SYSTEMATIC REVIEW

Infrapatellar Fat Pad-Derived Mesenchymal Stem Cells as an Alternative Cell Source for Cell-based Osteoarthritis Treatment: A Systematic Review on Preclinical and Clinical Evidence

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ABSTRACT

Introduction: There is still no definitive treatment to either inhibit the degradation process or restore the damaged cartilage in osteoarthritis (OA). Various cell sources have been studied and in vitro studies showed that infrapatellar fat pad-derived mesenchymal stem cells (IFPDMSCs) exhibit higher chondrogenic potential than other adipose-derived cells. Still, very few in vivo studies on IFPDMSCs for cartilage healing in OA have been reported. **Aims:** This systematic review will analyze the therapeutic potential of IFPDMSCs for cartilage healing in osteoarthritis from preclinical and clinical studies. **Design, Methods, and Data Source:** Using the PubMed, EMBASE, and Cochrane Library database up to November 30, 2020, a systematic review according to PRISMA reporting guideline was conducted on IFPDMSCs application to treat osteoarthritis *in vivo* studies. Inclusion criteria were *in vivo* preclinical and clinical studies from January 2010 to November 2020 involving the OA model or cases using IFPDMSCs to promote healing. **Results:** *In vivo* studies are scarce. Only four studies are included: two animals and two clinical studies. All included studies demonstrate favourable results of IFPDMSCs in osteoarthritis, but there is heterogeneity in outcome measurement among all studies. **Conclusion:** The *in vitro* and currently limited *in vivo* studies showed that infrapatellar fat pad-derived mesenchymal stem cells offer an alternative cell source with promising chondrogenic healing potential. **Impact:** More preclinical and clinical *in vivo* studies should be encouraged to explore and support the efficacy of IFPDMSCs in cell-based OA treatment to prove the promising result as those of the *in vitro* studies.

Keywords: Osteoarthritis, *In vivo,* Infrapatellar fat pad, Mesenchymal stem cells, Cell-based treatment

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INTRODUCTION

Osteoarthritis (OA) involves not only the degradation of articular cartilage but also the intraarticular inflammatory process. The degenerative process progression may eventually result in permanent disabling conditions, affecting an individual's daily activity and quality of life (1,2). Current treatments, both pharmacological and surgical, aim to improve patients' quality of life by reducing pain, but no definitive treatment to either inhibit the degradation process or restore the damaged cartilage has been agreed upon. One of the emerging efforts to delay the disease progression is the application of cell-based therapy using mesenchymal stem cells (MSCs), thanks to their abilities of multipotency, self-renewal, and immunomodulation. These abilities differ according to cell sources (3–6).

Adipose-derived mesenchymal stem cells (ADMSCs) are believed to have more edges than the more conventional bone marrow mesenchymal stem cells (BMSCs) due

to their advantages in abundance, ease of harvesting, higher differentiation and proliferation potential, and resilience over multiple culture passages. Among the ADMSCs, the cells harvested from the infrapatellar fat pad (IFP) are reported to yield higher chondrogenic potential. *In vitro* studies on the chondrogenic potential of IFP-derived mesenchymal stem cells (IFPDMSCs) showed encouraging results of larger cell volume and higher proliferative capacity (7–9). Still, very few in vivo studies on IFPDMSCs for cartilage repair in OA have been reported. This systematic review aims to analyze the therapeutic potential of IFPDMSCs for cartilage healing in osteoarthritis from preclinical and clinical studies.

METHODS AND MATERIALS

Study Design

This systematic review has been registered on PROSPERO (no. 256996) and follows the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (10). The research question was formulated according to PICO method: the population (P) was *in vivo* studies either preclinical or clinical that involve osteoarthritic model or clinical cases; the intervention (I) was the treatment with infrapatellar fat pad-derived mesenchymal stem cells (IFPDMSCs); the Comparison (C) involved control, placebo, or any other methods of treatment standardized for osteoarthritis; and the outcome (O) was the preclinical or clinical efficacy of the treatment method.

Search Protocol

The search was performed using the PubMed, EMBASE, and Cochrane Library database from January 2010 up to November 30, 2020, with the following keywords: *"osteoarthritis"* AND (*"infrapatellar fat pad stem cells" OR "infrapatellar fat pad-derived stem cells" OR "infrapatellar fat pad-derived stromal cells"*). Any updates of the recruited studies were also followed up and included.

Study Selection

According to PRISMA guidelines, three independent reviewers (KUH, JIF, and DW) conducted the screening process and the analysis of the papers. Any disagreement in opinion was resolved through discussion with the senior reviewers (KIS, DS, and DNU). The inclusion criteria for selection included only English language articles that reported in vivo studies of any level of evidence using osteoarthritis knee model (preclinical studies) or osteoarthritis cases (clinical studies) and application of cells derived from IFP. For preclinical studies, osteoarthritic models permit the use of any surgical or chemical method to induce OA. The exclusion criteria were articles of conference proceedings, inaccessible full text, reviews, and studies that did not use or analyze the efficacy of IFPDMSCs. Before screening the full text, all articles were initially screened by titles and abstracts. Screening through the bibliography of the included articles was also conducted to recruit more studies. The flowchart that describes the process is shown in Figure 1.

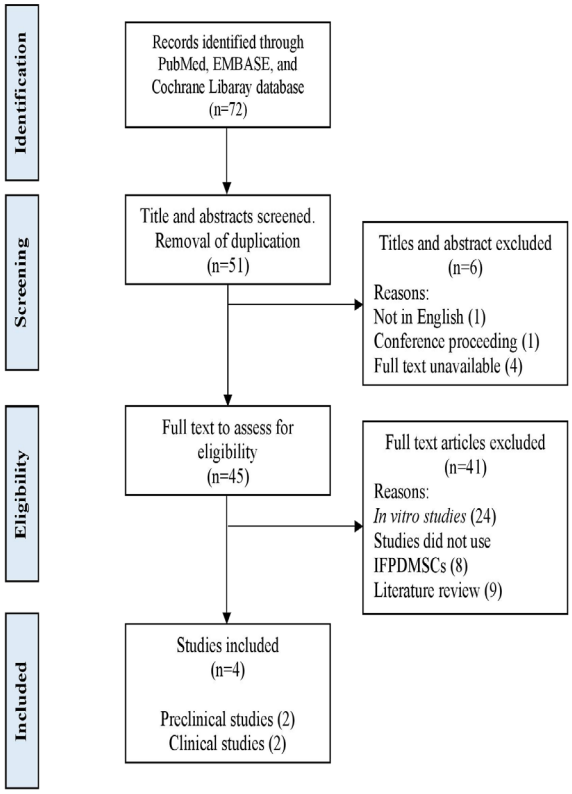

Figure 1: The flowchart that describes the process

Data Extraction and Synthesis

Relevant data from the included studies were extracted, organized, summarized, and analyzed. The data that includes the author, study type, study design, IFPDMSCs processing, delivery method, and the result were extracted. For preclinical studies, any results on cartilage quality, subchondral changes, histological evaluation, or immunohistochemical examination were extracted. For clinical studies, the extracted results include all clinical scores or MRI assessments. Two independent reviewers extracted the data. Due to the high heterogeneity and scarcity of the recruited studies, it was not possible to perform a meta-analysis.

Quality and Risk of Bias Assessment

Assessment of quality and risk of bias (RoB) of all preclinical studies were performed according to the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines and a modification of the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) respectively (11,12). SYRCLE's tool includes several domains such as baseline characteristics, allocation concealment, random housing, blinding, and outcome reporting. For the clinical studies, the quality and

RoB assessment were conducted using the Cochrane tool (13). The quality and RoB of all included studies were assessed as having "clearly insufficient/possibly sufficient/clearly sufficient" and "low/high/unclear RoB", respectively (14).

RESULTS

According to the previously described search strategy, 72 articles were initially found in PubMed, EMBASE, and Cochrane Library databases. After removal of duplication, forty-five articles were further screened after six titles, and abstracts were excluded. After removing *in vitro* studies, literature review, and studies that did not describe the use of IFPDMSCs, two preclinical animal studies and two clinical studies were included. Quality and RoB assessment showed that the selected studies were of good quality with low risk of bias, except for one case series in which the assessment was not applicable (Table 1). The characteristics of the included studies are displayed in Table 2.

Table I. Assessment of quality and risk of bias

	Quality assessment	Risk of bias assessment
Toghraie et al., 2011, *The Knee* (15)	high[a]	low[b]
Ude et al., 2014, *PLoS One* (16)	high[a]	low[b]
Koh and Choi, 2012, *The Knee* (17)	clearly sufficient[c]	low[d]
Koh et al., 2013, *Arthroscopy* (18)	n.a.[e]	n.a.[e]

[a]ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines; [b]SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation); [c]Cochrane tool for quality assessment; [d]ROBINS-I (Risk of Bias in Non-randomised Studies - of Interventions); [e]not assessed for case series

The two preclinical studies used different types of animals. A study from Toghraie et al. used IFPDMSCs retrieved from the knees of adult New Zealand White rabbits. Transection of anterior cruciate ligament (ACL) was chosen to create an OA model in the animals. Both groups received treatment to the medial compartment of the operated knee joints. Injection of 10^6 cells suspended in 1 ml of medium was used in the study group, whereas 1 ml of medium without cells was given to the control group. Both groups were evaluated for plain x-rays and histological evaluation. X-rays confirmed the induction of OA in all knees at twelve weeks. At sixteen weeks, another x-ray was taken and compared to that of the twelve weeks. In the study group, the radiological score of OA showed a slight decrease or remained unchanged, but there was an increase in the radiological score of OA in the control group. Another x-ray was taken at the twenty weeks. Osteophyte and subchondral sclerosis formation showed a further decline compared to 12

Table II. Data extraction of the included studies

	Study type	Study design	IFPDMSCs processing	Delivery method	Results
Toghraie et al., 2011, *The Knee* (15)	Experimental animal study (Rabbit)	Two groups induced with ACLT: (1)IFPDMSCs, (2)The control group (medium only)	Expanded homologous. Cell source: New Zealand white rabbit's infrapatellar fat pad adipose mesenchymal stem cells	Injection	The study group showed better quality of regenerated cartilage with lower subchondral changes and less prominent OA features as shown by better mean histological score in 12 and 20 weeks (p=0.01 and 0.008, respectively).
Ude et al., 2014, *PLoS One* (16)	Experimental animal study Sheep)	Three groups, induced with ACLT and meniscus removal: (1) IFPDMSCs, (2) BMSCs, and (3) control group.	Expanded chondrogenic-induced autologous. Cell source: sheep's infrapatellar fat pad adipose mesenchymal stem cells	Injection	ICRS score showed no difference between IFPDMSCs and BMSCs. IFPDMSCs showed more rapid cell proliferation (p=0.01)
Koh and Choi, 2012, *The Knee* (17)	Case control	Comparative study between two groups with knee OA: (1) study group (25 patients), treated with an injection of PRP+IFPDMSCs; (2) control group (25 patients), treated with PRP only. The average follow-up of 16.4 months.	Cell source: human adipose synovium from infrapatellar fat pad from arthroscopic surgery	Injection	The short-term results demonstrated that IFPDMSCs therapy with intraarticular injections is safe and aids in pain reduction and functional improvement in patients with knee OA. Significant improvement in all clinical scores of Lysholm and Tegner (p=0.01 and 0.003, respectively). No significant difference at the final follow-up.
Koh et al., 2013, *Arthroscopy* (18)	Case series	Case series of 18 patients with knee OA. All patients received one injection of IFPDMSCs + PRP after debridement. Average follow-up of 24.3 months.	Cell source: human adipose synovium from infrapatellar fat pad from arthroscopic surgery	Injection	Pre- and post-treatment evaluation of :ysholm and MRI scores. At the final follow-up, both Lysholm and MRI scores demonstrated significant improvement (p=0.011 and 0.005)

ACLT, anterior cruciate ligament transection; BMSCs, bone marrow mesenchymal stem cells; ICRS, International Cartilage Research Society; IFPDMSCs, infrapatellar fat pad-derived mesenchymal stem cells; MRI, magnetic resonance imaging; OA, osteoarthritis; PRP, platelet-rich plasma.

weeks in the study group. The radiological score of the study group showed a better result than the control group (15). Histologically, the study group demonstrated a significant reduction in the mean histological score of cartilage lesions twenty weeks after the surgery compared to the control group (15).

The other study by Ude et al. used IFPDMSCs from the sheep model. This study included three groups: the study group with IFPDMSCs, the study group with BMSCs, and the control group. Induction of OA model at the sheep's right knee was carried out by complete resection of the ACL and removal of the medial meniscus. The harvested IFDSCs from the sheep's right infrapatellar fat pad were cultured, expanded, and chondrogenically induced. The BMSCs were processed from aspirated bone marrow at the iliac spine. The two study groups were treated with a 5-ml injection of IFPDMSCs and a 5-ml of BMSCs, respectively. The control group was given a 5-ml injection of culture medium. Macroscopically, both study groups showed comparable de novo regeneration of cartilages after six weeks of treatment. Comparing further between IFPSDCS and BMSCs, there was evidence that IFPDMSCs showed a significantly higher proliferation rate than BMSCs. Interestingly, expressions of chondrogenic specific genes, such as collagen II, SOX9, and aggrecan, were higher in the BMSCS group than that of IFPDMSCs. Based on the International Cartilage Repair Society (ICRS) score, no significant difference was observed between the two groups (16).

A clinical study of case-control by Koh and Choi compared two groups with knee osteoarthritis. Arthroscopic debridement was performed on both groups before injection. The study group received an intraarticular injection of IFPDMSCs (a mean of 1.89 x 10^6 stem cells) and 3 ml of platelet-rich plasma (PRP). The control group received only 3 ml of PRP. Preoperative and postoperative evaluation using Lysholm score, Tegner activity scale, and visual analog scale (VAS) were performed in both groups to evaluate the treatment's efficacy. The study group that received both the cells and PRP demonstrated significant improvement of the mean Lysholm score, Tegner activity scale, and VAS scores by the last follow-up visit compared to the control group (mean follow-up period of 16.4 months). This study also evaluated the safety of IFPDMSCs injection. There was no record of adverse events related to the injections during the treatment and follow-up periods in both groups. This study concluded that intraarticular injection of IFPDMSCs showed favorable short-term outcomes of good safety, better pain reduction, and improved function in patients with knee osteoarthritis (17).

Koh et al. reported a case series that involved eighteen patients with knee osteoarthritis (average age of 54.6 years old) who received intraarticular injections of autologous IFPDMSCs after the patients underwent arthroscopic debridement. A mean of 1.18 x 10^6 cells were injected into the knees with 3 ml of PRP. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lysholm score, and visual analog scale were recorded preoperatively and at the final follow-up for clinical outcome evaluation. Radiological evaluation using magnetic resonance imaging (MRI) was carried out before the treatment and at the final follow-up for Comparison. The mean follow-up was 24.3 months (range of 24 to 26 months). The WOMAC score showed a significant decrease from 49.9 points to 30.3 points at the final follow-up. There was also a significant improvement of the Lysholm scores from 40.1 points to 73.4 points. Improvement of VAS score was also recorded in all patients during the follow-up period. Radiological assessment using MRI score demonstrated significant improvement from 60.0 to 48.3 points by the end of the follow-up period. This study concluded that intraarticular injection of IFPDMSCs showed encouraging results as shown by satisfying pain reduction, improved knee function, and better radiological evaluation in patients with knee osteoarthritis (18).

DISCUSSION

Mesenchymal stem cells have been studied extensively for regeneration in various tissue (19–22). Conventionally, mesenchymal stem cells have been isolated from bone marrow. The isolation of stem cells from the bone marrow is considered tedious and gives a low yield (21,23). Recent evidence demonstrated that the adipose tissue of the infrapatellar fat pad or Hoffa's pad could be an alternative source of mesenchymal stem cells. The adipose tissue harvested from the IFP differs from the adipose tissue recovered from liposuction, as the IFP consists of a higher composition of dense collagenous tissue (24,25). This characteristic of IFP tissue can provide a more abundant source of progenitor cells for cell-based therapies or another tissue engineering. Therefore, the isolation of mesenchymal stem cells from the IFP can produce a comparatively larger cell volume (26,27). A 30-ml bone marrow aspirate may produce approximately 1 x 10^5 cells, whereas every 100 cm^3 of IFP may yield approximately 3.3 x 10^6 cells (28,29).

There was also evidence of the multipotent nature and chondrogenic potential of stem cells derived from the infrapatellar fat pad. The chondrogenic potential of IFPDMSCs was independent of donor age. The cells will not be affected by aging when expanded *in vitro*. Procurement of IFPDMSCs also showed to have lower donor-site morbidity. The donor well tolerates resection and removal of IFP since this is a routine procedure in total knee arthroplasty. IFPDMSCs are also accessible by a minimally invasive procedure of knee arthroscopy. No complication or sequelae was ever recorded after partial resection or removal of IFP in routine knee arthroscopy (30–32).

Various *in vitro* studies showed favorable results of infrapatellar fat pad-derived mesenchymal stem cells in terms of chondrogenic potential (33–35). IFPDMSCs have a higher proliferation capacity compared to BMSCs (36,37). Furthermore, IFPDMSCs are more resistant to apoptosis than BMSCs *in vitro* conditions (38). However, *in vivo* studies on the application of IFPDMSCs are still scarce and vastly heterogeneous. In this study, only two animals and two clinical studies on OA used IFPDMSCs. These results showed that there is still a minimal number of studies on the efficacy of IPFDSCs in osteoarthritis treatment. The studies' heterogenicity varies from the type of cell source, the number of cells used, and outcome measurement. The two animal studies used cells from different animals: rabbits and sheep. Different types of cells applied to different knee models would hardly provide an exact comparison for subsequent extrapolation of the result (39).

The outcome measurement of the included studies was also heterogeneous. In animal studies, only one study used a more objective histological score. In the clinical study, only one study used a control group as a comparison. The other study was a case series comparing pre and post-treatment assessments. Unfortunately, there has been no randomized control study to evaluate the efficacy of IFPDMSCs in patients with knee OA. Therefore, for future studies both in animal and clinical, standardized measurement tools with control groups should be used to understand better the efficacy of IFPDMSCs in osteoarthritis (16–18,31).

There is some limitation in this study. Firstly, the number of the included studies is small. Secondly, this study includes both animal and human studies. The reason is that IFPDMSCs are a relatively new cell source of cartilage tissue engineering, and therefore, studies on this topic are still limited.

Infrapatellar fat pad-derived mesenchymal stem cells might provide an alternative cell with promising chondrogenic potential, as demonstrated by the in vitro studies (1,17,27–29,39,40). However, due to the minimal number of *in vivo* studies, concluding the efficacy of IFPDMSCs as an alternative to cell-based therapy for OA is still a long journey. Therefore, to provide more firm evidence of the efficacy of IPDSCs as an alternative treatment to OA, the direction of future studies should focus on both preclinical studies and clinical trials with more homogenous methods, intervention, evaluation parameters, and scoring tools.

CONCLUSION

There are currently a limited number of studies on infrapatellar fat pad-derived mesenchymal stem cells (IFPDMSCs) use for cell-based osteoarthritis treatment. Two preclinical studies showed encouraging results on the use of IFPDMSCs in animal models, as shown by the better quality of regenerated cartilage in radiological and histological evaluation. A comparative study and a case series also showed promising post-treatment outcomes in the clinical setting. Therefore, IFPDMSCs can be considered as an alternative cell source for cartilage tissue regeneration although the efficacy of IFPDMSCs in cell-based osteoarthritis treatment still needs to be explored and proven further with more *in vivo* studies, both preclinical and clinical, to yield the same promising result as those of the *in vitro* studies.

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