Systematic Review

The Role of Platelet-Rich Plasma in Cartilage Pathology: An Updated Systematic Review of the Basic Science Evidence

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Purpose: To review the basic science studies on platelet-rich plasma (PRP) for cartilage and determine whether there has been an improvement in methodology and outcome reporting that would allow for a more meaningful analysis regarding the mechanism of action and efficacy of PRP for cartilage pathology. **Methods:** The PubMed/MEDLINE and EMBASE databases were screened in May 2017 with publication dates of January 2011 through May 2017 using the following key words: "platelet-rich plasma OR PRP OR autologous conditioned plasma (ACP) OR ACP AND cartilage OR chondrocytes OR chondrogenesis OR osteoarthritis OR arthritis." Two authors independently performed the search, determined study inclusion, and extracted data. Data extracted included cytology/description of PRP, study design, and results. **Results:** Twenty-seven studies (11 in vitro, 13 in vivo, 3 in vitro and in vivo) met the inclusion criteria and were included in the study. All of the studies (100%) reported the method by which PRP was prepared. Two studies reported basic cytologic analysis of PRP, including platelet, white blood cell, and red blood cell counts (6.7%). Nine studies reported both platelet count and white blood cell count (30.0%). Twelve studies reported platelet count alone (40.0%). Nine studies (30.0%) made no mention at all as to the composition of the PRP used. PRP was shown to increase cell viability, cell proliferation, cell migration, and differentiation. Several studies demonstrated increased proteoglycan and type II collagen content. PRP decreased inflammation in 75.0% of the in vitro studies reporting data and resulted in improved histologic quality of the cartilage tissue in 75.0% of the in vivo studies reporting data. **Conclusions:** Although the number of investigations on PRP for cartilage pathology has more than doubled since 2012, the quality of the literature remains limited by poor methodology and outcome reporting. A majority of basic science studies suggest that PRP has beneficial effects on cartilage pathology; however, the inability to compare across studies owing to a lack of standardization of study methodology, including characterizing the contents of PRP, remains a significant limitation. Future basic science and clinical studies must at a minimum report the contents of PRP to better understand the clinical role of PRP for cartilage pathology. **Clinical Relevance:** Establishing proof of concept for PRP to treat cartilage pathology is important so that high-quality clinical studies with appropriate indications can be performed.

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Cartilage injuries and osteoarthritis are debilitating conditions that represent significant treatment challenges owing to the avascularity of chondrocytes and their limited capacity for repair.[1-3] Injury to cartilage is common and can occur both in the normal aging process and via traumatic injury. In the United States the rate of knee articular cartilage surgery is increasing at about 5% annually and is the most common diagnosis for which arthroscopic procedures are performed.[4] As a result, there is growing interest in nonoperative treatments and biological adjuncts to surgical treatments to promote cartilage healing and curb degeneration.

Platelet-rich plasma (PRP) is an autologous blood product that is centrifuged to isolate and concentrate platelets to a level at least 3 to 5 times higher than endogenous serum levels.[5] PRP contains a unique composition of growth factors and cytokines, including vascular endothelial growth factor (VEGF), fibroblast growth factor, platelet-derived growth factor, insulin-like growth factor-1, interleukin-1B, interleukin-10, and tumor necrosis factor-B. These biological mediators are known to be involved in healing through mechanisms such as angiogenesis, collagen synthesis, and immune response regulation.[1,5-7] Over the past decade, orthopaedic research and treatments using PRP have become increasingly popular owing to literature demonstrating its anti-inflammatory and restorative function in musculoskeletal tissues such as bone, tendon, ligament, and cartilage.[1,5,8-11]

Owing to the relative ease of obtaining a serum sample and the safety of its autologous origin, PRP has gained significant interest as an adjunct to surgery and as a nonoperative treatment.[12-15] PRP's potential effects in regulating the immune response, promoting angiogenesis, and inducing cell differential make it an intriguing option for the treatment of cartilage lesions. However, the optimal clinical use of PRP for cartilage pathology requires a better understanding of PRP's mechanism of action as both an adjunct to cartilage repair as well as a nonoperative treatment modality for osteoarthritis. A previous systematic review of the basic science literature on PRP for cartilage pathology performed by Smyth et al.[11] demonstrated the need for standardization across study design so that meaningful analysis and comparisons could be made. Literature regarding PRP for cartilage pathology published prior to 2012 is heterogenous in methodology and outcome reporting. The purpose of this study is to update a previous systematic review by Smyth et al.[11] of basic science studies on PRP for cartilage pathology by reviewing the literature published since 2012. This systematic review will determine whether there has been an improvement in methodology and outcome reporting that would allow for a more meaningful analysis regarding the mechanism of action and efficacy of PRP for cartilage pathology. The authors hypothesized that recent literature on PRP for cartilage pathology will be more consistent and comprehensive in reporting methodology and outcome measures, including the contents of PRP. It was also hypothesized that this will allow a more detailed analysis of PRP's role in treating cartilage pathology that ultimately will demonstrate several in vitro and in vivo benefits of PRP for cartilage pathology.

Methods

Literature Search

This systematic review was conducted in accordance with the guidelines set forth in the Cochrane Handbook.[16] Two authors (M.P.F., J.C.M.) independently searched and selected eligible studies from the EMBASE and PubMed/MEDLINE electronic database systems with publication dates of January 2011 through May 2017. The search was performed in May 2017. A starting date of January 2011 was chosen so that any studies that may have been published during the time frame of the previous search by Smyth et al.[11] but not yet indexed on either EMBASE or PubMed would be identified. The following key words were used in the search: "cartilage OR chondrocyte OR chondrogenesis OR osteoarthritis OR arthritis" AND "platelet-rich plasma OR PRP OR autologous conditioned plasma OR ACP"; these key words were identical to those of the Smyth et al.[11] review. The reference list of all publications, including reviews identified in the search, were screened for additional articles potentially not identified through the EMBASE or PubMed/MEDLINE search.

Exclusion and Inclusion Criteria

Studies were included if they met the following criteria: they (1) studied the effect of PRP in cartilage and chondrocytes and not in other tissue; (2) analyzed the use of PRP, as defined by Smyth et al.,[11] for the treatment of cartilage damage or injury and not in the context of intervertebral disc disease or meniscal tears; (3) used PRP that was not mixed with another reagent or material; (4) were published in a peer-reviewed journal; (5) were written in English; (6) used a control to compare PRP. Articles that used PRP in the form of leukocyte platelet-rich plasma (L-PRP), PRP gels, PRP releasate, and/or activated PRP were included as long as they met the previous inclusion criteria. All studies included in the previous systematic review were excluded. Additionally, all review articles, articles not written in English, and clinical studies were excluded from the review.

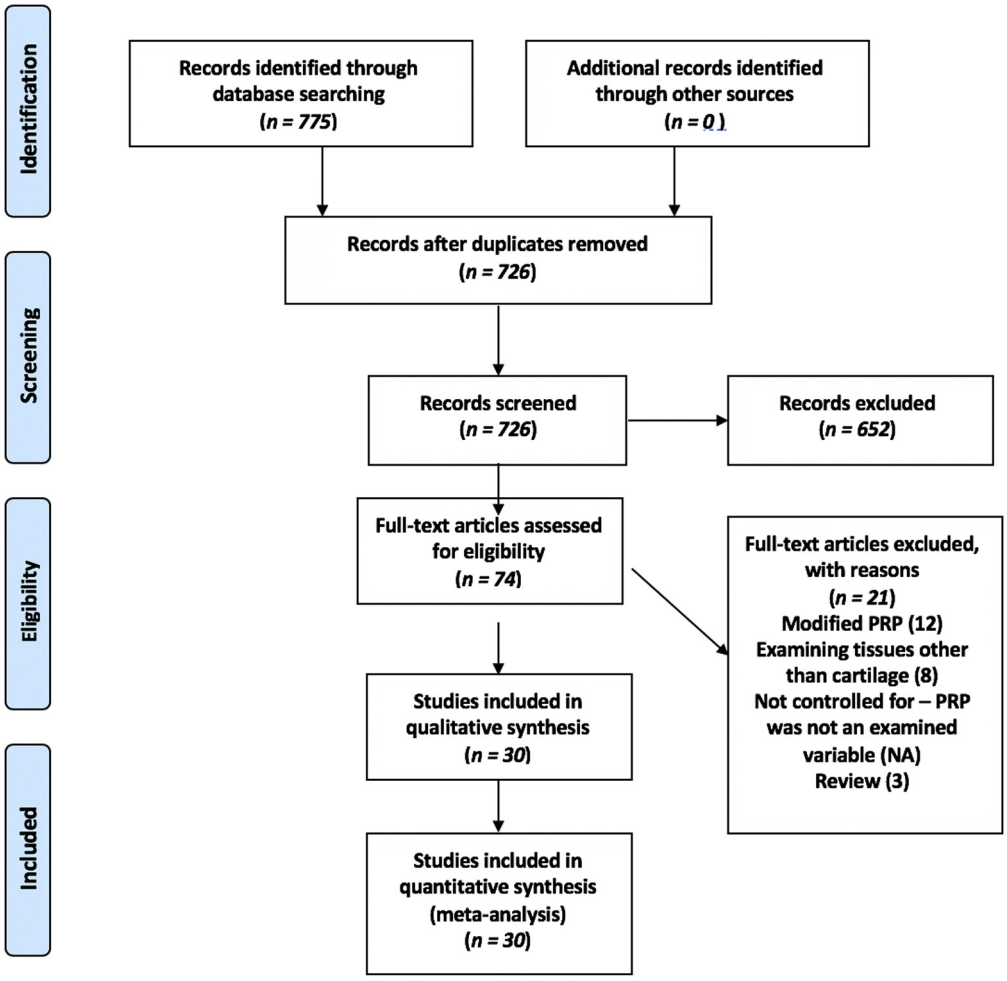

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram representing the process of individual study inclusion after application of the study algorithm and each of the exclusion criteria.

Two authors (M.P.F., J.C.M.) individually performed the search, determined which studies met the exclusion and inclusion criteria, and extracted data in accordance with the PRISMA guidelines (Fig 1). Final results were compared at the end of each stage to ensure accuracy and compliance. For any articles that were not agreed upon, a third author (C.P.H.) was consulted to make an independent decision.

Data Extraction

A large-scale standardized data sheet was developed, and 2 authors performed the data extraction. Data collected included the description of PRP (platelet concentration, white blood cell [WBC] concentration, and red blood cell [RBC] concentration), growth factor concentration, adhesive protein concentration, clotting factor concentration, fibrinolytic factors, proteases and antiproteases, basic proteins, membrane glycoproteins, dense granule bioactive molecules, proinflammatory cytokine concentration, anti-inflammatory cytokine concentration, and other proteins.

In vitro studies were analyzed for cell viability, cell proliferation, proteoglycan and type II collagen content, gene expression, cell migration, cell differentiation, and inflammatory mediation. In vivo studies were analyzed for cell viability, gene expression, gross appearance of cartilage repair, histologic assessment of cartilage repair, proteoglycan content, collage type II deposition, cartilage stiffness, and inflammatory mediation.

Results

A total of 775 articles were identified by the electronic search; 49 duplicates were eliminated, and the remaining 726 relevant articles were screened. After abstract review, 652 articles were excluded because they failed to meet the inclusion criteria. The remaining 74 articles were then analyzed for full-text review, and an additional 47 articles did not meet inclusion criteria (Fig 1). Thus, 27 articles met the inclusion criteria and were included in the study.[3,13,17-41] Of the 27 articles, 11 were strictly in vitro studies[13,20,22,23,25,26,31,36,38-40] (Table 1), and 13 were strictly in vivo

Table 1. In Vitro Studies on Platelet-Rich Plasma (PRP) for Cartilage Pathology Since 2011

Study	PRP Cytologic Findings	Study Design	Outcomes Measured	Results
Cavallo et al.[23] (2014)	Mean P-PRP platelet concentration: 1.94 × 10^5/mm^3; mean L-PRP platelet concentration: 9.29 × 10^5/mm^3; mean P-PRP WBC concentration: 5.5 × 10^3/mm^3; mean L-PRP WBC concentration: <200/mm^3.	Chondrocytes were isolated from 4 human male subjects and then seeded in 12-well plates at a density of 0.25 × 10^5 cells/cm^2 and cultured for 7 days in P-PRP, L-PRP, or PPP at different concentrations (5, 10, 20% vol/vol). Chondrocyte growth was evaluated after 0, 3, and 7 days of culture.	Cell proliferation, matrix production, expression of specific genes.	PRP contained several prochondrogenic molecules such as TGF-B1 and FGF-B. All 3 formulations induced a dose-dependent enhancement of chondrocyte growth. On day 7, P-PRP stimulated greater cell proliferation compared with L-PRP and PPP. Higher levels of hyaluronan were secreted by chondrocytes grown in the presence of L-PRP compared with other formulations, but effects of L-PRP and P-PRP on secretion of lubricin were similar.
Pereira et al.[18] (2013)	Mean platelet concentration: 1 × 10^7/mL.	Chondrocytes were isolated from 4 men and 4 women from femoral condyles, and isolated cells were cultured in Coon's modified Ham's F12 with either 10% FCS or 5% PL. The number of cell doublings was calculated for each passage.	Cell proliferation, ability to maintain redifferentiation chondrogenic potential, proinflammatory potential of platelet lysate.	Cells maintained in presence of PL had more than 20 doublings compared with 4 for the 10% FCS condition. Chondrocytes cultured in the presence of PL maintained a chondrogenic potential and presented with the typical chondrocyte appearance. PL promotes proinflammatory cytokine expression and secretion. Platelet lysate is a source of growth factors able to induce a selective chondrocyte recruitment.
Xie et al.[13] (2015)	Average platelet concentration: 1.9-2.1 × 10^9/mL; average mononuclear cell concentration: 11.8-16.2 × 10^6/mL.	PRP was prepared from 3 cows, and chondrocytes were isolated from adult bovine knees. The day before cyclic tensile strain, chondrocytes were seeded onto 6-well plates. A pulsed waveform from 0%-16% elongation at 0.5 Hz frequency was continuously applied for 48 hours, and after another 24 hours of incubation the chondrocytes and supernatant medium were collected.	Concentration of platelets and mononuclear cells in PRP, effects of cyclic tensile strain on chondrocytes.	PRP increased type II collagen and aggrecan messenger RNA expression. PRP mitigated the increased matrix metalloproteinase-3 production and decreased tissue inhibitor of metalloproteinase 1 secretion. PRP ameliorated multiple cycle tensile strain-mediated catabolic and inflammatory responses in chondrocytes. Early PRP application is more beneficial than late PRP application.
Petrera et al.[20] (2013)	Average platelet concentration: 1.22 × 10^6/mL.	Chondrocytes were isolated from articular cartilage harvested from 6- to 9-month old bovine metacarpal-phalangeal joints. They were seeded on calcium polyphosphate cylinders at a density of 160,000 cells/mm^2 and supplemented with fetal bovine serum, PRP, or PPP at 5%. On day 5, the concentration was increased to 20% and supplemented with ascorbic acid. After 2 weeks of culture, constructs were photographed and cartilage heights determined.	Platelet count, mechanical properties of PRP treated cartilage, GAG content, hydroxyproline content.	PRP in the culture media enhances the in vitro formation of cartilage, with increased GAG content and greater compressive mechanical properties while maintaining characteristics of hyaline phenotype.

(continued)

Table 1. Continued

Study	PRP Cytologic Findings	Study Design	Outcomes Measured	Results
Hildner et al.[25] (2015)	Average thrombocyte concentration: 1.0-2.0 × 10^9/mL	Articular cartilage was from the femoral head of patients undergoing total hip arthroplasty after femoral neck fracture. Cells were expanded with 5% PL or 10% FCS. ASCs from 8 donors and HACs from 3 donors were used to evaluate chondrogenic (re) differentiation of ASCs and HACs. Micromass pellets cultured for 5 weeks. Histologic evaluation was performed on day 35.	Characterization of PL, effect of PL on ASC and HAC proliferation, GAG quantification, qRT-PCR gene analysis.	Both HACs and ASCs cultured with PL showed strongly enhanced proliferation rates. Redifferentiation of HACs was possible for cells expanded up to 3.3 population doublings. PL-expanded HACs demonstrated better redifferentiation potential than FCS-expanded cells. GAG quantification and qRT-PCR of 10 cartilage related markers demonstrated a tendency for increased chondrogenic differentiation of PL-expanded ASCs compared with cells expanded with FCS. PL strongly induces proliferation of ASCs, whereas the chondrogenic differentiation potential is retained.
Kreuz et al.[26] (2015)	Average ACP platelet concentration: 2- to 3-fold increase. Average PRP-A platelet concentration: 0.6-1.3 × 10^{10}/mL; average PRP-C platelet concentration: 0.7-1.8 × 10^9/mL; average PRP-A WBC concentration: <0.3 × 10^4/mL. Average PRP-C WBC concentration: <0.5 × 10^4/mL.	Human subchondral MPCs were isolated from corticospongious bone of human femoral heads post mortem. Chondrogenic differentiation of MPCs was performed under serum-free conditions in high-density pellet cultures. Migration of MPCs on stimulation with PRP was analyzed in 96-multiwell plates.	Determination of total protein content of PRP concentrates, tissue-forming effects of PRP on human subchondral MPCs, PRP-mediated chondrogenic differentiation of human subchondral MPCs, measurement of candidate chondrogenic growth factor content in PRP by ELISA.	MPCs cultured in the presence of 5% ACP, the Regen ACR-C Kit, or the Dr. PRP Kit formed fibrous tissue, whereas MPCs stimulated with 5% PRP-A or PRP-C developed compact and dense cartilaginous tissue rich in type II collagen and proteoglycans. All platelet concentrations significantly stimulated migration of MPCs. All platelet concentrates except for Dr. PRP showed a proliferative effect on MPCs.
Sakata et al.[31] (2015)	NA	Cartilage tissue samples were obtained from the lateral femoral condyle of 3-month-old bovine stifle joints. Cells were seeded in a monolayer at 10^5 cells/well in a 12-well culture plate in medium A with 1%ITS + Premix containing either 10% PRP or no PRP for 3 days. Media was harvested 3 days after PRP treatment.	Cell proliferation, SZP synthesis in knee joint tissues, presence of SZP in PRP, lubrication properties of PRP.	PRP stimulated proliferation in cells derived from articular cartilage, synovium, and anterior cruciate ligament. PRP enhanced SZP secretion from synovium and cartilage-derived cells. Nonactivated and thrombin-activated PRP decreased the friction coefficient compared with saline and high molecular weight hyaluronan. PRP contains endogenous SZP.
Sundman et al.[22] (2014)	Mean platelet concentration: 331 × 10^3/μL ± 231 × 10^3; mean WBC concentration: 3.41 × 10^3/mL ± 2.47 × 10^3; mean red blood cell concentration: 3.8% ± 2.4%.	Human knee cartilage, subchondral bones, and joint capsules (n = 21) were from osteoarthritis patients undergoing total knee arthroplasty. Three treatment groups were established (HA, PRP [2.5 mL] and untreated control). Total cellular RNA was extracted from the synoviocytes. Before culture, 1 cartilage explant from each sample was fixed and stained.	Histologic analysis of cartilage, radiographic scores of bone contour, cytokine concentration in media (IL-1B), cartilage matrix gene expression (aggrecan), synoviocyte gene expression.	Both PRP and HA treatments of osteoarthritic joint tissues result in decreased catabolism, but PRP treatment also resulted in a significant reduction in MMP-13, an increase in HAS-2 expression in synoviocytes, and an increase in cartilage synthetic activity. PRP acts to stimulate endogenous HA production and decrease cartilage catabolism. PRP showed similar effects as HA in the suppression of inflammatory mediator concentration and expression of their genes in synoviocytes and cartilage.

(continued)

Table 1. Continued

Study	PRP Cytologic Findings	Study Design	Outcomes Measured	Results
Xie et al.[33] (2014)	NA	Articular cartilage was removed from the knees and hip joints of rabbits. Cell cultures used different concentrations of PRP (0%, 5%, 10%, 20%, 30%). Cells were washed and resuspended in PRP at 5×10^7 cells/mL. A constant compressive strain rate of 1 mm/min was applied, until a maximal force of 100 N was achieved to test the biomechanical analysis.	Scanning electron microscopy analysis of chondrocyte-autologous platelet-rich plasma gel scaffolds, quantification of growth factors in PRP, effect of different concentrations of PRP on cell proliferation, collagen and GAG content analysis, biomechanical analysis of cartilage.	PRP may provide a suitable environment for the proliferation and maturation of chondrocytes and can be used as a promising bioactive scaffold for cartilage regeneration. PRP provides a high level of growth factors such as TFG-B1 and FGF that can enhance cell proliferation and/or matrix production.
Carmona et al.[40] (2016)	Mean platelet concentration: P-PRP: $9.87 \times 10^4/\mu L$; L-PRP: $3.128 \times 10^5/\mu L$. Mean WBC concentration: P-PRP: $1.1 \times 10^2/\mu L$; L-PRP: $3.51 \times 10^4/\mu L$	30 cartilage explants were obtained from each horse; 6 experimental groups were set up (1 cartilage explant healthy control without lipopolysaccharide, ` cartilage explant challenged with lipopolysaccharide, 4 cartilage explant groups cultured with L-PRG and P-PRG supernatants at 2 different concentrations [25% and 50%]). After 1 hour of incubation, L-PRG and P-PRG supernatants were added to obtain concentrations. All groups were cultured at 96 hours.	Histology via hematoxylin and eosin staining, chondrocyte apoptosis gene expression via qRT-PCR.	25% L-PRG has the most important anti-inflammatory (MMP-13, ADAMTS-4, NF-kB) and anabolic effect; 25% P-PRG supernatant has important anabolic effects, but it induces a high degree of chondrocyte apoptosis.
Durant et al.[39] (2016)	Mean platelet concentration: $184.13 \times 10^3/\mu L$; mean WBC concentration: $0.75 \times 10^3/\mu L$.	Peripheral blood from 8 human volunteers was obtained and PRP was isolated. Human chondrocytes were treated with PRP alone or PRP plus corticosteroids or local anesthetics. Chondrocyte viability was analyzed at 0, 5, 10, 30 minutes, and proliferation was analyzed at 120 hours.	Luminescence and radioactive thymidine assays were used to determine viability and proliferation of chondrocytes treated with PRP.	PRP significantly limited the negative effect on chondrocyte viability at tested time points for those treated with anesthetics or corticosteroids. PRP improves chondrocyte proliferation.
Moussa et al.[38] (2017)	NA	Chondrocytes were cocultured with different concentrations of PRP (5%, 10%, 20%) that was derived from 12 healthy human volunteers. Cells were then analyzed for proliferation, autophagy, apoptosis, and intracellular levels of different genes via flow cytometry.	Proliferation, autophagy, apoptosis, gene expression via flow cytometry, and ELISA.	PRP increases the proliferation of chondrocytes and decreases apoptosis. PRP decreases MMP3, MMP13, ADAMTS-5, IL-6, and COX-2 in a dose-dependent manner. PRP increased TGF-B, aggrecan, and COL2A1, IL-4, IL-10, and IL-13.
Xu et al.[37] (2017)	Mean platelet concentration: $2{,}000 \times 10^9/L$; mean WBC concentration: $0.15 \times 10^9/L$.	Rabbit bone marrow stem cells were harvested from 6-week old New Zealand white rabbits and L-PRP and P-PRP was obtained. PRP scaffolds and transplanted constructs were prepared as per Xie et al. Whole blood analyses were performed to determine platelet and leukocyte concentrations of whole blood and PRP. Bone marrow stem cells were seeded onto cell culture plates to determine the effects of PRP on the NF-kB pathway.	Cell proliferation and constituent components of PRP was analyzed; effects of PRP on NF-kB were determined.	P-PRP has significantly lower concentrations of leukocytes and proinflammatory cytokines compared with L-PRP. P-PRP promotes growth and chondrogenesis of rabbit bone marrow stem cells.

(continued)

Table 1. Continued

Study	PRP Cytologic Findings	Study Design	Outcomes Measured	Results
Yang et al.[36] (2016)	Mean platelet concentration: 1-1.5 × 10^{12}/L	Chondrocytes were isolated from cartilage tissue in the knee joints of three 4-week-old male Sprague-Dawley rat neonates. They were characterized by immunohistochemical staining of collagen type II. PRP was derived from the patient's own blood. Five different concentrations of PRP was studied (1%, 2%, 5%, 10%, 25% volume/volume). Total RNA was isolated from the cells using TRIzol reagent reverse transcription and was run according to the manufacturer's protocol.	Cell proliferation was monitored using the colorimetric water-soluble tetrazolium salt (CCK8) assay; total RNA was used for qPCR of specified genes, western blotting for protein expression, flow cytometry.	10% PRP increased chondrocyte proliferation. Il-1B induces cell apoptosis, but treatment with PRP reduces overall apoptosis in IL-1B treated chondrocytes. PRP significantly reduces MMP production and promotes anabolism of cartilage extracellular matrix under IL-1B treatment.

ASC, adipose-derived stem cells; FCS, fetal calf serum; GAG, glycosaminoglycan; HA, hyaluronan; HAC, human articular chondrocytes; L-PRG, leukocyte- and platelet-rich gel; L-PRP, leukocyte PRP; MPC, mesenchymal progenitor cell; NA, not applicable; PL, platelet lysate; PPP, platelet-poor plasma; P-PRG, pure platelet-rich gel; P-PRP, pure PRP; PRP-A, PRP by apheresis; PRP-C, PRP by centrifugation; qRT-PCR, quantitative reverse-transcriptase-polymerase chain reaction; SZP, superficial zone protein; TGF-B1, transforming growth factor-B1; WBC, white blood cell.

studies[3,17,19,21,24,27-30,32,34,35,41] (Table 2). Three articles included both in vitro and in vivo studies.[18,33,37] The in vitro and in vivo components of each of these studies were treated as separate studies for data analysis for a total of 30 studies evaluated.

All of the studies (100%) reported the method by which PRP was prepared; however, there were multiple variations of the PRP preparation methods used. Two studies reported basic cytologic analysis of PRP, including platelet, WBC, and RBC counts (6.7%). Nine studies reported both platelet count and WBC count (30.0%). Twelve studies reported platelet count alone (40.0%). Nine studies (30.0%) made no mention at all as to the composition of the PRP used (Table 3).

In Vitro Studies

Of the 14 in vitro studies analyzed, 10 examined the effect of PRP on chondrocytes (4 human,[18,23,38,39] 3 bovine,[13,20,31] 1 rabbit,[33] 1 horse,[40] 1 rat[36]), 1 examined the effect on human subchondral mesenchymal progenitor cells,[26] 1 examined the combined effect on human adipose-derived stem cells and chondrocytes,[25] 1 examined the effect on rabbit bone marrow stem cells,[37] and 1 examined the combined effect on human chondrocytes and synoviocytes[22] (Table 1).

Three (21.4%) of the studies[23,36,39] reported the influence of PRP on cell viability, with all 3 studies demonstrating significant increases. Cell proliferation was examined in 10 (71.4%) of the studies,[18,23,25,26,31,33,36-39] and all of the studies showed that PRP significantly increased proliferation of either chondrocytes, mesenchymal progenitor cells, adipose-derived stem cells, and/or synoviocytes.

The propensity for cell migration was reported in 2 (14.3%) studies,[18,26] and both demonstrated that PRP increased cell migration activity. Likewise, the potential for cell differentiation was reported in 3 (21.4%) studies,[18,25,26] and in each of the studies there was a significant increase in the differentiation capacity (Table 4).

The effect of PRP on proteoglycan and type II collagen content was less clear. Six of the 14 in vitro studies reported data on proteoglycan and type II collagen content (42.9%).[18,20,22,23,25,26] Three of the studies revealed a significant increase in the synthetic capability of chondrocytes,[20,25,26] 2 of the studies demonstrated no significant change,[18,22] and 1 reported a significant decrease in type II collagen content.[23]

Finally, gene expression and inflammatory mediation were also analyzed. Three of the 9 studies reporting gene expression, including COL1 and COL2, showed PRP to have a significant increase,[18,23,25] whereas 6 additional studies revealed that some genes significantly increased and others significantly decreased.[13,22,36-38,40] Two of the 8 studies describing inflammatory mediation reported

Table 2. In Vivo Studies on Platelet-Rich Plasma (PRP) for Cartilage Pathology Since 2011

Study	PRP Cytologic Findings	Study Design	Outcomes Measured	Results
Liu et al.[28] (2014)	Average platelet concentration: 6.8-fold that of whole blood.	Subchondral bone defect in 3 groups of rabbits (n = 60 knees). PRP injections 1×/week for 3 weeks; 6 and 12 weeks after injection rabbits were sacrificed and distal femurs were dissected.	Platelet number, concentrations of growth factors of P-PRP and whole blood, IL-1B concentration in joint fluid, histologic assessment (Mankin's scoring system).	Platelet concentration in P-PRP is 6.8-fold of that in the whole blood. IL-1â level in the P-PRP group was lower than in the HA and control groups ($P < .01$). Restoration of the defective cartilage as well as the subchondral bone was better in the P-PRP group than in the HA group or the control group ($P < .05$). P-PRP is better than HA in promoting the restoration of the cartilage and alleviating the arthritis caused by cartilage damage.
Pereira et al.[18] (2013)	Average platelet concentration: 1×10^7/mL	Platelet lysates from 4 men and 4 women were prepared from femoral condyles. Three-dimensional micromass pellets were maintained for 2-3 days in vitro before subcutaneous implantation in athymic mice. PL samples were compared with those grown with only 10% FCS. Ectopic cartilage formation was analyzed after 10 or 20 doublings in culture first.	Cell proliferation, histologic assessment.	Cells maintained in presence of PL had more than 20 doublings compared to 4 for the 10% FCS condition. PL promotes proinflammatory cytokine expression and secretion. Platelet lysate is a source of growth factors able to induce a selective chondrocyte recruitment.
Serra et al.[21] (2013)	NA	Medial parapatellar arthrotomy of the medial femoral condyle in rabbits (n = 12). PRP-treated animals received 7 injections of .25 mL PRP in both knees, and placebo group animals received 7 injections of .25 saline. Animals sacrificed at 16 and 19 weeks.	Macroscopic analysis of condylar surface, microscopic study of defect filling with normal matrix staining and cell morphology, biochemical study of load and shearing strengths.	Tissue treated with autologous PRP showed a positive tendency over time, whereas the placebo group was negative. At 19 weeks of age the PRP treatment did not show better results than the placebo. None of the treatments produced a repair tissue that compared to the control model (healthy cartilage).
Kutuk et al.[27] (2014)	Average platelet concentration: 5.24-fold that of whole blood.	Standard round burr defects made in rabbit temporomandibular joint. Right joints received PRP and left joints saline. After 4 weeks the rabbits were sacrificed.	Histologic assessment via light microscopy, scanning electron microscopy analysis of the ultrastructure of the temporomandibular joint.	Although the regeneration of the fibrocartilage and hyaline cartilage was greater in the PRP group, no statistically significant difference was found between the 2 groups. Scanning electron microscopy showed better ultrastructural architecture of the collagen fibrils in the PRP group.
Manafi et al.[29] (2012)	Mean PRP platelet count: 900,000/mm^3	Skin and perichondrium was removed from rabbit's ear and divided into 4 pieces (2 diced, 2 intact) and treated with PRP or saline. Rabbits were sacrificed at 12 weeks, and cartilage was harvested.	Measurement of weight and volume of implanted cartilages, cartilage viability via H&E staining.	In both the intact and diced cartilages adding PRP resulted in increased regeneration of chondrocytes. Adding PRP to intact cartilages had a significant effect in maintaining the graft's weight and volume.
Carneiro et al.[30] (2013)	Platelet concentration range: 1.2-2.5 × 10^5/μL	An osteochondral defect was made in the trochlear groove of sheep on both knees. The left knee was left alone, and the right knee was filled with PRP gel. At 12 weeks sheep were sacrificed and distal femurs were analyzed.	Macroscopic analysis of cartilage appearance, microscopic analysis for cartilage differentiation.	PRP has reparative properties of the joint cartilage of sheep knees, but mostly by stimulating the formation of fibrocartilaginous tissue. Macroscopic appearance was not uniform among animals, nor was it different between the right and left knees (PRP and control).

(continued)

Table 2. Continued

Study	PRP Cytologic Findings	Study Design	Outcomes Measured	Results
Zhou et al.[34] (2016)	Mean platelet concentration: 2.5×10^7/mL	Osteoarthritis-like arthritis was induced by intra-articular injections of monosodium iodoacetate into both knee joints of rats. Chondrocytes incubated with or without platelets were injected into the articular cavity 2 weeks after injury. Rats were sacrificed at 4 or 8 weeks after transplantation.	Chondrocyte gene expression, chondrocyte protein expression and phosphorylation, histologic and macroscopic evaluation of cartilage repair.	Platelets significantly promote the proliferation of chondrocytes while mildly influencing anabolic and catabolic activity. Chondrocytes cocultured with platelets showed significantly increased production of BMP7, which is responsible for proliferation of chondrocytes. Transplantation of platelet-treated chondrocytes showed better cartilage repair than the controls.
Milano et al.[24] (2011)	NA	A medial parapatellar arthrotomy was made at the medial femoral condyle of sheep (n = 30). Group 1 (n = 15) had 5 intra-articular injections of ACP into the operated knee with the first at 24 hours after surgery and the rest every week after for 4 times. Group 2 (n = 15) had untreated operated knees. Animals were sacrificed at 3, 6, and 12 months after treatment.	Histologic analysis (tissue morphology, chondrocyte clustering, matrix staining) of cartilage development using H&E and Safranin-O staining.	Histologic evaluation at 3 and 6 months showed that ACP-treated animals had significantly higher O'Driscoll scores than control animals. At 12 months no statistically significant difference was observed between groups. Local injection of ACP for treatment of full-thickness cartilage injuries did not produce hyaline cartilage, although it did promote the reparative response of cartilage defect until 6 months after treatment.
Bulam et al.[19] (2015)	NA	6 cartilage grafts of rabbits (2 block circular grafts, 2 crushed cartilage grafts, 2 crushed cartilage grafts wrapped with oxidized regenerated cellulose) were prepared and weighed. Pockets were dissected through 2 cm incisions on the dorsum of rabbits. 0.5 mL autologous PRP for experimental groups and 0.5 mL 0.9% NaCl for control groups were injected into the pockets where the cartilage grafts were placed. Grafts were removed 8 weeks later and then weighed.	Weight loss/gain of cartilage grafts, histopathologic evaluation.	Although PRP-treated block cartilages lost less percentage of weight, no significant difference was found in histologic markers of cartilage viability between PRP-treated and non-treated cartilage grafts.
Danieli et al.[3] (2014)	Average platelet concentration: > 10^6/c	Lesions were made on rabbit knees at the medial femoral condyle. The left knee was filled with PRP gel, and the right knee was left untreated. Animals were euthanized 180 days after surgery.	Histologic analysis of cell morphology, surface regularity, chondral thickness and lateral integration.	PRP significantly improved cell morphology, surface regularity, chondral thickness, and repair tissue integration compared with control. Repair tissue was histologically superior after 180 days when treated with the platelet gel compared to untreated group.

(continued)

Table 2. Continued

Study	PRP Cytologic Findings	Study Design	Outcomes Measured	Results
Boakye et al.[17] (2015)	Mean platelet concentration: $> 1.1 \times 10^6/\mu L$	Rabbit knees were randomly treated with an injection of 0.5 mL of either PRP or saline. Osteochondral grafts were soaked in PRP or saline for 10 minutes prior to implantation. Rabbits were sacrificed at 3, 6, or 12 weeks following surgery.	Histologic assessment of articular cartilage via TGF-B1 levels, histologic assessment of synovium.	Articular cartilage of rabbits treated with autologous osteochondral transplantation and PRP exhibit increased TGF-B1 expression compared with those treated with autologous osteochondral transplantation and saline. There was a higher percent concentration of chondrocytes staining in the superficial cartilage of PRP treated joints than controls. Synovial tissue specimens demonstrated hypertrophy in the PRP-treated group when compared with the saline-treated group microscopically.
Xie et al.[33] (2014)	NA	Articular cartilage was removed from the knee and hip joints of rabbits and enzymatically digested. Different concentrations of PRP (0%, 5%, 10%, 20%, 30%) were used. Composites were subcutaneously implanted into BALB-c nude mice and harvested at 6 weeks. A constant compressive strain rate of 1 mm/min was applied, until a maximal force of 100 N was achieved to test the biomechanical analysis.	Scanning electron microscopy analysis of chondrocyte-autologous platelet-rich plasma gel scaffolds, quantification of growth factors in PRP, gross evaluation of the in vivo engineered composites, histologic analysis of cartilage formation, collagen and GAG content analysis, biomechanical analysis of cartilage.	PRP may provide a suitable environment for the proliferation and maturation of chondrocytes and can be used as a promising bioactive scaffold for cartilage regeneration. PRP provides a high level of growth factors such as TFG-B1 and FGF that can enhance cell proliferation and/or matrix production.
Smyth et al.[32] (2013)	Mean platelet concentration: $817.6 \pm 155.0 \times 10^3/\mu L$; mean white blood cell concentration: $10.0 \pm 3.2 \times 10^3/\mu L$; mean red blood cell concentration: $10.1 \pm 1.8 \times 10^3/\mu L$.	An osteochondral lesion was created at the lateral femoral condyle of the left knee of every rabbit. An osteochondral lesion was created in the right knee and implanted with a graft harvested from the left knee. Grafts soaked in either 1 mL of PRP or saline solution for 10 minutes before placement into the osteochondral lesion; 0.5 mL of PRP or saline solution was additionally administered as an intra-articular injection. Rabbits were sacrificed at 3, 6 or 12 weeks after initial surgery.	Cytologic analysis of whole blood and PRP aliquots, macroscopic and histologic appearance of the osteochondral graft, GAG content analysis.	When assessing graft integration, the mean score for the PRP-treated group was significantly higher than that for the control group. PRP may improve the integration of an osteochondral graft at the cartilage interface and decrease graft degeneration in an in vivo animal model. There is increased GAG content in PRP-treated samples, as well as greater type II collagen immunoreaction compared with the control group.

(continued)

Table 2. Continued

Study	PRP Cytologic Findings	Study Design	Outcomes Measured	Results
Bahmanpour et al.[41] (2016)	NA	Full-thickness defect in the trochlear groove was made in 36 bilateral knees of 18 mature male rabbits. They were randomly divided into 6 groups (I: control; II: PRP; III: PRF; IV: gelatin+SDF1; V: PRP+SDF1; VI: PRF+SDF1). After 4 weeks the specimens were evaluated.	Macroscopic examination and histologic grading, immunofluorescent staining for collagen type II, cartilage marker genes by reverse transcription-polymerase chain reaction	Macroscopic evaluation revealed PRF+SDF1 was the highest, but PRP alone showed significant improvement. Microscopic analysis showed cartilage repair with PRP alone was not significant. Immunofluorescent staining for collagen II demonstrated no change with PRP, but significant distribution in the Gel+SDF1, PRP+SDF1, and PFR+SDF1 groups. Reverse transcription-polymerase chain reaction analysis revealed that mRNA expression of SOX9 and aggrecan were significantly greater in the PRF+SDF1, PRP+SDF1, Gel+SDF1, and PRF groups but not the PRP group alone.
Xu et al.[37] (2017)	Mean platelet concentration: $2{,}000 \times 10^9$/L; mean white blood cell concentration: 0.15×10^9/L.	Rabbit bone marrow stem cells were harvested from 6-week old New Zealand white rabbits and leukocyte PRP and pure PRP were obtained. PRP scaffolds and transplanted constructs were prepared as per Xie et al. Whole blood analyses were performed to determine platelet and leukocyte concentrations of whole blood and PRP; 27 male mature New Zealand white rabbits were used, and a lateral para-patellar skin incision was made. PRP translates were introduced into the incisions and analyzed.	Macroscopic evaluation of cartilage repair, micro-computed tomography of mineralized bone, histologic analysis via H&E staining.	PRP provides better cartilage regeneration based on histologic examination when compared to leukocyte PRP.
Yokoyama et al.[35] (2017)	NA	Platelet-activated serum was collected from 5 Japanese white rabbits aged 12 weeks using CellAID. PRP was injected into the right knees of Japanese white rabbits (12 weeks) under anesthesia. Knees were injected with 1 mL of the treatment (phosphate-buffered saline, platelet activated serum, Avastin, platelet activated serum+Avastin) solutions in phosphate-buffered saline weekly from weeks 1-7 and weight distribution ratios were measured. Rabbits were killed at 12 weeks after surgery by intravenous overdose of anesthesia. Medial and lateral tissues from the femoral and tibial ends of the right knees were collected and fixed and processed for histology and staining.	Growth factor concentrations were determined for VEGF, PDGF-BB, and TGF-B; histologic evaluation was performed 12 weeks after ACL transection; weight distribution ratios of the damaged limbs were determined, and pain was evaluated during weeks 1-7.	PRP showed therapeutic effects on cartilage histologic repair and pain relief; Avastin with PRP did not provide synergistic effects.

ACP, autologous conditioned plasma; FCS, fetal calf serum; GAG, glycosaminoglycan; HA, hyaluronan; H&E, hematoxylin and eosin; PL, platelet lysate; TGF-B1, transforming growth factor-B1.

Table 3. Platelet-Rich Plasma Cytology Reporting in Basic Science Studies on Cartilage Repair Published Since 2011

Component	Reported Studies, n (%)	Studies Not Reporting, n (%)
Platelet count	21 (70.0)	9 (30.0)
WBC count	9 (30.0)	21 (70.0)
RBC count	2 (6.7)	28 (93.3)
Platelet + WBC + RBC count	2 (6.7)	28 (93.3)
Platelet + WBC count	9 (30.0)	21 (70.0)
Platelet count without WBCs or RBCs	12 (40.0)	18 (60.0)
No reference to Platelet, WBC or RBC count	9 (30.0)	21 (70.0)

RBC, red blood cell; WBC, white blood cell.

PRP to have a significant increase,[18,23] and the remaining 6 studies demonstrated a significant decrease.[13,22,36-38,40]

In Vivo Studies

The in vivo studies included used the following animal models: 11 rabbit,[3,17,19,21,27-29,32,35,37,41] 2 sheep,[24,30] 2 mice,[18,33] and 1 rat.[34] PRP treatment was studied in the context of focal cartilage lesions, and most studies characterized factors such as histologic appearance, biochemical matrix content, and/or load and shearing strengths (Tables 1 and 5).

Of the 16 in vivo studies, only 1 study[33] reported data on cell viability (6.3%), and the results showed no significant change. Nine of the studies (56.3%) described the effects that PRP had on the gross appearance of cartilage repair. Five of those studies reported a significant improvement in gross appearance[28,29,34,37,41] with "restoration of the defected cartilage as well as the subchondral bone."[28] The other 4 studies stated that there was no significant change in the gross appearance of the cartilage with the use of PRP.[21,30,32,33]

Proteoglycan content of cartilage repair with PRP treatment was assessed histologically in 3 studies (18.8%). Two of the studies showed a significant increase in proteoglycan content,[32,34] whereas the third study described no change.[33] Type II collagen deposition was also analyzed in 7 studies (43.8%). Four studies reported no significant change in deposition,[33,34,37,41] and 3 studies found significant increases.[27,32,35] Kutuk et al.[27] specifically demonstrated that there was improved organization of type II collagen with PRP treatment in addition to the deposition.

All 16 studies (100%) reported a histologic assessment of cartilage repair. Twelve of the studies reported significant improvement in the quality of cartilage repair tissue with PRP treatment,[3,17,18,24,27-30,32,34,35,37] and 4 studies demonstrated no change.[19,21,33,41] One study that reported significant improvement in the quality of cartilage tissue repair after PRP treatment found that this was not maintained over time.[24]

Two studies (12.5%) reported data on the strength and stiffness of cartilage when treated with PRP. One study reported no significant change,[33] whereas the other study reported both decreased strength and no significant change depending on the test administered.[21] Finally, only 1 study (6.3%) reported data on inflammatory mediation, and the data revealed a significant decrease.[28]

We also evaluated more than 100 additional parameters, including growth factors, adhesive proteins, pro- and anti-inflammatory cytokines, and anabolic and catabolic cytoskeletal molecules, in an attempt to further identify factors of interest for future studies to assess PRP efficacy. We were unable to find a single parameter that was reported in >40% of studies (Appendix 1).

Table 4. Variables Reported in Vitro

Outcome	Studies Reporting, n (%)	Significant Increase, n	No Significant Change, n	Significant Decrease, n
Cell viability	3 (21.4)	3	0	0
Cell proliferation	10 (71.4)	10	0	0
Proteoglycan and type II collagen content	6 (42.9)	3	2	1
Gene expression	9 (64.3)	3 (6 studies had some genes increase and others decrease)	0	6 (6 studies had some genes increase and others decrease)
Cell migration	2 (14.3)	2	0	0
Cell differentiation	3 (21.4)	3	0	0
Inflammatory mediation	8 (57.1)	2	0	6

Table 5. Variables Reported in Vivo

Outcome	Studies Reporting, n (%)	Significant Increase, n	No Significant Change, n	Significant Decrease, n
Cell viability	1 (6.3)	0	1	0
Gene expression	4 (25.0)	3 (1 study had some genes increase and others decrease)	0	1 (1 study had some genes increase and others decrease)
Gross appearance of cartilage repair	9 (56.3)	5	4	0
Histologic assessment of cartilage repair	16 (100)	12 (1 study showed short term growth increase, but long term no change)	4	0
Proteoglycan content	3 (18.8)	2	1	0
Type II collagen deposition	7 (43.8)	3	4	0
Cartilage stiffness	2 (12.5)	0	1	1 (showed both decreased strength and no change)
Inflammatory mediation	1 (6.3)	0	0	1

Discussion

Although the number of basic science articles published on PRP for cartilage pathology has more than doubled since 2012, the quality of the literature remains significantly limited by the lack of reporting of recommended data. In the original systematic review by Smyth et al.[11] that included 21 studies, only 1 (4.7%) reported a full cytology of PRP. In this updated review of the original review by Smyth et al.,[11] 27 articles were included, but only 2 (6.7%) studies reported a full cytology of PRP. Moreover, 70.0% of studies reported the platelet count, 6.7% of studies reported the RBC count, and only 30.0% reported the WBC counts within PRP. Furthermore, 30.0% of the studies analyzed in this paper failed to document any of the 3 parameters within their studies.[19,21,24,31,33,35,38,41] In all studies, the protocol of preparation and contents of the PRP used should be clearly articulated and reproducible so that results across studies can be compared. Journals should consider establishing guidelines that require all submitted studies on PRP to report the method by which PRP was produced as well as a detailed analysis of the biological contents.

When comparing studies on PRP in cartilage repair, cell proliferation,[18,23,25,26,42-47] cell differentiation,[18,25,26,44,45] and type II collagen and glycosaminoglycan deposition[18,20,22,23,43,46-49] have consistently been used to evaluate PRP efficacy in in vitro studies, whereas histologic assessment[3,19,21,27,28,30,34,50-54] and gross appearance[21,28,29,32-34,50,53,54] have been the standard of evaluation of PRP in in vivo studies. Although the contents of PRP reported in basic science literature remains limited, a majority of the evidence suggests that PRP has several effects on these parameters when treating cartilage pathology. All of the in vitro studies (100%) that reported cell proliferation demonstrated that PRP significantly increases the proliferative capacity of treated cells.[18,23,25,26,31,33,36-39] The 2 studies (1 in vivo and 1 in vitro)[23,35] that reported on the effect of PRP on VEGF expression found that VEGF levels were increased, thus providing a potential mechanism for induction of proliferation that was not identified in the prior review by Smyth et al.[11] In addition, 3 of the 6 in vitro studies reporting data on proteoglycan and type II collagen content demonstrated a significant increase when treated with PRP,[20,25,26] with only 1 study showing a significant decrease.[23] Of the in vivo studies, 12 of the 16 studies reporting on the histologic assessment of cartilage demonstrated a significant increase in the quality of cartilage repair,[3,17,18,24,27-30,32,34,35,37] with the remaining 4 studies finding no change at all.[19,21,33,41] Some of the aspects used to define quality of cartilage repair included chondral thickness, tissue integration, cell morphology, and surface regularity. Collectively, these findings suggest that PRP has some benefit to the overall growth and differentiation of the treated chondrocytes in cartilage repair models, supporting its use as an adjunct to bone marrow stimulation and autologous osteochondral transplantation. However, the extrapolation of these results to the efficacy of PRP for treatment of osteoarthritis should be made with caution. Only 2 basic science studies have specifically looked at the use of PRP in an osteoarthritic model.[22,34] In the setting of osteoarthritis, PRP has been shown to have several anti-inflammatory effects, which may result in improved clinical symptoms; however, there is a lack of research on PRP's efficacy in preventing osteoarthritis disease progression.

In addition to its ability to increase chondrocyte proliferation, PRP has been shown to induce chondrogenic differentiation and matrix development. Petrera et al.[20] suggest that it is the ability of PRP to increase the overall glycosaminoglycan content that promotes cartilage repair. Although some studies demonstrated that this repair maintains the hyaline phenotype characteristic

and increases the overall compressive mechanical properties of the tissue, other studies found that PRP did not induce hyaline cartilage formation but was still able to induce a reparative response.[24] Transforming growth factor-B1 and fibroblast growth factor, both found to be notably elevated in PRP, seem to facilitate the overall matrix production and chondrocyte proliferation by generating a scaffold that permits regeneration and improved growth.[23,33] The ability of PRP to stimulate endogenous hyaluronan production and decrease cartilage catabolism may further promote matrix synthesis.[22,31]

The observed ability of PRP to inhibit catabolic processes may also play a meaningful role in its efficacy especially in osteoarthritis treatment. Matrix metalloproteinases (MMPs) are enzymes with the potential to degrade multiple extracellular matrix proteins and may inhibit the development of matrix formation during the healing process. The ability of PRP to significantly reduce MMP-3 and MMP-13 activity when administered shortly after injury improves matrix formation and the healing process.[13,22] However, this process seems to be time dependent since delayed administration of PRP after injury shows less effect and may, in fact, increase MMP-13 activity.[13] This suggests that PRP's effects are multifactorial and that the time of administration may change the overall efficacy and anti-inflammatory potential, which is important when considering its clinical implications. However, the effect of PRP on the inflammatory milieu is not clearly understood. Some studies have argued that PRP's ability to induce transitory proinflammatory cytokines promotes cell migration postinjury via chemoattractant effects that seem to be chondrocyte specific.[18] Conversely, other studies have shown that PRP inhibits inflammatory cytokines and have concluded that this leads to a decrease in secondary matrix damage mediated by the proinflammatory process.[13,22]

Limitations

The greatest limitation of this study that prevents detailed analysis and comparison across studies is the lack of consistent methodology and outcome reporting as previously discussed. In addition, the study is limited by the databases chosen to search, which may lead to selection bias. There are also several limitations inherent to in vivo and in vitro studies. For in vivo studies, cartilage lesions are distinctly different in animals than humans. The lesions in animals are typically smaller, and the thickness of cartilage is also thinner. This study is also limited by a lack of evaluation of the risk of bias of included studies. Unfortunately, there are no validated tools to evaluate the presence of bias in basic science research. A validated tool to independently assess the quality and risk of bias in these studies would provide a more objective evaluation for future systematic reviews of the topic. Owing to these limitations, it is difficult to extrapolate results to a clinical setting; however, basic science research is still critical to evaluate for proof of concept for PRP for cartilage therapy.

Conclusions

Although the number of investigations on PRP for cartilage pathology has more than doubled since 2012, the quality of the literature remains limited by poor methodology and outcome reporting. A majority of basic science studies suggest that PRP has beneficial effects on cartilage pathology; however, the inability to compare across studies owing to a lack of standardization of study methodology, including characterizing the contents of PRP, remains a significant limitation. Future basic science and clinical studies must at a minimum report the contents of PRP to better understand the clinical role of PRP for cartilage pathology.

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Appendix 1. Variables Reported in Basic Science Studies on Platelet-Rich Plasma for Cartilage Pathology Published Since 2011

	No. of Studies Reporting	Increase, Decrease, or No Change?
Growth factor concentrations		
Epidermal growth factor (EGF)	2 (1 in vivo; 1 in vitro)	Increase
Platelet-derived growth factor A+B (PDGF A+B)	9 (4; 5)	Increase
Transforming growth factor-B1 (TGF-B1)	12 (5; 7)	Increase (1 in vivo study found no change)
Insulin-like growth factor- I, II (IGF- I, II)	3 (1; 2)	Increase
Vascular endothelial growth factor (VEGF), endothelial cell growth factor (ECGF)	2 (1; 1)	Increase
Basic fibroblast growth factor (bFGF)	2 (1; 1)	Increase (in vivo); no change (in vitro)
Fibroblast growth factor-2 (FGF-2)	2 (0; 2)	Increase
Fibroblast growth factor-18 (FGF-18)	0	NA
Bone morphogenetic protein-2 (BMP-2)	1 (0; 1)	No change
Bone morphogenetic protein-7 (BMP-7)	1 (1; 0)	Increase
Hepatocyte growth factor (HGF)	1 (0; 1)	Increase
Adhesive protein concentration		
Fibrinogen	0	NA
Fibronectin	0	NA
Vitronectin	0	NA
Thrombospondin-1	1 (0; 1)	Decrease
Clotting factor concentration		
Factor V	0	NA
Factor XI	0	NA
Protein S	0	NA
Antithrombin	0	NA
Fibrinolytic factors		
Plasminogen	0	NA
Plasminogen activator inhibitor	0	NA
Alpha-2 antiplasmin	0	NA
Proteases and antiproteases		
Tissue inhibitor of metalloproteinases (TIMP-4)	1 (0; 1)	Increase
Metalloprotease-4	0	NA
Alpha1-antitrypsin	0	NA
Basic proteins		
Platelet factor 4	0	NA
B-thromboglobulin	0	NA
Endostatins	0	NA
Membrane glycoproteins		
Cluster of differentiation CD40 ligand (CD40L)	0	NA
P-selectin	0	NA
Dense granule bioactive molecules		
Serotonin	0	NA
Histamine	0	NA
Dopamine	0	NA
Adenosine diphosphate (ADP)	0	NA
Adenosine triphosphate (ATP)	0	NA
Ca2+	0	NA
Catecholamines	0	NA
Proinflammatory cytokine concentration		
Interleukin-1 alpha (IL-1a)	0	NA
Interleukin-1 beta (IL-1b)	5 (2; 3)	Increase (1: in vitro); decrease (4: 2 in vivo and 2 in vitro)
Interleukin-2 (IL-2)	0	NA
Interleukin-6 (IL-6)	4 (0; 4)	Increase (2); no change (1); decrease (1)
Interleukin-7 (IL-7)	0	NA
Interleukin-8 (IL-8) (CXCL8)	2 (0; 2)	No change
Tumor necrosis factor-alpha (TNF-a)	4 (1; 3)	No change (2 in vitro); decrease (2: 1 in vivo and 1 in vitro)
Interferon-alpha (IFN-a)	0	NA
Interleukin-12 (IL-12)	0	NA
Interleukin-15 (IL-15)	0	NA
Interleukin-17 (IL-17)	0	NA
Interleukin-18 (IL-18)	0	NA

(continued)

Appendix 1. Continued

	No. of Studies Reporting	Increase, Decrease, or No Change?
Natural killer B-cell cytokines (NK-B cytokines)	3 (1; 2)	No change (2: 1 in vivo and 1 in vitro); decrease (1 in vitro)
Anti-inflammatory cytokine concentration		
Interleukin-1 receptor antagonist (IL-1RA)	0	NA
Interleukin-4 (IL-4)	1 (0; 1)	Increase
Interleukin-5 (IL-5)	0	NA
Interleukin-10 (IL-10)	2 (0; 2)	Increase
Interleukin-13 (IL-13)	1 (0; 1)	Increase
Interferon-gamma (IFN-g)	0	NA
Other proteins		
Activin A	0	NA
Advanced glycosylation end product (AGE)	0	NA
Agrin	0	NA
Brain-derived neurotrophic factor (BDNF)	0	NA
Chemokine (C-C motif) ligand 2 (CCL2)	0	NA
Chemokine (C-C motif) ligand 5 (CCL5)	0	NA
Chemokine (C-C motif) ligand 20 (CCL20)	0	NA
Chemokine (C-X-C motif) ligand 1 (CXCL1)	0	NA
Chemokine (C-X-C motif) ligand 2 (CXCL2)	0	NA
Chemokine (C-X-C motif) ligand 3 (CXCL3)	0	NA
Chemokine (C-X-C motif) ligand 5 (CXCL5)	0	NA
Chemokine (C-X-C motif) ligand 7 (CXCL7)	0	NA
Chemokine (C-X-C motif) ligand 10 (CXCL10)	0	NA
Ciliary neurotrophic factor (CNTF)	0	NA
Cluster of differentiation 86 (CD86)	0	NA
Colony-stimulating factor 2 (CSF2)	0	NA
Fas ligand	0	NA
Fractalkine	0	NA
Intercellular adhesion molecule 1 (ICAM1)	0	NA
Interleukin 1 receptor-like 2 (IL1RL2)	0	NA
L-selectin	0	NA
Leptin	0	NA
Matrix metalloproteinase 1 (MMP1)	2 (0; 2)	No change (1); decrease (1)
Matrix metalloproteinase 2 (MMP2)	0	NA
Matrix metalloproteinase 3 (MMP3)	3 (0; 3)	No change (2); decrease (1)
Matrix metalloproteinase 8 (MMP8)	0	NA
Matrix metalloproteinase 9 (MMP9)	1 (0; 1)	No change
Matrix metalloproteinase 13 (MMP13)	7 (1; 6)	Increase (1); no change (1); decrease (4: 1 in vivo and 4 in vitro)
Prolactin receptor	0	NA
Tissue inhibitor of metalloproteinases 1 (TIMP1)	3 (0; 3)	Increase
Regulated on activation, normal T cell expressed and secreted (RANTES)	0	NA
Monocyte chemoattractant protein-1 (MCP-1)	0	NA
Macrophage inflammatory protein-1a (MIP-1a)	0	NA
Granulocyte-colony stimulating factor (G-CSF)	0	NA
Granulocyte-macrophage colony stimulating factor (GM-CSF)	0	NA
Eotaxin	0	NA
Macrophage inflammatory protein-1b (MIP-1b)	0	NA
Cartilage oligomeric matrix protein (COMP)	2 (0; 2)	No change (1); decrease (1)
Collagen type 1 (COL1A1)	6 (2; 4)	No change (3: 1 in vivo and 2 in vitro); decrease (3: 1 in vivo and 2 in vitro)
Collagen type 2 (COL2A1)	12 (6; 6)	Increase (6: 3 in vivo and 3 in vitro); no change (6: 3 in vivo and 3 in vitro)
Collagen type 3 (COL3A1)	0	NA

(continued)

Appendix 1. Continued

	No. of Studies Reporting	Increase, Decrease, or No Change?
A disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5)	3 (1; 2)	Decrease
Aggrecan	9 (3; 6)	Increase (5: 2 in vivo and 3 in vitro); no change (2: 1 in vivo and 1 in vitro); decrease (2 in vitro)
Protein 10 (IP-10)	0	NA

NA, not applicable.