

The Current Perspectives of Stem Cell Therapy in Orthopedic Surgery

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Received 2016 April 07; Revised 2016 June 16; Accepted 2016 June 23.

Abstract

Context: Musculoskeletal injuries may be painful, troublesome, life limiting and also one of the global health problems. There has been considerable amount of interest during the past two decades to stem cells and tissue engineering techniques in orthopedic surgery, especially to manage special and compulsive injuries within the musculoskeletal system.

Evidence Acquisition: The aim of this study was to present a literature review regarding the most recent progress in stem cell procedures and current indications in orthopedics clinical care practice. The Medline and PubMed library databases were searched for the articles related with stem cell procedures in the field of orthopedic surgery and additionally the reference list of each article was also included to provide a comprehensive evaluation.

Results: Various sources of stem cells have been studied for orthopedics clinical care practice. Stem cell therapy has successfully used for major orthopedic procedures in terms of bone-joint injuries (fractures-bone defects, nonunion, and spinal injuries), osteoarthritis-cartilage defects, ligament-tendon injuries, femoral head osteonecrosis and osteogenesis imperfecta. Stem cells have also used in bone tissue engineering in combining with the scaffolds and provided faster and better healing of tissues.

Conclusions: Large amounts of preclinical studies have been made of stem cells and there is an increasing interest to perform these studies within the human population but preclinical studies are insufficient; therefore, much more and efficient studies should be conducted to evaluate the efficacy and safety of stem cells.

Keywords: Stem Cells, Orthopedic Surgery, Mesenchymal Stem Cells, Adipose Derived Stem Cells, Bone Marrow Derived Stem Cells

1. Context

Musculoskeletal injuries may be painful, troublesome, life limiting and also one of the global health problems. Various treatment modalities are available for treating these problems; however, the most effective method is controversial (1-3). Current research has focused on identifying novel and effective methods of addressing the morbidity associated with musculoskeletal injuries. Stem cells are a promising and growing area of researches within the medical field (4).

Stem cells are described as to have a potential to differentiate more than 200 different cell types in the body. They are specific cell types that can create new cells in existing healthy tissues and may help to repair tissues in those structures that are injured or damaged when they differentiate into multi lineages and becoming multipotent under appropriate conditions (5). They primarily create progenitor cells and these cells have capability of more specialized functions, such as brain cells, red blood cells, bone or cartilage (2). Among the different sources for cell therapy, mesenchymal stem cells (MSCs) are the most preferred source because they can differentiate to many different tissues, in

terms of muscles, bones, fat and cartilage (6), and can be obtained from many sources, such as bone, tendon, skin, adipose tissue, umbilical cord, blood and amnion (7-11).

Over the past 15 years, orthopedic surgeons have focused their attention to MSCs therapies (12, 13). There are plenty of animal studies that have successful results and there is an increasing concern about their use in human studies. In these studies, stem cell procedures have been focused on promoting fracture healing and nonunion, regenerating articular cartilage in degenerated joints, healing ligaments or tendon injuries, and replacing degenerative vertebral disks (6).

2. Evidence Acquisition

The aim of this study was to present a literature review regarding the most recent progress in stem cell procedures and current indications in orthopedics clinical care practice. The inclusion criteria for this review were all the study types related with orthopedics surgery and stem cell therapy. Studies evaluating different methods, and stem cell procedures nonrelated with orthopedic surgery were excluded. The Medline and PubMed library databases (1946

to the 15th of December 2015) were searched for the articles related with stem cell procedures in the field of orthopedic surgery and additionally the reference list of each article was also included to provide a comprehensive evaluation.

3. Results

3.1. Types of Stem Cells

3.1.1. Embryonic Stem Cells

James Thompson firstly described embryonic stem cells in 1988 (14). These cells can be obtained from blastocysts during in-vitro fertilization especially on the fifth days of fetal life, and they are characterized as pluripotent cells. They can be proliferated easily in the cell culture, and differentiate into every different cell type, and thus controlling stem cell growth and differentiation is difficult. Embryonic stem cells are usually preferred for transplantation, but the rejection risk is higher. Only a limited number of animal studies have been conducted on embryonic stem cells.

3.1.2. Mature Stem Cells

Mature stem cells were described in the 1960's. They can be obtained from body tissues, the umbilical cord or placenta after birth and they are characterized as multipotent cells. In this type of stem cells, differentiating is limited and these cells are similar to the cells from which they originate. They are not perceived as foreign by the immune system. Tissue and organ regeneration and repair are enhanced by these cells.

Stem cells are also classified into 4 types according to differentiating potential; totipotent cells are only be present in early embryo, pluripotent cells can differentiate to every cells, multipotent cells can differentiate to limited number of cells and unipotent cells are the mature form (15)(Figure 1).

3.2. Stem Cell Procedures in Orthopedic Surgery

Stem cell therapy has recently become popular in orthopedics surgery, especially in the musculoskeletal injuries. Musculoskeletal injuries can involve tendons and ligaments, bone, the meniscus and cartilage. When not treated properly, patients can have long-lasting symptoms such as large bone defects, pseudoarthrosis and nonunions (16, 17).

Therapeutic applications can be performed using stem cells as progenitor cells, and they are primarily aspired from bone marrow then injected directly into tissues to enhance the repair process. Mesenchymal stem cells that are obtained from bone marrow have chondrogenic, osteogenic and radiogenic potentials (18). After differentiation to mesenchymal progenitor cells, these cells support

to bone formation by osteogenesis; adipose tissue by adipogenesis; cartilage formation by chondrogenesis; muscle formation by myogenesis; tendon/ligament formation by tendo/ligamentogenesis; and neuron-like cell formation by neurogenesis.

Many sources of stem cells have been studied for orthopedic procedures; however, the optimal source of stem cells has not yet been clearly defined (Figure 2).

3.2.1. Sources of Stem Cells Used for Orthopedic Procedures

3.2.1.1. Bone Marrow Derived Mesenchymal Stem Cells (BM-MSCs)

Bone is the most common used stem cell source that can differentiate into musculoskeletal system cells (trabecular bone, tendon, articular cartilage, ligaments) in the suitable environment as an origin of multipotent cells (19, 20). However, bone marrow aspiration can be painful, and various complications have been stated by many authors (21).

3.2.1.2. Adipose Derived Stem Cells (AD-MSCs)

Adipose tissue has recently described as a reliable source for MSCs (22, 23). The procedure is less invasively as a lipo-aspiration (24, 25). Recent studies have shown that AD-MSCs have a considerable potential for proliferation, and maximal strength to serum deprivation-induced apoptosis (26, 27).

3.2.1.3. Synovial Tissue-Derived Stem Cells (ST-MSC)

Synovial tissue is another source of stem cells used for orthopedic procedures (28). There are few studies available in the literature about synovial tissue-derived stem cells. Many of them have reported better outcomes in the functional scores, pain and patient satisfaction in especially cartilage repair procedures (29).

3.2.1.4. Peripheral Blood-Derived Progenitor Cells

MSCs can be also prepared from peripheral blood. Automated cell separator (apheresis) used in this procedure for collecting progenitor cells. The first two clinical studies were published in 2011 by Saw et al. (30). Both of the studies demonstrated successful results in the treatment of regenerated cartilage. In the histological evaluation, proteoglycan and type II collagen proportion was substantially increased and achieved 95% of the normal articular cartilage score (31).

3.2.1.5. Bone Marrow Concentrate

This procedure was proposed by Buda et al. (32) and Gobbi et al. (33) and the iliac crest is used for this technique. Bone marrow is aspirated and then centrifuged.

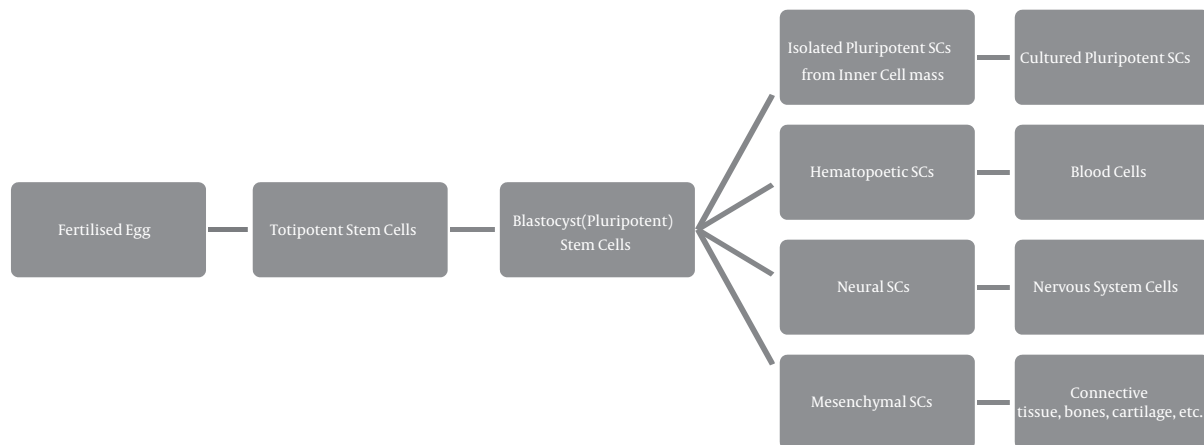


Figure 1. Types of Stem Cells According to Differentiating Potential

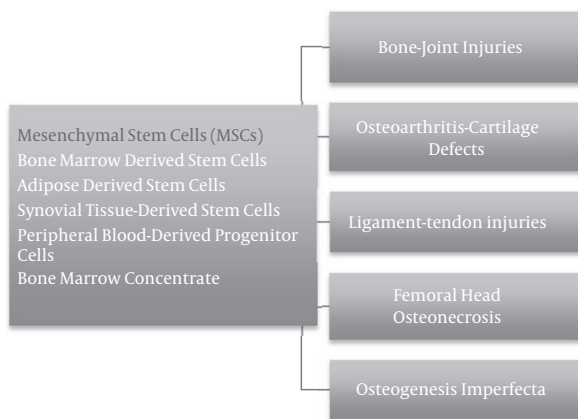


Figure 2. Mesenchymal Stem Cell Sources and the Most Preferred Conditions in Orthopedic Surgery

Both of the studies reported satisfactory clinical results, especially in cartilage regeneration.

AD-MSCs and BM-MSCs have been most preferred sources of MSCs; however, there is a controversy about the most effective source of MSCs for orthopedic procedures (34). Joseph et al. (35) comprised human cortical bone fraction (CBF-MSCs), BM-MSCs and AD-MSCs, and declared that CBF-MSCs's osteogenic potential was superior to BM-MSCs and AD-MSCs in normoxia and hypoxia. Veriter et al. (36) used AD-MSCs in 11 patients with bone nonunion and 7 patients of nonhealing chronic wounds and obtained successful results in both of the situations and did not face with serious side effects or adverse events.

3.3. Stem Cells in Bone Tissue Engineering Studies

In light of the previous studies, stem cells have been used in bone tissue engineering. Bone tissue engineering promises alternative tools that develop a microenvironment that holds osteogenic, osteoinductive and osteoconductive properties. In the recent studies, researchers have developed strategies of combined use of MSCs and three-dimensional biodegradable polymeric scaffolds. In addition, Udehiya et al. (37) declared that combined use of hydroxyapatite scaffolds and BM-MSCs provides faster and better healing of bone segmental defects in a rabbit model, when compared to hydroxyapatite alone. Muwan Chen et al. (38) declared that in vitro bone marrow human mesenchymal stem cells that combined with hyaluronic acid and b-Tri calcium phosphate-coated polymeric scaffold provided enhanced osteogenic differentiation and cellular proliferation and reorganization of the cellular matrix.

Colosimo et al. (39) isolated BM-MSCs from 8 New Zealand white adult rabbits than combined scaffold-BM-MSCs and compared to cells cultured in absence of scaffolds. They obtained promising results for bone marrow regeneration in vitro and in vivo settings. There are a few studies available in the literature in this area; therefore, further studies are needed to investigate the most efficient cell-scaffold combination approach.

3.4. Orthopedic Indications of Stem Cells (Table 1)

3.4.1. Bone-Joint Injuries

Bone fractures and trauma-related joint injuries are the primary issue of orthopedic surgery and account for a large number of surgical procedures. The management and treatment methods have developed in consistent with

the increasing number of scientific researches and technological possibilities, thus patient satisfaction, and quality of regenerated tissue have increased, and recovery time and treatment related complications have decreased. Nonetheless, complications such as non-union, delayed union, pseudoarthrosis, infections, loss of range of motion, and articular damage and bone defects have been continued; therefore, there is a need for new techniques that fasten fracture healing especially in the patients with comorbidities or complicated fractures. Recently stem cell procedures have investigated in the field of orthopedics to deal such these problems and successful results were obtained.

3.4.1.1. Fractures-Bone Defects

After high-energy trauma or gunshot injuries, bone defects may occur from extrusion of bony fragments. Bone defects are one of the major challenging situations of orthopedic surgery. In this area, the first stem cell study was performed by Masquelet (40, 41) and then by Henrich et al. (42), they used membranes that contain MSCs for the femoral defects, and declared vascular endothelial growth factor, BMP-2, TGF β and were significantly elevated in the membranes. This raises the question of whether BMDSCs can be used to repair bone defects. Lio et al. (43) investigated the results of preclinical studies that used BMDSCs (bone marrow derived stem cells) for fracture healing in their systematic review, and stated that BMDSCs enhance bone formation and increase bone mineral density.

3.4.1.2. Nonunion

In ABD 6.2 million fractures occurred per year and 5% - 10% of them resulted as nonunion. This is one of the devastating problems and accounts for higher rates of patient morbidity and mortality (44, 45). There is an increasing concern about stem cell studies in this area and successful results have been reported. Bajada et al (46). used BM-MCSs and a calcium sulphate to a patient with tibial nonunion. His fracture was refractory to other treatments and he underwent 6 previous unsuccessful operations. They declared complete union in a short time period with BM-MCSs and a calcium sulphate (46). Giannotti et al. (47) used BMDSCs for nonunion of long bones of 7 patients and obtained successful results. Grgurevic et al. (48) stated that combined BMDSCs and BMP1-3 increase type-I collagen and osteocalcin in the nonunion of rat long bones.

3.4.1.3. Spinal Injuries

Traumatic spinal cord injury is one of the most common reasons of severe neurological damage and recovery

rates are very low (49). Recently, stem cells have been conducted for axonal regeneration. Sykova et al. (49) performed BMDSCs for 20 patients whom had spinal cord injury and declared beneficial outcomes with this method. Ya-jing Zhou et al. (50) used bone marrow mesenchymal stem cell transplantation in combination with propofol for spinal cord injury of rats and stated that the effectiveness of bone marrow mesenchymal stem cell transplantation increased with propofol in the treatment of spinal cord injury in rats.

3.4.2. Osteoarthritis-Cartilage Defects

Osteoarthritis is the debilitating, degenerative joint disorder. The disease commonly affects the weight bearing joints, formed 40%-60% of the musculoskeletal disorders (51-53). In the early stages of the disease, the joint cartilage is degenerated and joint space become narrow thus affects the patient comfort and physical activity. Recently, stem cell studies have obtained promising results in this area and provided remarkable regeneration of joint cartilage and became a considerable alternative of the nonsurgical options (54, 55).

3.4.2.1. Cartilage Defects

Regeneration capacity of damaged hyaline cartilage is very limited; therefore, some materials are needed for efficient and faster repair. Mesenchymal cells are the novel methods and many authors have recommended them because they have a reliable and reproducible effect on cartilage repair recently. Human bone marrow stem cells (hMSCs) have shown to have chondrogenic and regenerative potential in the considerable number of studies (54-56). Mesenchymal stem cells have a potential to produce a cartilage-like tissue with a matrix based on type II collagen and aggrecan under suitable culture conditions (57, 58). In the clinical practice, isolated chondrocytes have been prepared from healthy cartilage tissue and cultured with the cell culture and then, they intra-articularly injected to knees.

Wakitani firstly reported clinical application of MSCs in the treatment of osteoarthritic knees and declared better arthroscopic and histological outcomes (59). Murdoch et al. (60) stated that cultured human bone marrow mesenchymal stem cells with Transwell permeable membranes as specific growth and a differentiation factor, provided rigid translucent cartilaginous discs and expressed cartilage-specific structural proteins as aggrecan and type II collagen. Zhu et al. (61) preferred the combination of BM-MCSs and a connective tissue growth factor, and they stated that the regenerated hyaline cartilage was similar to normal hyaline cartilage after the treatment. Guo et al. (62) used BM-MSCs combined with TGF-beta in the treatment

Table 1. Major Orthopedic Indications of Stem Cells

Major Orthopedic	Problems		
Bone-Joint Injuries	Osteoarthritis-Cartilage Defects	Ligament-Tendon Injuries	Other Conditions
Fractures-Bone defects	Cartilage Defects	Rotator cuff lesions	Meniscopathy
Nonunion	Osteoarthritis	Anterior cruciate ligament lesions	Femoral Head Osteonecrosis
Spinal Injuries		Achilles Tendon Rupture	Osteogenesis Imperfecta
		MCL Lesions	

of full-thickness defects of articular cartilage and declared successful results. Reyes et al. (63) stated that BMDSCs combined with BMP had successful results in the repair of rabbit's osteochondral defects.

3.4.3. Ligament-Tendon Injuries

A nearly half of the musculoskeletal injuries involve soft tissue injuries such as ligaments or tendons (64). Complete ligament and tendon healing require a wider period of time up to 1 to 2.5 years postinjury and the healed tissue may have less organized collagen fibrils that resulted in decreased mechanical strength; therefore, re-injury and re-rupture risks are increased (65-68).

In general, most of the authors have stated that stem cell therapy fasten and improve ligament-tendon healing; however, some literatures have contradictory results (69-71). Saether et al. (72) stated that MSCs can provide improved healing of ligament-tendon injuries. However, lower doses of MSCs are more efficient to improve healing when compared to higher doses. In this area stem cell studies were lower and have contradictory results. So, there is a need for continued research to optimize stem cell protocols, enhance beneficial outcomes and reduce the risk of re-injury.

3.4.3.1. Rotator Cuff Lesions

Rotator cuff lesions are very common in the adults and elderly. Patients are often subjected to rotator cuff injury at a rate of 58% after shoulder trauma (73, 74). Tears within the rotator cuff are associated with muscle pathology, such as weakness or impingement (75). The ruptures successfully treated with open or arthroscopic techniques; however, re-rupture rates were high (76, 77). Yokoya et al. (78) treated infraspinatus lesions of the rats with polyglycolic acid combined with BM-MSCs or isolated polyglycolic acid. They determined successful results in the combined group when compared to the isolated group.

3.4.3.2. Anterior Cruciate Ligament Lesions

Knee injuries are very common and 17%-61% of them required surgical repair (79). Mesenchymal stem cells and

ACL fibroblasts are determined to have regenerative effects on anterior cruciate ligament lesions (80).

3.4.3.3. Achilles Tendon Rupture

Achilles tendon ruptures are common in adults. Adams et al. (81) compared the effectiveness of sutures with BMDSCs and without BMDSCs on histological and mechanical strength in the treatment of Achilles ruptures of rats, and stated that sutures with BMDSCs had significantly better results than sutures without BMDSCs.

3.4.3.4. Medial Collateral Ligament Lesions

Saether et al. (69) evaluated the effectiveness of MSCs in the treatment of medial collateral ligament (MCL) injury of rats and stated that primed MSCs resulted in less inflammation and provides high quality of healing in the short time period.

3.4.4. Other Conditions

3.4.4.1. Meniscopathy

Meniscopathies are common in every age group. In the progressive stages of meniscopathies, biomechanics of knee deteriorate, and if it is not properly treated eventually osteoarthritic changes occur in the knee joint. Hat-sushika et al. (82) performed BM-MSCs to the porcine massive meniscus defect model and evaluated with MRI and stated that BM-MSCs can promote meniscus regeneration.

3.4.4.2. Femoral Head Osteonecrosis

It is one of the progressive diseases that commonly seen in the younger adults by disruption of femoral head nutrition and joint degeneration. Papakostidis et al. (83) comprised the results of core decompression and local MSC in treatment of femoral head avascular necrosis and found that MSC therapy decreases the requirement of total knee arthroplasty in the patents with femoral head AVN.

3.4.4.3. Osteogenesis Imperfecta

It is one of the genetic disorders of mesenchymal cells and characterized by generalized osteopenia, bone deformity and fractures. Complete cure is impossible with the

current treatment methods. Horwitz et al. (84) stated that bone mineral density increased and long-term fractures were decreased in the patients with osteogenesis imperfecta with the treatment of BM-MSCs.

4. Conclusions

There has been considerable amount of interest during the past two decades to stem cells and tissue engineering techniques in orthopedic surgery, especially to manage special and compulsive injuries within the musculoskeletal system. Large amounts of preclinical studies have been made of stem cells and there is an increasing interest to perform these studies within the human population but preclinical studies are insufficient, thus more research should be conducted to evaluate the safety and efficacy of stem cells.

Footnotes

Authors' Contribution: All authors contributed to and approved the manuscript.

Conflict of Interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

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