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Review Article

Mesenchymal stem cells for articular cartilage repair treatment of the knee. A review of clinical studies

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Abstract

Knee cartilage lesions are a common source of pain and progressive debilitation affecting individuals in all age groups. Treatment of these lesions remains a challenge due to the poor healing capacity of the articular cartilage. Numerous techniques with various improvements in terms of pain and function have been published and only few of them have been proven to be valuable. Mesenchymal stem cells provide a new option for treatment due to their differentiation properties into several connective tissues. They can be isolated from several human tissues such as bone marrow, adipose tissue, synovial tissue, peripheral blood and periosteum. When applied in combination with proper biomaterials used as scaffolds as well as growth and other stimuli factors, they represent a promising treatment strategy. Aim of our study is to review the clinical trials which evaluate the current status of MSCs application for the management of knee cartilage lesions.

Keywords: Articular cartilage, Knee, Mesenchymal stem cells

Introduction

Knee cartilage lesions are common injuries and can affect patients of all age groups. One review of 31,516 knee arthroscopies, found that 63% of patients had chondral lesions with most of patients aged less than 40 years, presenting with a solitary lesion[1]. They result in severe pain and loss of function of the affected knee and are associated with the development of osteoarthritis in the long term[2]. The problem with these lesions is that despite conservative and surgical methods applied, they remain highly irreversible and only inferior repair is possible. Fibrous repair tissue is formed, (fibrocartilage) which is not characterized by the same biomechanical properties as hyaline cartilage. It is susceptible to failure under high compressive forces during knee movements, deteriorates over time and can lead to the previous symptoms experienced by the patient[3].

While conservative treatment of these lesions remains unchanged over time, there is a wide variety of options available once surgical intervention is decided. These include cartilage repair with osteochondral autograft tranfer, microfracture, autologous chondrocyte implantation(ACI), matrix induced ACI, use of growth factors, platelet rich plasma, bone morphogenetic proteins, magnetically labeled synovium derived cells M-SDCs and chondroprotection with pulsed electromagnetic fields[4-12]. However, there is increasing evidence in the literature and an emerging focus on the management of these lesions with the use of mesenchymal stem cells. It seems that their unique characteristics may give them an advantage compared to other treatment modalities.

Mesenchymal stem cells (MSCs) have been first reported in bone marrow in 1966 and took their name in the early 90s[13]. MSCs are undifferentiated cells which can differentiate into cartilage, fat, bone, ligament, marrow stroma etc[14]. Therefore, all these tissues consist potential sources of MSCs. They have self-renewal capacity, plasticity and most importantly can suppress the immune system

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through various mechanisms such as suppression of natural killer(NK) cell activation and inhibition of T and L lymphocute activation[15].

Their first application for osteochondral defect treatment was performed in rabbits with their first use in humans reported in 2001 by Quarto et al.[16,17]. Bone marrow derived stem cells use has been reported in animal and human research studies[18,19]. Bone marrow has a high MSC density and these cells seems to favor differentiation of deep articular cartilage zone close to healthy bone[20]. Synovium is another great source of MSCs with chondrogenesis potential, while peripheral blood is characterized by low MSC density, difficulty during cell isolation and poor results[21]. MSCs are mostly injected in the affected knee or applied with the use of scaffold implantation combined with growth or transcription factors like TGF-β, BMP-7, hyaluronic acid and others[22,23].

Our focus in this study was to provide a short review of the available evidence concerning the use of MSCs for articular cartilage repair treatment of the knee in humans.

Materials and mehods

We searched pubmed studies focused on articular repair treatment of the knee with the use of mesenchymal stem cells. The keywords we searched were the following: cartilage, bone marrow-derived MSCs, articular cartilage repair, mesenchymal stem cells, synovial-derived MSCs, adipose-derived MSCs knee, articular regeneration. Our search included only articles in English language of the last 10 years.

Results

Along with the advantage of the ease of collection of the cells, bone marrow-derived MSCs (BMSCs) are mostly used in the studies identified[24]. BMSCs can be used as cultured cells or as a bone marrow concentrate (BMC)[25,26]. BMC offers the advantage of a greater number of progenitor cells but a lower number of MSCs compared to cultured cells[27]. Additionally, cultured amplification of MSCs has several limitations. Except for the fact that it can be considered as a pharmaceutic administration, thus raising ethical issues, the risk of bacterial contamination, hypertrophy of the cells and cellular transformation cannot be overlooked[28,29].

To modify progenitor cells, viral vectors are commonly used. Recombinant adeno-associated viruses (rAAV) are characterized by lower toxicity and oncogene activation compared to other adenoviral and retroviral vectors and are widely used[30].

Most studies involving the use of bone marrow-derived mesenchymal stem cells (BMSCs) in the human knee are case series studies and case reports. In their comparative study in 24 patients with knee osteoarthritis and medial femoral condyle cartilage lesions, Wakitani et al. used cultured BMSCs in a type I collagen gel scaffold and a periosteal flap. Their control group of 12 patients received no cells in the scaffold. At 16 months follow-up, although no clear clinical result was shown between the two groups, the histological and arthroscopic grading score was better in the MSC group then in the cell-free control group[31]. In 2004, the same group reported on two individuals with full thickness patellar lesion. The same technique was used, leading to satisfactory results for both patients in terms of pain and function and clinical improvement lasted for 4 and 5 years respectively[32]. Three more patients with a total of nine full thickness patellofemoral cartilage defects have been treated from the same group with the above technique, reporting significant improvement at follow-up (17-27 months) with additional complete coverage of the defect on MRI and histology signs of repair[33].

Haleem et al. placed BMSCs on platelet-rich fibrin glue in the operating theatre and then covered them with an autologous periosteal flap to deal with full thickness articular cartilage lesions of the femoral condyle in 5 patients. After 6 and 12 months, all patients presented with reduced pain and better functional outcomes. Two patients were treated arthroscopically at 1 year follow-up and showed ICRS scores close to normal. MRI of five patients was evaluated 12 months post-transplantation with 3 of them revealing complete surface congruity and defect coverage and 2 incomplete congruity despite the satisfactory clinical result[34].

A recent cohort study compared autologous chondrocyte implantation (ACI) with BMSC treatment for the management of these knee lesions in 72 age and lesion matched patients. Patients were followed for 3, 6, 9, 12, 18 and 24 months after the operation. All patients showed significant clinical improvement with men showing a greater benefit from surgery. Interestingly, patients, less than 45 years old scored better when ACI was chosen. Authors came to the conclusion that BMSCs can have similar effect as ACI for the treatment of knee cartilage lesions while offering the advantage of a single lower cost knee operation with limited donor-site morbidity[35].

Satisfactory cartilage regeneration was also noted in case reports when cultured BMSCs on hydroxyapatite ceramic or collagen scaffold alone was used[36,37].

Injection techniques of cultured BMSCs have also been studied for the treatment of cartilage knee lesions. Emadedin et al. reported on six patients with osteoarthritis of the knee joint who underwent an injection of cultured BMSCs. Up to six months post-injection, there was a clear improvement in terms of pain, function and walking distance with MRI findings revealing an increase in cartilage thickness[38]. Satisfactory outcome was shown by Davatchi et al. with the use of the same technique[39].

Bone marrow concentrate (BMC) has also been used in knee cartilage defects instead of BMSCs. However, there is little evidence to support its use. In a comparative study of 50 patients, half of them underwent arthroscopic debridement for knee OA and the rest BMC injection along with debridement for the same disease. It was reported that patients on the injection group had better visual analogue

scale and osteoarthritis outcome scores and better quality of life than the debridement alone group[40]. Buda et al. implanted BMC on hyaluronic acid membrane and platelet rich fibrin in 20 patients with knee osteochondral defects with an arthroscopic technique. At 24 months, clear clinical improvement along with cartilage repair and subchondral bone regeneration was observed[41]. Finally, a case series of 5 patients with medial femoral condyle lesions who were treated with arthroscopic autologous matrix-induced chondrogenesis (AMIC) augmented with BMC revealed nearly normal arthroscopic appearance on second look arthroscopy at 12 months follow-up. Moreover in 4 out of 5 patients a mixture of hyaline/fibrocartilage was identified histologically[42].

Synovial-derived MSCs have also been reported as an alternative source of cells for cartilage repair. Unfortunately from our search, no clinical study in humans was identified. On the other hand, we identified two clinical studies using adipose-derived MSCs (ADMSCs) for the management of knee osteoarthritis. In a case series study, two Korean women with knee osteoarthritis were treated with ADMSCs along with PRP, hyaluronic acid, calcium chloride and 1ng of dexamethasone injections. At three months follow-up, the authors report an increase in cartilage thickness on MRI with clear improvements in pain score and functional properties[43]. Additionally, Koh et al. reported on a comparative study where two different groups of patients were examined. The study group of 25 individuals received infrapatellar fat pad derived MSCs along with arthroscopic debridement for knee osteoarthritis. The control group was treated with debridement and PRP injections alone. Although the study group patients had poorer knee and pain scores preoperatively, clinical results were reported to be similar at the latest follow-up exam, 16 months after surgery[44].

No clinical studies involving periosteum derived MSCs are available to date for the management of knee cartilage lesions.

Discussion

Stem cells are matured from cells of the germ layer. Mesenchymal stem cells (MSCs) can be derived from tissues such as bone marrow, synovial tissue fat and periosteum[45]. There is emerging evidence in the literature concerning the use of mesenchymal stem cells for the treatment of osteochondral lesions of the knee. However, most of the studies are conducted in animals and few of the advances presented preclinically have also been applied in the clinical practice[46-48]. Additionally, low quality clinical studies are available, mostly due to problems with methodology, few patients and not adequate follow up period. Thus, there is still room for quality scientific research in this topic and many aspects of their use have not yet been clarified.

The optimal source of mesenchymal stem cells is still under debate with its type having its advantages and drawbacks. For example, preclinical data show that adipose-derived MSCs have the best potential for adipogenesis, synovial-derived MSCs may be a valuable option for regeneration of the chondral tissue and bone marrow and periosteum derived cells are superior for osteogenesis[49,50]. Recently, Koga et al. showed that synovial and bone marrow derived MSCs are superior to adipose and muscle-derived ones for full thickness articular cartilage lesions[51].

Moreover, it is yet to be determined whether these cells should be cultured or concentrated, which is the appropriate quantity of cells that should be used, which is the best technique for implantation, open or minimally invasive as well as which biological factor or scaffold should be used for the best possible result.

Except for all these unanswered questions, other aspects that should be determined include the potential risks of MSCs use. Researchers must be able to control hypertrophic differentiation of the cells as well as differentiation in unwanted tissue such as endochondral ossification in some parts of cartilage repair tissue[52]. Controversy exists in the literature concerning the safety of the use of MSCs with studies reporting no side effects even in the long term and others raising concerns about the possible transformation of the cells while they have been cultured[53,54]. In any case, their effectiveness and overall safety is not yet convincingly proven leaving a cause for concern. Long term, multicenter, double-blind randomized control studies will help us understand the biological pathway of these cells and provide sufficient evidence to clarify all the above controversial issues. The fact is that regeneration of natural articular cartilage has not yet been reported. The challenge of the upcoming years will be to try to assemble all these different and complicated aspects in order to put into clinical practice an effective and most importantly safe technique.

Conclusion

Our study tried to summarize current data from clinical studies available reporting on the treatment of knee cartilage lesions with mesenchymal stem cells. Despite growing interest on this subject, low quality studies with small number of patients are mostly available. Until long term randomized controlled multicenter studies are available to provide definite conclusions, the use of these cells, derived from different human tissues, will be a great area for scientific research and controversy.

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