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Review

Mesenchymal stem cells in human meniscal regeneration: A systematic review

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ABSTRACT

Background: Stem cell regeneration is the holy grail of meniscal tissue repair. Currently, the best treatment is to preserve the original meniscus but if it fails, a partial meniscectomy is indicated to delay the onset of osteoarthritis.

Materials and methods: The authors present a systematic review to determine the up-to-date evidence underlying the use of mesenchymal stem cells for meniscal regeneration in humans. A search was conducted using the electronic databases of MEDLINE/Pubmed, Google scholar, and the Cochrane Collaboration. Search keywords included human, meniscus, stem cells and regeneration.

Results: After screening 10 non-duplicate studies, 5 were identified based on title and abstract. 4 were included in the analysis. There were marked differences in the method of stem cell harvest techniques. 3 studies administered stem cells through percutaneous injection into the knee and 1 study used a collagen scaffold. MRI analysis, functional scores and safety were assessed and the longest follow-up period was 2 years. The Visual Analogue Score (VAS) was most commonly used to assess function and patients generally showed an improvement. There were no reported adverse events.

Conclusion: Despite positive results from animal models, there is currently a lack of evidence in humans to conclude that stem cells can form durable neotissue similar to original human meniscus. There is a need for standardisation of protocol before further trials are considered. Initial outcomes from human studies are promising and mesenchymal stem cells may play an important role in meniscal repair in years to come.

1. Background

The holy grail of meniscal repair lies within the realms of meniscal regeneration. Most meniscal injuries are associated with a more active lifestyle and the damage of meniscal tissue renders young patients at a higher risk of undergoing meniscal surgery and hence osteoarthritis [1].

Established options for the management of a torn meniscus include partial or complete meniscectomy, meniscal allograft transplantation and synthetic meniscus transplantation. Other more conservative options include conduit treatment, abrasion therapy, platelet-rich-plasma therapy and more recently, meniscus tissue engineering [2]. Tissue engineering involves the use of cells with regenerative potential to augment the healing process following a meniscal injury. Cells that have been studied include articular chondrocytes, meniscal fibrochondrocytes, and mesenchymal stem cells (MSCs) [2]. Within orthopaedics, MSCs are mainly derived from bone marrow. However, other sources include synovial membrane [3], adipose tissue [4], meniscus-derived MSCs [4] and extra-articular tissues such as dermis [5]. Adult MSCs are particularly attractive due to their potential for multilineage differentiation, immunomodulation and ability to migrate towards sites of injury [6]. One concern regarding MSCs is that the cartilage formed from MSCs has different mechanical properties to native meniscal tissue and inferior content in the extracellular matrix [6]. Further questions yet to be definitively answered include the optimal delivery method and scaffold choice [7].

A large volume of pre-clinical data exists, and stem cells in meniscal regeneration have been widely studied in animal models. Few studies, however, have assessed the in-vivo use of MSCs in human meniscal injuries. Limited understanding of the interplay between MSCs and stimulatory factors involved in meniscal regeneration is currently one of the factors contributing to regulatory burdens and their limited clinical use [8].

In this review, we explore the current studies which investigate the use of MSCs for meniscal regeneration in humans. Our objectives were:

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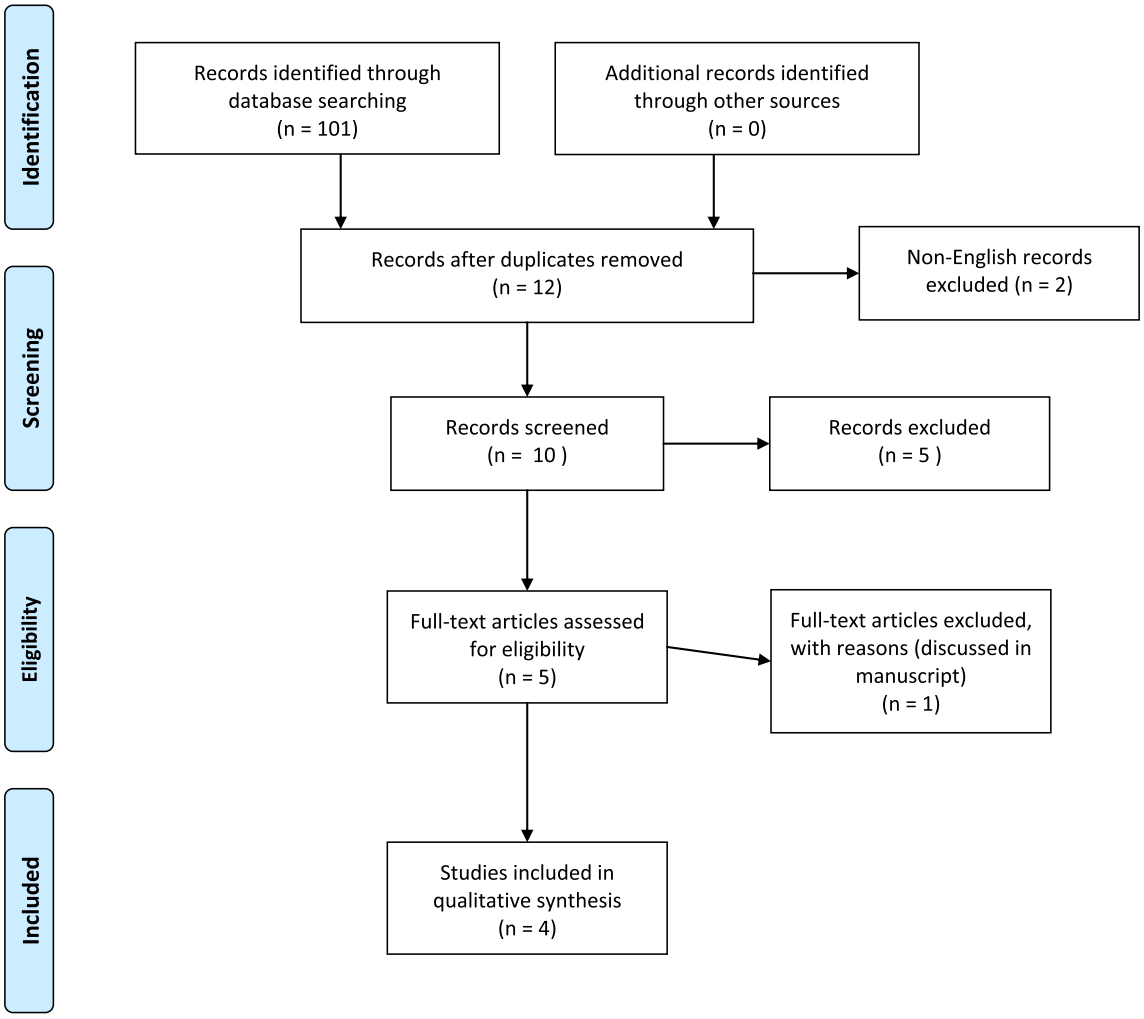

Fig. 1. PRISMA 2009 flow diagram.

to determine the efficacy of using human mesenchymal stem cells to repair damaged meniscus; to critically review all studies to date involving the application of mesenchymal stem cells into the human adult knee joint and to identify improvements for future human studies.

2. Materials and methods

A systematic review of literature for meniscal regeneration in the human model was performed and reported according to the PRISMA criteria (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [9]. Searches were carried out on 1st July 2017 of MEDLINE/Pubmed and Google Scholar using the following search string: Human AND (meniscal OR meniscus OR menisci OR knee) AND (tear OR injury) AND (stem cell OR mesenchymal OR MSC). The inclusion period was January 1st, 2000 to July 1st, 2017 (see Fig. 1).

Studies were then screened by title and abstract using the following inclusion criteria:

1. Mesenchymal stem cells used for meniscus repair, tested in human models only regardless of how cells were extracted or delivered.
2. Participants of any age, any nationality, male or female were included.
3. Participants must also have had MRI evidence of meniscal degeneration, meniscal tear or osteoarthritis, pre-stem cell application.

Studies involving the application of human stem cells in animal models, in-vitro experiments, reviews, articles in languages other than English and articles with missing full texts were excluded. Each study was independently reviewed by the authors RP and EC, with relevant details recorded on a data extraction sheet.

3. Results

A total of 45 studies from MEDLINE, 55 studies from Google Scholar and 1 study from the Cochrane Collaboration were obtained from the literature search. After excluding 89 duplicated results and 2 non-English studies, 10 studies were analysed using their title and abstract, of which 5 studies were excluded as they involved the application of human stem cells in animal models. The full text of the remaining 5 articles were screened and 1 study was excluded as it was a study assessing the safety of stem cell administration. A total of 4 studies met the inclusion criteria in this review amounting to a total of 67 patients. 2 studies were case reports [10,11], 1 study was a case series [12] and 1 study was a double-blind randomized control trial [13]. The average patient age was 38. Gender distribution generally had more males than females. Table 1 outlines the methods of extraction and delivery of stem cells and Table 2 summarises the objectives and results of each study.

3.1. Method of obtaining stem cells

Vangsness Jr et al.'s study used a preparation of ex-vivo cultured adult human mesenchymal stem cells derived from bone-marrow aspirates, obtained from unrelated donors who were not human leukocyte antigen (HLA)-matched to recipients. The donors were also between 18