients. There are ethical concerns regarding the use of embryonic stem cells. Despite these challenges, stem cell therapy shows great promise as a treatment option for a multitude of injuries and diseases. With continued research and development, stem cell therapy is likely to become an important aspect of the field of medicine.

Cost

While the potential of stem cell therapy for rotator cuff injuries is evident, the cost of such therapies is an important consideration. Stem cell therapy can cost anywhere from \$5,000 to \$50,000 [59]. There are many different prices for different types of stem cell therapy but typically with orthopedic conditions it is lower ranging from \$5000 to \$8000 and can be used in rotator cuff tendonitis [59]. The cost can be influenced by the condition being treated, the type of stem cells, how many cells a person is receiving, the quality of the cells and the source of the stem cells [59]. Dr. Verma charges \$3000 for stem cell therapy in rotator cuff tears [60]. The cost is of concern because stem cell therapy is still considered experimental, so it is not covered under insurance and is extremely variable by clinic and doctor [59].

Ethical Concerns

With all developments in medicine there is concerns that come up regarding the new form of treatment. Stem cell therapy does bring forth a few ethical concerns. One of the primary ethical concerns is related to the source of stem cells, embryonic stem cells in particular have raised debates due to the destruction of embryos for their extraction [61]. There is also an ethical concern in stem cell therapy due to the limited research and lack of long-term research to determine the safety of stem cell therapy in years to come [62]. There are also ethical concerns regarding rejection and tumor development [63]. Despite these concerns, stem cell therapy shows great promise as a treatment option for a multitude of injuries and diseases. With continued research and development, stem cell therapy is likely to become an important aspect of the field of medicine.

Summary of Objectives and Findings

This paper's primary objective was to review current literature on stem cell therapy in rotator cuff injuries and its application to the treatment of them. The goal was to outline the possible advantages of stem cell therapy for these injuries while simultaneously examining the drawbacks and dangers of the procedure. In order to encourage additional study, this publication should have given readers a better understanding of the current state of the field of stem cell therapy for rotator cuff injuries. Stem cell therapy has shown great promise as a treatment option for rotator cuff injuries. Stem cells have the potential to promote tissue regeneration, enhance healing rates and reduce pain in patients. However, stem cell therapy is still a developing field with limited research and there are challenges. Nevertheless, with more research stem cell therapy could become a common treatment option for rotator cuff injuries.

Importance of Continued Research

Continued research in stem cell therapy for rotator cuff injuries is important due to the potential of stem cells to revolutionize the treatment of such injuries. Rotator cuff injuries pose a significant challenge and existing treatment options typically fall short in achieving sustained healing [48]. Stem cells have shown promise in enhancing the healing process of rotator cuff injuries. Studies have illustrated that stem cell therapies can accelerate the restoration of tensile strength of tendons and alleviate the progression of rotator cuff injuries [64]. The regenerative potential of stem-cell based therapies has been underscored, emphasizing the need for further clinical research in this area [65]. In human clinical trials it was found that there were enhanced

rate of tendon healing and decreases in the occurrence of retearing [28]. There is an important need for increased research because although human clinical trials have shown promising results, they have limited participants and limited long term results. The continued research in stem cell therapy for rotator cuff injuries holds immense promise for advancing the treatment of these injuries. The diverse approaches and significant findings from various studies underscore the importance of further exploration and development of stem cell-based therapies for rotator cuff injuries.

Conflict of Interest

The authors have no conflict of interest to declare.

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