Peripheral Blood-Derived Stem Cells for the Treatment of Cartilage Injuries: A Systematic Review

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Background: The treatment of cartilage damage is a hot topic at present, and cell therapy is an emerging alternative therapy. Stem cells derived from peripheral blood have become the focus of current research due to the ease of obtaining materials and a wide range of sources.

Methods: We used a text search strategy using the ["mesenchymal stem cells" (MeSH term) OR “MSC” OR “BMMSC” OR “PBMSC” OR “PBMNC” OR “peripheral blood stem cells"] AND (cartilage injury [MeSH term] OR “cartilage” OR “chondral lesion”). After searching the literature, through the inclusion and exclusion criteria, the last included articles were systematically reviewed.

Result: We found that peripheral blood-derived stem cells have chondrogenic differentiation ability and can induce chondrogenic differentiation and repair in vivo and have statistical significance in clinical and imaging prognosis. It is an improvement of academic differences. Compared with the bone marrow, peripheral blood is easier to obtain, widely sourced, and simple to obtain. In the future, peripheral blood will be a more potential cell source for cell therapy in the treatment of cartilage damage.

Conclusion: Stem cells derived from peripheral blood can repair cartilage and are an important resource for the treatment of cartilage damage in the future. The specific mechanism and way of repairing cartilage need further study.

Keywords: peripheral blood-derived stem cells, cartilage injuries, PBMSC, BMSC, PBMNCs

1 INTRODUCTION

Cartilage is a special, low-friction articular surface tissue that is essential for weight absorption and smooth gliding of the articulating surfaces in diarthrodial joints, whose primary function is to absorb, cushion, and protect the underlying bone from the forces that arise when the joint is being used. Chondral lesions can lead to direct contact with bone, ultimately leading to osteoarthritis (Rackwitz et al., 2014). Due to the lack of native blood vessels and lymphatic return, the spontaneous healing capacity of cartilage is low and is generally replaced by fibrocartilage (Frisch et al., 2017a). The newly generated fibrocartilage can withstand far less mechanical stress than the original cartilage tissue (Hunziker, 2002). Numerous studies have reported that the newly formed fibrocartilage tends to deteriorate over time (Orth et al., 2014). Therefore, the treatment of chondral lesions is currently an important research topic in traumatology.
Conservative treatment of cartilage damage usually includes corticosteroids, nonsteroidal anti-inflammatory drugs, hyaluronan, and polysulfated glycosaminoglycan (Ferris et al., 2011). However, the abovementioned drugs can only control the symptoms and cannot prevent the occurrence of osteoarthritis (Frisbie et al., 2009). Marrow stimulation techniques, including microfracture and microdrilling, have been widely reported as promoting chondral healing, with microfracture being the most commonly performed (Madry et al., 2011). It penetrates the underlying subchondral bone marrow through drilling, allowing bone marrow mesenchymal stem cells (MSC) and other progenitor cells to enter the cartilage defect for repair and present good clinical outcomes (Bieback et al., 2008). However, after bone marrow stimulation, the joint normally covered by hyaline cartilage is repaired by fibrocartilage, which is biochemically and mechanically inferior to hyaline cartilage.
Continued stress can lead to tissue degeneration and deteriorating results in the long term (Vinatier et al., 2009). Therefore, improving the quality of prosthetic tissue has become a new issue.

The application of autologous mesenchymal stem cells in the joint cavity shows the effect of enhancing cartilage repair in a lasting way (Saw et al., 2013; Skowronski and Rutka, 2013; Reissis et al., 2016). Thus, lately researchers have focused on cell therapy as a therapeutic alternative (Brittberg et al., 1994). There are many sources of mesenchymal stem cells, including bone marrow, adipose tissue, skin, or peripheral blood, or from an umbilical cord donor (Kassis et al., 2006; Larochelle et al., 2006; Huang et al., 2009). While bone marrow (BM) MSCs show a decline in the number and differentiation potential of MSCs with aging or transformation in long-term in vitro culture, the peripheral blood mononuclear cell fraction has been shown to enhance cartilage repair in an ovine osteochondral defect model (Emadedin et al., 2012; Hopper et al., 2015a). The use of peripheral blood may provide workable and less invasive translational procedures as this resource also contains MSC with the same potency for chondrogenic differentiation as that of bone marrow MSC (Zvaifler et al., 2000; Huang et al., 2009; Raghunath et al., 2010; Al Faqeh et al., 2012). The purpose of this systematic review is to evaluate the potential of peripheral blood-derived stem cells in the treatment of cartilage injury by collecting relevant literature on the treatment of cartilage injury with peripheral blood-derived stem cells in the past two decades, including in vitro and in vivo experimental articles.

2 MATERIALS AND METHODS

2.1 Data Sources and Search Strategy

We conducted a systematic review based on the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines (Moher et al., 2009). We used a text search strategy using the ["mesenchymal stem cells" (MeSH term) OR "MSC" OR "BMMSC" OR "PBMSC" OR "peripheral blood stem cells"] AND [cartilage injury (MeSH term) OR "cartilage" OR "chondral lesion"]. Specifically, we searched the PubMed, Embase, and OVID databases from inception to 20 April 2022. We also assessed the bibliographies of identified studies to seek additional articles. We did not add language restrictions.

Along with the database search, we examined the references of included studies and previously published systematic reviews to identify additional studies. We also checked the International Clinical Trials Registry Platform Search Portal and ClinicalTrials.gov (https://clinicaltrials.gov/) to identify the currently ongoing or recently completed trials.

2.2 Inclusion and Exclusion Criteria

2.2.1 Inclusion

1. Any basic English-language scientific studies of the PB-derived primitive cells that exhibited chondrogenic or multipotent mesenchymal differentiation abilities.

2. *in vivo* animals using PB as a source of chondrogenic progenitor cells for cartilage regeneration were also included.

3. Human studies using PB as a source of chondrogenic progenitor cells for cartilage regeneration were also included.

4. Any study that has at least one outcome that can be documented.

2.3 Exclusion

Any studies of primitive cells that were not chondrogenic or not derived from the PB and *in vivo* studies that only used non-PB sources were excluded.

2.4 Quality Assessment

The risk of bias graph in Review Manager 5.3 was used to evaluate the methodologic quality of included RCT studies in this systematic review. This seven-element checklist qualitatively assesses various aspects of trial quality (random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias) using an ordinal scoring system comprising high risk, low risk, or unclear risk response options for each statement in Review Manager 5.3. A higher score obtained with the Review Manager 5.3 is indicative of higher methodological study quality.

QUADAS (Quality Assessment of Diagnostic Accuracy Studies) was used to evaluate the methodologic quality of other studies. The detailed items of the scale are as follows:

1. Was a consecutive or random sample of patients enrolled? Yes/No/Unclear
2. Was a case-control design avoided? Yes/No/Unclear
3. Did the study avoid inappropriate exclusions? Yes/No/Unclear
4. Could the selection of patients have introduced bias? RISK: LOW/HIGH/UNCLEAR
5. Is there a concern that the included patients do not match the review question? CONCERN: LOW/HIGH/UNCLEAR
6. Were the index test results interpreted without the knowledge of the results of the reference standard? Yes/No/Unclear
7. If a threshold was used, was it prespecified? Yes/No/Unclear
8. Could the conduct or interpretation of the index test have introduced bias? RISK: LOW/HIGH/UNCLEAR
9. Is there a concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW/HIGH/UNCLEAR
10. Is the reference standard likely to correctly classify the target condition? Yes/No/Unclear
11. Were the reference standard results interpreted without the knowledge of the results of the index test? Yes/No/Unclear
12. Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW/HIGH/UNCLEAR
13. Is there a concern that the target condition, as defined by the reference standard, does match the review questions? CONCERN: LOW/HIGH/UNCLEAR
### TABLE 1 | PBSCs in Cartilage Injury

| First author          | Species               | Number | Character                  | Type of study     | Evaluation method                                      | Injury site(number)                          | Degree of damage                        |
|-----------------------|-----------------------|--------|----------------------------|-------------------|--------------------------------------------------------|---------------------------------------------|------------------------------------------|
| Henson et al. (2021)  | Welsh Mountain sheep  | 40     | 3-4 year-old (adult) (mean age 3.2 years), 40-42 kg | Comparative study | MRI, Gross Morphology, Histology, and Immunohistochemistry | the medial femoral condyle defects of 8 mm diameter | Full-thickness chondral defects |
| Broeckx et al. (2019) | Horse                 | 75     | 22 mares, 16 geldings and 37 stallions | RCTs              | visual lameness assessment, flexion test               | Fetlock joint                              | Early staged fetlock disease            |
| Broeckx et al. (2019) | Horse                 | 12     | 3 geldings and 9 mares (median age 8.5 years) | RCTs              | weekly joint assessment, AAEP score, an inertial sensor-based system, X-ray, Synovial fluid analysis, OARSI, and Immunohistochemistry | Metacarpophalangeal OA                      | Surgically induced OA                   |
| Fu et al. (2014)      | Rabbit                | 30     | New Zealand White rabbits, aged about 4 months clinical lameness for at least 3 months | Controlled laboratory study | histological scoring, histochemical staining, and immunohistochemistry | the trochlear groove of the distal femur | Full-thickness articular osteochondral defects (5 mm in diameter and 1-2 mm in depth) |
| Broeckx et al. (2014) | Horse                 | 50     | 4 year-old (adult) (mean age 3.2 years) | Preliminary study | Cytological Staining, Immunocytochemistry, Flow Cytometry, RT-PCR, and AAEP Clinical lameness; locomotory disorder; and positive flexion test | fetlock | NA                                 |
| Broeckx et al. (2014) | Horse                 | 165    | NA                          | Pilot study       | Clinical outcome Imaging results Experimental results | Degenerative joint disease                |                                           |

| First author          | Cell source             | Cultivation and extraction methods | Cell character markers | number of cells | Cell implantation method | Surgical approach |
|-----------------------|-------------------------|-----------------------------------|------------------------|-----------------|--------------------------|-------------------|
| Henson et al. (2021)  | Autologous G-CSF activated PB | Apheresis                        | CD34, CD45, CD73, CD90, and CD105 | NA              | intra-articular injections | intra-articular injections |
| Broeckx et al. (2019) | Chondrogenic induced PBMSCs | DGC and PA                        | CD44, MHC II, CD29, CD44, and CD90 | 2 x 10⁶ cells/ml | Articular injection      | Articular injection |
| Broeckx et al. (2019) | Chondrogenic induced PBMSCs | DGC and PA                        | Aggrecan+, Col II+, COMP+, p63+ and GAG+; decrease in Ki67. CD44, CD45, and MHC II | 2 x 10⁶ cells/ml | Articular injection      | Articular injection |
| Fu et al. (2014)      | Autologous G-CSF activated PB | Erythrocyte Lysis and PA          | CD44, CD45, and MHC II | 4 x 10⁶ cells/scaffold | Surgical implantation | Establishment of animal model |
| Broeckx et al. (2014) | PB-MSCs (native or chondrogenic induction) | DGC and PA                        | Coll II, Ki67 p63, vimentin, and MHCII aggrecan | NA              | Single IA injection      | PB-MSCs with or without PRP injection |
| Broeckx et al. (2014) | PB-MSCs (native or chondrogenic-induced) | DGC and PA                        | Coll II, Ki67 p63, vimentin, and MHCII aggrecan | NA              | Single IA injection      | PB-MSCs with PRP injections |

| First author          | Time | Postoperative treatment | Clinical outcome | Imaging results | Experimental results | Adverse event |
|-----------------------|------|-------------------------|-----------------|-----------------|---------------------|---------------|
| Henson et al. (2021)  | 8 weeks | NA | NA | SPION labeled cells could not be detected within the defect at any of the time points studied despite using MRI sequences | NA | No adverse event |
| Broeckx et al. (2019) | 1 year | Dexmedetomidine hydrochloride and Ketoprofen | Improved AAEP score*, Flexion score* and Pan score* | radiographic changes were not significantly different | higher viscosity score*, less wear lines were present in the intervention group*, higher COMP in the cartilage adjacent* | 3 mild infections of the upper respiratory tract |
| Broeckx et al. (2019) | 11 weeks | Dexmedetomidine hydrochloride | AAEP scores in week 7* | | | 1 horse had an increase in local temperature 2 horses had a limited range of motion |
| Fu et al. (2014)      | 24 weeks | allowed to move freely and had free access to food pellets and water | NA | NA | | | (Continued on following page) |
14. Was there an appropriate interval between index test(s) and reference standard? Yes/No/Unclear
15. Did all patients receive reference standard? Yes/No/Unclear
16. Did patients receive the same reference standard? Yes/No/Unclear
17. Were all patients included in the analysis? Yes/No/Unclear
18. Could the patient flow have introduced bias? RISK: LOW /HIGH/UNCLEAR

2.5 Data Extraction
A single reviewer screened all the citations and abstracts generated by the literature search and applied the selection criteria. Identified randomized trials were assessed for inclusion by two reviewers. Any disagreement between them on the eligibility of certain studies was resolved through discussion with a third reviewer. The titles of journals and names of authors were not masked during the study selection process.

Each investigator independently extracted the following data:

1. Study characteristics, including species, number, character of included species, type of study, evaluation method, injury site, and degree of damage.
2. Experimental details including cell source, cultivation and extraction methods, cell character markers, number of cells, cell implantation method, and surgical approach.
3. Experimental results and adverse events.

3 RESULT

3.1 Basic Characteristic
According to our retrieval strategy abovementioned, we retrieved a total of 3,076 articles. After a brief reading of the abstracts and titles, duplicate articles and irrelevant articles were excluded, and a total of 296 articles were reviewed in detail (Figure 1). After excluding articles that do not contain related stem cells, we ultimately included 24 articles between 2008 and 2022 for the systematic review (Jancewicz et al., 1995; Pufe et al., 2008; Saw et al., 2011; Casado et al., 2012; Chong et al., 2012; Kim et al., 2012; Skowroński et al., 2012; Saw et al., 2013; Skowroński and Rutka, 2013; Turajane et al., 2013; Broeckx et al., 2014a; Fu et al., 2014a; Broeckx et al., 2014b; Fu et al., 2014b; Fu et al., 2014b; Turajane et al., 2014; Hopper et al., 2015b; Frisch et al., 2017b; Broeckx et al., 2019a; Broeckx et al., 2019b; Monckeberg et al., 2019; Ying et al., 2020; Henson et al., 2021). The data from 24 studies were analyzed, including seven fully in vitro studies and 17 in vivo studies (Table 1). The experimental subject includes humans, sheep, rabbits, and horses. A total of nine articles included in vitro experiments, all (100%) of which confirmed the tendency of peripheral blood-derived stem cells to differentiate into chondrocytes. In terms of cell sources, 10 articles used G-CSF-stimulated PBMSCs, four articles used chondro-induced PBMSCs, and eight articles directly used the peripheral blood stem cells afterapheresis or gradient centrifugation. In vivo experiments include three comparative studies, one prospective study, three RCTs, five case reports, one preliminary study, and one pilot study. Cartilage defects in nine of the studies were graded with ICRS and were all greater than grade 3. All characteristics of the included literature are listed in Tables 1, 2, 3. Figures 2, 3 demonstrates the basic experimental procedure. Table 1 and Figure 4 show the methodological quality evaluation results. The detailed results of the quality evaluation are shown in Figure 4 and Table 4.

3.2 PBMSC in Humans
We included nine studies with human subjects, including one prospective study, three comparative studies, 4 case reports, and one RCTs (Jancewicz et al., 1995; Saw et al., 2011; Skowroński et al., 2012; Saw et al., 2013; Skowroński and Rutka, 2013; Fu et al., 2014b; Turajane et al., 2014; Monckeberg et al., 2019; Ying et al., 2020). A total of 225 people were included. Most injuries are concentrated in the patella and femoral condyle, and a few in the hip joint. Cartilage damage in all patients included in the study was degenerative. Except for the study conducted by Ying et al.
### Table 2: PBSCs in human.

| First author       | Species | Number | Character | Type of Study | Evaluation method | Injury site(number) | Degree of damage |
|--------------------|---------|--------|-----------|---------------|-------------------|---------------------|------------------|
| Monckeberg et al.  | Human   | 37(15 males) | age range 31–64 years | prospective study | HHS, µCT Scanning, Histochemistry, Immunohistochemistry (IHC), and Immunofluorescence analyses, 1.Trochlea(9) 2.Femoral condyle(5) 3.Patella(6) | hip | microfracture and/or cystic degeneration existed between cartilage and subchondral bone ICRS grade>3 |
| Fu et al.          | Human   | 1      | 19 years old | case report | X-rays, CT and MRI, Tegner, Lysholm, and IKDC 2000 scores. | Lateral femoral trochlea | Full-thickness cartilage defects(ICRS grade IV) |
| Turajane et al.    | Human   | 5      | 52–59 years old | Case report | WOMAC and KOOS | Medial condyle (4) and patellofemoral (1) | Early-stage OA(ICRS grade III and IV) |
| Saw et al.         | Human   | 46     | 7–52 years old (average age: 26 years) | Comparative study | KOOS and Lysholm and VAS scales | Medial femoral condyle | Osteochondral lesions(ICRS grade IV) |
| Saw et al.         | Human   | 50     | 22–50 years old | RCTs | IKDC, MRI scan, and ICRS | Knee | Chondral defects(ICRS grade III and IV) |
| Skowroński and Rutka, | Human   | 52     | 16–55 years old | Case report | KOOS, Lysholm and VAS scales, and MRI | Patella (22), medial femoral condyle (38), and lateral femoral condyle (8) | Cartilage lesions (ICRS grade III and IV) |
| Saw et al.         | Human   | 5      | 19–52 years old | case report | Second-Look Arthroscopy and Histology clinical examination, Magee score, and MRI | Knee | Chondral defects (ICRS grade III and IV) |
| Jancowicz, P.      | Human   | 9      | NA | Case report | KOOS, Lysholm and VAS scales, and MRI | Patella (22), medial femoral condyle (38), and lateral femoral condyle (8) | Cartilage lesions (ICRS grade III and IV) |

| First author       | Cell source | Cultivation and extraction methods | Cell characteristic markers | Number of cells | Cell implantation method | Surgical approach |
|--------------------|-------------|-----------------------------------|-----------------------------|-----------------|--------------------------|-------------------|
| Monckeberg et al.  | PBSCs       | autologous PB (Apheresis)         | N/A                         | 430,000 PBSC = 270,000/ml | articular injection with PRP | Knee arthroscopy |
| Fu et al.          | Autologous G-CSF mobilized PB | Blood cell separation | NA | 3.496 × 10^7 cells/ml | Surgical implantation | Debridement + PBSCs with autologous periosteum flap cover |
| Turajane et al.    | Autologous G-CSF activated PB | Leukapheresis | CD34^+ CD105^+ | 2.67–5.99 × 10^5 cells/injection | Repeated IA injections | Debridement + BMS + repeated IA injections |
| Skowroński and Rutka, | Autologous G-CSF activated PB, | Apheresis | NA | 1.26 × 10^5–5.2 × 10^6 cells/ml | Surgical implantation | Debridement + modified sandwich technique |
| Skowroński et al.  | Autologous G-CSF mobilized PB | Apheresis | NA | 2.0 × 10^7 cells/injection | Repeated IA injections | Debridement + BMS + HTO(1) + repeated IA injections |
| Saw et al.         | Autologous G-CSF activated PB | Blood cell separation | CD34^+ | NA | Surgical implantation | Debridement + sandwich technique |

| First author       | Time | Postoperative treatment | Clinical outcome | Imaging results | Experimental results | Adverse event |
|--------------------|------|------------------------|------------------|----------------|---------------------|---------------|
| Monckeberg et al.  | 5 years | Nonsteroidal anti-inflammatory drugs and acetaminophen, rehabilitation protocol | Improved IKDC score and lower VAS score | Improved IKDC score* | Improved ICRS score* | 2: myalgia and fever |
| Fu et al.          | 7.5 years | Strict rehabilitation program | Improved IKDC 2000 subjective score, Lysholm score and Tegner score | CT: subchondral bone recovery; MRI: near-normal cartilage and tissue regeneration | Regenerated articular cartilage with a smooth surface, but with a slightly | NA |

(Continued on following page)
TABLE 2 | (Continued) PBSCs in human.

| First author | Time | Postoperative treatment | Clinical outcome | Imaging results | Experimental results | Adverse event |
|--------------|------|-------------------------|------------------|----------------|---------------------|--------------|
| Turajane et al. (2013) | 6 months | Nonweight bearing | Improved WOMAC and KOOS* Succeeded in regenerating articular cartilage | NA | Improved MRI morphologic scores | NA | Mild swelling and discomfort |
| Skowroński and Rutka. (2013) | 5 years | Passive and active exercises, nonweight to full-weight bearing | Improved KOOS and Lysholm scales, relief of VAS scale*; | 92% of patients with good results MRI: satisfactory reconstruction of the cartilaginous surface and good regenerative integration | NA | NA |
| Saw et al. (2013) | 18 months | NA | No IKDC score difference compared to the control group | Improved MRI morphologic scores | Improved total ICRS II histologic scores | Deep vein thrombosis (1 patient in the control group) | NA |
| Saw et al. (2013) | 10–26 months | Crutch assisted partial to full weight-bearing | NA | X-ray: reappearance of medial articulation | generated full-thickness articular hyaline cartilage | Minimal discomfort from PBSCs harvesting and IA injection |

* means statistically different.

(2020), which did not report the degree of cartilage damage, the rest of the studies reported that cartilage damage and the ICRS grade was greater than grade 3. The evaluation methods include International Knee Documentation Committee score (IKDC), visual analog scale (VAS), and International Cartilage Repair Society morphologic score system (ICRS) for subjective scoring; X-ray and Magnetic Resonance Imaging (MRI) for imaging examination; and tissue biopsy and Immunohistochemistry for laboratory examination. Seven studies used the G-CSF-stimulated peripheral blood stem cells, and two studies used apheresis peripheral blood stem cells. The preparation process uses red blood cell lysis and gradient centrifugation, which has been proven to be effective in isolating PBMSCs (Kim et al., 2012). All studies used the intra-articular injection for cell implantation. Five articles report on postoperative treatment, including drug therapy: acetaminophen, NSAIDs, and Dexmedetomidine, and different types of rehabilitation programs. Seven studies reported clinical outcomes, except Ying, J (Ying et al., 2020), who reported no significant difference in HH3s between the two groups at 36 months followup. However, clinical results of the remaining six studies reported a significant improvement in clinical scores (KOOS, VAS, The Western Ontario, and McMaster Universities Osteoarthritis Index (WOMAC)) after the peripheral blood-derived stem cells were injected into the defect site. Similarly, in the imaging results and laboratory test results, except for Ying, J, all the other reported studies showed a statistically significant improvement after peripheral blood stem cell transplantation. In terms of adverse events, except for a case of deep vein thrombosis reported by Saw, K. Y, which is a high-risk event, all the other adverse events are low-risk events, including fever and joint adhesion (Saw et al., 2013). The detailed information is shown in Table 2.

3.3 PBMSC in Animals

Six animal studies were included in our systematic review, including two RCTs, one comparative study, one controlled laboratory study, one preliminary study, and one pilot study (Broeckx et al., 2014a; Fu et al., 2014a; Broeckx et al., 2014b; Broeckx et al., 2019a; Monckeberg et al., 2019; Henson et al., 2021), and subjects included sheep, horses, and rabbits. The lesions are mainly concentrated in the lower extremity joints or the metacarpophalangeal joints. The cartilage defects of the experimental subjects of Fu, W. L (Fu et al., 2014a), Henson, F. (Henson et al., 2021), and Broeckx, S. Y (Broeckx et al., 2019b) were all using experimental modeling, and the cartilage defects of the experimental subjects of other researchers were all caused by degenerative diseases. Grade of cartilage damage was not reported. Two studies used the G-CSF-stimulated peripheral blood stem cells, and four studies used chondrogenic induced PBMSCs. Gradient centrifugation was used for cell isolation in all experiments, and plastic adhesion was also used in some experiments. All studies did not impose strict requirements on the postoperative rehabilitation of experimental animals and did not limit their range and intensity of activities. Only Broeckx, S. Y. in the 2019 experiment gave experimental animals postoperative drug treatment for sedation and analgesia. In experiments where flow cytometry was performed, Henson, F. et al. (2021) detected: CD34, CD45, CD73, CD90, and CD 105, and Broeckx, S. Y. et al. (2019) detected: CD45, MHC II, CD29, CD44, and CD90, Fu, W. L. et al. (2014) detected: CD44, CD45, and MHC II. All studies used intra-articular injection for cell implantation. In the
### TABLE 3 | PBSCs in vitro.

| First author     | Species | Number | Character | Type of study | Evaluation method                                                                 | Injury site (number) | Degree of damage |
|------------------|---------|--------|-----------|---------------|------------------------------------------------------------------------------------|----------------------|------------------|
| Frisch, J. (2019) | in vitro | 4 donors age 42 ± 27 | Basic Medical Experiment | Biochemical analyses, Histological and immunohistochemical analyses, Histomorphometry, and Real-time RT-PCR analyses | NI                  | NA               |
| Hopper, N. (2015) | in vitro | 12 young (32.9 ± 9.3 years) volunteers | Basic Medical Experiment | Scratch assay, xCELLigence assay, Cell proliferation, Cell proliferation, mRNA expression, PCR array, and Quantitative real-time PCR | NI                  | NA               |
| Turajane, T. (2014) | in vitro | 10 patients (median age 58 years, range 56–60 years, eight females) | Basic Medical Experiment | Attachment and proliferation assays, Flow cytometry analysis, RT-PCR analysis, Scanning electron microscopy, and Histology | NI Half ICRS grade = 2 Remainder ICRS grade >3 | |
| Kim, J. (2012)    | in vitro | NA | Basic Medical Experiment | In vitro differentiation, Classification of differentially regulated proteins, western blot, and real-time RT-PCR analysis, and Immunofluorescent-staining | NI                  | NA               |
| Chong, P. P. (2012) | in vitro | NA | Basic Medical Experiment | Biochemical Assays, Morphological Analysis of Chondrogenic, Osteogenic, and Adipogenic, and Gene Expression Analysis, rt-PCR, | NI                  | NA               |
| Casado, J. G. (2012) | in vitro | Large White pigs aged between 3 and 4 months | Basic Medical Experiment | flow cytometry, adipogenic, chondrogenic and osteogenic differentiation, and Quantitative RT-PCR Immunohistochemistry, Electron Microscopy, and Enzyme-Linked Immunosorbent Assay, rt-PCR, | NI                  | NA               |
| Pufe, T. (2008)   | in vitro | NA | Basic Medical Experiment | NA                  | NA                  | NA               |

### Table continued...

| First author     | Cell source | Cultivation and extraction methods | Cell character markers | Number of cells | Cell implantation method | Surgical approach |
|------------------|-------------|----------------------------------|------------------------|-----------------|--------------------------|-------------------|
| Frisch, J. (2019) | rAAV transferred PB MSC PBSCs | DGC and PA | IGF-I, aggrecan, COL2A1, and SOX9 | NA              | NA                       | NA               |
| Hopper, N. (2015) | PBSCs | DGC | C5a, CXCL1, ICAM-1, IL-1β, IL-1ra, IL-6, IL-8, IL-13, IL-16, CXCL10, CXCL11, CCL2, MIF, CCL5, and PAI-1 | NA              | NA                       | NA               |
| Turajane, T. (2014) | Autologous G-CSF activated PB PBMSC | DGC | CD34, CD29, CD44, CD45, CD90, and CD105 | NA              | NA                       | NA               |
| Kim, J. (2012)    | PBMSC | NA | CD34, CD45, CD133, CD73, CD90, CD105, PDGF-B, and HLA-ABC | CD105, CD166, and CD29 | NA              | NA               |
| Chong, P. P. (2012) | Peripheral blood mononuclear cells | NA | CD29+, CD44+, CD45+, CD90+, and CD105+ | NA              | NA                       | NA               |
| Casado, J. G. (2012) | Peripheral blood mononuclear cells | Erythrocyte lysis, DGC and PA | NA | NA | NA | NA |
| Pufe, T. (2008)   | Peripheral blood mononuclear cells | DGC and PA | NA | NA | NA | NA |

### Table continued...

| First author     | Time | Postoperative treatment | Clinical outcome | Imaging results | Experimental results | Adverse event |
|------------------|------|------------------------|------------------|-----------------|----------------------|---------------|
| Frisch, J. (2019) | NA   | NA                     | NA               | Enhanced proliferative and chondrogenic activities, Significantly increased cellularity, Enhanced levels of chondrogenic marker expression | NA              | NA               |
| Hopper, N. (2015) | NA   | NA                     | NA               | The wound closure rate at the 3 h time point was significantly higher* no significant difference between the PBMC-stimulated and non-stimulated test groups in the total DNA amount The mRNA levels for these genes were upregulated by the 24 h PBMC stimulus: SOX9 and COL2A1 | NA              | NA               |
| Turajane, T. (2014) | 7 days | NA                     | NA               | Cell proliferation on day 7 showed statistically significant differences* increase in cell attachment and cell proliferation* Sox9 increased in days 7 and 14, Sox9 increased on days 7, Aggrecan increases were statistically significant on days 7 and 14 | NA              | NA               |
| Kim, J. (2012)    | NA   | NA                     | NA               | MSC from PB also shows the differentiation of chondroitin | NA              | NA               |

(Continued on following page)
Table 3 | (Continued) PBSCs in vitro.

| First author | Time | Postoperative treatment | Clinical outcome | Imaging results | Experimental results | Adverse event |
|--------------|------|-------------------------|------------------|----------------|---------------------|---------------|
| Chong, P. P. | NA   | NA                      | NA               | NA             | MSCs from PB maintain similar characteristics and have similar chondrogenic differentiation potential to those derived from BM while producing comparable s-GAG expressions to chondrocytes | NA            |
| Casado, J. G. | 2 weeks | NA                      | NA               | NA             | PBMSC have both chondrogenic and adipogenic potential | NA            |
| Pufe, T. | 6 weeks | NI                      | NI               | NI             | A strong accumulation of collagen type II after a 6 weeks found chondrogenic differentiation with a continuous expression of collagen type II mRNA and protein | NA            |

* means statistically different.

Figure 2 | The general process of human peripheral blood-derived stem cell experiments (in vivo).

Postoperative results, the clinical results showed a consistent trend of improvement, whether it was objective indicators or subjective scores. In the imaging results, except for the study done by Broeckx, S. Y in 2019, the radiographic changes were not significantly different. The rest showed improvements after the use of peripheral blood-derived stem cells. In the absence of laboratory validation, only three articles showed increased levels of cartilage-related matrix or components around damaged cartilage tissue, such as type II collagen and cartilage oligomeric matrix protein. The detailed information is shown in Table 1.

3.4 PBMSC In Vitro

In this systematic review, we included a total of seven articles from in vitro studies (Pufe et al., 2008; Casado et al., 2012; Chong et al., 2012; Kim et al., 2012; Turajane et al., 2014;...
Hopper et al., 2015b; Frisch et al., 2017b). Among them, the donors of three experiments were humans, the donors of one experiment were pigs, and the peripheral blood donors were not specified in the remaining experiments. The validation methods for in vitro experiments include scratch experiments, immunohistochemistry, flow cytometry, RT-PCR, and more.
The authors described the peripheral blood-derived stem cells used in the article, including the peripheral blood mononuclear cells, PBMSC, autologous G-CSF activated PB, and peripheral blood stem cells (PBSCs). CD105+ was found in all experiments with flow cytometry results, but CD34+ was found in all experiments by Turajane, T. et al., may indicate that the cells used in the experiments are the nonmesenchymal presence of stem cells. Other experiments uncovered the secretion of many chemokines, which may also be largely involved in the induction of cartilage repair. In terms of results, all studies have proved that the peripheral blood-derived stem cells can differentiate into cartilage and have
the potential to repair cartilage damage. Hopper, N, and Turajane, T. all found the upregulation of SOX-9 in their experiments, indicating that the peripheral blood-derived stem cells have a regulatory effect on cartilage differentiation. The formation of the extrachondral matrix was found in all in vitro studies, which is important for cartilage repair. The detailed information is shown in Table 3.

4 DISCUSSION

According to the research on stem cells derived from peripheral blood in vitro, they have the same or similar chondrogenic differentiation ability as that of the bone marrow mesenchymal stem cells in the process of culture and passage in vitro, as Chong, P. P. showed in his research. (Chong et al., 2012; Gong et al., 2021).
Combined with the human and animal research reports on its improved in vivo results, this systematic review shows that peripheral blood-derived stem cells have chondrogenic differentiation ability and can induce chondrogenic differentiation and repair in vivo, and have statistical significance in the clinical and imaging prognosis. There is improvement of academic differences. Compared with bone marrow, the peripheral blood is easier to obtain, widely sourced, and simple to obtain. In the future, peripheral blood will be a more potential cell source for cell therapy in the treatment of cartilage damage.

However, some studies have contrary results. In the study of Ying, J. et al. (Ying et al., 2020), peripheral blood-derived stem cells did not show improvement in the clinical and imaging results in the treatment of femoral head necrosis, and combined treatment in histology. The bone destruction in the group was more severe than that in the control group. But a previous study showed that combination therapy with an intra-arterial infusion of G-CSF activated PB has the potential for cartilage damaged by the peripheral blood stem cells alone may not be able to offset the overall damage caused by the inflammatory response. Moreover, in this study conducted by Ying, J. et al., although the injection of PBSCs into the internal circumflex artery did not improve the survival rate of femoral head necrosis, it had a good effect on relieving pain and improving the joint function. This result can also reflect that peripheral blood-derived stem cells have a repairing effect on intra-articular cartilage damage, although it cannot be reflected in the histology of this study (Hopson and Siverhus, 1988). This makes us think that in the treatment of some diseases with more complex mechanisms than simple cartilage damage, the use of stem cells derived from peripheral blood alone may not have a good prognosis, and more combined treatment or surgical treatment is needed. But not being able to cure the disease is not the same as denying its effect on the repair of cartilage damage.

**Figure 5.**

The cell types and potential repair mechanisms are detailed in **Figure 5, 6.** At present, the cell source used in most research is G-CSF activated PB or chondrogenic-induced PBMSCs. It has been demonstrated in the previous literature that G-CSF and CXCR4 antagonists can mobilize mesenchymal stem cells into peripheral blood (Pelus, 2008; Kolonin and Simmons, 2009). It can improve the success rate of subsequent mesenchymal stem cell culture, and the density of mesenchymal stem cells is also an important feature to evaluate cartilage repair. Moreover, in the other literature, a simple injection of G-CSF can make bone marrow and peripheral blood mesenchymal stem cells home to the joint cavity and help cartilage regeneration (Sasaki et al., 2017; Turajane et al., 2017). The literature included in this systematic review also showed that G-CSF activated PB has the potential for chondrogenic differentiation and repair and is a good alternative.
the research results subject to influence. In the statistics of cell phenotype, no further analysis was performed for the events whose cells highly expressed CD34+ and some studies did not express the mesenchymal stem cell marker CD105+. This means that, in some of the included studies, it is not only mesenchymal stem cells that perform cartilage repair, but may also be mononuclear cells or other stem cells in peripheral blood. Therefore, here, we refer to them as the peripheral blood-derived stem cells and use this fully as a resource for cartilage repair.

5 CONCLUSION

Stem cells derived from peripheral blood have the ability to repair cartilage and are an important resource for the treatment of cartilage damage in the future. The specific mechanism and way of repairing cartilage need further study.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by YZ. The first draft of the manuscript was written by YZ and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Stem cells have many advantages and can effectively treat cartilage damage; for example, they have strong self-renewal capacity, pluripotency, and plasticity. However, the properties of MSCs may be altered by various elements of the local microenvironment that influence differentiation, may cause reduced chondrogenic activity or differentiation into other tissues, so they may suffer from disadvantages such as eventual hypertrophy or tumorigenesis (Chen and Tuan, 2008; Chen, 2018; Broeckx et al., 2014a; Koh et al., 2014; Pandey et al., 2022). However, in the studies we included, adverse events were mild and there was no worsening change in the imaging findings. This may indicate that stem cells derived from peripheral blood have stable differentiation (Chong et al., 2012). This also proves our point that peripheral blood-derived stem cells are an important source of cells to repair cartilage damage.

This article also has certain limitations. In the selection of literature, due to the continuous updating of preparation methods and repair mechanisms, we only included relevant literature after 2008, excluding some studies in older periods, which may make

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