Journal of Health, Medicine and Nursing
ISSN 2422-8419 An International Peer-reviewed Journal
Vol.40, 2017

Role of Stem Cells in Orthopaedic Surgery: Theoretical Survey

DR. FAISAL KHALAF D. ALSHAMMARI DR. MUATH ABDULGHANI A ALTURKISTANI
DR. SAMI AHMED H ALANAZI DR. OMAR MOHAMMED J ALBURAIDI
DR. IBRAHIM SAEED G ALGHAMDI DR. AYAD YOUSIF ALAHMADI
DR. MOHAMMED OMAR ALREHAILI DR. MOHAMMED SAUD ALJOHANI
DR. FAHAD MATAR A ALZAHRANI

Abstract
This study aims at analyzing the Stem cell application is a burgeoning field of medicine that is likely to influence the future of orthopaedic surgery. Stem cells are associated with great promise and great controversy. For the orthopaedic surgeon, stem cells may change the way that orthopaedic surgery is practiced and the overall approach of the treatment of musculoskeletal disease. Stem cells may change the field of orthopaedics from a field dominated by surgical replacements and reconstructions to a field of regeneration and prevention. This review will introduce the basic concepts of stem cells pertinent to the orthopaedic surgeon and proceed with a more in depth discussion of current developments in the study of stem cells in orthopaedic surgery.
Keywords: Stem cell, orthopaedic, surgery.

1.1 Introduction

With an expanded accentuation on confirm based medication, there has been an expanding center around the pathophysiology of orthopedic wounds and illness forms, and their effect on general result. Customary treatment methodologies are developing to envelop custom-made methodologies that record for age, occupation and patient desire. More current methodologies for administration are routinely executed and urged with an end goal to enhance persistent results. It is to accomplish these targets that regenerative solution which uses the utilization of undifferentiated organisms and tissue designing has recently developed (Huang, Gronthos & Shi, 2009).

A test to the orthopedic specialist in the 21st century is the yearning of the maturing patient to remain physically and rationally dynamic and to keep on contributing to society. More youthful patients are taking an interest in more physically requesting wearing exercises, bringing about wounds that require organic arrangements which can enable them to keep on being dynamic all through their lifetime (Lee & Hui, 2006).

Significant advantages have come about because of the biomechanical arrangements of the previous 50 years, with better biomaterials and inserts for joint substitutions, more exact instrumentation and PC helped route strategies. Be that as it may, inserts have a limited life expectancy inferable from relaxing or different methods of disappointment and may require assist surgery including expanded dismalness for the patient. The future lies in regenerative solution, with the possibility to develop new tissues and organs to supplant harmed or infected ones by using undeveloped cells, which have the ability to self-recharge and separate into a wide range of sorts of tissue. Despite the fact that this territory of research holds unending guarantee, it is likewise impacted by logical, moral, moral and political contentions. This audit means to give a superior comprehension of the issues concerning undifferentiated organism examine, and also the potential remedial utilization of these cells in orthopedic surgery (Veronesi, Giavaresi, Tschon, Borsari, Nicoli & Fini, 2012).

Stem cells are depicted as to can possibly separate more than 200 distinctive cell sorts in the body. They are particular cell sorts that can make new cells in existing healthy tissues and may repair tissues in those structures that are harmed or damaged when they separate into multi ancestries and getting to be noticeably multipotent under fitting conditions (Akpancar, Tatar, Turgut, Akyildiz & Ekinci, 2016).

Tissues such as muscle, cartilage, tendon, ligaments, and vertebral discs show limited capacity for endogenous repair. Therefore, tissue engineering techniques are being developed to improve the efficiency of repair or regeneration of damaged musculoskeletal tissues.

Over the past 15 years, orthopedic surgeons have focused their attention to MSCs therapies. There are plenty of animal studies that have successful results and there is an increasing concern about their use in human studies6. 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 (Desiderio, De Francesco, Schiraldi, De Rosa, La Gatta & Paino, 2013).

1.2 Problem statement

Essential science and test look into on stem cells has expanded exponentially in the most recent decade. Our present learning about stem cells science is better than anyone might have expected sometime recently. This new outlook change in inquire about has been reflected in the field of orthopedic surgery (Guan, Yao, Liu, Lam, Nolta & Jia, 2012).

Various experimental models have suggested a potential application of stem cells for different orthopaedic conditions, and early clinical results of stem cell use have been encouraging. The problem of this study lies in

analyzing these cells to be easily isolated, processed and made available for clinical use. From healing of bone defects caused by trauma, tumor or infection to cartilage defects, nerve, tendon and ligament healing, stem cell use has the potential to revolutionize orthopaedic practice.

1.3 Objectives of the study

Efforts must be made to ensure safe, economical, efficient and effective introduction of stem cells for regular clinical use. Well-developed, randomized, prospective, clinical studies that build on the existing animal data will provide us with much needed information for the correct application of this field of science to well documented needs of orthopaedic surgeons.

Therefore, the objectives of this study are to orient a general orthopaedic surgeon towards the current use and clinical applications of stem cell based therapy in orthopaedics and to provide a complete overview of the clinical advances in this field. And analyzing the regenerative medicine with the use of stem cells as expected to revolutionize patient treatment. Besides analyzing their utilization for bone tissue engineering with appropriate scaffolds provides us with exciting opportunities for research and development.

1.4 Terminology

Stem Cells: Undeveloped biological cells capable of proliferation, self-renewal, conversion to differentiated cells and regenerating tissues (Mafi, Hindocha, Mafi, Griffin & Khan, 2011).

Totipotent cells: These are cells that can develop into all cell types in the human body and can also form extra embryonic and placental cells. The cells of the early stages of the embryo are the only totipotent cells and are not in clinical use due to ethical concerns (Shostak, 2006).

Pluripotent cells: Cells that can develop into cells of all the three germ layers (endoderm, ectoderm or mesoderm). Cells of late stages of embryo after the blastocyst stage are pluripotent cells (Shostak, 2006).

Multipotent cells: These are cells that can develop into more than one but not all germ layers. Adult stem cells and cord blood cells are multipotent cells (Shostak, 2006).

1.5 Types of Stem Cells:

Embryonic Stem Cells (Pre-natal): These cells are obtained from the blastocyst stage of the embryo. Pluripotent in the truest sense, they have a capacity to form into any tissue of the body and multiply in an unlimited manner. This is predominantly due to the phenomenon of asymmetric division – production of one stem and one non-stem daughter cell. These properties, however, also make them prone to tumorigenesis. This and the necessity of harvest from embryos causes safety and ethical dilemma.

Adult Stem cells (Post-natal): These cells are obtained later in life after the embryonic stage. They are multipotent, undifferentiated cells located among specialized tissues with a primary function of their maintenance and repair. Mesenchymal stem cells (MSC), which originate from the mesoderm, are a type of adult stem cells that have a good potential to develop into adipocytes, chondrocytes, myoblasts and osteoblasts.

1.6 Methods and procedures

Stem cells might be "unselected cells" acquired from autologous bone marrow after centrifugation or "chose" and upgraded in culture using their fondness to tissue plastics. Cost included, time to culture, risk of infection and loss of capacity in vitro are factors counteracting consistent clinical utilization of refined MSCs. It should be noted that absolute number and the purity of cells obtained from cultures is higher, an important factor for clinical effect. The posterior iliac crest has been shown to have a higher yield for MSCs as compared to anterior in case of bone marrow aspiration (Hernigou, Poignard, Manicom, Mathieu & Rouard, 2005).

Stem cells may be directly applied into a lesion either surgically or via local injection with a suitable scaffold/carrier. MSCs may be taken through initial phases of differentiation, forming bone or cartilage precursors under laboratory conditions and then implanted into lesions. In addition, MSCs may be administered intravenously. Their ability to migrate systemically and colonize the bone marrow after a peripheral injection has been utilized for treatment of Osteogenesis Imperfecta (Horwitz, Prockop, Gordon, Koo, Fitzpatrick & Neel, 2001).

1.7 Study mechanism

In addition to differentiation into bone, muscle, cartilage, ligament or tendon cells, MSCs also have a paracrine effect whereby they secrete growth factors and cytokines such as bone morphogenic proteins (BMPs), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF). These play an important role in angiogenesis, repair, cell survival and proliferation. MSCs also have the ability to migrate to the site tissue injury to modulate an inflammatory response. Genetically modified MSCs for long term release of growth factors are being currently developed (Giuliani, Lisignoli, Magnani, Racano, Bolzoni & Dalla Palma, 2013).

1.8 Study techniques

1.8.1 Role of Mesenchymal Stem Cells in Orthopaedic Surgery

MSCs have a capacity to form into any mesodermal tissue. In this way, they can be incited to frame antecedent cells to form into tissues including bone, ligament, muscle, ligament, and tendon. The utilization of foundational stem cells for different orthopedic difficulties is sketched out beneath:

1.8.1.1Trauma and bone defects

Nonunion/Delayed union and bone deformities following injury, tumor or disease are testing parts of orthopedic surgery that may require biologic enlargement for ideal recuperating. Autologous cancellous join is the current `gold standard', yet constrained supply and contributor site grimness restrict their utilization. Allografts and bone join substitutes are routinely used to enlarge bone mending. In any case, poor join incorporation and osteonecrosis of the unite stay essential issues with this technique.

Bone marrow aspirates that contain stem cells in a proportion of 1:10,000 to 1:1,000,000 of nucleated cells have been successfully used to enhance healing of non-unions 5. Tissue engineering, involving the use of stem cells with scaffolds such as hydroxyapatite (HA), demineralized bone matrix (DBM) and tri-calcium phosphate (TCP), have been studied and found to be useful for bridging bone defects 9. Due to absence of an extracellular matrix to grow on, MSCs alone have not proven to be beneficial for filling defects caused by simple/aneurysmal bone cysts. Healing rates, are however, enhanced when these are used in conjunction with scaffolds (Wright, Yandow, Donaldson & Marley, 2008).

1.8.1.2 Spine and peripheral nerve surgery

Spine Fusion*:* Neen *et al*, in a prospective study, showed that unselected stem cells used with HA scaffolds had similar healing rates as autologous grafting; thereby preventing donor site morbidity. Similar results were obtained by Gan et al using β-TCP12.

Intervertebral Disc Degeneration*:* Intervertebral disc degeneration is one of the most common causes of backache in a young productive population. Despite the high prevalence there is no treatment available which reverses the primary pathology. Animal experiments have shown increased proteoglycan content and maintenance of disc height with percutaneous stem cell injections (Miyamoto, Muneta, Tabuchi, Matsumoto, Saito & Tsuji, 2010).

Spinal cord and peripheral nerve injuries*:* Spinal cord and peripheral nerve injuries have a significant impact on quality of life of affected individuals. Animal studies have highlighted some positive effects of MSC use via intrathecal and local administration, however, the response seen in clinical studies is mixed. In an animal study, Tamaki *et al*, demonstrated that muscle derived MSCs aided in successful regeneration of a crushed peripheral nerve. Further prospective clinical studies are necessary to establish the role of MSCs in managing these patients.

1.8.1.3 **Articular cartilage**

Articular cartilage is a highly specialized tissue with a poor intrinsic capacity to repair itself. The goal of any cartilage procedure is to restore its integrity so that it can withstand the wear and tear of daily activity.

Focal cartilage damage*:* Since Pridie introduced subchondral drilling in the late 1950s, various procedures such as microfracture and abrasionplasty have been developed to recruit MSCs from adjacent bone marrow to proliferate into chondrocytes. Unfortunately, these procedures result in the formation of an inferior quality nonhyaline cartilage. Data on use of MSCs with suitable scaffolds in cartilage healing is mostly based on animal studies, with a few human case series showing improved healing and better function after autologous MSC implantation techniques (Nejadnik, Hui, Feng, Choong, Lee & Tai, 2010).

Osteoarthritis (OA): Due to their role in inhibiting the catabolic activity of matrix metalloproteinases (MMP), MSCs have been shown to have a beneficial effect in OA 18. In a recent study, Sato *et al* showed that guinea pigs with age related OA treated with MSC laden hyaluronic injections had better cartilage regeneration with higher type II collagen and lower MMP content 19. Except for a few case series which show some clinical improvement there is a paucity of trials with human subjects which study the effect of MSCs on OA.

High tibial Osteotomy (HTO) and Arthoplasty*:* In a randomized control trial, Dallari *et al* showed that lyophilized bone chips treated as grafts with platelet gels and MSCs had higher rate of osteointegration in HTOs. With appropriate use of nanotechnology to make optimum implant surfaces, MSCs have a great potential to revolutionize joint replacement surgery by facilitating osteointegration. Three dimensional scaffolds with MSCs may be used in the future to form autologous osteochondral grafts suitable for a `biologic' arthroplasty.

1.8.1.4 Wound Healing

Although not typical in orthopaedic practice, poorly healing wounds are commonly encountered in treating patients with risk factors such as diabetes or open fractures. MSC treatment of acute and chronic wounds results in accelerated wound closure with increased epithelialization, granulation tissue formation and angiogenesis.

1.8.1.5 Bone-Tendon interface and Tendon Healing

Numerous commonly employed surgical procedures such as anterior cruciate ligament reconstruction, rotator cuff repair or retro calcaneal bursa excisions depend on optimum healing of the bone-tendon interface.

Fibrovascular scar formed during healing possesses inferior biochemical and mechanical properties. MSCs have been shown to promote early healing of the bone tendon interface by increasing the proportion of Sharpey's fibers. MSCs used with bone morphogenic protein 2 (BMP-2) are associated with improved biomechanical properties of the bone tendon interface including stiffness and maximal load. A recent study by Adams *et al* showed that rats with Achilles tendon tear treated with stem cell-bearing sutures have higher failure strength and better histological properties. Unselected MSCs were used for ultrasound-guided injections in a case series by Pascual-Garrido *et al* for chronic patellar tendinopathy with good clinical results.

1.8.1.6 Paediatric Orthopaedics

Cellular therapy has gained an increasing popularity in recent years. Mesenchymal stem cells (MSCs) have the potential to differentiate into bone, cartilage, or fat tissue. In recent studies, these cells have also shown healing capability by improving angiogenesis and preventing fibrosis, which could have a role in tissue repair and tissue regeneration. Preclinical and clinical orthopedic studies conducted in the adult population support the use of MSCs for bone-healing problems, early stages of osteonecrosis, and local bone defects. Only a few published studies support the use of MSCs in pediatric osteoarticular disorders, probably due to the unknown long-term results of cellular therapy. The purpose of this review is to explain the mechanism by which MSCs could exhibit a therapeutic role in pediatric osteoarticular disorders. Several pediatric osteoarticular disorders can have lifelong consequences on the patient. Scientists and physicians believe that cellular therapy with multipotent mesenchymal stem cells (MSCs) have the potential to cure these disorders, or at least significantly alleviate their symptoms and sequelae (Norambuena, Khoury & Jorgensen, 2012).

Osteogenesis Imperfecta (OI):This is a heterogenous group of diseases with abnormality of type I collagen primarily leading to increased susceptibility to fractures, slow growth and loss of bone mass. Systemic infusion of allogenic MSCs by Horwitz *et al* in six children with OI showed improvement in bone mass and bone growth acceleration.

Physeal injuries: Bone bridge formation is an adverse complication following traumatic, infectious or other insult on the Physeal, leading to angular and/or longitudinal deformities. In a pig study, Planka *et al* showed that MSCs with scaffolds used in physical defects differentiated into chondrocytes forming hyaline cartilage and prevented bony bridge formation. Currently, there are no clinical studies to support this.

1.8.1.7 Stem Cells in Fracture Healing

The role of stem cells in fracture healing has now been well established. Although stem cells have applications throughout the field of orthopaedics, a discussion of each topic is beyond the scope of this article. We will use the example of the role of stem cells in fracture healing as an example of the advancement in the knowledge and application of stem cells in orthopaedics. Bone has the ability to heal itself when fractured. Bone healing is a complex and well-orchestrated process that depends on many factors: cellular, molecular, and mechanical. Unlike other adult tissues, which generate scar tissue at the site of an injury, the skeleton heals by forming new bone that is indistinguishable from uninjured bone. Recently, the role of stem cells of various origins has been demonstrated.

A combination of adult mesenchymal stem cells and parathyroid hormone (PTH) significantly increased new bone formation and may speed the healing process for human bone fractures caused by osteoporosis. The therapeutic effect of the stem cells-PTH combination was compared with the results of stem cell therapy alone, PTH injections alone, and no treatment. Bone regeneration in vertebral defects was monitored at several time points with computed tomography scan. Some studies showed increased bone volume density and healthy bone formation only in the lab animals treated with both stem cells and hormone therapy (Morigi, Introna, Imberti, Corna, Abbate, Rota & Rambaldi, 2008).

The enhancement or exploitation of this can enhance bone repair and regeneration. The osteogenic potential of MSCs has already been verified. Two approaches have been used for cell delivery: bone marrow aspiration and direct introduction at the lesion or expansion ex vivo before implantation. Percutaneous autologous bone marrow grafting has been shown to be an effective treatment for tibial diaphyseal nonunion in one study. The efficacy is influenced by the amount of progenitor cells in the harvested graft, as harvested iliac crest bone marrow graft appears to contain a suboptimal concentration of cells. In vitro studies have shown that myoblastic cell lines in mice can differentiate into osteoblastic lineage cells upon stimulation with bone morphogenic protein. Lee et al showed that their highly purified muscle derived MSCs (preplate technique) differentiated into osteogenic lineage,33 suggesting that subpopulations of muscle-derived stem cells are capable of bone healing. Shen and colleagues were able to show that IGF-1 transduced mesenchymal cells were able to return and repopulate the bone marrow with a preferential recolonization of the fracture site in a mouse in vivo model.

They have also shown an accelerated fracture healing by demonstrating a greater average mineralized matrix and progression to osseous callus. This demonstrates, as earlier studies have shown, that MSCs are attracted to fracture sites and that there may be a role in systemic administration of stem cells in certain instances, for example, with fractures that have a relatively high non-union rate or in elderly patients who have been shown to have a decreased concentration of MSCs.

1.9 Conclusion and Summary

The treatment of musculoskeletal disease at this point of time concentrates on the concepts of reconstruction and replacement. A large amount of musculoskeletal pathology is thought to be due to inadequate or absent regenerative potential of a variety of musculoskeletal tissues. The field of stem cells has the potential to change this completely. Stem cells are far from replacing the orthopaedic surgery that we know today, but they will augment our ability to treat pathologic processes that continue to be problematic to our everyday practice. Developments in orthopaedic surgery will soon revolutionize the treatment and have the ability to possibly eradicate the problem of non-unions. Other developments may be farther off, but the developments that are possible and that are being studied now should become familiar to all orthopaedic surgeons.

References

Akpancar, S., Tatar, O., Turgut, H., Akyildiz, F., & Ekinci, S. (2016). The Current Perspectives of Stem Cell Therapy in Orthopedic Surgery. *Archives of trauma research*, *5*(4).

Desiderio V, De Francesco F, Schiraldi C, De Rosa A, La Gatta A, Paino F, et al. Human Ng2+ adipose stem cells loaded in vivo on a new crosslinked hyaluronic acid-Lys scaffold fabricate a skeletal muscle tissue. J Cell Physiol. 2013;228(8):1762–73.

Gan Y, Dai K, Zhang P, Tang T, Zhu Z, Lu J. The clinical use of enriched bone marrow stem cells combined with porous betatricalcium phosphate in posterior spinal fusion. *Biomaterials.* 2008; 29: 3973-3982.

Giuliani N, Lisignoli G, Magnani M, Racano C, Bolzoni M, Dalla Palma B, *et al.* New insights into osteogenic and chondrogenic differentiation of human bone marrow mesenchymal stem cells and their potential clinical applications for bone regeneration in pediatric orthopaedics. *Stem Cells Int.* 2013; 2013: 312501.(Level V).

Guan M, Yao W, Liu R, Lam KS, Nolta J, Jia J, *et al.* Directing mesenchymal stem cells to bone to augment bone formation and increase bone mass. *Nat Med.* 2012; 18: 456-462.

Hernigou P, Poignard A, Manicom O, Mathieu G, Rouard H. The use of percutaneous autologous bone marrow transplantation in nonunion and avascular necrosis of bone. *J Bone Joint Surg Br*. 2005; 87: 896-902.

Horwitz EM, Prockop DJ, Gordon PL, Koo WW, Fitzpatrick LA, Neel MD, *et al.* Clinical responses to bone marrow transplantation in children with severe osteogenesis imperfecta. *Blood.* 2001; 97: 1227-31.(Level III).

Horwitz EM, Prockop DJ, Gordon PL, Koo WW, Fitzpatrick LA, Neel MD, et al. Clinical responses to bone marrow transplantation in children with severe osteogenesis imperfecta. Blood. 2001; 97: 1227-31

Huang, G. J., Gronthos, S., & Shi, S. (2009). Mesenchymal stem cells derived from dental tissues vs. those from other sources: their biology and role in regenerative medicine. *Journal of dental research*, *88*(9), 792-806.

Lee, E. H., & Hui, J. H. P. (2006). The potential of stem cells in orthopaedic surgery. *Bone & Joint Journal*, *88*(7), 841-851.

Mafi R, Hindocha S, Mafi P, Griffin M, Khan WS. Sources of adult mesenchymal stem cells applicable for musculoskeletal applications - a systematic review of the literature. *Open Orthop J.* 2011; 5 Suppl 2: 242-8.

Miyamoto T, Muneta T, Tabuchi T, Matsumoto K, Saito H, Tsuji K, *et al.* Intradiscal transplantation of synovial mesenchymal stem cells prevents intervertebral disc degeneration through suppression of matrix metalloproteinase-related genes in nucleus pulposus cells in rabbits. *Arthritis Res Ther.* 2010; 12: R206.

Neen D, Noyes D, Shaw M, Gwilym S, Fairlie N, Birch N. Healos and bone marrow aspirate used for lumbar spine fusion: a case controlled study comparing healos with autograft. *Spine (Phila Pa 1976).* 2006; 31: E636-40.

Nejadnik H, Hui JH, Feng Choong EP, Tai BC, Lee EH. Autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation: an observational cohort study. Am J Sports Med. 2010; 38: 1110-1116.

Planka L, Srnec R, Rauser P, Stary D, Filova E, Jancar J, et al. Nanotechnology and mesenchymal stem cells with chondrocytes in prevention of partial growth plate arrest in pigs. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2012; 156: 128-34.

Shostak S. (Re) defining stem cells. *Bioessays*. 2006; 28: 301-308.

Tamaki T, Hirata M, Soeda S, Nakajima N, Saito K, Nakazato K, *et al.* Preferential and comprehensive reconstitution of severely damaged sciatic nerve using murine skeletal muscle-derived multipotent stem cells. *PLoS One.* 2014; 9: e91257.

Veronesi, F., Giavaresi, G., Tschon, M., Borsari, V., Nicoli Aldini, N., & Fini, M. (2012). Clinical use of bone marrow, bone marrow concentrate, and expanded bone marrow mesenchymal stem cells in cartilage disease. *Stem cells and development*, *22*(2), 181-192.

Wright JG, Yandow S, Donaldson S, Marley L, Simple Bone Cyst Trial Group. A randomized clinical trial comparing intralesional bone marrow and steroid injections for simple bone cysts. *J Bone Joint Surg Am.*

2008; 90: 722-730.

Morigi, M., Introna, M., Imberti, B., Corna, D., Abbate, M., Rota, C., ... & Rambaldi, A. (2008). Human bone marrow mesenchymal stem cells accelerate recovery of acute renal injury and prolong survival in mice. *Stem cells*, *26*(8), 2075-2082.

Norambuena, G. A., Khoury, M., & Jorgensen, C. (2012). Mesenchymal stem cells in osteoarticular pediatric diseases: an update. *Pediatric research*, *71*(4-2), 452-458.