Cartilage repair techniques in the knee: stem cell therapies

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Abstract Among the surgical options for large full-thickness chondral injuries, cell-based therapy has been practiced and its satisfactory outcomes have been reported. One area that appears promising is cell-based therapies utilizing stem cells. Various tissues within the human body contain mesenchymal stem cells (MSCs) from where these can be harvested. These include bone marrow, adipose, synovium, peripheral blood, and umbilical cord. In this article, both preclinical animal studies and clinical studies dealing with the use of MSCs for cartilage repair of the knee are reviewed. Majority of the clinical papers have shown promising results; however, there are a limited number of studies of high evidence level. Clinical significance of the stem cell therapy as compared to other surgical options as well as optimization of the procedure in terms of cell type and delivery method is still to be determined.

Keywords Stem cell · Cartilage repair · Knee

Introduction

Chondral injury to the knee is a major cause of short- and long-term disability. Various surgical treatment options for chondral restoration are available to the treating surgeon including marrow stimulating techniques, osteochondral autografting and allografting, and various cell-based therapies such as autologous chondrocyte implantation (ACI) and DeNovo-NT (Zimmer). One area that appears promising is cell-based therapies utilizing stem cells [1•, 2–5]. Mesenchymal stem cells (MSCs) are able to differentiate into many mesenchymal phenotypes and maintain their multipotency during culture expansion [6, 7]. These cells are able to be delivered into the knee and to the site of injury via a single-stage injection of a MSC suspension into the joint, single-stage implantation into the joint, as well as implanted into a matrix after preculture and cell line expansion. Various tissues within the human body contain MSCs from where these can be harvested. These include bone marrow, adipose, synovium, and umbilical cord [8–10]. We will focus our systematic review on the use of MSCs for chondral injuries in preclinical animal studies and clinical studies.

Literature search

First, a literature search was carried out for preclinical animal studies dealing with the use of stem cell for cartilage repair in the knee. Using the PubMed database, relevant articles published to date (August 2015) were searched based on the following key words: stem cell, cartilage repair, knee, and animal study. Consequently, 104 articles were retrieved. Thereafter, publication in English language that reported repair of articular cartilage using stem cells for cartilage defect in the knee was selected. In addition, hand search for relevant articles

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were performed. Finally, 42 papers were included in this review.

Second, a literature search for clinical studies was carried out for relevant articles using the PubMed database based on combination of the following keywords: stem cell, cartilage repair, knee, human, and clinical. In total, 82 articles were retrieved. Among those, articles written in English which report clinical outcomes of stem cell therapy for cartilage repair and regeneration were exclusively selected. In addition, hand search for relevant articles were performed. Consequently, 19 articles were selected for review of recent clinical studies. Eleven of those are level IV case series articles, while there are eight level II or III comparative studies.

Preclinical animal studies of stem cell therapy for knee cartilage repair

A number of preclinical animal studies have been conducted to examine efficacy and feasibility of stem cell application to knee cartilage repair. Various experimental conditions regarding animal model, cell source, cell delivery procedure, scaffold, healing enhancement, and evaluation method have been employed and tested in these studies.

Small animal studies

Wakitani and associates reported a study for mesenchymal cell-based repair of full-thickness cartilage defect in a rabbit model [11]. In this study, bone marrow-derived and periosteum-derived mesenchymal cells were implanted into the defect with collagen gel, and regeneration of cartilage and subchondral bone was observed. Subsequent to 2000, increasing number of studies using a rabbit model has been published. [11–31]. In general, these studies report satisfactory cartilage regeneration after stem cell implantation showing efficacy of this treatment strategy. The predominant cell source was bone marrow, while other sources such as periosteum, synovium, placenta, and amnion have also been studied. Tay and associates compared applications of allogenic bone marrow-derived MSC with autologous chondrocyte application and demonstrated comparable efficacy in both groups implying the potential implication for the use of allogenic stem cells [23]. Various materials such as collagen [11, 22], hyaluronic acid [14, 17], polyglycolic acid [18], poly-(lactic-co-glycolic) acid [29, 30], and silk fibroin [24] have been used as scaffolds; however, the superiority of one scaffold over another is as of yet unproven. Efficacy of cell differentiation prior to implantation has been examined in several studies. Dashtdar and associates and Reyes and associates compared the use of predifferentiated and undifferentiated MSCs showing no significant difference in histological and biochemical evaluations between the groups [21, 28]. Zhu and associates demonstrated that combined use of growth factor and scaffold could enhance healing of the articular

cartilage defect with superior histological and mechanical properties with regeneration of hyaline-like cartilage compared to the control group in rabbits [30].

Rat and mouse models have been used in some studies [32–36]. In those animal models, in general, rather novel approaches to the stem cell therapy such as magnetically labeled MSC, gene transfer, uses of induced pluripotent stem (iPS) and embryonic stem (ES) cells were examined for their future possibilities.

Large animal studies

With the intent of evaluation with models that is more relevant to clinical condition in humans, large animals such as pig and sheep have been used as experimental subjects [37–52]. Among those, a (mini)pig model has been most frequently employed in previous studies [37–44]. Various cell types and materials were tested in the studies. Zhang et al. compared bone marrow-derived MSC and uncultured bone marrow-derived nucleated cells (bone marrow concentrate) in a pig model and reported that the results of both groups were comparable [40]. The results of this study seem to support the feasibility of a one-step procedure in a clinical setting. Jung showed that enhancement of cartilage repair with the use of collagen type I/III membrane significantly improves the repair tissue quality in minipigs [37]. In addition, use of allogenic MSC and xenotransplantation of human umbilical cord blood-derived MSC were tested in this animal model, showing induction of cartilage healing by those cell types [42, 44]. Efficacy of MSC/scaffold constructs have been shown in other large animals such as sheep, horse, and goats [45–49]. In regards the cell delivery method, enhancement of cartilage healing after bone marrow stimulation techniques (microfracture or drilling) by postoperative intraarticular injection of MSCs was shown in horse and goat models [48, 49].

Clinical studies of stem cell therapy for knee cartilage repair (Table 1)

Bone marrow-derived MSC

Chondrogenic potential of human bone marrow-derived stem cell was confirmed by cell culture studies and reported in 1998 [52, 53].

Clinical application of these cells was first reported by Wakitani in 2002 [11]. Twenty-four knees with osteoarthritis undergoing high tibial osteotomy were included in the study. The outcomes of 12 knees with concomitant two-stage cell transplantation were compared to 12 knees with osteotomy alone. In the cell transplantation group, adherent cells in bone marrow aspirates were culture expanded, embedded in

Table 1 Clinical studies of stem cell therapy for knee cartilage repair

Authors (year)	Study type	Cell source	Location	Size (cm ²)	Age (years)	Number of patients	Follow-up period	Delivery methods and concomitant procedures	Outcome measures	Summary of results
Wakitani et al. (2002) [11]	Randomized comparative study	Bone marrow	Femoral condyle	Mean 4.9	Mean 63 (49–70)	12	Mean 16 months	Implantation of MSCs embedded in collagen gel with a periosteal patch HTO with and without cell transplantation.	HSS, arthroscopy	No significant difference in clinical score between the group; better cartilage healing in the cell transplantation group
Kuroda et al. (2007) [55]	Case report	Bone marrow	Femoral condyle	6	31	1	7 months	Implantation of MSCs embedded in collagen gel with a periosteal patch		Satisfactory cartilage regeneration with functional recovery
Wakitani et al. (2007) [56]	Case series	Bone marrow	Patellofemoral	1.7	31–45	3	17–27 months	Implantation of MSCs embedded in collagen gel with a periosteal patch	IKDC, arthroscopy, MRI	Satisfactory cartilage healing in arthroscopy and MRI
Haleem et al. (2010) [57]	Case series	Bone marrow	Femoral condyle	Mean 5.8 (3–12)	Mean 25.4	5	Mean 14.2 (12–16) months	Cell implantation with fibrin glue and a periosteal patch	Lysholm, HSS, arthroscopy, MRI	Satisfactory cartilage healing in arthroscopy and MRI
Nejadnik et al. (2010) [58]	Nonrandomized cohort study	Bone marrow	Various sites	Mean 4.6	Mean 44	36 (Comparative group 36)	24 months	Cell implantation with collagen and a periosteal patch ACI versus stem cell implantation; concomitant procedures: PF realignment, HTO, ACL reconstruction, meniscectomy	SF-36, Lysholm, IKDC, Tegner	No significant difference in outcome between the groups
Kasemkijwattana et al. (2011) [59]	Case series	Bone marrow	Femoral condyle	2.2 and 2.5	24, 25	2	31 months	Cell implantation with collagen and a periosteal patch; concomitant procedure: ACL reconstruction, meniscal repair	KOOS, IKDC, arthroscopy	Satisfactory clinical improvement with full integration in arthroscopy
Lee et al. (2012) [60]	Prospective matched pair analysis	Bone marrow	Femoral condyle patellofemoral multiple	Not specified	Mean: 44	70 (N 35 in each group)	24 months MRI at 12 months	Arthroscopic microfracture with intraarticular MSC injection versus open MSC implantation	ICRS, SF-36, IKDC Lysholm, Tegner, MRI	No significant difference in clinical results
Wong et al. (2013) [61]		Bone marrow	Not specified	Not specified	Median 51 (36–54)	28 (Control group 28)	Mean 24.8 months	HTO with intraarticular MSC injection (control)	Lysholm, IKDC,	

Table 1 (continued)

Authors (year)	Study type	Cell source	Location	Size (cm ²)	Age (years)	Number of patients	Follow-up period	Delivery methods and concomitant procedures	Outcome measures	Summary of results
	Prospective randomized study						MRI at 1 year	group: without injection)	Tegner, MRI	Better clinical and MRI results in the cell-recipient group
Koh et al. (2014) [62]	Case series	Adipose tissue	Not specified	Mean 5.4 (2.3–8.9)	Mean 57.4	37	Mean 26.5 months	Implantation of cell suspension under arthroscopic control	ICRS, IKDC, Tegner, arthroscopy	Overall satisfaction in 94 % (nearly) normal cartilage healing in 24 %
Koh et al. (2014) [63]	Prospective comparative study	Adipose tissue	Not specified	Not specified	Mean 54.2	21 (Control 23)	Mean 24.6 months arthroscopy at 14–24 months	Injection of MSCs with PRP HTO with PRP + MSC versus PRP alone	KOOS, Lysholm, VAS for pain, arthroscopy	Better clinical score and cartilage regeneration in the cell therapy group
Kim et al. (2015) [64]	Cohort study	Adipose tissue	Not specified	Mean 5.7	Mean 57.5	54 (Fibrin glue group 17)	Mean 28.6 months arthroscopy at 12.3 months	Implantation of cell suspension versus cells loaded in fibrin glue	ICRS, IKDC, Tegner, arthroscopy	Clinical improvement in both groups with better cartilage repair in knees implanted with fibrin glue
Sekiya et al. (2015) [65]	Case series	Synovial tissue	Femoral condyle	Mean 2 (0.25–5)	Median 41 (20–43)	10	Mean 52 (37–80) months MRI at 18 months	Suspension of MSCs placed in the cartilage defect under arthroscopic control	Lysholm, Tegner, MRI, arthroscopy	Improvement in clinical score with satisfactory cartilage repair confirmed by MRI and arthroscopy
Algun et al. (2015) [66]	Prospective randomized study	Synovial tissue	Femoral condyle	Mean 2.9 (2.1–4.3)	Mean 32.3 (18–41)	7 (Comparative group 7)	Clinical assessment and MRI at 24 months	Implantation of MSC/collagen membrane construct fixed with fibrin sealant and sutures MSC versus chondrocyte	KOOS, VAS, MRI	Better clinical and MRI outcomes in the MSC group
Saw et al. (2013) [67]	Prospective randomized study	Peripheral blood	Not specified	Not specified	Mean 45 (22–50)	24 (Control 24)	IKDC at 24 months MRI and arthroscopy at 18 months	Intraarticular injection of stem cells (eight times) following arthroscopic drilling Injection of hyaluronic acid with and without stem cells	IKDC, MRI, arthroscopy, histology	No significant difference in IKDC score; better cartilage regeneration at 18 months in the stem cell therapy group
Turajane et al. (2013) [69]	Case series	Peripheral blood	Medial femoral condyle 4, patellofemoral 1	Median 7.0 (5–8.8)	Median 56 (52–59)	5	Median 6 (6–12) months	Arthroscopic microdrilling followed by weekly intraarticular injection of stem cell, growth	WOMAC, KOOS, histology	Clinical improvement achieved in all patients; histologic confirmation of increased

Table 1 (continued)

Authors (year)	Study type	Cell source	Location	Size (cm ²)	Age (years)	Number of patients	Follow-up period	Delivery methods and concomitant procedures	Outcome measures	Summary of results
Fu et al. (2014) [70]	Case report	Peripheral blood	Femoral trochlea	4	19	1	7.5 years	factor, and hyaluronic acid (three times) Implantation of cell suspension with a periosteal patch concomitant with tibial tubercle transfer	Lysholm, Tegner, IKDC, MRI	proteoglycan and glycosaminoglycan Satisfactory outcome with return to sports; cartilage regeneration on MRI at 7.5 years
Saw et al. (2015) [71]	Case series	Peripheral blood	Not specified	Not specified	Mean 52.9 (15–58)	8	Arthroscopy and biopsy at 25.9 months (mean)	Intraarticular injection of stem cells (eight times) following HTO with arthroscopic drilling and abrasion chondroplasty	Histological evaluation based on the ICRS II score	Histologic score of 95 % compared to normal articular cartilage value; confirmation of proteoglycan and type II collagen.
Buda et al. (2010) [72]	Case series	Bone marrow concentrate	Femoral condyle	Not specified	Not specified	20	24 months	Transplantation of hyaluronic acid scaffold filled with bone marrow concentrate (one-step surgery); concomitant procedures: meniscectomy, HTO, ACL reconstruction	IKDC, KOOS, MRI, histology	Satisfactory results in clinical score, MRI score (MOCART), and histology
Gobbi et al. (2014) [73•]	Case series	Bone marrow concentrate	Femoral condyle 40.5 %, patella 24.5 %, trochlea 21.5 %	Mean 8.3 (2.5–22)	Mean 46.5 (32–58)	25	Mean 41.3 months	Transplantation of bone marrow aspirate concentrate clot covered with a collagen membrane (one-step surgery)	IKDC, KOOS, Lysholm, Tegner, Marx, MRI	Significant improvement in clinical scores; satisfactory cartilage healing observed in MRI and arthroscopy

MSC mesenchymal stem cell, HTO high tibial osteotomy, HSS Hospital for Special Surgery (Knee Rating Scale), IKDC International Knee Documentation Committee, SF-36 Short Form-36, PF patellofemoral, KOOS Knee Injury and Osteoarthritis Outcome Score, ICRS International Cartilage Repair Society, PRP platelet-rich plasma, MOCART Magnetic Resonance Observation of Cartilage Repair Tissue, VAS visual analog scale, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

collagen gel, and transplanted into the articular cartilage defect. They reported that arthroscopic and histological findings were better in the cell transplantation group, while no significant difference in clinical results (evaluated with the Hospital for Special Surgery Knee Rating Scale) was demonstrated.

Following this study, several cases series dealing with the use of bone marrow-derived MSC with scaffold for cartilage repair have been reported with satisfactory clinical improvement and cartilage healing [54–59]. Nejadnik reported results of a nonrandomized study comparing two-stage MSC and chondrocyte implantation with collagen and a periosteal patch and showed comparatively satisfactory results assessed by SF-36, Lysholm, and International Knee Documentation Committee (IKDC) scores without intergroup difference [58].

In a recent clinical trial, Lee et al. conducted a prospective matched pair analysis study that compared arthroscopic microfracture with intraarticular injection of bone marrow-derived MSCs/hyaluronic acid versus open microfracture with periosteal patch in surgical treatment of cartilage defect [60]. At the final follow-up of 24.5 months on average, clinical results (SF-36, IKDC, and Lysholm scores) significantly improved in both groups without significant intergroup difference. Based on the study results, the authors concluded that the arthroscopic procedure with MSC injection provided advantages of minimal invasion over the open procedure.

Wong et al. conducted a prospective randomized trial to compare the outcomes of high tibial osteotomy with and without intraarticular injection of bone marrow-derived MSCs [61]. Fifty-six knees in 56 patients who underwent high tibial osteotomy for varus osteoarthritis were randomly allocated to the cell-recipient and control groups. Consequently, both clinical (IKDC and Lysholm scores) and MRI results were better in the cell-recipient group up to 2 years.

Adipose tissue-derived MSC

Subcutaneous adipose tissue is another readily available source of MSCs. Two clinical studies were published in this category. In these studies, adipose tissue was harvested from the patient's buttock through tumescent liposuction.

In 2014, Koh et al. reported second-look arthroscopy study for patients with chondral defect in osteoarthritic knees [62]. Thirty-seven knees in 35 patients were included in the study. Cartilage lesion was arthroscopically debrided, and the defect was filled with suspension of cultured adipose tissue-derived MSCs. Thereafter, the knee was held in a stationary position with subsequent local adherence of MSCs to the cartilage lesion. Overall satisfaction was attained in 94 % of the patients, while normal or nearly normal cartilage healing in second-look arthroscopy assessed by International Cartilage Repair Society (ICRS) repair grading was observed for only 24 % of the subjects.

Koh et al. conducted a prospective comparative study that compared outcomes of high tibial osteotomy with intraarticular injection of platelet-rich plasma (PRP) alone and MSC injection with PRP [63]. Forty-four patients were included in the study, and clinical results at 2 years and arthroscopic findings were compared between the groups. Consequently, it was shown that the cell therapy group exhibited greater clinical improvement assessed by Knee Injury and Osteoarthritis Outcome Score (KOOS) and Lysholm score as well as better cartilage regeneration compared to the control group.

Kim et al. reported clinical and second-look arthroscopic outcomes of the two-stage implantation of adipose tissue-derived MSCs loaded in fibrin glue [64]. Fifty-six knees in 54 patients were included in the study. Chondral defect in early osteoarthritic knees were implanted with MSC suspension alone or MSCs with a fibrin glue scaffold. At the final follow-up after a minimum period of 2 years, clinical results (ICRS and IKDC scores) had improved in both groups while the second-look arthroscopy revealed better cartilage repair in knees implanted with MSCs and scaffold.

Synovial tissue-derived MSC

Synovial tissue is an alternative source of stem cells utilized for cartilage repair procedure [9]. There have been two studies reporting clinical results of synovial tissue-derived MSC.

Sekiya et al. performed two-stage transplantation of synovial MSCs for cartilage defect of the femoral condyle [65]. Following debridement, a suspension of MSCs was placed in the cartilage defect under arthroscopic control. Ten patients were included in the study. The follow-up evaluation at the 52 months on average showed improved clinical (Lysholm) score with satisfactory cartilage repair as confirmed by MRI and second-look arthroscopy.

Akgun conducted a prospective randomized study that compared two-stage matrix-induced synovial MSC implantation versus matrix-induced chondrocyte implantation in treatment of chondral defect [66]. Fourteen patients were included in the study and randomized into two groups. Up to 2 years after surgery, the MSC group achieved better outcomes in the KOOS and visual analog scale (VAS) for pain.

Peripheral blood-derived progenitor cells

Five clinical studies dealing with the use of peripheral blood-derived MSCs (progenitor cells) have been published. MSCs in those studies were obtained from peripheral blood. In the stem cell harvesting procedure, progenitor cells were collected by automated cell separator (apheresis) following administration of human granulocyte colony-stimulating factor for a period of 1 week.

In 2013, Saw et al. reported the results of a randomized controlled trial that compared arthroscopic subchondral drilling followed by postoperative injections of hyaluronic acid with

and without peripheral blood-derived cells [67]. This study was conducted based on a pilot clinical study published in 2011 [68]. In total, 50 patients were included in the study. Sequential intraarticular injections were performed eight times after the surgery in both groups. Second-look arthroscopy and histological examination of the core biopsy specimen at 18 months showed significantly better cartilage regeneration in the stem cell therapy group. Turajane et al. expanded the use of these cells into treatment of early osteoarthritic knees [69]. In this study, peripheral blood-derived stem cells were intraarticularly injected with growth factor and hyaluronic acid following arthroscopic microdrilling. Five patients were included in this case series, and clinical improvements assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and KOOS were achieved in all patients with histologic confirmation of increased proteoglycan and glycosaminoglycan. There were two studies that examined cartilage regeneration following the realignment procedures combined with cell therapy. Fu et al. reported the case of a 19-year-old patient who underwent patellofemoral realignment procedure combined with two-stage peripheral blood-derived cells and periosteal flap transplantations [70]. Second-look arthroscopy showed a smooth surface at the repair site, and the patient resumed sports activities at 7.5 years after surgery. Saw et al. reported second-look arthroscopy and histologic results for eight patients who underwent high tibial osteotomy combined with intraarticular injections (eight times) of peripheral blood-derived stem cell [71]. They showed that histologic score of the regenerated cartilage approached 95 % of the normal articular cartilage score with confirmation of substantial amount of proteoglycan and type II collagen.

Bone marrow concentrate

With the intent of eliminating the process of cell culture or apheresis, Buda et al. [72] and Gobbi et al. [73•] proposed the procedure of “one-step surgery.” In this technique, bone marrow of the iliac crest is aspirated at the time of cartilage repair surgery. The harvested bone marrow is centrifuged, and the bone marrow concentrate containing bone marrow-derived cells is obtained. During the surgery, the concentrated aspirate is transplanted to the chondral defect with scaffold made of hyaluronic acid or collagen. Both studies reported satisfactory cartilage regeneration with clinical improvement (IKDC, Lysholm, and KOOS scores). These authors addressed the advantage of the one-step surgery over conventional cell therapy procedures requiring cell culture and two-stage surgeries.

Future directions

Other cell sources

In addition to the tissues described above, there are other potential sources of MSCs. Muscle-derived MSC has been

investigated as a cell source [74], and potentials of other sources such as placenta [75], amnion [76], umbilical cord blood [77], and ear elastic cartilage [78] have been tested in previous in vitro and animal studies.

Use of pluripotent cells such as embryonic stem cell and iPS cell is another subject toward the future clinical application. Chondrogenic properties of these cells have been confirmed by recent studies [36, 79–81]. Utilization of iPSC can afford abundant availability of cell source as well as allogenic transplantation, which reduces invasion and cost.

Biological enhancement of cartilage regeneration

Various growth factors and biofactors such as insulin-like growth factor, transforming growth factor- β , and SOX9 have been reported to enhance chondrogenesis of MSCs, and gene transfer of these factors to MSCs through viral vector system has also been investigated [33, 82–85].

Healing enhancement by growth factors and gene transfer as well as use of pluripotent cells seem promising; however, the researchers and physicians should overcome the conflict with government regulation before the actual clinical application [86].

Compliance with ethics guidelines

Conflict of interest Dr. Yoshiya has received money from the Arthroscopy Journal for serving as an Associate Editor.

Dr. Dhawan has received money from the Arthroscopy Journal for serving as an Associate Editor and for lectures and serving as a consultant for Smith & Nephew, Arthrex, and BioMet.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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