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Review article

Assessment of Therapeutic Potential Effect of Autologous Bone Marrow Derived Mesenchymal Stem Cell Transplantation in Patients with Knee Osteoarthritis

Reham Salama

Department of clinical pathology, Faculty of Medicine Benha University, Egypt.

Corresponding to: Reham Salama, Department of clinical pathology, Faculty of Medicine Benha University, Egypt.

Email: reham.s.elshinnawy@gmail.com

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ABSTRACT

Osteoarthritis (OA) is a degenerative joint disease, it is additionally referred to the most common type of arthritis. OA is graded collectively as one of the leading causes of disability among the elders. An ideal therapy ought to deal with both inflammatory and tissue degeneration processes in the joint building tissue. Regenerative medicine is an exciting potential non-invasive therapeutic alternative to total joint replacement for treating osteoarthritis. Encouraging results of pre-clinical and clinical trials that provided initial proof of efficacy and safety in the therapeutic impact of using mesenchymal stem cell therapies for the treatment of knee osteoarthritis.This review study aimed to discuss the safety and efficacy of autologous mesenchymal stem cells (MSCs) intra-articular injection in treating patients with knee OA classified grade II and III according to Kellgren and Lawrence system. Assessment of potential therapeutic effect of autologous bone marrow derived mesenchymal stem cells transplantations in patients with osteoarthritis.This review concluded that, Mesenchymal stem cells (MSCs) are the most used for therapeutic cause and cartilage regeneration, and their safety and effectiveness have been demonstrated in basic research and clinical studies. There are many clinical experiments of stem cells showing a satisfactory healing effect in cartilage damage repair, but further studies are still required to test the effectiveness and safety of stem cells for cartilage repair.

Key words: Mesenchymal stem cells, Cartilage regeneration, knee osteoarthritis.

Introduction:

Osteoarthritis is a degenerative disease most often occurring in the aged population, joints are affected by slowly progressive course, where hyaline cartilage exposed to dysfunctional tissue damage that has no ability of self- repair (1)**.**

Cartilage damage leads to loss of smooth glide at the joint, during movement bone surface friction, subchondral bone remodeling, tissue loss, marginal osteophytes, and loss of joint space may occur. Bone frictional rubbing result in pain, swelling and stiffness at the joint and eventual muscle strain due to difficult movement of the joint (2)(3)**.**

Current treatments for knee osteoarthritis achieve poor clinical results with no ability to heal damaged cartilages. Joint replacement is the terminal line of treatment options, bearing enormous effort and expenses on the patients (4).

Disability due to musculoskeletal disorders has raised by 45% from 1990 to 2010 and osteoarthritis is listed as the fastest increasing major health condition and ranked second as cause of disability by World Health Organization (WHO) (5).

Regenerative medicine is an exciting potential minimally invasive therapeutic alternative to total joint replacement for treating osteoarthritis. Encouraging results of pre-clinical and clinical trials that provided initial proof of efficacy and safety in the therapeutic effect of using mesenchymal stem cell therapies for the treatment of knee osteoarthritis (6)**.**

Review of literature:

Osteoarthritis:

The definition of Osteoarthritis is: "a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity (7).

Osteoarthritis of the knee is the most common form of arthritis that cause pain, stiffness, decreased function, and one of leading causes of disability among non-institutionalized adults. More than 50 modalities of pharmacological, non-pharmacological, and surgical treatment are reported in the literature. However, the current most common treatments for osteoarthritis except for joint replacement have at best modest albeit clinically relevant effects and can endanger substantial adverse events or costs, or both (8)**.**

Prevalence of knee OA in men is lower compared with women .This was shown in a meta-analysis of males and females in which the incidence of knee OA in males aged <55 years was lower than females. Females, particularly those ≥55 years, tended to have more severe OA in the knee but not in other sites. The results of this study demonstrated sex differences incidence of knee OA particularly after menopausal age (9)**.**

The etiology and pathogenesis of osteoarthritis (OA) are poorly understood,

although proinflammatory cytokines are known to be critically implicated in the disease. the role of proinflammatory cytokines, particularly interleukin (IL) 1β, tumor necrosis factor and IL 6 in the pathophysiology of OA (10).

Previously OA was believed to be a normal consequence of aging and the physiologic consequence of "wear and tear," thereby leading to the term degenerative joint disease. However, it is now realized that OA results from a, complex pathophysiology and multifactorial process involving effect of constitutional and mechanical factors, including joint trauma, chronic experience of joint stress , genetic predisposition, local inflammation, and cellular and biochemical processes (11).

Knee OA is closely related to age, as radiographic evidence of OA occurs in most people by age 65 years and continue increasing to more than 75% of individuals older than 75 years old. Even though there are many associations and mechanisms that are mentioned in literature, for example it has been reported that there is a higher prevalence of OA among elderly women (12).

Treatment designed for knee OA should aim to alleviate pain, improve knee function, and limit motion disabilities. Knee OA treatment is usually driven by the patient's symptoms and the potential to improve quality of life. Non-operative treatments of knee OA are often useful for patients with Kellgren and Lawrence Grades I to III, which are early stages of OA. However, surgical treatments are generally needed to cure or ameliorate advanced stages of knee OA (13).

Treatment may include options: lowering body mass index, modifying the intensity of the activities performed, strengthening muscles by regular exercises, osteopathic treatment, application of cold or hot bandages, pharmaceutical treatment including non-steroidal anti-inflammatory drugs NSAIDs, and visco supplementation with hyaluronic acid injections, corticosteroid injections, glucosamine intakes, and platelet-rich plasma injections (PRP). PRP is derived from a sample of the patient's own blood and then injected directly into the diseased knee joint to alleviate pain, improve joint function, and possibly repair the cartilage (5)

Stem cells:

Stem cells are non-differentiated cells, which have the capacity to renew themselves through cell division, when a stem cell divides, each new cell has the potential either to remain a stem cell or to differentiate to any other type of cell with a more specialized function (14).

Stem cells have the potential to develop into variety of cell types in the body during early life and during growing process. Additionally, in many tissues they serve as a sort of spare cells used for internal repair process, dividing essentially without limit to replenish other cells as long as the individual is still alive. When a stem cell divides, each new cell has a possibility to remain a stem cell or become another type of cell performing specific function, such as a muscle cell, liver cell, or blood cells (15).

Sources of Stem Cells based on the developmental stage; (I) Embryo-derived

stem cells: The blastocyst is the pre-implantation stage in embryos aged one week approximately. The blastocyst is a complex structure made by the trophectoderm, an outer layer of cells forming a cavity filled with fluid and a cluster of cells in the interior layer known as inner cell mass (ICM) (16).

Embryonic stem cells (ESCs) are contained in the ICM and generate the organism, whereas the surrounding trophoblast cells contribute to the placental chorion. Traditionally, ESCs are capable of a self-renewal and differentiation into cells of all tissue lineages (5)

ESCs can be cultured and maintained for a long time (1-2 years with cell division every 36-48 hours) in an undifferentiated phenotype. (16).

(II) Fetal stem cells; these stem cells present in fetus. At about 9 weeks, a maturing embryo enters into the fetal stage of development. Fetal stem cells are found in fetal tissues, blood and bone marrow. They have the ability to develop into almost any type of cell (17).

(III) Induced pluripotent stem cells; commonly abbreviated (iPSCs) are a type of pluripotent stem cell artificially derived from a non-pluripotent cell, typically an adult somatic cell by inducing a forced expression of specific genes. Induced pluripotent stem cells are similar to natural pluripotent stem cells, such as embryonic stem cells, in many aspects, such as the expression of certain stem cell genes and proteins. This has been cited as an important advance in stem cell research, as it may allow researchers to obtain pluripotent stem cells, which are important in research and potentially have therapeutic uses, without the controversy use of embryos (18).

(IV)Adult stem cells (AsCs); An adult stem cell is thought to be an undifferentiated cell, found among differentiated cells in tissue or organ that can renew it and can differentiated to yield some or all of the major specialized cell types of the tissue or organ (19).

ASCs have the ability to self–renew and give rise to mature cell types with specialized function. This usually happens through the differentiation of intermediate cell types called progenitors and precursors, before forming fully differentiated cells (20).

MSCs possess two important properties, which are essential to distinguish stem cell from other normal cell; the capacity of long term self-renewal and potential ability to differentiate to variety of cell lineages, such as muscle, bone, cartilage, and adipose cells. Even though their presence is scarce in bone marrow aspirate (the the average frequency of MSCs in the whole bone marrow of skeletally mature adults ranges from 1 in 50 000 to 1 in 100 000 cells, corresponding to a yield of a few hundred MSCs/milliliter of marrow), mesenchymal stem cells are easily expandable through standard culture techniques (21). Upon cultivation, they assume a spindly shaped morphology. MSC primary tissue culture has been reported to be heterogeneous, containing multiple colonies with different specialization capacities; nearly one-third of these colonies have the capacity to differentiate to; osteocytes , adipocytes, and chondrocytes, while the other two thirds showed either

bipotent or unipotent capacity to differentiate into osteogenic, chondrogenic and adipogenic lineages, respectively (22).
The capacity for self-renewal and the potential for multiple differentiation of stem cells, such as ESCs, iPSCs, and MSCs, have been studied widely in the field of tissue regeneration. Furthermore, studies including MSCs have been applied in the clinical application. In this review, we focus on the cartilage treatment strategies and studies of stem cells in the field of cartilage regeneration (23).

Method

In this review article we followed the PRISMA statement guidelines during the preparation of this review.
Literature search strategy; we searched for published, randomized, controlled trials in medical electronic databases including: PubMed, Scopus, Embase, and web of science from 2012 to January 2019, using the following query: "potential therapeutic effect of autologous mesenchymal stem cell transplantation in patients with knee osteoarthritis". No language restrictions were imposed.

Inclusion criteria: interventional studies, performed on human, using mesenchymal stem cells in therapy of osteoarthritis.

Exclusion criteria; studies performed on animals, using hematopoietic or embryonic stem cells.

Key Words used: Mesenchymal stem cells, Osteoarthritis, Cartilage regeneration.

Data extraction:

Data extracted according to year of study, study design, type and source of cells used, number of studied population and conclusion of studies performed as shown in the table.

Study design and ID	Cell type	Number of joints	Results/conclusion
Case series (24)	Bone marrow derived mononuclear cells (BM-MNCs)	34patients received intraarticular injection of BM-MNCs	A single dose BM MNC reduces clinical signs of the knee OA stage II/III and in some cases, diminished degenerative changes in the joint over 12-month period.
Randomized control trial (25)	Bone marrow derived mesenchymal stem cells (BM-MSCs)	30 patients divided to 3 groups: 10 received BM-MSCs 10 received Hyaluronic acid injection 10 control	Our study shows that the single intraarticular injection of in vitro cultured and expanded autologous BM-MSCs together with HA is a safe and effective procedure that proved successful in a clinical and functional improvement of knee OA after a follow up of 4 years.
Prospective randomized control trial (26)	Bone Marrow derived mononuclear cells (BM-MNCs)	56 patients divided into 2 groups: 28 received BM-MNCs 28 received Hyaluronic acid	A statistically significant improvement was observed in the mononuclear cell group over the baseline point in all scores. At the endpoint at month 12, the KOOS score improved significantly. Indicating safety and efficacy of cellular therapy.
Prospective cohort. (27)	Mesenchymal Stem Cells (MSCs)	20 patients received MSCs	Considering the encouraging clinical and MRI outcomes and the significant correlations between the clinical and MRI outcomes, MSC transplanting seems to be fruitful for cartilage lesions regeneration in OA knees.
Case series (28)	Adipose tissue derived stromal cells	30 patients received ADSCs	Adipose-derived stem cell therapy for elderly patients with knee OA was effective in cartilage repair, alleviating pain, and improving function. Therefore, ADSCs appears to be valid choice for OA treatment in elderly patients.
Prospective cohort study (29)	Mesenchymal Stem Cells	109 patients followed up aster knee surgeries 20 received mesenchymal stem cells	Utilizing MSC implantation for knee OA resulted in better clinical sequel and second-look arthroscopic than non-injected patients.
Case report (30)	Peripheral blood Mesenchymal stem cells	1 received with autologous PBSCs	CT and MRI showed better results. Eight months after the surgery, the second arthroscopy showed that the regenerated cartilage had a smooth surface. The patient returned to practicing sports.
Case series (31)	Peripheral blood derived stem cells (PBSCs)	5patients received PBSCs	No adverse events and all clinical scores got improved. PBSC group has a better quality of regenerated cartilage than the control group on histological and MRI Assessment
Cohort study (32)	Adipose tissue derived stromal cells	65 patients 31 injected with ADSCs	Among patients above 50 years of age, the effect of marrow stimulation + ADSCs was better therapeutic intervention than marrow stimulation alone. ADSCs showed better regeneration results.
Randomized control trial (33)	Peripheral Blood Stem Cells (PBSCs)	50 patients received PBSCs	There were no adverse events to be noted. After arthroscopic subchondral drilling into grade 3 and 4 chondral lesions, intra-articular injections of autologous PBSC in combination with HA resulted in an improvement of the articular cartilage regeneration over the same treatment without PBSC, as proved by histologic and MRI evaluation.
Therapeutic case-control study (34)	Autologous adipose derived stem cells and Platelet Rich Plasma (ADSCs+ PRP)	25 MSCs injections combined with arthroscopic debridement were administered to patients with knee OA.	ADSCs of the infrapatellar fat pad were useful for alleviating articular pain and improving knee joint function.

Discussion:

Osteoarthritis (OA) is a progressive, destructive joint disease in which the articular cartilage injury initiation may be attributed to intensive, or repetitive physical stress that started mechanical disruption of joint tissues. However, progressive changes are dependent on active cell-mediated processes that can be observed or inferred during the generally long time-course of the disease often with disabling symptoms of arthritis as the end result. (35)

Treatment of the early stages of the knee-joint osteoarthritis continues challenging doctors in orthopedic practice. Current accepted medical treatment strategies are aimed at symptom control rather than disease modification. Surgical options including joint replacement are conjoint with possible significant complications, this treatment strategies have had limited success in these patients (6).

The goal is to develop therapeutic modlaities that either prevent the destruction in the first place or promote repair to replicate the physiological and functional properties of the original cartilage. Encouragingly scientists are increasing their intention to regenerative medicine, led by an improved understanding of the role of mesenchymal stem cells in healing and tissue repair, has seen recent concentrated efforts to explore the potential of stem cell therapies in the active management of symptomatic osteoarthritis (36) (35).

This study aimed to investigate the safety and efficacy of autologous bone marrow (BM)-derived mesenchymal stem cells (MSCs) intra-articular injection in treating patients with knee OA.

In a case series study was conducted on 46 patients by Goncarset,al. 2018, performed intra-articular (BM-MNC) injection, majority of cases provides a statistically and clinically significant improvement of knee osteoarthritis of stage II-III symptoms at the 12-month period, the clinical effect measured by the KOOS and KSS score, similar improvement levels were reported. The intra-articular injection of the BM MNCs was reported as a safe manipulation with no serious side effects over the 12-month period (24).

A prospective randomized clinical trial was carried out by Gongars et,al.2017. compared safety and clinical efficacy of intra-articular injection of (BM-MNC) versus hyaluronic acid, concluded that intra-articular injection of the BM MNC seems to be a safe manipulation with no side effects during the 12-months follow-up period, treatment with single intra-articular injection of BM-MNC in grade II and III OA had a statistically significant superiority in pain relief between baseline and 12 months after, compared to the control group; treated with 3 hyaluronic acid injections(26).

Moreover, Rodriguez-fontan et.al. found that intra-articular injections of BMC considered a safe symptomatic treatment for early knee or hip osteoarthritis. However, variable outcomes predictable, since only 63.2% of the patients were satisfied after the treatment (38).

Conclusion:

Stem cells research is vital and basic in research topics concerned with cartilage healing and regeneration, by reviewing literature significant improvement of signs and symptoms of knee osteoarthritis is proven statistically. Moreover adult mesenchymal stem cells proven safety, and is can be valid effective safe option alternating joint replacement therapy in knee osteoarthritis cases. Bone marrow derived mesenchymal stem cells is considered safe and effective intervention in treatment of grade II and III osteoarthritis.

However more clinical trials with larger sample size and longer follow up period are still needed for better evidence practice.

Abbreviation table:

OA	Osteoarthritis
MSCs	Mesenchymal Stem Cells
WHO	World Health Organization
IL	Interleukin
NSAIDs	Non-steroidal anti-inflammatory drugs
ECs	Embryonic Stem Cells
ICM	Inner Cell Mass
ASCs	Adult Stem Cells
iPSCs	Induced pluripotent stem cells
BM-MNCs	Bone marrow derived mononuclear cells
BM-MSCs	Bone marrow derived mesenchymal stem cells
ADSCs	Adipose tissue derived stromal cells
PBSCs	Peripheral blood mesenchymal stem cells
PRP	Platelet Rich Plasma

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