

Biologic Augmentation for the Operative Treatment of Osteochondral Defects of the Knee

A Systematic Review

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Background: Various surgical treatment options exist for repairing, replacing, or regenerating tissue to fill osteochondral defects. Biologic augmentation has been increasingly studied as an adjunct in the surgical treatment of osteochondral defects of the knee in animal and human models.

Purpose/Hypothesis: The purpose of the study was to systematically review use of platelet-rich plasma (PRP) and bone marrow concentrate (BMC) augmentation in the surgical treatment of osteochondral knee defects and to describe the outcomes. It was hypothesized that both PRP and BMC augmentation will result in improved outcomes in osteochondral knee surgery in both animal and human models.

Study Design: Systematic review.

Methods: PubMed, MEDLINE, and Embase were searched for studies relating to PRP or BMC and treatment of osteochondral defects of the knee, from database inception to February 1, 2020. Included were articles that (1) studied PRP or BMC augmentation; (2) used osteochondral autograft, allograft, or biologic scaffold; and (3) treated osteochondral defects in the knee. Data on use of PRP or BMC, outcomes assessed, and results were recorded for each publication.

Results: Of the 541 articles identified initially, 17 were included in the final review. Five articles studied osteochondral grafts in animals, 5 studied biologic scaffolds in animals, and 7 studied scaffolds or allografts in humans; the combined sample size was 202 patients. Of 4 histologic scaffold studies, 3 PRP-augmented scaffold studies identified histologic improvements in regenerated cartilage in animal models, while 1 BMC study demonstrated similar improvement in histologic scores of BMC-augmented scaffolds compared with controls. Three studies associated greater collagen type 2 and glycosaminoglycan content with PRP treatment. Comparative studies found that both augments increase osteogenic proteins, including bone morphogenetic protein-2 and osteoprotegerin. Two of 3 studies on BMC-augmented osteochondral allografts reported no difference in radiographic features postoperatively. Long-term improvement in clinical and radiographic outcomes of PRP-augmented scaffolds was demonstrated in 1 human study.

Conclusion: Animal studies suggest that biologics possess potential as adjuncts to surgical treatment of osteochondral knee defects; however, clinical data remain limited.

Keywords: osteochondral; biologics; PRP; BMP; augmentation

Osteochondral lesions of the knee are a localized abnormality of the subchondral bone and articular cartilage that can result from traumatic injury, osteochondritis dissecans, subchondral insufficiency fractures, or violation of the

subchondral bone plate from prior surgery, resulting in a spectrum of symptoms and disability.^{4,7,8,10} In some reports, up to 60% of knees may possess such defects at the time of arthroscopy.^{4,6,7,10} These can lead to pain, functional limitation, and ultimately the accelerated progression of osteoarthritis if left untreated.^{4,6,8,10,11,15,20}

Consequently, attempts have been made to repair, replace, or regenerate tissue to fill osteochondral defects

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in the knee. Various surgical treatment options exist and are continually evolving.^{4,6,8,10,11,15,20} As the field of orthobiologics begins to expand, enhancing the growth and repair potential of these lesions has attracted additional attention as well.^{2,4,10,11,15,20,23,25} Biologic adjuvants such as platelet-rich plasma (PRP) and bone marrow (aspirate) concentrate (BMC) have piqued the interest of many orthopaedic surgeons attempting to best restore native anatomy in their patients.^{2,8,23,25} Particularly when considering the young age of many of these patients, providing a durable solution that will maintain its function under high levels of activity and physical stress is of the utmost importance.^{4,8,10,11,20,23,25}

While investigation has begun into ways to enhance the healing of osteochondral defects of the knee, it is currently unclear exactly how biologic augmentation may affect clinical outcomes.^{8,23,25} It was therefore the aim of the present study to systematically review the current preclinical and clinical evidence relating to PRP and BMC augmentation in the surgical treatment of osteochondral defects in the knee. The ultimate goal was to determine the potential utility of biologics and identify the optimal substance for augmentation, with the hypothesis that both PRP and BMC will result in improved outcomes in osteochondral knee surgery.

METHODS

PubMed, MEDLINE, and Embase were searched for studies relating to PRP and/or BMC augmentation in operative treatment of osteochondral defects of the knee, published from database inception until February 1, 2020. The search terms “osteochondral,” “chondral,” “PRP,” “platelet rich plasma,” “bone marrow concentrate,” “bone marrow aspirate,” “bone marrow aspirate concentrate,” “bone marrow,” “knee,” “distal femur,” “tibia,” and “patella” were used (see Appendix 1 for detailed search strategy). Titles, abstracts, and articles were evaluated independently by 2 reviewers (D.V.C., P.D.M.) on the basis of predefined inclusion and exclusion criteria. For studies using the same patient data, only the most recent publication was included. Consensus on disagreements was reached through discussion among reviewers and, if necessary, by using a third reviewer (senior author, S.L.S.) as the tie-breaking vote.

Included in the review were articles that (1) studied PRP or BMC augmentation (2) using osteochondral autograft, allograft, or biologic scaffold to (3) treat osteochondral defects in the knee. Excluded were articles that (1) studied

chondral-only defects or defects outside of the knee, (2) did not use osteochondral graft or biologic scaffold, or (3) were review articles, meta-analyses, technique articles, or case reports. For studies reporting on identical cohorts at multiple time points, each publication was included.

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria were used to guide reporting from those studies that met all of the above criteria. Kappa statistics were calculated for each stage of screening to quantify interreviewer agreement: 0.81-0.99, excellent; 0.61-0.80, substantial; 0.41-0.60, moderate; 0.21-0.40 fair; and ≤ 0.20 , slight. Agreement and/or disagreement was calculated based on initial results obtained by each reviewer before discussion of specific studies.

The 2 reviewers collected data regarding defect specifications, use of BMC or PRP, graft/scaffold characteristics, outcomes assessed, and results of each publication. Studies were organized by participant type (animal/in vitro vs human) and use of graft versus scaffold. Outcomes were categorized as microscopic, protein expression, cytokine expression, macroscopic, clinical, or radiographic.

RESULTS

After removal of duplicate search results, 541 publications were identified for potential inclusion. After review of titles and abstracts, 42 full-text manuscripts were screened, and 17 articles were identified that satisfied all inclusion and exclusion criteria. The results of the review process are presented in Figure 1. The kappa statistics for interreviewer agreement were 0.89 and 0.91 for the abstract and manuscript stages, respectively, indicating excellent agreement at both stages.

Pertinent aspects of the included studies are summarized in Appendix Tables A1 to A3. Five studies investigated osteochondral grafts (4 autograft^{3,5,16,22}; 1 allograft²⁴) and 5 examined biologic scaffolds (3 polylactic-co-glycolic acid [PLGA],^{9,25,28} 1 collagen,²⁶ and 1 both PLGA and collagen/glycosaminoglycan [CGAG]¹²) in nonhuman participants. Of these 10 nonhuman studies, 8 used rabbits,^{3,5,9,16,22,25,26,28} 1 used dogs,²⁴ and 1 in vitro as the study specimen.¹² Eight studied PRP,^{3,5,9,12,16,22,25,28} 1 studied BMC,²⁶ and 1 studied both PRP and BMC augmentation.²⁴ Of the 7 human studies, 4 reported data on human patients treated with scaffolds.^{15,19-21} One study presented 12-month follow-up results in 23 patients comparing BMC and PRP,¹⁵ and 3 presented subsequent results of a single 52-patient cohort treated with PRP at

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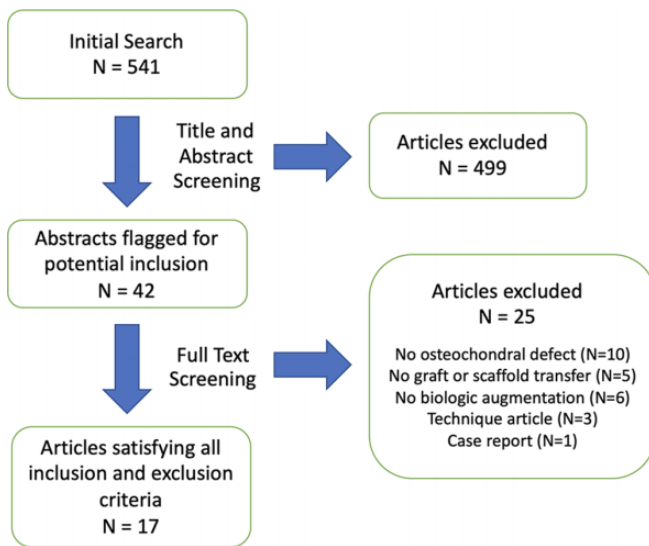


Figure 1. Results of the search process for articles included in this review following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

multiple time points ranging from 3 months to 5 years postoperatively.¹⁹⁻²¹ The remaining 3 human studies investigated BMC augmentation of osteochondral allografts, with 6 to 12 months of follow-up.^{1,18,27}

Microscopic Examination Results

Eight animal studies reported results of postoperative microscopic examination.^{3,5,16,22,24-26,28} Four studies^{3,5,16,22} found that treatment of osteochondral autografts with PRP during surgery resulted in short-term improvements over controls. Enhancements were specifically noted in histologic integration and surface regularity that were reflected in the histological scoring systems used by the respective authors. However, in all 3 studies that tested for differences at multiple time points, significant differences were noted only at 3 weeks and were not sustained at longer-term follow-up of 6 to 12 weeks. One study by Stoker et al²⁴ examined osteochondral allografts from dogs treated with either PRP, BMC, or saline. BMC resulted in higher colony-forming unit (CFU) concentration than PRP and yielded viable cells in both deep and superficial portions of the graft. On the other hand, neither PRP nor saline resulted in viable cells in any part of the osseous portion of the grafts.

Two articles published comparisons of PLGA scaffold implantation with and without PRP augmentation.^{25,28} Both noted significant differences in the results at 4 and 12 weeks postoperatively. Higher histological scores were found by Sun et al²⁴ and Zhang et al²⁸ at both time points, and both studies noted the increased presence of chondrocyte-like cells and hyaline-like cartilage in the PRP-augmented groups compared with controls. One publication by Chang et al⁹ compared results of treating osteochondral defects in the trochlear grooves of rabbits with either PRP, PRP and PLGA scaffold, or PRP, PLGA

scaffold, and continuous passive motion (CPM). PRP alone resulted in fibrous tissue with inflammatory cells and some persistent defects, while PRP with scaffold yielded fibrocartilaginous tissue with some chondroblasts and small chondrocytes in a newly formed chondral layer. The addition of CPM led to the production of a smoother articular surface, with improved chondrocyte alignment and mature bone and vasculature in the subchondral region. One additional study evaluated the microscopic results of BMC augmentation of collagen scaffold implantation, finding statistically significant improvements in histological scores and improved appearance and organization of hyaline cartilage at both 3 and 6 months.²⁶

Siclari et al¹⁹⁻²¹ performed histologic examinations in 52 humans treated with polyglycolic acid–hyaluronan scaffold immersed in PRP. Notably, all 52 patients were also treated with bone marrow stimulation before PRP treatment. They found good integration of the scaffold, with hyaline-like cartilage in the defects after 9 months and predominantly hyaline cartilage rich in chondrocytes at further follow-up examination between 18 and 24 months postoperatively.

Protein Expression

Six studies analyzed protein expression at the defect sites.^{9,16,19-22,25,28} Among the 2 studies that used osteochondral autografts,^{16,22} 1 noted that PRP resulted in increased presence of type 2 collagen and glycosaminoglycan compared with controls.²² The other reported greater safranin-O staining at 3 weeks resulting from insertion of a platelet-rich fibrin clot into the osteochondral defect before graft placement, but no differences in safranin-O or type 2 collagen staining at 12 weeks.¹⁶

The 2 studies that compared PLGA scaffold with and without PRP augmentation found that PRP resulted in higher expression of type 2 collagen, safranin-O, and aggrecan than scaffold alone.^{25,28} Differences in type 2 collagen expression were sustained at the 12-week follow-up.^{25,28} In a comparison of PRP with and without PLGA scaffold, Chang et al⁹ reported higher glycosaminoglycan content and type 2 collagen content in the PRP scaffold group at both 4 and 12 weeks postoperatively. The addition of CPM further increased both glycosaminoglycan and type 2 collagen expression and decreased type 1 collagen expression at both time points as well. In their comparative study of BMC applied to collagen scaffolds versus scaffold alone, Veronesi et al²⁶ found significant decreases in type 1 collagen at 3 months and increases in type 2 collagen associated with BMC augmentation at 3 and 6 months postoperatively.

Siclari et al¹⁹⁻²¹ reported that PRP and bone marrow stimulation in addition to scaffold implantation in humans yielded high expression of proteoglycans and type 2 collagen. However, no control participants were evaluated for comparison in this study.

Cytokine Expression

Cytokine expression was evaluated in 5 studies.^{5,9,12,13,24} Boakye et al⁵ reported that chondrocyte expression of transforming growth factor–beta 1 (TGF- β 1) was higher

at all time points (3, 6, and 12 weeks) after augmentation of osteochondral autografts with PRP. No significant differences were identified between PRP augmentation and controls with respect to synovial expression of TGF- β 1 in this study, but synovial expression of TGF- β 1 was significantly associated with a decrease in histological appearance of the graft and defect postoperatively.⁵ Chang et al⁹ found that PRP applied alone to osteochondral defects resulted in high expression of tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and matrix metalloproteinase-3 (MMP-3), with the addition of PLGA scaffold decreasing these to modest levels at 12 weeks postoperatively. Combining PRP, scaffold, and CPM further decreased the levels of these proinflammatory cytokines at both 4 and 12 weeks compared with the other treatment groups.⁹ Getgood et al¹² compared PRP with and without PLGA or CGAG scaffolds in vitro, finding that fibroblast growth factor-2, platelet-derived growth factor-AB (PDGF-AB), and TGF- β 1 each demonstrated a burst release pattern in the initial 24 hours and that PRP with scaffold resulted in greater growth factor production than PRP alone. Additionally, their results suggest that CGAG scaffold may result in greater PRP activation than PLGA scaffold based on an increase found in PDGF-AB release.¹² In comparisons of collagen scaffold with or without BMC, an association was identified between BMC addition and both increased insulin growth factor-1 and decreased MMP-1 expression.²⁶ Stoker et al²⁴ used osteochondral allografts from dogs to compare treatment with BMC, PRP, and saline and found that both BMC and PRP increased the expression of osteogenic proteins, bone morphogenetic protein-2 (BMP-2), and osteoprotegerin (OPG), compared with controls after 3 days of culture. BMC also resulted in higher expression of Dickkopf-related protein-1 (DKK-1) at 3 days after treatment.²⁴ However, only BMC maintained increased release of BMP-2 and OPG after 7 days, while no significant differences were found between PRP-treated groups and controls at this time point.²⁴

Macroscopic Examination

Macroscopic examination was performed in 7 studies.^{3,9,16,22,25,26,28} None of the 3 that compared osteochondral autograft with and without PRP found significant differences in the macroscopic appearance of grafts during examination between 6 and 12 weeks postoperatively.^{3,16,22} However, among the 2 that evaluated PLGA scaffold implantation with and without PRP, both found improved gross integration with less distinct margins between defect and surrounding cartilage in the PRP-treated animals at the 12-week examination.^{25,28} Chang et al⁹ quantified tissue repair in rabbits based on combined histological and gross appearances and found significant differences at 4 and 12 weeks favoring PRP with PLGA scaffold and CPM over either PRP with scaffold or PRP alone. PRP with scaffold also scored significantly higher in the tissue repair score than PRP alone at both time points.⁹ Finally, Veronesi et al²⁶ examined osteochondral defects in rabbits and reported significant improvements in International Cartilage Regeneration & Joint Preservation Society

(ICRS) scores associated with BMC augmentation of collagen scaffolds at both 3 and 6 months.

Clinical Results

Clinical outcomes were available from only a single cohort published at 3 different time points by Siclari et al.¹⁹⁻²¹ Using the Knee injury and Osteoarthritis Outcome Score (KOOS) in 52 patients treated with scaffold augmented with PRP and bone marrow stimulation, they reported statistically significant and clinically meaningful improvements in all KOOS subcategories at 3 months, which continued to progress until 12 months postoperatively.¹⁹⁻²¹ These improvements were sustained at 2 and 5 years, with their overall mean KOOS of 50.3 preoperatively and 85.0 at 5 years postoperatively.¹⁹⁻²¹

Radiographic Results

Four studies published results of postoperative microtomography after implantation of scaffolds in rabbits.^{9,25,26,28} Both articles that compared PLGA scaffold with or without PRP found greater subchondral bone formation in the PRP-treated groups.^{25,28} Chang et al⁹ found greater mineralization and bone volume/tissue volume ratios in their combined treatment group using PRP, PLGA scaffold, and CPM compared with PRP alone. Veronesi et al²⁶ similarly identified improvements in this ratio through augmentation of collagen scaffold with BMC.

Siclari et al¹⁹⁻²¹ used MOCART (magnetic resonance observation of cartilage repair tissue) scores applied by a radiologist to conclude that 20 of 21 human knees treated with PLGA scaffold and PRP augmentation had excellent radiographic results 4 years postoperatively. Two studies found no difference on 6-month magnetic resonance imaging (MRI) according to the Osteochondral Allograft MRI Scoring System (OCAMRISS) in patients treated with osteochondral allograft and BMC augmentation compared with allograft alone.^{1,27} One study by Wang et al²⁷ also obtained MRI scans at 12 months and again identified no difference in OCAMRISS scores. In another study of BMC augmentation of osteochondral allograft implantation, Oladeji et al¹⁸ evaluated radiographs and identified higher scores for graft integration associated with BMC augmentation at 6 weeks, 3 months, and 6 months. They additionally reported decreased graft sclerosis in the BMC-treated group, but this was statistically significant only at 6 weeks and 3 months postoperatively.¹⁸

Krych et al¹⁵ qualitatively and quantitatively compared 12-month postoperative MRI results among 23 human patients treated with either scaffold, scaffold augmented with PRP, or scaffold augmented with BMC. Qualitatively, PRP and BMC groups were found to have superior cartilage filling compared with controls, with no differences between the 3 groups in bony incorporation.¹⁵ Quantitative T2 mapping revealed that there was no difference between PRP and control groups, but BMC resulted in mean values significantly closer to those of superficial hyaline cartilage than either of the other treatments.¹⁵

DISCUSSION

The present systematic review suggests that PRP and BMC augmentation may enhance the outcomes of surgical treatment of osteochondral defects of the knee when scaffold implantation is employed, as evidenced by postoperative microscopic, macroscopic, and radiographic examinations in animal studies. However, clinical data remain limited. PRP does not appear to enhance the outcomes of osteochondral transfer in a sustained manner, and there exists mixed evidence regarding the effect of BMC in these operations. While there also exists significant heterogeneity in the ways in which these biologics were utilized and outcomes were assessed, there are a number of scientifically and clinically meaningful conclusions that can be drawn by researchers and orthopaedic surgeons when considering all of the evidence in aggregate.

First, it appears that PRP affects outcomes of osteochondral graft transfer differently than biologic scaffold implantation.^{3,5,9,15,19-22,24,25,28} PRP augmentation results in short-term improvements in the microscopic and macroscopic appearances of defects, as well as protein expression profiles, in both osteochondral graft and biologic scaffold implantation.^{3,5,9,15,20,22,24,25,28} However, PRP appears to have sustained impact only on those scaffolds. On microscopic examination, short-term enhancements were noted with the addition of PRP to osteochondral graft transfer, but were not sustained at longer-term follow-up of 6 to 12 weeks in animal models.^{3,5,14,16,22,24,25,28} Microscopic examination after scaffold implantation augmented with PRP, on the other hand, resulted in higher histological scores and increased the presence of chondrocyte-like cells and hyaline-like cartilage at both short- and long-term follow-up.^{3,5,16,22,24,25,28} Macroscopic examination appeared to reveal a similar trend.^{3,5,16,25,28} None of the 3 studies comparing osteochondral autograft with and without PRP augmentation identified significant differences in the gross appearances of the surgical site during postoperative examinations at 6 to 12 weeks.^{3,16,22} Conversely, both studies that tested PLGA scaffold implantation with and without PRP augmentation found significant improvements in the appearances of the PRP-treated groups at 12 weeks.^{25,28} This trend is further supported by protein expression profiles, which demonstrated that PRP augmentation of osteochondral grafts yielded higher safranin-O staining and type 2 collagen expression at short-term examination, but no differences at 12-week testing.^{9,16,20,22,25,28} Meanwhile, for PLGA scaffold implantation, similar short-term increases resulted from PRP augmentation in the expression of type 2 collagen, safranin-O, and aggrecan, but the increase in type 2 collagen was sustained at 12 weeks.^{9,16,20,22,25,28}

There appears to be a similar theme presenting in the limited data obtained for BMC augmentation.²⁶ Collagen scaffold treated with BMC before implantation in rabbits yielded improved macroscopic and microscopic results at 3 and 6 months, along with more favorable protein and cytokine expression profiles.²⁶ However, in 3 clinical studies of BMC treatment of osteochondral allografts,^{1,18,27} 2 found

no MRI differences in the appearance of cartilage, degree of osseous integration, or appearance of relevant ancillary features, including subchondral cysts at the graft-host junctions.^{1,27} The third study did report improvements in degree of graft integration and sclerosis in the BMC-augmented group, but it used radiographs rather than advanced imaging modalities.¹⁸

The reasons for these findings are as of yet unclear, but they are noteworthy as evidence of key differences between the interactions of PRP and BMC with grafts versus scaffolds in the surgical treatment of osteochondral defects. Based on these results, it would appear that both PRP and BMC augmentation have some impact on osteochondral defects treated with scaffolds, while their effects may be more limited when osteochondral defects are treated with osteochondral grafts.^{8,11-19,21,25-27}

In this review, the use of PRP and BMC appears to have a positive impact on the osseous integration of scaffolds and regeneration in the area of the defect, as demonstrated by multiple studies evaluating results of microtomography.^{9,25,26,28} Also noteworthy is that there likely exists a synergistic effect between PRP and biologic scaffolds, as demonstrated by the decrease in proinflammatory cytokines TNF- α and IL-6, as well as in MMP-3 when PRP and scaffold are combined.^{9,12} Furthermore, the *in vitro* study by Getgood et al¹² appears to confirm that both PRP and scaffold are needed in combination for optimal growth factor release.

The question of whether to augment operative treatment of osteochondral lesions with biologics in humans cannot be definitively answered from these data alone. However, the data suggest that PRP and BMC may play a beneficial role in the treatment of osteochondral defects with scaffold implantation. Still, there remains the clinically relevant question of which option, prepared in which way, is the optimal choice of biologic adjunct to such treatment. Although extensive comparative data are lacking, the protein and cytokine expression profiles identified by Stoker et al²⁴ suggest that BMC may result in an increased, sustained release of osteogenic proteins when interacting with osteochondral allograft that is greater than that associated with PRP. Additionally, BMC augmentation was found to yield a greater number of viable cells on and in the osseous portions of grafts.²⁴ However, this has not necessarily manifested as a positive difference in the clinical literature, as recent clinical publications by Ackermann et al¹ and Wang et al²⁷ have demonstrated no differences in any OCAMRISS scores in humans when evaluating graft integration using comparative imaging analysis of osteochondral allograft with and without BMC augmentation. Furthermore, a recent systematic review and critical analysis of the evidence regarding BMC treatment of chondral lesions in the knee reported inconsistent outcomes from animal studies and clinical studies that were limited in both quality and quantity on the topic.⁷

The cohort treated by Siclari et al¹⁹⁻²¹ obtained excellent clinical, radiographic, and histologic outcomes with their use of scaffold and PRP at a follow-up of 5 years, but all patients were also treated with bone marrow stimulation.

Additionally, no control group was included, which unfortunately limits the ability to identify the extent to which any single factor of the treatment protocol contributed to their very promising outcomes.¹⁹⁻²¹ The comparative study performed by Krych et al,¹⁵ although limited by its lack of clinical correlation, does suggest that while both PRP and BMC augmentation of scaffold implantation appear to improve cartilage fill, BMC may be more efficacious in yielding articular cartilage most similar to that of a native knee.

The present review contributes to the understanding of biologic augmentation in the operative treatment of osteochondral defect of the knee. However, it is not without its own limitations. There was significant variability in the ways in which biologics were applied, and there was limited standardization of the biochemical composition and preparation of PRP or BMC used in each study. In the 14 studies using PRP, 6 studies^{9,16-21} published the platelet count and leukocyte concentration of the prepared PRP, and 1 study²⁴ described the PRP preparation as “leukocyte-reduced” without providing measurements. Specifically, the average platelet count was $713 \times 10^3/\mu\text{L}$ (range, $199 \times 10^3/\mu\text{L}$ to $1190 \times 10^3/\mu\text{L}$), and the average leukocyte concentration was $4.24 \times 10^3/\mu\text{L}$ (range, $0.92 \times 10^3/\mu\text{L}$ to $6.1 \times 10^3/\mu\text{L}$). The remaining 7 PRP studies^{3,5,12,15,22,25,28} only referenced the manufacturer protocol to describe their methods of PRP preparation. Meanwhile, of the 4 studies investigating BMC, only Oladeji et al¹⁸ reported their quantitative evaluation of the bone marrow in terms of CFUs, reporting an average of 36 CFUs/mL in BMC; the remaining articles^{1,15,27} cited only the manufacturer protocol for the aspiration kit. The heterogeneity in preparing PRP and BMC highlights the continued need for standardizing how authors report the composition of the biologics. Furthermore, variation existed in the postoperative rehabilitation protocol for the human studies with regard to immediate postoperative weightbearing status (non-weightbearing vs toe-touch weightbearing), use of a CPM machine, and timeline progression to full return to recreational activity (range, 6 weeks–8 months).^{1,15,19-21,27}

By employing predefined inclusion and exclusion criteria to our systematic review, we attempted to address these limitations and biases, recognizing that there does still exist some degree of expertise and spectrum bias, particularly in the clinical studies included here. Nevertheless, this review does summarize the most current knowledge on a topic of clinical relevance and ongoing research activity and establishes the foundation upon which future studies may build.

Further work is needed to more accurately determine the true impact of biologics on the treatment outcomes for these injuries. Establishing standardized manufacturing methods and biochemical profiles of PRP and BMC would address the heterogeneity of biologic treatments and allow for more meaningful comparisons between studies. Additionally, clinical studies are limited in quantity but would likely be of substantial benefit, especially if comparisons can be made between PRP and BMC as forms of augmentation.

CONCLUSION

Although current data were limited, studies of PRP and BMC augmentation suggest that they may enhance the outcomes of surgical treatment of osteochondral defects of the knee when scaffold implantation is employed, as evidenced by postoperative microscopic, macroscopic, and radiographic examinations in animal studies.

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APPENDIX

Appendix 1. Search Strategy

PubMed Strategy: (((osteochondral OR chondral))) AND ((prp OR platelet rich plasma) OR (bone marrow concentrate OR bone marrow aspirate OR bone marrow aspirate concentrate OR bone marrow)) AND ((knee OR distal femur OR tibia OR patella))

Retrieved: 439 results

Embase Strategy: (((osteochondral OR chondral))) AND ((prp OR platelet rich plasma) OR (bone marrow concentrate OR bone marrow aspirate OR bone marrow aspirate concentrate OR bone marrow)) AND ((knee OR distal femur OR tibia OR patella)) AND [embase]/lim

Retrieved: 487 results

MEDLINE Strategy: (((osteochondral OR chondral))) AND ((prp OR platelet rich plasma) OR (bone marrow concentrate OR bone marrow aspirate OR bone marrow aspirate concentrate OR bone marrow)) AND ((knee OR distal femur OR tibia OR patella)) AND [medline]/lim

Retrieved: 322 results

TABLE A1
Osteochondral Grafts: Basic Science Articles^a

Lead Author (Year)	Study Group	Graft/ Scaffold	Defect	Biologic Use	Outcome	Result	Conclusions
Altan (2014) ³	6 rabbits	Osteochondral autograft	Femoral groove of PF joint ($\phi = 4$ mm, depth = 4 mm)	(1) 1 mL PRP into defect before fixation (2) 1 mL PRP into joint after closure	(1) Microscopic exam - Pineda's histological grading (2) Macroscopic exam - regularity, continuity, arthritic change	(1) Microscopic 3 wk: PRP: Better histologic integration ($P < 0.05$); 6/6 sufficient regeneration, integration Control: 4/6 thinner cartilage ($P < 0.05$) 6 wk: no difference; 100% excellent interdigitation w/host (2) Macroscopic 3 wk: PRP group: shiny white, no arthritic changes Control: 1/6 linear margin, 2/6 superficial fissures and opaque white 6 wk: Similar appearance	PRP may stimulate local healing response.
Boakye (2015) ⁵	12 rabbits	Osteochondral autograft	Weightbearing portion of lateral femoral condyle ($\phi = 2.7$ mm, depth = 5 mm)	(1) 0.5 mL PRP into joint (2) Graft soaked in PRP $\times 10$ min before implantation	(1) Chondrocyte TGF- $\beta 1$ expression (2) ICRS Score (3) Synovial TGF- $\beta 1$ expression	(1) PRP: Higher percentage of chondrocytes positive for TGF- $\beta 1$ at all time points ($P \leq 7.3 \times 10^{-3}$) (2) PRP: Higher ICRS score (18.2 vs 13.5, $P = 2 \times 10^{-3}$) (3) Synovium positive for TGF- $\beta 1$ associated w/lower ICRS Score (14.6 vs 18.3, $P = 8 \times 10^{-3}$) (4) Synovium positive for TGF- $\beta 1$ - PRP 6/12, Control 4/12 (not significant)	Adjunctive PRP increases TGF- $\beta 1$ expression by chondrocytes.
Maruyama (2017) ¹⁶	6 rabbits	Osteochondral autograft	Patellar groove ($\phi = 5$ mm, depth = 2 mm)	1 mL PRP into joint after closure	(1) Macroscopic exam - ICRS Score (2) Microscopic exam - Histologic Scoring System (Niederauer et al)	(1) Macroscopic 3 wk: PRF: Higher ICRS scores (PRF 6.6, PRP 5.0, control 4.8, $P = 4 \times 10^{-3}$); no difference between PRP and control 12 wk: All grafts integrated and similar to host No differences in ICRS scores (PRF 11.5, PRP 11.7, control 11.2, $P = 0.98$) (2) Microscopic 3 wk: PRF: normal cellularity, higher safranin O ($P < 0.05$) than PRP, control -PRF: Higher histologic scores (PRF 26.3, PRP 22.6, Control 23.1, $P = 4 \times 10^{-3}$) -PRP, PRF: Surface regularity better than control ($P < 0.05$) -PRF: superior structural integrity to PRP ($P < 0.05$) -All groups: normal type II collagen staining on graft cartilage 12 wk: All groups: normal type II collagen, safranin O staining, cartilage thickness of graft cartilage; normal subchondral bone and bony integration No differences in histologic scores (PRF 27.0, PRP 27.6, control 26.9; $P = 1.0$)	(1) PRF improved microscopic and macroscopic appearance of graft cartilage compared to PRP and controls at 3 wk, with no differences identified at 12 wk. (2) Benefit of OAT with PRP augmentation was not confirmed.
Smyth (2013) ²¹	12 rabbits	Osteochondral autograft	Weightbearing portion of lateral femoral condyle ($\phi = 2.7$ mm, depth = 5 mm)	(1) 0.5 mL PRP into joint (2) Graft soaked in PRP $\times 10$ min before implantation	(1) Macroscopic exam - ICRS Score (2) Microscopic exam - Modified ICRS Histological Scoring System	(1) Macroscopic PRP: Higher ICRS score, but not significant (11.2 vs 10.3, $P = 0.09$) PRP: Less fissuring and fibrillation compared to controls PRP: Grossly hypertrophied synovium (2) Microscopic PRP: Higher histological score overall (18.2 vs 13.5, $P = 2 \times 10^{-3}$) PRP: Higher histological score at each time point, but only significant at 3 wk PRP: Higher graft integration score (2.5 vs 1.6, $P = 4 \times 10^{-3}$) PRP: Greater type-II collagen immunoreaction, increased glycosaminoglycan content	PRP may improve integration of osteochondral autograft at cartilage interface.
Stoker (2018) ²³	12 dogs	Osteochondral allograft	—	Grafts: ($\phi = 8$ mm, depth = 8 mm) harvested from canine femur Stored for 21 d, osseous portion irrigated w/10 mL saline, dried, saturated w/0.5 mL PRP or BMC	(1) CFU analysis (2) Viable cell colonization (3) Media analysis	(1) CFU BMC higher CFUs/mL than PRP ($P = 0.029$) (2) Viable cell colonization BMC: all grafts had detectable viable cells on surface and in deep area of osseous portion PRP, control: no grafts with viable cells in any part of osseous portion (3) Media analysis BMP-2: Higher in BMC, PRP than controls at day 3; Higher in BMC than controls at day 7 DKK-1: Higher in BMC than controls at day 3 OPG: Higher in BMC, PRP than controls at day 3; Higher in BMC than controls at day 7; Higher in BMC than PRP at day 7 ALP: Lower in PRP than controls at day 3 ACTH: No differences BMP-7, OPN: Below detectable limits	(1) BMC may enhance the osseous integration potential of osteochondral allograft compared to PRP and controls. (2) BMC treatment increases the viable cells on and in the osseous portion of grafts, while PRP does not. (3) Both BMC and PRP treatments increase the delivery of osteogenic proteins compared to controls, although the increase is more sustained with BMC than PRP.

^aACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; BMC, bone marrow concentrate; BMP, bone morphogenetic protein; CFU, colony forming units; DKK-1, Dickkopf-related protein-1; ICRS, International Cartilage Repair Society; OAT, osteochondral autograft transplantation; OPG, osteoprotegerin; OPN, osteopontin; PF, patellofemoral; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; TGF- $\beta 1$, transforming growth factor- $\beta 1$.

TABLE A2
Biologic Scaffolds: Basic Science Articles^a

Lead Author (Year)	Study Group	Graft/ Scaffold	Defect	Biologic Use	Outcome	Result	Conclusions
Chang (2018) ⁹	52 rabbits (PG = 16 PP = 16 PPC = 20)	PLGA scaffold	Femoral trochlear groove (Ø = 3 mm, depth = 3 mm)	(1) PRP gel (PG group) (2) PRP + PLGA scaffold (PP group) (3) PRP + PLGA scaffold + CPM (PPC group)	(1) Micro-CT (2) Histology (3) Protein cytokine expression (4) Tissue repair score (combined histological and gross appearances)	(1) Micro-CT 4 wk: All groups: osseous tissue developed from outer area to center of defect - PPC: Greater bone volume/tissue volume ratio than PG 12 wk: PPC: Greater bone volume/tissue volume ratio, more mineral tissue at defect center than PG (2) Histology 4 wk: PPC: more chondroblasts, tissue coverage; more osteoid matrix, angiogenesis in repaired subchondral bone layer - PG, PP: disorganized fibrous tissue, fibroblast-like cells 12 wk: PPC: smoother articular surface, sound chondrocyte alignment, minimal inflammatory cells, mature trabecular bone with osteocytes and vasculature in subchondral bone region - PP: fibrocartilaginous tissue, chondroblasts, chondrocytes in newly formed chondral layer, disoriented collagen fibers - PG: persistent hollow defects w/fibrous tissue; inflammatory cells, osteoclasts (3) Protein/cytokine expression 4 wk: PPC: Higher GAG, COL II; Modest COL I, TNF- α , IL-6, MMP-3 - PG, PP: Less GAG; Higher COL I, TNF- α , IL-6, MMP-3 12 wk: PPC: Abundant GAG; High COL II; Modest COL I, TNF- α , IL-6, MMP-3 - PP: Moderate GAG - PG: Low GAG in repair site, loss of GAG in adjacent host cartilage; Highest COL I, TNF- α , IL-6, MMP-3 (4) Tissue repair scores 4 wk: PPC > PP > PG (15.9 vs 11.3 vs 6.8, P<0.02) 12 wk: PPC > PP > PG (26.1 vs 18.7 vs 10.7, P<0.02)	(1) PRP combined with biologic scaffold and continuous passive motion yields promising outcomes for tissue regeneration of osteochondral defects. (2) PRP in addition to scaffold results in better outcomes than PRP alone, but both may result in defect repair without significant regeneration.
Getgood (2011) ¹²	3 in vitro	(1) CGAG scaffold (2) PLGA scaffold	—	(1) Scaffold + 500 μ L PRP (2) Scaffold + 450 μ L PRP + 50 μ L bovine thrombin (3) Scaffold + 375 μ L PRP + 125 μ L autologous thrombin (4) 500 μ L PRP alone (no scaffold) Each sample then incubated, cultured	Expression of: (1) FGF-2 (2) PDGF-AB (3) TGF- β 1	(1) FGF-2 PRP + scaffold: greater release than in PRP + scaffold + autologous thrombin from 24 h onward PRP + scaffold: no significant difference in FGF-2 release compared to PRP + scaffold + bovine thrombin (2, 3) PDGF-AB, TGF- β 1 Increased release of each with scaffold-only versus with scaffold and thrombin at all time points (1-3) All growth factors show burst release pattern in initial 24 h (4) Scaffold comparison Increased PDGF-AB release in PRP + CGAG scaffold versus PRP+PLGA scaffold at all time points Minimal PDGF release in absence of scaffold	(1) Thrombin is not necessary for maximum PRP activation when used in conjunction with scaffold. (2) CGAG scaffold may result in greater PRP activation than PLGA scaffold. (3) PRP alone is not as active as PRP in conjunction with scaffold.
Sun (2009) ²⁴	16 rabbits	PLGA Scaffold	Femoral trochlear groove (Ø = 5 mm, depth = 4 mm)	PLGA scaffold + 20 μ L human thrombin + 80 μ L PRP	(1) Macroscopic examination (2) Micro-CT (3) Histology	(1) Macroscopic examination 4 wk: PRP+PLGA and PLGA only had similar appearances 12 wk: PRP+PLGA: no distinct margins; good gross integration - PLGA only: defects filled w/fibrocartilaginous tissue; clear margins - Untreated: irregular surface of defect; arthritic change adjacent (2) Micro-CT PRP+PLGA had greatest subchondral bone formation at 12 wk (3) Histology 4 wk: PLGA only: immature repair tissue; No safranin O staining - PRP+PLGA: neochondrogenesis within void; high safranin O staining; chondrocyte-like cells w/lacunae - Untreated: Fibrous tissue w/some new bone in defect 12 wk: PRP+PLGA: defects fully filled with regenerated tissue similar to hyaline cartilage; good integration with surrounding cartilage; +collagen II staining - PLGA only: Scaffolds completely absorbed; fibrocartilage in defect	(1) PRP combined with PLGA scaffold yielded promising results in regeneration of osteochondral defect. (2) Scaffold alone does not successfully regenerate osteochondral defect.

(Continued)

Lead Author (Year)	Study Group	Graft/ Scaffold	Defect	Biologic Use	Outcome	Result	Conclusions
Zhang (2017) ²⁷	6 rabbits	PLGA Scaffold	Medial femoral condyle (Ø =4 mm, depth = 4 mm)	PLGA scaffold + 80 µL PRP	(1) Macroscopic examination (2) Histology (3) Immunohistochemical Evaluation (4) qPCR (5) Micro-CT	(1) Macroscopic examination 4 wk: PRP+PLGA and PLGA only had similar appearances 12 wk: PRP+PLGA: no distinct margins; good gross integration; hyaline cartilage appearance - PLGA only: obvious margins; less smooth than PRP+PLGA group - PRP+PLGA: higher scores than PLGA only or untreated at both time points (2) Histology PRP+PLGA: higher O'Driscoll scores than PLGA and untreated at both time points ($P<0.015$) 4 wk: PRP+PLGA: neocartilage evident 12 wk: PRP+PLGA: significantly more cartilage and chondrocyte-like cells than PLGA and untreated groups (3) Immunohistochemical evaluation PRP+PLGA: highest expression of collagen II (4) Quantitative PCR PRP+PLGA: greater collagen II, aggrecan than PLGA only ($P\leq 0.002$) No significant differences in collagen I expression (5) Micro-CT All groups: subchondral bone regeneration detected; greatest in PRP+PLGA group	(1) PRP combined with PLGA scaffold yielded promising results in regeneration of osteochondral defect. (2) Scaffold alone does not successfully regenerate osteochondral defect.
Veronesi (2019) ²⁵	12 rabbits	Collagen Scaffold	Medial femoral condyle (3x5 mm)	Collagen scaffold + 1 mL BMC	(1) Macroscopic examination (2) Histology (3) Immunohistochemical evaluation (4) Micro-CT	(1) Macroscopic examination SC-BMC highest ICRS Score at both time points 3 mo: ICRS score: SC+BMC greater than SC (10.33 vs 5.33) 6 mo: ICRS score: SC+BMC greater than SC (11.33 vs 4.83) (2) Histology 3 mo: SC-BMC: highest O'Driscoll score ($P<0.05$ vs all groups) - SC, SC+MSCs, SC+SN-MSCs: fibrous tissue, no hyaline-like cartilage - SC+BMC: cartilaginous tissue w/organized cells - SC+SN-BMC: fibrous tissue, chondrocyte clustering at native edges 6 mo: SC-BMC: significantly better score than control ($P<0.05$) - SC+BMC: hyaline cartilage, normal cell organization - SC+SN-BMC: greater cartilage organization except at center of defect where minor organization seen - SC+MSC, SC+SN-MSC: fibrocartilaginous tissue with no cartilage ECM except at edges (3) Immunohistochemistry 3 mo: All treatments significantly less type I collagen than scaffold alone 3 mo, 6 mo: SC-BMC higher type II collagen than scaffold alone - SC-BMC: higher IGF-1, lower MMP-1 than scaffold (4) Micro-CT Bone volume/tissue volume: SC+BMC highest at both time points 6 mo: SC less than all other treatment options ($P<0.005$)	(1) BMC was the most beneficial augmentation method by macroscopic, histological, and micro-CT. (2) All forms of augmentation were superior to scaffold alone.

^aBMC, bone marrow concentrate; CGAG, collagen/glycosaminoglycan scaffold; COL, collagen; CPM, continuous passive motion; CT, computed tomography; FGF, fibroblast growth factor; GAG, glycosaminoglycan; IGF-1, insulin growth factor-1; IL, interleukin; MMP, matrix metalloproteinase; MSC, mesenchymal stem cells; PDGF-AB, platelet-derived growth factor-AB; PG, Platelet-rich plasma gel group; PLGA, polylactic-co-glycolic acid; PP, platelet-rich plasma and polylactic-co-glycolic acid scaffold group; PPC, platelet-rich plasma and polylactic-co-glycolic acid scaffold group with continuous passive motion group; PRP, platelet-rich plasma; qPCR, quantitative polymerase chain reaction; SC, collagen scaffold; SN, surnatant; TGF-β1, transforming growth factor-beta 1; TNF-α, tumor necrosis factor-alpha.

TABLE A3
Osteochondral Grafts and Biologic Scaffolds: Clinical Studies^a

Lead Author (Year)	Study Group	Graft/Scaffold	Defect	Biologic Use	Outcome	Result	Conclusions
Krych (2016) ¹⁵	23 humans	PLG scaffold	Outerbridge 3 or 4 Femoral lesion 1.5-6 cm ² (avg 3.92 cm ²)	(1) Scaffold soaked in PRP (2) PRP added to base of defect	(1) Qualitative MRI cartilage assessment (2) Quantitative T2 mapping (3) Qualitative assessment of bony incorporation	(1) Qualitative cartilage assessment PRP, BMC: superior cartilage fills compared to control (2) Quantitative T2 mapping PRP vs control not significant (49.1 vs 42.7 ms, P=0.07) BMAC significantly higher than PRP and control (60.5 vs 49.1 vs 42.7 ms, P=0.01) (3) No differences identified in qualitative assessment of bony incorporation	(1) PLG scaffold augmented with BMC shows greatest fill and maturation of cartilage with T2 values closest to those of native hyaline cartilage. (2) PRP augmentation may result in greater cartilage fill than scaffold alone.
Siclari (2011-2014) ¹⁸⁻²⁰	52 humans	Polyglycolic acid-hyaluronan scaffold (Note: all patients also treated w/bone marrow stimulation)	Outerbridge 3 or 4 Femoral or tibial lesion 1.5-5 cm ² (avg 2.75 cm ²)	(1) Scaffold immersed in 3 mL PRP	(1) KOOS (2) Histologic exam (3) MRI evaluation - MOCART score	(1) KOOS 3-12 mo: significant improvements at all time points 2 y: significant improvement from preop scores; no difference from 1 y postop 5 y: significant improvement from preop scores; no difference from 1- or 2-y postop scores (2) Histology 9 mo: hyaline-like cartilage, good integration 18-24 mo: hyaline-like to hyaline cartilage, rich in chondrocytes, proteoglycans, collagen II (3) MRI evaluation - MOCART: excellent in 20/21	Polyglycolic acid-hyaluronan scaffold treated with PRP and implanted after bone marrow stimulation results in durable clinical improvement, as well as histological and radiographic healing of defect.
Wang (2019) ²⁶	33 humans	Osteochondral allograft	Outerbridge 4 defect of distal femur	(1) Osteochondral graft saturated with 3-4 mL BMC for at least 4 mins immediately before implantation (2) 1-2 mL BMC placed in base of host defect immediately prior to implantation	MRI evaluation - OCAMRISS score	MRI evaluation 6 mo: OCAMRISS: no difference (BMC 3.0, control 3.3, P=0.76) Clefts at graft-host junction: no difference (BMC 71% vs control 81%, P=0.69) Cysts at graft-host junction: no difference (BMC 41% vs control 25%, P=0.46) 12 mo: OCAMRISS: no difference (BMC 2.7, control 2.9, P=0.97) Clefts at graft-host junction: no difference (BMC 44% vs control 63%, P=0.33) Cysts at graft-host junction: no difference (BMC 50% vs control 31%, P=0.32)	BMC augmentation of osteochondral allograft was not associated with improved osseous integration, decreased cystic changes, or decrease cleft formation at graft-host junction. No changes in bone, cartilage, or ancillary features was identified.
Oladeji (2017) ¹⁷	36 humans	Osteochondral allograft	Outerbridge 4 defect of distal femur (>2.5 cm ²)	Osseous portion of osteochondral graft saturated with BMC for at least 2 mins immediately before implantation	(1) Graft integration (2) Degree of sclerosis	(1) Graft integration 6 wk, 3 mo, 6 mo: BMC higher graft integration (43.1 vs 25.6, 67.2 vs 50.6, 84.1 vs 74.4, P<0.034) (2) Graft sclerosis 6 wk, 3 mo: BMC less graft sclerosis (1.4 vs 1.9, 1.2 vs 1.7, P<0.018) 6 mo: no difference (0.9 vs 1.3, P=0.20)	BMC augmentation may result in superior integration and less sclerosis during the first 6 mo after implantation. Treatment with BMC may decrease failure rate of allograft bone healing.
Ackermann (2019) ¹	58 humans	Osteochondral allograft	Full-thickness defect on femoral condyle, trochlea, or patella (>2 cm ² , avg 3.3 cm ²)	Subchondral bone of graft saturated with 4 mL of unprocessed BMC.	MRI evaluation	MRI evaluation (6 mo) 86% achieved osseous integration No difference between BMC vs control (P=0.128) 76% showed no cystic changes No difference between BMC vs control (P=0.539) No difference in OCAMRISS score or any subscale (P>0.05)	Osteochondral allografts showed excellent osseous integration at 6 mo. BMC augmentation did not result in superior imaging outcomes.

^aavg, average; BMAC, bone marrow aspirate concentrate; BMC, bone marrow concentrate; KOOS, Knee injury and Osteoarthritis Outcome Score; MOCART, magnetic resonance observation of cartilage repair tissue; MRI, magnetic resonance imaging; OCAMRISS, Osteochondral Allograft MRI Scoring System; postop, postoperative; PLG, polylactide-co-glycolide; PRP, platelet-rich plasma.