

Stem cell application for osteoarthritis in the knee joint: A minireview

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Abstract

Knee osteoarthritis is a chronic, indolent disease that will affect an ever increasing number of patients, especially the elderly and the obese. It is characterized by degeneration of the cartilage substance inside the knee which leads to pain, stiffness and tenderness. By some estimations in 2030, only in the United States, this medical condition will burden 67 million people. While conventional treatments like physiotherapy or drugs offer temporary relief of clinical symptoms, restoration of normal cartilage function has been difficult to achieve. Moreover, in severe cases of knee osteoarthritis total knee replacement may be required. Total knee replacements come together with high effort and costs and are not always successful. The aim of this review is to outline the latest advances in stem cell therapy for knee osteoarthritis as well as highlight some of the advantages of stem cell therapy over traditional approaches aimed at restoration of cartilage function in the knee. In addition to the latest advances in the field, challenges associated with stem cell therapy regarding knee cartilage regeneration and chondrogenesis *in vitro* and *in vivo* are also outlined and analyzed. Further-

more, based on their critical assessment of the present academic literature the authors of this review share their vision about the future of stem cell applications in the treatment of knee osteoarthritis.

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Key words: Multipotent adult mesenchymal stem cells; Osteoarthritis; Knee joint; Clinical trial

Core tip: Knee osteoarthritis is a common medical condition in the elderly and the obese. Despite the variety of available conventional treatments for this disease, in recent years stem cell therapy has been applied in an ever increasing number of clinical cases. Therefore the aim of this review is to outline the latest advances in stem cell therapy as a non-pharmacologic treatment for knee osteoarthritis. It also emphasizes on some of the challenges associated with stem cell therapy regarding knee cartilage regeneration and chondrogenesis *in vitro* and *in vivo*.

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INTRODUCTION

Osteoarthritis (OA) of the knee is a chronic, indolent disease that affects all genders, ages and races but is known to be most common in the elderly and in obese people. A degenerative disease of the connective tissue, it mainly affects the articular cartilage (Figure 1)^[1]. The definition of knee OA varies in reported studies and includes self-reported knee OA (obtained from a questionnaire), radiographic definitions of knee osteoarthritis, and symptom-

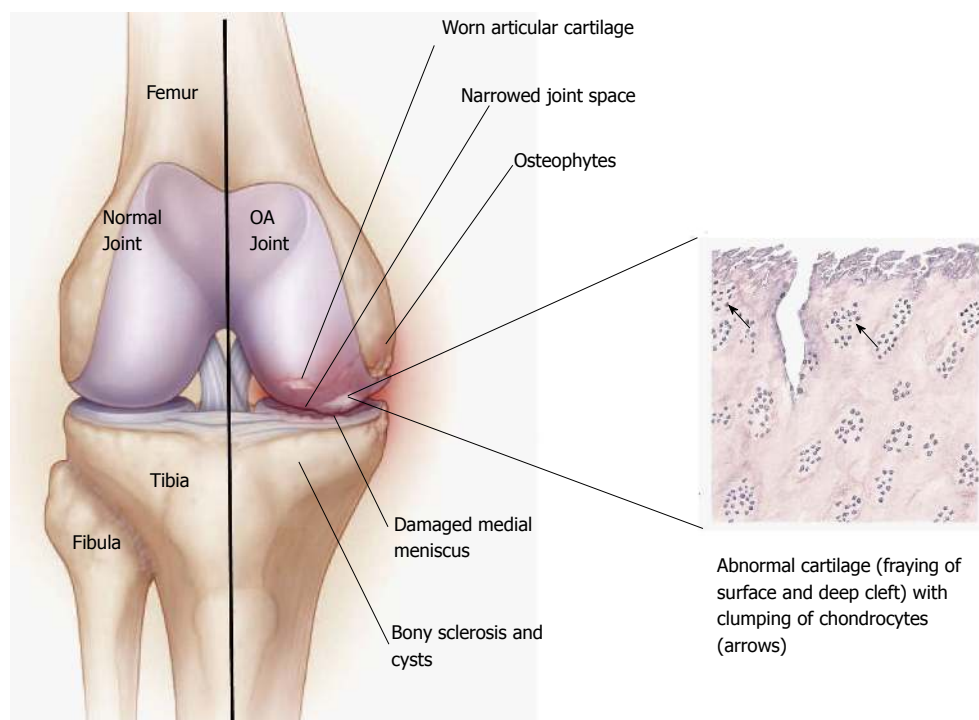


Figure 1 Pathophysiology of knee osteoarthritis. Comparison between a normal and diseased joint (Illustration created after Felson^[3] and Buja *et al*^[4])

atic knee OA (self-reported joint pain and radiographic evidence of OA)^[2]. Symptoms may include joint pain, stiffness and tenderness. Furthermore, as the cartilage substance decreases, the bone surface may also become affected. This results in development of osteophytes (bone spurs) and direct bone-bone contact. In addition to the stiffness of the joint, the patient tries to avoid pain by minimizing joint movement, which leads to muscle atrophy and laxity of the ligaments^[11-41].

The pathogenesis of knee OA have been linked to biomechanical and biochemical changes in the cartilage of the knee joint (*e.g.*, inability to withstand normal mechanical stresses, limited supply of nutrients and oxygen, inadequate synthesis of extracellular matrix components, increased synthesis of tissue-destructive proteinases (matrix metalloproteinases and aggrecanases) and overall apoptosis of chondrocytes)^[4-71]. Recently, synovial inflammation has also been accredited as a factor limiting knee cartilage repair. Moreover, it correlates to clinical signs of knee OA such as swelling of the knee and inflammatory pain^[7,81]. It is believed that synovial inflammation is a response of synovial macrophages to cartilage debris and catabolic mediators entering the synovial cavity^[8,91].

In regards to the epidemiology of knee OA (Table 1), studies indicate that knee osteoarthritis in men aged 60 to 64 is usually found in the right knee (23%) than in the left knee (16.3%), while distribution seems to be more evenly balanced in women of the same age (right knee, 24.2%; left knee, 24.7%)^[6,101]. A variety of endogenous (*e.g.*, age, sex) and exogenous (obesity, patient's lifestyle) risk factors for OA have also been outlined^[2,6,11-141]. Recently, a number of genome wide association studies (GWAS) (*e.g.*, Rotter-

dam GWAS^[15], Tokyo GWAS^[15], Chingford Study^[161]) have highlighted the significance of gene mutations (*e.g.*, in *GDF5*) for the development of knee OA^[15-211]. Additionally, cross-sectional studies indicate that the risk of knee OA is 1.9 to 13.0 times higher among underground coal miners when compared to a control population; presumably, due to frequent work in the kneeling or squatting position^[61]. Construction workers, especially floorers, also have a significantly elevated prevalence of knee OA^[61].

As of clinical diagnosis of knee OA, it is complex as during the physical examination of the patient it is needed to confirm and characterise joint involvement, as well as to exclude pain and functional syndromes linked to other causes (*e.g.*, inflammatory arthritis or damaged meniscus)^[3,11,221]. In addition to non-surgical treatments for this condition such as physiotherapy, diet rich in vitamin D and supportive sport (*e.g.*, swimming)^[10,23,241], there are several medicinal and homeopathic products on the market, which promise pain relief and a decrease in symptoms. However, researchers are keen to investigate new treatments to combat OA of the knee.

STEM CELL TREATMENT

Self-regeneration of the cartilage, which includes chondrocytes, ground substance (cartilage matrix) and elastin fibers, is a slow process which results in new cartilage substance that is not stable for intensive burdens. The fluid inside the joint contains mesenchymal stem cells (MSCs) which can differentiate into chondrocytes, but new deposited cartilage is very fragile and can be destroyed by applying a minimal amount of stress on the

Table 1 Worldwide prevalence (2005) of knee osteoarthritis

| | Knee OA prevalence |
|--------------------------|--------------------|
| Europe | |
| Western | 0.1689 |
| Central | 0.1889 |
| Eastern | 0.1914 |
| Asia | |
| Middle East | 0.1764 |
| South | 0.1563 |
| East | 0.1683 |
| Southeast | 0.1704 |
| Central | 0.1854 |
| Pacific | 0.1704 |
| Africa | |
| North | 0.1764 |
| West Sub-Saharan | 0.1574 |
| East Sub-Saharan | 0.1544 |
| Central Sub-Saharan | 0.1528 |
| South | 0.1822 |
| Australia and Oceania | |
| Australia | 0.1736 |
| Oceania | 0.1813 |
| North America | |
| United States and Canada | 0.1792 |
| Central America | 0.1777 |
| Caribbean | 0.1756 |
| South America | |
| Andean | 0.1751 |
| Tropical | 0.1691 |
| Southern | 0.1693 |

Combined value for male and female, aged 30-100 (Data adapted from March *et al*^[10]). OA: Osteoarthritis.

joint. Additionally there is only a limited quantity of MSCs in the joint available to differentiate and the process of differentiation is slow^[1,25].

STEM CELL MANAGEMENT

The aim in using stem cells is to support the self-healing process of the knee joint cartilage which results in relief from OA symptoms^[26-32]. This treatment should be used in conjunction with additional treatment in order to improve patients' functional status and quality of life. However, osteoarthritis cannot be cured by any radical treatment at the moment.

The stem cell candidates for use in these therapies are multipotent adult MSCs, because they are available in several tissues, including in the fluid inside the joint, and have the ability to differentiate into cells of the chondrogenic lineage^[33,34]. Pittenger *et al*^[35] have described that MSCs could be cultured without losing their multilineage differentiation potential and it has been shown that MSCs are capable of undergoing chondrogenic differentiation both *in-vitro* and *in-vivo*. MSCs can be harvested from bone marrow, periosteum, trabecular bone, adipose tissue, synovium, skeletal muscle and deciduous teeth^[36]. Regardless of their origin they have the capacity to differentiate into many cell types, including cells of connective tissue lineages, including bone, fat, cartilage and muscle^[26,37]. MSCs were first identified in the pioneering

studies of Friedenstein and Petrakova (1966)^[33] and are of major interest of research in the treatment of arthritis, in particular OA.

Multipotent adult mesenchymal stem cells are extensively investigated - in particular their behaviour in cell culture: how do they stay multipotent after several passages; how is chondrogenesis triggered in MSCs^[32]. There are no definitive markers identified for MSCs yet, but the immunophenotype is positive for the proteins and enzymes STRO-1, CD73, CD146, CD105, CD106, CD166 and negative for CD11b, CD45, CD34, CD31 and CD117. These are the most reliable for characterizing MSCs^[34,36].

There are several other criteria which must be considered when growing MSCs in culture. One of the most crucial criteria is the availability of characterized factors which stimulate the anabolic activity in cartilage including transforming growth factor (TGF)- β , bone morphogenetic protein (BMP), fibroblast growth factors (FGF), insulin growth factor (IGF)-1, hedgehog (hh) and Wntless (Wnt) proteins^[26]. These factors are signalling proteins that belong to the tyrosine kinase family of proteins (transmembrane proteins) that activate several downstream processes leading to cell proliferation, survival, growth and a reduction in apoptotic signalling.

Growth factors like FGF2 or transforming growth factor beta induce a positive differentiation of MSCs^[38]. Moreover, the development of methods was required to develop the cartilage phenotype without hypertrophy, fibrogenesis or ossification. In addition, a delivery system was devised to target cells in a lesion, but without inhibiting their chondrogenic differentiation or the integrity of repaired tissue^[39].

CLINICAL TRIALS

In recent years several clinical protocols for MSCs have been tested^[26-32,40]. In general, MSC related therapeutic approaches have a significant advantage to traditional surgical approaches such as autologous chondrocyte transplantation: no cartilage biopsy is necessary, thus no external stress and cellular damage are applied at the donor-site articular surface^[31]. Moreover, direct intra-articular injection of MSC is perceived as a technically simple way to treat advanced OA of the knee^[32].

Stem cells from patients

MSCs and platelet-rich plasma are harvested from the patient to be treated thus ensuring that the patient's immune system will not reject the cells^[41]. These cells are already specific for the patient's body but they have to be processed before intra-articular injection in the knee joint. This process includes separation of the MSCs by centrifugation and other purification steps. With the aim in mind of increasing cartilage build-up, chondrogenic activity of the harvested cells has to be evaluated, as well as glycosaminoglycan and type II collagen deposition, before reinjection^[29]. The MSCs are tested *in vitro* for their

ability to undergo chondrogenic differentiation under the previous described conditions. Glycosaminoglycan and type II collagen are components of the matrix of cartilage which induces and supports the differentiation of MSCs into chondrocytes. During this procedure it is important that the joint is stressed as little as possible because the newly differentiated cartilage is highly susceptible to damage.

In regards to recent advancements in the field, Neporent^[42] mentioned several pro and contra factors for stem cell injection in the knee joint. MSCs treatment offers the significant advantage of a quick and relatively uneventful recovery. Furthermore the majority of patients became ambulatory within 24 h. There are no reasonable arguments against treatment with the patient's stem cells, but there are several issues that have to be considered that are likely to make it financially less attractive. Firstly, at approximately \$4000 per knee for stem cell reinjection, which will not be covered by health insurance, this treatment is not for affordable by everyone. Secondly, there are several criteria for eligibility for treatment of osteoarthritis with stem cells preparations. For one thing, the body-mass-index (BMI) should not be more than 35. Obesity, as previously mentioned, is a high risk factor for OA, because of the high stress which results on the knee joint. Stem cell treatment is reasonable, if it can be ensured that there would be no high stress on the joint. Furthermore this treatment is applicable only if the degeneration of the cartilage is not complete. As long as cartilage and joint fluid is available, stem cells can differentiate, because of necessary factors are present in the fluid and matrix but in severe cases, with bone-bone contact, stem cell treatment is unlikely to work. Most important for the patient is to minimize physical activity in the immediate period after the therapy because the stress to the joint reduces the chance of successful recovery. Furthermore it is likely that more than one treatment session would be required, meaning a greater investment of time and money.

In addition to the intra-articular injection of MSCs, Nöth *et al.*^[32] also highlighted the use of MSCs as progenitor cells to engineer cartilage implants that can be used to repair chondral and osteochondral lesions, or as trophic producers of bioactive factors to initiate endogenous regenerative activities in the OA joint.

Stem cells from donors

Another potential source of stem cells, which can be used in therapies, is allogeneic MSCs. They are harvested from donated human umbilical cord tissue (HUCT) after normal, healthy births where the mother has been tested for infectious diseases and has a screened medical history. These harvested MSCs are then screened to International Blood Bank Standards (Stem Cell Institute, 2012).

Umbilical cord tissue provides an abundant supply of mesenchymal stem cells avoiding the requirement to harvest stem cells by invasive procedures such as liposuction or bone marrow aspiration. There is evidence show-

ing that mesenchymal stem cells from umbilical cords are more robust than those from other sources such as fat^[43].

Rush University Medical Center^[44], 2013, described the preparation of MSCs harvested from donated umbilical cord tissue: The cells are mixed with hyaluronan, a natural polymer that plays an important role in wound healing and deposition of cartilage, and are subsequently re-injected into the knee joint. In addition they also described a two-year Phase I/ II a clinical study in which a total of 12 participants aged 18 years and older, with a body mass index of less than 35 were enrolled. Initially, six individuals with lesions sized 2 to 5 cm were recruited into the study and an additional six volunteers with lesions larger than 5 cm were enrolled subsequently. Each participant went through an eligibility screening followed by a 12-mo observation period to determine the safety and efficacy of the therapy with an additional long-term follow-up evaluation at 24 mo.

Basically both treatment protocols, both for the MSCs from the patient and from a donor, were identical. Any differences in the MSCs and in some characteristics of the cells arose due to those from the patient themselves, from fat or bone marrow, being "older" than MSCs from umbilical cord and may therefore lack potential for proliferation and/or differentiation.

CONCLUSION

In recent years the role of stem cells in health and disease is a topic of high interest for biomedical research, especially regenerative medicine^[33,45,46], including non-pharmacologic treatment of knee OA^[25,40,47], and drug discovery^[48-50]. At the moment there is an increase in the number of clinical cases utilizing stem cell therapy for knee OA, however, many clinical protocols are still under development^[26,30,40].

Future perspectives about clinical trials with stem cells from patients

Based on the current status of clinical investigations regarding autologous stem cell therapy for OA of the knee some authors have expressed concerns about the issues of dosing, timing of intervention, type of MSCs, mode and route of delivery of MSCs in clinical studies^[51-56]. Therefore the need for a gold standard for autologous stem cell therapy for knee OA arises, which (hopefully) will be the aim of future clinical trials. Another interesting trend is the increased research interest in scaffold assisted or scaffoldless grafts of MSCs as a method to restore the structural and biomechanical characteristics of the OA affected knee^[57-62]. MSC grafts may even prove to be a viable alternative to total knee replacement in the near future. However, we still have to wait for a 100% effective and also low cost clinical procedure to be developed.

Future perspectives about clinical trials with stem cells from donors

The use of human umbilical cord-derived mesenchymal

stem cells (hUC-MSCs) in clinical trials for treatment of knee OA faces the same challenges as clinical trials with other types of MSC in terms of stem cell handling^[43]. There is also the need for more relevant clinical data, so it would be beneficial to have more clinical trials for knee OA, which utilize hUC-MSCs.

Future perspectives about basic research in knee cartilage regeneration and chondrogenesis *in vitro* and *in vivo*

Nowadays basic research in chondrogenesis *in vitro* and *in vivo* is primarily focus on increasing the efficacy of stem cells in terms of tissue repair^[57-62]. However, the issues of stem cell characterization and tumorigenesis *in vivo* are somewhat overlooked.

Until relatively recently, the genomic profile of the stem cell lines maintained *in vitro* was only assessed in terms of ploidy and karyotype, as it was known that cultured cells may exhibit loss or gain of chromosome fragments or whole chromosomes and/or genomic rearrangements^[63-65]. After the introduction of the concept for individual capacity for DNA repair and for maintenance of genomic integrity in research and diagnostic practice, its applicability as a complex marker for the proliferative potential and/or the differentiation capacity of undifferentiated cells has been extensively discussed^[66-69]. Some authors have advised that the minimal panel for characterisation of *in vitro* maintained pluripotent cell lines ought to include markers for individual capacity for repair of genotoxic damage and maintenance of genomic integrity^[69-71]. Some stem cells types (mesenchymal stem cells, haematopoietic cells from bone marrow and iPSC) have been shown to lose *TP53* gene copies during *in vitro* culturing (detected as loss of heterozygosity for markers at the *TP53* locus)^[72]. Shetzer *et al.*^[72] also reported that the cells with loss of heterozygosity were more often than not identified as the origin of the teratoma-like tumours developing after the cells were transplanted in mice.

All those findings in basic stem cell biology will likely influence the development of more advanced (in terms of cell characterization) stem cell culturing and differentiation protocols and lead to the development of a gold standard in clinical trials with MSCs.

Conclusion

In conclusion, stem cell therapy may not become a standard treatment for knee OA till the end of the decade due to various aspects regarding the clinical safety (*e.g.*, risk of complications after surgery, compatibility of donor stem cells) and the affordability of this treatment for the general public. Moreover, there is still no sufficient amount of clinical data on the effectiveness of stem cell therapy when compared with pharmacological treatments for this particular disease^[47]. There is also the emerging application of nutraceuticals as a possible alternative to drugs for knee osteoarthritis^[73,74]. So here comes the question: what will future clinical trials for knee OA and OA in general evaluate: novel pharmaceuticals, novel nu-

traceuticals, improved stem cell therapies?

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