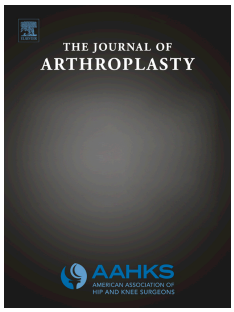

Biologic Therapies for the Treatment of Knee Osteoarthritis: An Updated Systematic Review

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Biologic Therapies for the Treatment of Knee Osteoarthritis: An Updated Systematic Review

Abstract

Background

Use of "orthobiologics" continues to expand for patients who have knee osteoarthritis (OA). We sought to perform a systemic review of biologic therapies relative to comparative groups, including: (1) platelet-rich plasma (PRP); (2) bone marrow-derived mesenchymal stem cells (BMSCs); (3) adipose-derived mesenchymal stem cells (ADSCs); and (4) amniotic-derived mesenchymal stem cells (AMSCs). We assessed: (1) study methodologies; (2) cell preparations and formulations; (3) patient-reported outcome scores (PROMs); and (4) structural changes.

Methods

PubMed, Cochrane Library, and Embase databases were queried (2013-2021) to conduct a systematic review of biologic therapies for knee OA, according to Preferred Reporting Items for Systematic-Reviews and Meta-Analyses (PRISMA) guidelines. Eighty-two studies were included: PRP (51); BMSC (15); ADSC (11); AMSC (five). Study evaluations were made using the Modified Coleman Methodological Score (MCMS). PROMs included the Western Ontario and McMaster Universities Arthritis Index, and the Visual Analog Scale. Structural change evaluations included ultrasounds, radiographs, or magnetic resonance imaging.

Results

PRP comprised a majority of the studies (n=51), most with "fair" to "good" MCMS. Studies had variable cell preparations and formulations, with comparison study results leading to

inconsistent PROMs, and structural changes. A limited number of studies were included for BMSC, ADSC, and AMSC, all with similar findings to PRP.

Conclusions

Available literature evaluating "orthobiologics" for knee OA remain non-superior to comparison cohorts. Higher level studies with larger sample sizes and improved methodologies are warranted to suggest differences. Despite a growth of "orthobiologics" in clinics, this updated systematic-review highlights the uncertain efficacy for use in knee OA.

Keywords: biologic therapies; orthobiologics; PRP; bone marrow; adipose; amnion; stem cells

Introduction

Rates of osteoarthritis (OA) continue to rise as the population ages, with the knee being the most affected weightbearing joint.[1] The global incidence of knee OA is estimated to be approximately 10% in men and 18% in women, causing substantial disability, reduced quality of life, and financial burden.[2] Non-operative management of knee OA continues to evolve, but delaying eventual total knee arthroplasty (TKA) remains challenging.[3] Current treatment regimens include exercise therapy, unloader bracing, and analgesic medications. The use of intra-articular injections has had a dramatic rise in recent years.[4] These include, but are not limited to corticosteroids and visco-supplementation; however, these formulations are often limited by short-lived improvements and the inability to demonstrate consistent superiority over placebos.[5–7] Within recent years, the use of other intra-articular knee injections has expanded to include an array of biologic options, or "orthobiologics." These have become part of many orthopaedic practices, despite a lack of concrete evidence.[8–10] The American Academy of Orthopaedic Surgeons (AAOS) currently lists the evidence for the use of biologic injections to treat knee OA as inconclusive due to the lack of consistent Level I and II studies.[7] However, existing literature regarding "orthobiologics" continues to expand, and an updated systematic review is warranted for proper evaluation.

Biologic therapies can be divided into blood-derived and cellular therapies. The former involves administration of blood or blood constituents to infuse supraphysiologic concentrations of cellular components and cytokines into the joint space. They theoretically stimulate chondrogenic proliferation and differentiation; examples include autologous whole blood cells and platelet-rich plasma (PRP).[11,12] The latter has garnered considerable attention over the past decade. Cellular therapies, including stem cells (e.g., bone marrow, adipose, and amniotic

cells) are theorized to have a more direct pathway in tissue regeneration via direct incorporation into tissue with capacity to promote growth and differentiation.[13] Despite the widespread use of these biologic therapies and their increasing allure, no gold standard for their preparation or administration exists.[14,15]

Non-operative management of knee OA continues to meet the increasing rate of patients requiring pain management, and the substantial rise of biologic therapies aims to fill this gap. Delanois *et al.* evaluated 16 studies assessing biologic therapies from March 2013 to March 2018, most of which were PRP related.[16] They concluded that there is insufficient evidence to justify the use of these therapies. However, since this publication (2019), the available literature has grown substantially, and an updated review is warranted.

Therefore, in this updated review, we sought to conduct a systematic review (between March 1, 2013 and November 30, 2021) evaluating: (1) level of evidence I and II platelet-rich plasma (PRP) studies; as well as level of evidence I to III; (2) bone marrow-derived mesenchymal stem cells (BMSCs); (3) adipose-derived mesenchymal stem cells (ADSCs); and (4) amniotic-derived mesenchymal stem cells (AMSCs) studies. We assessed: (1) study methodologies; (2) cell preparations and formulations; (3) patient reported outcome scores (PROMs); and (4) structural changes.

Methods

This systematic review of biologic therapies for the treatment of knee OA was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines utilizing PubMed, Cochrane Library, and Embase electronic databases

between April 1, 2018 and November 10, 2021. Registration with PROSPERO was also completed (CRD42021266982). This study serves to update a previous systemic review of biologic therapies that included studies until March 2018.[16]

Inclusion criteria consisted of studies published between March 1, 2013 and November 10, 2021, full text availability, and in English (**See Figure 1**). For PRP studies, exclusion criteria consisted of any cadaver studies, animal studies, conference abstracts, conference reviews, letters to the editor, surveys, case reports, case series, reviews, or otherwise levels of evidence III or lower. For BMSCs, ADSCs, and AMSCs, exclusion criteria consisted of similar criteria as above except for the inclusion of retrospective studies or otherwise levels of evidence I to III. A decision was made to include lower levels of evidence studies for the non-PRP biologic reports to account for the limited availability in these categories. Of note, studies from a previous review by Delanois *et al.* [16] were assessed for inclusion.

Two authors (J.C. and D.C.) independently performed the initial query. They then applied the search criteria and assessed relevance to identify the appropriate full text publications. Duplicates were removed after this initial search. A third author (O.S.) reconciled any existing discrepancies. For completeness, the selected articles' references were reviewed and appraised for possible inclusion. Funding or a third party was not deemed necessary for data collection.

Initial screening for the use of PRP, BMSC, ADSC, and AMSC as treatment for knee OA yielded 689 studies. Of these, 622 were excluded for the following reasons: (1) only discussed non-knee joints and/or separate pathologies other than OA; (2) involved non-human study models; or (3) were editorials/commentaries/letters to the editor. A total of 15 studies met inclusion criteria from a previous review [16]. This left 82 remaining studies: PRP (51), BMSC (15), ADSC (11), and AMSC (5).

Summary Statements

Following critical review of all included studies, a summary statement for each "orthobiologic" therapy was provided at the end of each result section. This served the purpose to provide readers with concise, take-home messages for each section.

Study Methodology

The included studies were stratified according to levels of evidence, study models, cohorts, formulations, follow-up durations, as well as clinical and radiographic outcomes. A quality assessment was conducted using the Modified Coleman Methodology Score (MCMS), scaled from 0 to 100.[17] The MCMS provides an objective methodological assessment by accounting for sample sizes, follow-up times, and clinical effect measurements (**See Table 1**). Scores were specifically categorized as "excellent" (85 to 100), "good" (70 to 84), "fair" (55-69), and "poor" (<55), as reported by Cowen *et al*.[17]

Results

Platelet-Rich Plasma Therapy

Methodology

Grading the 51 PRP studies using the MCMS yielded: four (8%) "excellent" [29,42,56,57], 14 (27%) "good"[27,30,32,34,39,40,43,48–51,58,60,61]**,** 25 (49%) **"**fair"[19,20,22,23,25,26,31,33,35,37,38,41,44,45,47,53–55,62–68], and eight (16%) "poor"[18,21,24,28,36,46,52,59] quality reports.

Preparations and Cellular Formulations

An autologous venous blood draw can be prepared for PRP through differential centrifugation whereby centrifugal forces separate cellular components based on their specific gravities. In one method, autologous blood undergoes two centrifugations to ultimately separate concentrated platelets. In a second method, the blood undergoes high speed centrifugation to collect the buffy coat layer. Among the studies included in this review, autologous venous blood was collected and delivered between 1 to 14 milliliters (mL) of PRP (**See Table 2**).

A total of 19 studies [19,20,45,46,50,51,55,62,63,65,67,22–25,32,34,37,42] described the platelet count, while only seven [19,23,45–47,50,56] detailed growth factor counts (platelet-derived growth factor (PDGF) and/or vascular endothelial growth factor (VEGF)) of the cellular content of the PRP preparations (**See Table 3**).

The majority utilized a lateral intra-articular approach for PRP delivery. The presence of leukocytes in the PRP preparation may not be desired given their pro-inflammatory activity, and their potential benefits on proliferation, differentiation, immunity, and infection is not well-understood [98]. Eleven of the studies [18,20,66,28,34,42,49,50,52,55,62] reported leukocyte-rich PRP, while 17 studies [22,23,57,59–61,63,67,99,25,27,39,43,47,51,53,56] reported leukocyte-poor PRP. The remaining did not report specify leukocyte presence.

Patient Reported Outcome Measures

A total of 24 out of 51 studies compared PRP to hyaluronic acid (HA) (**See Table 4**). Of these, 12 studies reported greater improvement in Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores among PRP patients [23,25,68,99,42,43,50,56,57,61,62,64]. Six studies reported WOMAC score equivalency between PRP and HA [24,27,40,44,46,63], and

another reported inferior scores [29]. Eleven studies reported higher Visual Analog Scale (VAS) scores among PRP patients (range 0 to 10, higher scores correspond to increased pain) [18,24,64,25,27–29,34,42,56,57]. Six studies reported equivalency between PRP and HA regarding VAS scores [40,44,46,47,50,99], while two studies showed PRP combined with HA as being superior to PRP alone.[63,67] Another study evaluated the VAS sub-scores and found PRP to be superior to HA in VAS resting pain, while PRP was equivalent to HA in VAS movement pain.[40]

Ten out of 51 (20%) studies compared PRP to corticosteroid (CS) [26,33,35,39,48,49,52,65,99,100]. Of these, four studies reported higher WOMAC scores among PRP patients [35,48,65,99], while one study found WOMAC score equivalency between PRP and CS [100]. Four studies reported higher VAS scores among PRP patients [33,48,52,65]. Four studies reported VAS score equivalency between PRP and CS [39,49,99,100]. Another examined the synergistic effects of CS with PRP, but found no meaningful WOMAC or VAS score differences.[26]

Seven (14%) studies compared PRP to normal saline (NS) [32,37,43,45,51,54,66]. Of these, six reported superior WOMAC scores among PRP patients [32,37,43,45,51,66]. The four studies reporting VAS scores all demonstrated greater pain improvements among the PRP patients [32,37,45,51].

Six (12%) studies compared PRP to either: BMSC; exercise therapy; radiofrequency ablation/shockwave therapy; autologous conditioned serum/dextrose; and ozone [29,53,55,57,68,76]. In relation to BMSC, WOMAC scores were found to be equivocal or inferior to PRP.[20,76] Among the two studies evaluating exercise therapy, one reported higher WOMAC and VAS scores among PRP[55], and the other reported higher WOMAC scores

among the exercise group.[19] One study reported higher VAS and Lequesne scores in PRP compared to radiofrequency ablation of the genicular nerve.[30] Conversely, another study reported higher VAS and Lequesne score among a shockwave therapy group.[31] PRP was found to be superior to dextrose, and ozone when assessing WOMAC and VAS scores [29,36,53,57]. In comparison to autologous conditioned serum (ACS), PRP was found to have inferior WOMAC and VAS scores.[53]

Structural Changes

Four (10%) studies reported radiographic outcomes after PRP use. As compared to HA, PRP demonstrated higher synovial vascularity and hypertrophy[18], but another study reported no differences in joint space width.[23] Relative to HA, PRP was reported to have an insignificantly higher patello-femoral cartilage volume.[50] A study comparing PRP to exercise therapy found superior radiographic outcomes among PRP users, including: patello-femoral cartilage volume, synovitis percentage, subarticular bone marrow abnormality, and medial/lateral meniscal disintegrity.[55]

PRP Summary Statement

Numerous studies assessed PRP in relation to NS, HA, CS, and other comparative groups. A substantial number were considered to have: (1) “poor” to “fair” methodology (as measured by the MCMS); (2) highly variable cell preparation, technique, and formulations; (3) inconsistent pain, function, and stiffness scores; as well as (4) inconsistent structural outcomes as measured by either ultrasound, radiograph, or MRI evaluations. Overall, the literature assessing PRP use for knee OA remains inconclusive.

<u>Bone Marrow Stem Cells</u>

Methodology

Grading the 15 BMSC studies using the MCMS yielded: seven "good"[69,72,75,76,78,79,82]**,** four **"**fair"[20,71,74,81]**,** and four "poor"[70,73,77,80] quality reports.

Patient Reported Outcome Measures

Three of the 11 BMSC studies were compared to PRP [20,76,101] (**See Table 5**). Of these, BMSC was not superior to PRP in International Knee Documentation Committee (IKDC) and WOMAC scores[20,101], but demonstrated significant improvements when combined with PRP ($p>0.05$).[76] Three studies compared BMSC to HA, but no improvement differences were demonstrated [72,75,82]. As compared to NS, BMSC demonstrated higher WOMAC pain scores but equivocal VAS scores [70,78]. As compared to exercise therapy, BMSC provided equivalent range of motion and VAS, Short Form 12-Item (SF-12), Levels of Emotional Awareness Scale (LEAS), as well as Knee Society Score (KSS) at three months follow-up.[69] Four other studies reported general improvements from baseline without a comparison group.[74,77,80,81]

Radiographic Changes

Three studies reported radiographic changes after BMSC injection.[73,74,79] When comparing BMSC versus saline injected knees, no differences were reported in cartilage compositions of the medial and lateral femoral condyles as measured by T2 mapping.[79] In a study comparing microfracture alone to microfracture with BMSC, no significant differences in coronal or sagittal alignment were reported.[73] A study assessing the effectiveness between subchondral versus intra-articular injection found no differences in changes of articular cartilage

morphology, subchondral cysts, bone marrow edema, articular profile, marginal osteophytes, meniscal integrity, and synovitis (WORMS).[74]

BMSC Summary Statement

Few studies assessed BMSC for the treatment of knee OA. Preparation and administration of these cells varied widely in the assessed studies (see Table 2). The majority had: (1) "poor" to "fair" methodology (as measured by the MCMS); (2) inconsistent pain, function, and stiffness scores; as well as (3) inconsistent structural outcomes as measured by either ultrasound, radiograph, or MRI. Overall, the literature assessing BMSC use for knee OA remains inconclusive.

Adipose Derived Stem Cells

Methodology

Grading the ten ADSC studies using the MCMS yielded: two "good"[86,87]**,** eight **"**fair"[45,83–85,88–91], and one "poor"[92] quality reports. Similar to the other stem cell types, preparation and administration of these cells varied widely in the assessed studies (see Table 2).

Patient Reported Outcome Measures

Ten ADSC studies reported non-superior results as compared to PRP, HA, a combination of PRP/HA, or NS cohorts [45,83–86,88–92] (**See Table 6**). As compared to NS, pain improvement was reported for WOMAC and VAS; however, other parameters resulted in equivocal findings.[88] In a comparison to HA, ADSC demonstrated improved WOMAC and

VAS scores from baseline [87]. When compared to a combination of PRP and HA, ADSC had equivocal VAS scores, but more improved KOOS and Tegner scores [83].

Structural Changes

Of the included studies, studies evaluated cartilage wear utilizing the Outerbridge classification as well as MRI Osteoarthritis Knee Score (MOAKS) and found no differences when compared to either NS or varying doses of SVF injection.[85,86] A RCT compared microfracture alone versus microfracture with SVF of ADSC also found no differences according to the Outerbridge classification.[90] When assessing ADSC versus NS, the size of cartilage defect decreased more in the ADSC group.[88] Comparison of low, mid, and high ADSC doses yielded no differences in WORMS at 48-weeks post-injection.[92] Additionally, no differences were noted in T2 mapping sequences of cartilage in groups of ADSC mixed with either NS, or high or low density PRP.[45] Another study found higher articular cartilage volume after ADSC injection compared to baseline.[89]

ADSC Summary Statement

Only ten studies assessed ADSC for the treatment of knee OA. Almost all were considered to have: (1) “fair” methodology (as measured by the MCMS); (2) inconsistent pain, function, and stiffness scores; as well as (3) inconsistent structural outcomes as measured by either ultrasound, radiograph, or MRI. Overall, the literature assessing ADSC use for knee OA remains inconclusive.

<u>Amniotic-Derived Mesenchymal Stem Cells</u>

Methodology

Grading the five AMSC studies using the MCMS yielded: one "good"[97]**,** two "fair"[95,96]**,** and two "poor"[93,94]**,** quality reports.

Patient Reported Outcome Measures

Five studies evaluated AMSC as compared to HA and NS [93–97] (**See Table 7**). In the form of amniotic suspension allograft, AMSC was reported to show improved KOOS, VAS, EQ-5D-5L, Single Assessment Numerical Evaluation (SANE), and Tegner score, compared to groups.[95] Another study demonstrated improvements regarding WOMAC and VAS scores compared to HA, but SF-36 scores yielded no differences.[97]

Structural Changes

One study evaluated WORMS and found greater improvements among the AMSC groups compared to HA; however, a repeated AMSC injection offered no further improvement.[97] Another study compared ADSC to HA and found no differences when assessing mild or severe OA treated with AMSC.[94]

ADSC Summary Statement

Only five studies assessed AMSC for the treatment of knee OA. All, but one were considered to have: (1) "fair" and "poor" methodology (as measured by the MCMS); (2) inconsistent pain, function, and stiffness scores; as well as (3) inconsistent structural outcomes as measured by either ultrasound, radiograph, or MRI. Overall, the literature assessing AMSC use for knee OA remains inconclusive.

Discussion

Intra-articular knee injections of "orthobiologics" have garnered considerable attention as a non-operative modality to manage knee pain. Its use in orthopaedic practices globally continue to expand.[103,104] In fact, the growth of studies warrants an updated systematic review to adequately apprise current understanding from a previous review of 16 studies by Delanois *et al.,* in 2019.[16] Therefore, we sought to evaluate all level of evidence I to III studies (levels I and II for PRP) evaluating intra-articular biologic injections for knee OA in an update, with inclusion of eligible studies from the previous review [16]. Only 82 of the 644 (87.3%) studies screened met inclusion criteria. Despite an increased focus on "orthobiologics" in recent years, studies continue to demonstrate non-superiority to comparisons groups.

Several limitations exist in this systematic review. The number of available levels I and II studies were limited among non-PRP groups (BMSC, ADSC, and AMSC). Therefore, the authors decided to include up to level III studies for this review to capture the existing breadth of literature available. The number of studies included continue to be skewed towards PRP, likely due to its attraction and availability over other forms of biologics. The formulations, injection techniques, and reported outcomes varied across all studies. Thus, study comparisons were challenging. To offset these limitations, the authors divided the groups such as PRP versus CS or PRP versus HA, in an attempt to arrive at more meaningful conclusions. Additionally, the methodology scores were widely varied, with the majority of studies failing to reach "excellent" or "good" methodologic scores. It is challenging to understand the cost-benefit of administering these treatment modalities given their high cost variability and limited available clinical efficacy. For example, the out of pocket costs for a single PRP injection ranges from $300 to $2,500, with a mean of $750.[105] As orthopaedic surgeons continue to choose alternative payment models,

the cost of various intra-articular injections for the treatment of knee OA may be of increasing importance. Perhaps the greatest cost reduction may result from the ability for injection-based therapies to delay TKA. A recent report evaluated the treatment costs for patients who had knee OA.[106] Among patients with eventual TKA, they found that intra-articular injections of HA was associated with a substantially decreased costs compared to those not treated with HA. HA recipients also underwent eventual TKA later than non-HA recipients (16- to 17-month delay versus 5- to 6-month delay). The strength of our review is that it provides an updated account of the literature regarding treatment of knee OA with intra-articular biologic injections.

Conclusions

Recent years have seen an amplified interest in "orthobiologics" in the form of increased available literature. However, these studies remain inconclusive for multiple reasons: varying levels of methodology scores; cell preparations; as well as inconclusive pain, function, stiffness, and structural outcomes (as measured by ultrasound, radiograph, or MRI). Standardization protocols for cell preparations are required to adequately compare studies. Despite a growth of "orthobiologics" in orthopaedic clinics, this updated systematic review highlights the uncertain efficacy for use in knee OA.

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Figure Legend

Figure 1. PRISMA Flow Diagram

Table 1. Modified Coleman Methodology Scores

Study	Score
PRP	
Ahmad et al. (2018) [18]	54
Akan et al. (2018) [19]	62
Anz et al. (2020) [20]	66
Ayeni et al. (2019) [21]	31
Baki et al. (2021) [22]	55
Bansal et al. (2021) [23]	67
Basnaev et al. (2021) [24]	45
Buendía-López et al. (2018) [25]	61
Camurcu et al. (2018) [26]	62
Cole et al. (2017) [27]	76
Di Martino et al. (2019) [28]	53
Duymus et al. (2017) [29]	86
Elawamy et al. (2021) [30]	74
Elgendy et al. (2020) [31]	57
Elik et al. (2020) [32]	70
Elksniņš-Finogejevs et al. (2020) [33]	63
Filardo et al. (2015) [34]	74
Freire et al. (2020) [35]	57
Gaballa et al. (2019) [36]	47
Ghai et al. (2019) [37]	55
Huang et al. (2019) [38]	64
Jubert et al. (2017) [39]	84
Kesiktas et al. (2020) [40]	73
Khan et al. (2018) [41]	65
Lana et al. (2016) [42]	89
Lin et al. (2019) [43]	70
Lisi et al. (2018) [44]	65
Louis et al. (2021) [45]	58
Louis et al. (2018) [46]	43
Montañez-Heredia et al. (2016) [47]	67
Nabi et al. (2018) [48]	73
Paterson et al. (2016) [49]	70
Park et al. (2021) [50]	77
Patel et al. (2013) [51]	82
Phul et al. (2018) [52]	42
Pishgahi et al. (2020) [53]	65
Qamar et al. (2021) [54]	69
Raeissadat et al. (January, 2020) [55]	62
Raeissadat et al. (June, 2020) [56]	86
Raeissadat et al. (2021) [57]	86
Rahimzadeh et al. (2018) [58]	71
Reyes-Sosa et al. (2020) [59]	47

Simental-Mendía et al. (2016) [60]	77
Smith et al. (2016) [61]	79
Su et al. (2018) [62]	69
Sun et al. (2021) [63]	55
Tavassoli et al. (2019) [64]	62
Uslu et al. (2018) [65]	65
Wu et al. (2018) [66]	62
Xu et al. (2020) [67]	64
Yu et al. (2018) [68]	67
BMSC	
Anz et al. (2020) [20]	66
Centeno et al. (2018) [69]	74
Emadedin et al. (2018) [70]	52
Estrada et al. (2020) [71]	61
Gupta et al. (2016) [72]	79
Jin et al. (2020) [73]	51
Kon et al. (2021) [74]	69
Lamo-Espinosa et al. (2016) [75]	78
Lamo-Espinosa et al. (2020) [76]	74
Rodriguez-Fontan et al. (2018) [77]	47
Shapiro et al. (2017) [78]	75
Shapiro et al. (2019) [79]	70
Themistocleous et al. (2018) [80]	53
Toan et al. (2020) [81]	56
Vega et al. (2015) [82]	78
ADSC	
Dallo et al. (2021) [83]	64
Ehlers et al. (2020) [84]	57
Freitag et al. (2019) [85]	69
Garza et al. (2020) [86]	71
Kuah et al. (2018) [87]	74
Lee et al. (2019) [88]	58
Louis et al. (2021) [45]	58
Lu et al. (2019) [89]	62
Tran et al. (2019) [90]	66
Yokota et al. (2019) [91]	55
Zhao et al (2019) [92]	51
AMSC	
Castellanos et al. (2019) [93]	50
Dilogo et al. (2020) [94]	54
Farr et al. (2019) [95]	61
Gomoll et al. (2021) [96]	69
Matas et al. (2018) [97]	70

PRP: Platelet-Rich Plasma; BMSC: Bone Marrow Derived Stem Cells; ADSC: Adipose Derived Stem Cells; AMSC: Amniotic Derived Stem Cells

Table 2. Biologic Therapy Study Characteristics and Cell Preparations

Study (stratified by cell type)	*Level of Evidence*	*N*	*Cohorts*	*Study Duration*	*Source Site*	*Collection Technique*	*Initial Volume*	*No. of Cells*	*Injection Site/Technique*	*Delivery Solution*	*Qualitative Cell Characterization, CD Markers*	*Successive Injections*
PRP												
HA												
Ahmad et al. (2018) [18]	I	90	PRP vs. HA	6 M	Venous blood	Blood draw	8 mL	NR	NR	2 mL	NR	None
Bansal et al. (2021) [23]	I	150	PRP vs. HA	1 Y	NR	NR	60 mL	Plt: 12.68 to 16.2 × 105 plt/µL, Leukocyte: 0, PDGF: 50,246 to 74,938 pg/mL; VEGF: 1348 to 2429 pg/mL	Superolateral	8 mL	IL-6, IL-8 and TNF-α	None
Basnaev et al. (2021) [24]	I	128	PRP, HA, chond. sulfate	6 M	NR	NR	NR	800 x 10^9/L	NR	NR	NR	1 injection/week for 1 M
Buendia-Lopez et al. (2018) [25]	I	98	PRP, HA, NSAID	12 M	Venous blood	Blood draw	60 mL	1,095,000/mL^3	NR	5 mL	NR	None
Cole et al. (2017) [27]	I	99	PRP vs. HA	1 Y	Venous blood	Blood draw	10 mL	790 WBCs/µL; PRP to peripheral blood ratio: 1.73	NR	4 mL	IL-1b, IL-1ra, IL-6, IL-8, TNF-a)	3 injections, 1 week intervals
Di Martino et al. (2019) [28]	I	192	PRP vs. HA	2 Y	Venous blood	Blood draw	150 mL	NR	NR	5 mL	NR	3 injections, 1 week intervals
Duymus et al. (2017) [29]	I	102	PRP vs. HA vs. ozone	1 Y	Venous blood	Blood draw	14 mL	NR	Suprapatellar	5 mL	NR	2 injections, 1 M interval
Filardo et al. (2015) [34]	I	183	PRP vs. HA	1 Y	Venous blood	Blood draw w/ sodium citrate	150 mL	Plt: 4.6 x baseline; leuk: 1.1 x normal	NR	NR	NR	3 injections, 1 week intervals
Huang et al. (2019) [38]	I	120	PRP vs. HA vs. CS	1 Y	Venous blood	Blood draw	8 mL	NR	Suprapatellar	4 mL	NR	None
Kesiktas et al. (2020) [40]	I	54	PRP vs. HA	3 M	NR	2.2 mL anticoag.	17 mL (women) ; 16 mL (men)	NR	Suprapatellar	2-3 mL	NR	None
Lana et al. (2016) [42]	I	108	PRP vs. HA vs. PRP+HA	1 Y	Venous blood	Blood draw with citric acid, sodium citrate, dextrose	60 mL	Plt range: 155 to 315 mm^3	Lateral mid-patellar	5 mL	NR	3 injections, 2 week intervals
Lin et al. (2019) [43]	I	53	PRP vs. HA vs. NS	1 Y	NR	Blood draw	10 mL	NR	Anteromedial	2 mL	NR	None
Lisi et al. (2018) [44]	I	50	PRP vs. HA	6 M	Whole blood	NR	20 mL	NR	Superolateral	NR	NR	3 injections at 4 week intervals
Louis et al. (2018) [46]	II	34	PRP vs. HA	6 M	Blood draw	NR	52.5 mL (men) or	Plt: 800x10^9/L.	NR	3 mL	PDGF+TGF-B+VEGF	None

							37.5 mL (women)	WBC: 0.86x10^9/L. Plt: Increase factor >2 compared with blood, 2,400 x 10^6; WBC: 3 x 10^6				
Montañez-Heredia et al. (2016) [47]	I	53	PRP vs. HA	6 M	Venous blood	NR	NR	HGF: 183.11 pg/mL; EGF 270.09 pg/mL; FGF-2 60.70 pg/mL; PDGF-B 1337.99 pg/mL	NR	NR	HGF, EGF, FGF-2, PDGF-B	3 injections, interval NR
Paterson et al. (2016) [49]	I	19	PRP vs. HA	3 M	Venous blood	Blood draw	48.5 mL, UV light	NR	Anteromedial	3mL	NR	None
Park et al. (2021) [50]	I	110	PRP vs. HA	6 M	Venous blood	Blood draw	54 mL	Plt count: 976,000 /µL; Leukocyte count: 29,400µL; RBC count: 900,000µL	Superolateral	3 mL	PDGF, TGF-B1, VEGF, EGF, bFGF, IGF-1, IL-1B, MMP-13, IL-1ra	None
Raeissadat et al. (June 2020) [56]	I	119	PRP vs. HA	1 Y	NR	NR	35 mL	PDGF: 279±52.1ng/mL; VEGF: 312±23.2ng/mL	Lateral	5 mL	PDGF, IGF, TGF-β1, TGF-β 2	3 injections with 1 week intervals
Raeissadat et al. (2021) [57]	I	238	PRP vs. PRGF vs. HA vs. Ozone	1 Y	Venous blood	18-G needle; +5 mL acid citrate dextrose	35 mL	NR	Lateral mid-patellar, and medial/lateral infrapatellar	3.5 mL	NR	2 doses with 3 weeks interval
Smith et al. (2016) [61]	I	30	PRP vs. HA	1 Y	Venous blood	Blood draw	15 mL	NR	Lateral parapatellar	Range 3 to 8 mL	NR	3 injections with 1 week intervals
Su et al. (2018) [62]	I	86	PRP vs. HA	18 M	Venous blood	50-mL injectors w/ 4 mL sodium citrate	45 mL	Plt count in peripheral whole blood and PRP: 140.73 × 10^9/L; Plt and PRP: 789.68) × 10^9/L; leukocyte counts in the peripheral whole blood and PRP were 5.25 × 10^9/L and 29.92 × 10^9/L	Superolateral	2 mL	NR	None
Sun et al. (2021) [63]	I	85	PRP vs. HA	6 M	Venous blood	NR	7 mL	Plt count: 463.83 ± 75.39 × 10^3	NR	3 mL	NR	None
Tavassoli et al. (2019) [64]	I	95	PRP vs. HA	3 M	Venous blood	18-G needle; +5 mL of acid citrate dextrose	40 mL	NR	Superolateral or midpatellar tendon	4-6 mL	NR	Double dose group had the PRP injections 3 weeks apart
Xu et al. (2020) [67]	II	150	PRP vs. HA	2 Y	Venous blood	Blood drawn	36 mL	Plt: 95.0 ± 17.3 × 10^4	Lateral	4 mL	IL-1B, TNF-a, MMP-3, TIMP-1	3 total injections at half M intervals
Yu et al. (2018) [68]	I	360	PRP vs. HA	1 Y	NR	NR	8 mL or 14 mL	NR	NR	8 mL or 14 mL	TNF-a, IL-1B, IL-6, IL-17a, RANKL, PD-ECGF, VEGF, IL-10	PRP 2, 4, 8, 10, 12, 14mL and PRP 8mL
CS												
Camurcu et al (2018) [26]	I	132	PRP vs. CS	1 Y	Venous blood	Blood drawn	18 mL	NR	Suprapatellar	3 mL	NR	None
Elksniņš-Finogejevs et al. (2020) [33]	I	40	PRP vs. CS	1 Y	Venous blood	NR	18 mL	NR	Anterolateral	8 mL	NR	None
Freire et al. (2020) [35]	I	50	PRP vs. CS	6 M	Venous blood	5 mL vacuum tubes +	15 mL	NR	Superolateral	5 mL	NR	None

						3.2% sodium citrate						
Jubert et al. (2017) [39]	II	64	PRP vs. CS	6 M	Venous blood	Collected in tubes of citrated dextrose	60 mL	NR	Medial compartment	4 mL	NR	None
Khan et al. (2018) [41]	I	103	PRP vs. CS	6 M	NR	NR	NR	NR	Superolateral	5 mL	NR	2-6 M, every 2 weeks
Nabi et al. (2018) [48]	I	67	PRP vs. CS	6 M	NR	Blood draw	50 mL	4- to 6-fold increase in plt count	Superolateral	5 mL	NR	3 injections, 1 M apart
Phul et al. (2018) [52]	I	80	PRP vs. CS	3 M	Venous blood	18µG needle	35–40 mL	NR	Suprapatellar or medial	4–6 mL	NR	None
Uslu et al. (2018) [65]	I	50	single dose PRP, triple dose PRP, CS	6 M	Venous blood	18-G needle	18 mL	Plt: 875 10^9; WBC: 8.67 10^9	Lateral-parapatellar	NR	NR	None
NS												
Elik et al. (2020) [32]	I	57	PRP vs. NS	6 M	NR	NR	10 mL	Plt: 900,000–1,100,000; WBC: 5,000–10,000	Lateral	4 mL	NR	3 doses at one-week intervals
Ghai et al. (2019) [37]	I	40	PRP vs. NS	6 M	Venous blood	Blood draw	50-60 mL	Plt: 310.14 x 10^3	Superolateral	8 mL	NR	None
Louis et al. (2021) [45]	II	27	microfat PRP high density, microfat PRP low density, microfat NS	6 M	Venous blood	Blood draw	45 mL	Plt: PRP HD: 3.0 x 109, PRP LD: 1.1 x 10^7; WBC: PRP HD: 20.1 x 10^6, PRP LD: 5.1 x 10^6	Lateral patellofemoral	5 mL	IL-1b+TNFa+IL-6+IFNg+IL-10+IL-1Ra+PDGF+VEGFa+NGF+EGF+EGF+FGF2+TGFb1	None
Patel et al. (2013) [51]	I	75	Single PRP vs. double PRP vs. NS	6 M	Venous blood	Blood draw	100 mL with CPD-A1	Plt: 310.14 3 10^3/µL	Superolateral	8 mL	NR	2nd injection interval NR
Qamar et al. (2021) [54]	I	100	PRP vs. NS	6 M	Venous blood	Blood draw	20 mL	NR	Superolateral	5 mL	NR	3 injections, 1 week apart
Wu et al. (2018) [66]	I	20	PRP vs. NS	6 M	Venous blood	Blood draw	10 mL	NR	Inferolateral	NR	NR	None
Others												
Ayeni et al. (2019) [21]	I	45	PRP, PRP+NSAID, and NSAID only	6 M	Venous blood	Blood draw	20 mL	NR	NR	3 mL	NR	1 injection/4 weeks for a max of 3 injections
Baki et al. (2021) [22]	II	100	PRP vs. chondro-protective meds.	6 M	Venous blood	Blood draw	30 mL	Plt: 2.56 X 10^6	NR	5 mL	NR	2 injections one week apart
Reyes-Sosa et al. (2020) [59]	II	60	PRP vs. celecoxib	1 Y	Venous blood	NR	10 mL	NR	NR	3 mL	NR	2 injections 15 days apart
Simental-Mendía et al (2016) [60]	I	65	PRP vs. acetaminophen	4 M	Venous blood	Blood draw w/ sodium citrate	27 mL	NR	NR	3 mL	NR	3 injections over 6 weeks (1 every 2 weeks)

Akan et al. (2018) [19]	I	60	PRP+exercise vs. exercise alone	6 M	Venous blood	NR	20 mL	Plt yield: 6.36	Anterolateral	1 mL	PDGF+TGF-B+IGF+VEGF+EGF	3 injections at 3- week intervals
Anz et al. (2020) [20]	II	90	PRP vs. BMSC	1 Y	Venous blood	Blood draw	60 mL	1,216 X 10^6	Superolateral	7 mL	CD34+ and CFU-F	None
Elawamy et al. (2021) [30]	I	200	PRP, pulsed RF	12 M	Venous blood	Blood draw	30 mL	NR	Superolateral	4-5 mL	NR	2 injections one M apart
Elgendy et al. (2020) [31]	I	45	PRP, SWT, PT	Post-procedure	Venous blood	Blood draw	36 mL	NR	Superolateral	6 mL	NR	None
Gaballa et al. (2019) [36]	I	60	PRP, ozone, rehab	3 M	NR	NR	15 mL	NR	NR	NR	NR	1 injection/week for 2 weeks
Pishgahi et al. (2020) [53]	I	92	PRP vs. dextrose vs. ACS	6 M	Venous blood	Blood draw	20 mL	NR	Superolateral	NR	NR	2 total injections at 1 week interval
Raeissadat et al. (2020) [55]	I	46	PRP vs. Exercise	8 M	NR	NR	NR	NR	NR	NR	NR	2 sessions with 4-weeks intervals
Rahimzadeh et al. (2018) [58]	I	42	PRP, prolotherapy	6 M	NR	NR	20 mL	NR	Superolateral	7 mL	NR	1 then 4 weeks later
BMSC												
Anz et al. (2020) [20]	II	90	BMSC vs. PRP	1 Y	PSIS	Jamshidi needle	60 mL	NR	Superolateral	7 mL	CD34+ and CFU-F	None
Centeno et al. (2018) [69]	I	48	BMSC vs. Exercise	1 Y	PSIS or IC	NR	60-90 mL	NR	NR	5-7 mL	NR	None
Emadedin et al. (2018) [70]	I	47	BMSC vs. NS	1 Y	IC	Aspiration	NR	40 x 10^6 MScs	NR	5 mL	NR	None
Estrada et al. (2020) [71]	II	89	BMSC vs. ATDSC vs. PRP	1 Y	IC	NR	45 mL	NR	NR	NR	NR	None
Gupta et al. (2016) [72]	I	60	BMSC million cell dose groups (25, 50, 75, 150) vs. HA	1 Y	NR	NR	NR	NR	Lateral midpatellar	NR	NR	None
Jin et al. (2020) [73]	III	131	Microfracture with BMSC vs. Microfracture	2 Y	ASIS	60 mL heparinized syringe	40 mL	NR	Mini-arthrotomy	NR	NR	None
Kon et al. (2021) [74]	II	30	BMSC	1.8 Y	ASIS	Two syringes coated w/ glucose citrate	NR	NR	Superolateral	9 mL	NR	None

Lamo-Espinosa et al. (2020) [76]	I	60	BMSC vs. PRP	1 Y	IC or pelvis	NR	100 mL	100 x 10^6 BMSC, PRP NR (8mL)	Lateral patellar	8 mL	NR	PRP only group: 3 doses of 8mL, 1 week each
Rodriguez-Fontan et al. (2018) [77]	II	19	BMSC	2 Y	IC	Aspiration needle	120 mL	NR	NR	12 mL	NR	None
Shapiro et al. (2017) [78]	II	25	BMSC vs. NS	6 M	IC	11-G Jamshidi, with citrate dextrose	26 mL	31.4 WBCs 1000/μL, 4.4 x 10^6 HSCs, 34,400 MSCs with 97% cellular viability	Superolateral	15 mL	NR	None
Shapiro et al. (2019) [79]	I	25	BMSC vs. NS	6 M	IC	11-G Jamshidi, with citrate dextrose	26 mL	150 x 10^6 WBC, 4.4 x 10^6 HSCs, and 34,000 MSCs	Superolateral	15 mL	NR	None
Themistocleous et al. (2018) [80]	III	121	BMSC	1 Y	IC	Bone access needle	80 mL	NR	Anterolateral	10 mL	NR	None
Toan et al. (2020) [81]	II	46	BMSC	2 Y	PSIS or IC	NR	120 mL	NR	NR	10 mL	NR	None
Vega et al. (2015) [82]	I	30	BMSC vs. HA	1 Y	Iliac spine	11-G trocar	80 mL	NR	Medial parapatellar	40 x 10^6 cells/ knee from a 5 x 10^6 cell/mL suspension	NR	None
ADSC												
Dallo et al. (2021)[83]	II	50	ADSC vs. PRP+HA	1 Y	Abdomen	Lipoharvest	60 mL	NR	Suprapatellar	NR	NR	None
Ehlers et al. (2020)[84]	III	89	PRP vs. PRP+ ADSC	1 Y	NR	NR	NR	NR	Suprapatellar, medial, or lateral	8 mL	NR	None
Freitag et al. (2019)[85]	I	30	ADSC vs. conservative management	1 Y	Abdomen	Lateral abdominal approach	60 mL	100 x 10^6 ADMSCs	Superolateral	3 mL	CD90, CD73, CD105, CD14, CD19, CD34, CD45	2 total injections, 6 M apart
Garza et al. (2020)[86]	I	39	SVF vs. non-SVF	1 Y	Abdomen	NR	75 mL	3.0 X 10^7 SVF cells or 1.5 X 10^7 SVF cells	Superolateral	3-4 mL	NR	None
Lee et al. (2019)[88]	I	24	ADSC vs. NS	6 M	Abdomen	Lipoaspiration through tumescent technique	20 mL	1 x 10^8 ADMSC	NR	3 mL	CD31, CD34, CD45, CD73, CD90	None

Louis et al. (2021) [45]	II	27	microfat PRP high density, microfat PRP low density, microfat NS	6 M	Abdomen	Liposuction with local anesthetic	NR	Plt: PRP HD: 3.0 x 109, PRP LD: 1.1 x 10^7; WBC: PRP HD: 20.1 x 10^6, PRP LD: 5.1 x 10^6	Lateral	5 mL	IL-1b+TNFa+IL-6+IFNg+IL-10+IL-1Ra+PDGF+VEGFa+NGF+EGF+EGF+FGF2+TGFb1	None
Lu et al. (2019)[89]	I	53	haMPC vs. HA	1 Y	Abdomen	Liposuction with local anesthetic	NR	5×10^7 haMPCs	NR	2.5 mL	NR	2 total injections, 3 weeks apart
Tran et al. (2019)[90]	II	33	SVF vs. Microfracture	2 Y	Abdomen	Liposuction	50-100 mL	90-120 x 10^6	NR	6 mL	NR	None
Yokota et al. (2019)[91]	III	80	ASC vs. SVF	6 M	NR	Liposuction	100-200 mL	NR	NR	5 mL	NR	NR
Zhao et al. (2019)[92]	II	24	ADSC	48 W	Abdomen	Liposuction	50g	1 x 10^7	NR	NR	CD29, CD73, CD90, and CD49d	2 total injections, 3 weeks apart
AMSC												
Castellano et al. (2019)[93]	II	20	AMSC	24 W	NR	NR	NR	NR	Lateral	50 mg	NR	NR
Dilogo et al. (2020)[94]	II	33	AMSC	6 M	Umbilical cord	Dissection	NR	10 x 10^6	NR	2 mL	NR	None
Farr et al. (2019)[95]	I	200	ASA vs. NS vs. HA	6 M	NR	NR	NR	NR	NR	4 mL	NR	None
Gomoll et al. (2021)[96]	I	200	ASA	1 Y	Inner layer of placenta	Cesarean section	NR	NR	NR	2 mL	NR	None
Matas et al. (2018)[97]	I	29	AMSC vs. HA	1 Y	Placentas	Cesarean section	NR	20×10^6	NR	3 mL	CD73, CD90, and CD105, CD45, CD34, CD14, and Human Leukocyte Antigen-DR isotype (HLA-DR)	None

ADMSC: adipose derived mesenchymal stem cells; AMSC; amnionic stem cells; ASA: amniotic suspension allograft; BMSC: bone marrow stem cell; CPD-A1: citrate phosphate dextrose and adenine; EGF: epidermal growth factor; IGF-1: insulin-like growth factor; IL: interleukin; IL-1B: interleukin 1B; MSC: mesenchymal stem cells; mL: milliliters; MMP-13: matrix metalloproteinase 13; NSAIDs: non-steroidal anti-inflammatory drugs; PDGF: platelet derived growth factor; PRP: platelet rich plasma; RF: radiofrequency; SWT: shockwave therapy; TGF-B1: transforming growth factor B1; TNF: tumor-necrosis factor; UC-MSC: umbilical cord mesenchymal stem cells; VEGF: vascular endothelial growth factor

Table 3. Cell Formulations in Platelet-Rich Plasma

Study	*Platelet Count*	*Leukocyte count*	*PDGF concentration*	*VEGF concentration*	*RBC concentration*	*Leukocyte Rich/Poor*
Ahmad et al. (2018) [18]	NR	NR	NR	NR	NR	Rich
Akan et al. (2018) [19]	6.36 (plt yield)	8.25 (leuk yield)	190927.96 ± 36619.33 (pg/mL)	10381.33 ± 413.1 (pg/mL)	NR	NR
Anz et al. (2020) [20]	1,216 X 10^6/mL	14.7 X 10^6/mL	NR	NR	0.12 X 10^6/mL	Rich
Ayeni et al. (2019) [21]	NR	NR	NR	NR	NR	NR
Baki et al. (2021) [22]	2.56 X 10^6	NR	NR	NR	NR	Poor
Bansal et al. (2021) [23]	12.68 to 16.2 × 10^5/μL	0	50,246 to 74,938 pg/mL	1348 to 2429 pg/mL	NR	Poor
Basnaev et al. (2021) [24]	800 x 10^9/L	NR	NR	NR	NR	NR
Buendia-Lopez et al. (2018) [25]	1,095,000/mL^3	NR	NR	NR	NR	Poor
Camurcu et al. (2018) [26]	NR	NR	NR	NR	NR	NR
Cole et al. (2017) [27]	NR	NR	NR	NR	NR	Poor
Di Martino et al. (2019) [28]	NR	NR	NR	NR	NR	Rich
Duymus et al (2017) [29]	NR	NR	NR	NR	NR	NR
Elawamy et al. (2021) [30]	NR	NR	NR	NR	NR	NR
Elgendy et al. (2020) [31]	NR	NR	NR	NR	NR	NR
Elik et al. (2020) [32]	900,000–1,100,000/mm	5,000–10,000/mm^3	NR	NR	NR	NR

Elksniņš-Finogejevs et al. (2020) [33]	NR	NR	NR	NR	NR	NR
Filardo et al. (2015) [34]	4.6 x baseline	1.1 x normal	NR	NR	NR	Rich
Freire et al. (2020) [35]	NR	NR	NR	NR	NR	NR
Gaballa et al. (2019) [36]	NR	NR	NR	NR	NR	NR
Ghai et al. (2019) [37]	310.14 x 10^3/mL	NR	NR	NR	NR	NR
Huang et al. (2019) [38]	NR	NR	NR	NR	NR	Poor
Jubert et al. (2017) [39]	0.99x10^6 platelets/µL	NR	NR	NR	NR	Poor
Kesiktas et al. (2020) [40]	NR	NR	NR	NR	NR	NR
Khan et al. (2018) [41]	NR	NR	NR	NR	NR	NR
Lana et al. (2016) [42]	Range: 155 to 315 mm^3	NR	NR	NR	NR	Rich
Lin et al. (2019) [43]	NR	Low	NR	NR	NR	Poor
Lisi et al. (2018) [44]	NR	NR	NR	NR	NR	NR
Louis et al. (2021) [45]	Plt: PRP HD: 3.0 x $10^{9:}$ PRP LD: 1.1 x 10^9	PRP HD: 20.1 x 10^6, PRP LD: 5.1 x 10^6	90.8 (MF/Saline), 499.7 (PRP LD), 1046.4 (PRP HD)	64.5 (MF/Saline), 66.2 (PRP LD), 13.3 (PRP HD)	90x10^6 (PRP LD), 210x10^6 (PRP HD)	NR
Louis et al. (2018) [46]	800x10^9/L. 2,400 x 10^6	0.86x10^9/L. 3 x 10^6	30,431 ng/mL	606 pg/mL	NR	NR

Montañez-Heredia et al. (2016) [47]	NR	NR	1,337.99 pg/mL	NR	NR	Poor
Nabi et al. (2018) [48]	NR	NR	NR	NR	NR	NR
Patel et al. (2013) [51]	310.14 3 10^3/μL	NR	NR	NR	NR	Poor
Paterson et al. (2016) [49]	NR	NR	NR	NR	NR	Rich
Park et al. (2021) [50]	9.76 × 10^5/μL	29,400/μL	AA: 1651.9; BB: 3801.6; AB: 10712.5 pg/mL	204.3 pg/mL	9.0 x 10^5 /μL	Rich
Phul et al. (2018) [52]	NR	NR	NR	NR	NR	Rich
Pishgahi et al. (2020) [53]	NR	NR	NR	NR	NR	Poor
Qamar et al. (2021) [54]	NR	NR	NR	NR	NR	NR
Raeissadat et al. (2020) [55]	4–6 x normal	4–6 x normal	NR	NR	NR	Rich
Raeissadat et al. (June 2020) [56]	NR	NR	279±52.1 ng/mL	312±23.2 ng/mL	NR	Poor
Raeissadat et al. (2021) [57]	NR	NR	NR	NR	NR	Poor
Rahimzadeh et al. (2018) [58]	NR	NR	NR	NR	NR	NR
Reyes-Sosa et al. (2020) [59]	NR	NR	NR	NR	NR	Poor
Simental-Mendía et al (2016) [60]	513.25 ± 189.3	0.52 ± 0.46	NR	NR	NR	Poor
Smith et al. (2016) [61]	NR	NR	NR	NR	NR	Poor
Su et al. (2018) [62]	(140.73) × 10^9 /L; in PRP: (789.68) × 10^9 /L,	5.25 × 10^9/L; in PRP 29.92 × 10^9/L.	NR	NR	NR	Rich

Sun et al. (2021) [63]	463.83 ± 75.39 × 10^3/ul	NR	NR	NR	NR	Poor
Tavassoli et al. (2019) [64]	NR	NR	NR	NR	NR	NR
Uslu et al. (2018) [65]	875x10^9/L	8.67x10^9/L	NR	NR	NR	NR
Wu et al. (2018) [66]	NR	NR	NR	NR	NR	Rich
Xu et al. (2020) [67]	95.0 ± 17.3 × 10^4 /μL	NR	NR	NR	NR	Poor
Yu et al. (2018) [68]	NR	NR	NR	NR	NR	NR

PDGF: platelet-derived growth factor; VEGF: vascular endothelial growth factor; RBC: red blood cell; Plt: platelet; PRP: platelet-rich plasma

Table 4. Patient Reported Outcome Measures using Platelet-Rich Plasma

Study	*WOMAC*	*VAS*	*KOOS*	*IKDC*	*Lysholm*	*SF-12*	*Lesquesne Index*	*SLS*	*6MWD*	*Isokinetic parameters*	*KSS*	*ROM*	*TUGT*
Ahmad et al. (2018) [18]	NR	Δ-1.66 (PRP), Δ-0.15 (HA), p=0.012.	NR	Δ26.5 (PRP), Δ18.4 (HA), p=.004.	NR	NR	NR	NR	NR	NR	NR	NR	NR
Akan et al. (2018) [19]	pain: Δ0.25 (PRP), Δ-2.95 (exercise) (p=0.001) (from baseline); stiffness: Δ1.25 (PRP), Δ-2.50 (exercise) (p=0.001) (from baseline); function: Δ1.23 (PRP), Δ-3.16 (exercise) (p=0.001) (from baseline)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Anz et al. (2020) [20]	Total: Δ-15.9 (BMSC), Δ-15.3 (PRP), p>0.05; pain: Δ-3.5 (BMSC), Δ-3.3, p>0.05; stiffness: Δ-1.5 (BMSC), Δ-1.6 (PRP), p>0.05; Function: Δ-10.1 (BMSC), Δ-10.0 (PRP), p>0.05	NR	NR	Δ19.3 (BMSC), Δ16.3 (PRP)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ayeni et al. (2019) [21]	total: Δ-28.45 (PRP), Δ-27.75 (PRP+NSAIDS), Δ-2.40 (NSAIDS) (p=0.001) (between groups at final follow-up)	Δ-4.0 (PRP), Δ-4.2 (PRP+NSAIDS), Δ-0.8 (NSAIDS) (p=0.001) (between groups at final follow-up)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baki et al. (2021) [22]	Δ-52.96 (PRP), Δ-8.66 (Chondro), p<0.001.	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bansal et al. (2021) [23]	Pain, stiffness, and physical function (PRP vs. HA); all *p*<0.01	NR	NR	Δ9.2 (PRP); Δ-1.5 (HA); *p*<0.001.	NR	NR	NR	NR	Δ120 (PRP); Δ4 (HA); *p*<0.001.	NR	NR	NR	NR
Basnaev et al. (2021) [24]	pain: Δ-121.96 (PRP), Δ-116.30 (HA), Δ-99.60 (chondroitin sulfate) (p<0.05) (from baseline); stiffness: Δ-51.8 (PRP), Δ-49.9 (HA), Δ-46.9 (chondroitin sulfate) (p<0.05)	-3.7 (PRP), -2.1 (HA), -2.0 (chondroitin sulfate) (p<0.05)	NR	NR	NR	NR	-8 (PRP), -6.4 (HA), -5.1 (chondroitin sulfate) (p<0.05) (from baseline)	NR	NR	NR	NR	NR	NR

	(from baseline); function: Δ-169.3 (PRP), Δ-166.4 (HA), Δ-155.6 (chondroitin sulfate) (p<0.05) (from baseline)	(from baseline)											
Buendia-Lopez et al. (2018) [25]	total: Δ-18.90% (PRP), Δ0.07% (HA), Δ0.20% (NSAID) (p<0.001) (between groups at final follow-up); pain: Δ-20.39% (PRP), Δ-1.03% (HA), Δ-6.40% (NSAID) (p<0.03) (between groups at final follow-up); stiffness: Δ-16.1% (PRP), Δ-0.7% (HA), Δ4.9% (NSAID) (p<0.001) (between groups at final follow-up); function: -19.0, 0.3, 0.9 (p<0.001) (between groups at final follow-up)	Δ-18.2 (PRP), Δ3 (HA), Δ-6.4 (NSAID) (p<0.001) (between groups at final follow-up)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cole et al. (2017) [27]	Δ-3.98 (PRP); Δ-3.52 (HA), (p>0.05)	At 1 Y: 44 ± 4.6 (PRP); 57.3 ± 3.8 (HA), p=.0039)	NR	At 1 Y: 57.6 ± 3.37 (PRP) vs 46.6 ± 3.76 (HA); p=.003	NR	NR	NR	NR	NR	NR	NR	NR	NR
Camurcu et al. (2018) [26]	Total: Δ-1 (PRP), Δ-1 (CS), Δ-3 (PRP + CS), p>0.05. Pain: Δ1 (PRP), Δ0 (PRP + CS), Δ2 (CS), p<0.05. Stiffness: Δ0 (PRP), Δ0 (PRP + CS), Δ2 (CS), p<0.05. Physical Function: Δ0 (PRP), Δ0 (PRP + CS), Δ-1 (CS), p>0.05.	Δ-1 (PRP), Δ0 (PRP, PRP+CS), p>0.05	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Di Martino et al. (2019) [28]	NR	Δ6.7 (PRP), Δ3.1 (HA).	NR	Δ14 (PRP), Δ11.8 (HA).	NR	NR	NR	NR	NR	NR	NR	NR	NR
Duymus et al (2017) [29]	Total: Δ+28.5 (PRP), Δ+36.1 (HA), Δ+45.9 (ozone), p<0.001	Δ+2.6 (PRP), Δ+4.2 (HA), Δ+4.1 (ozone), p<0.001	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Elawamy et al. (2021) [30]	NR	p = 0.04 (between groups (PRP, RF) at final follow-up)	NR	NR	NR	NR	p < 0.001 (between groups (PRP, RF) at final follow-up)	NR	NR	NR	NR	NR	NR
Eldendy et al. (2020) [31]	NR	Δ-5.64 (PRP), Δ-5.64 (SWT), Δ-3.31 (PT) (p=0.001)	NR	NR	NR	NR	total: Δ-61 (PRP), Δ-62.67 (SWT), Δ-26.2 (PT) (p=0.001) (from baseline)	NR	NR	NR	NR	Δ58.6, Δ59.8, Δ36.46 (p=0.001) (from	NR

		(from baseline)										baseline)	
Elik et al. (2020) [32]	total: Δ-31.53 (PRP), Δ-14.67 (NS) (p<0.001) (from baseline); pain: Δ-6.40 (PRP), Δ-3.26 (NS) (p<0.001) (from baseline); stiffness: Δ-2.67 (PRP) (p<0.001), Δ-1.07 (NS) (p=0.002) (from baseline); function: Δ-22.37 (PRP) , Δ-9.22 (NS) (p<0.001) (from baseline)	Δ-2.67 (PRP), Δ-1.56 (NS) (p<0.001) (from baseline)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Elksniņš-Finogejevs et al. (2020) [33]	NR	Δ-3.2 (PRP), Δ-0.9 (CS) *p=.0008.*	NR	Δ25.4 (PRP), Δ9.8 (CS), *p=.0002.*	NR	NR	NR	NR	Δ19 (PRP), Δ6.3 (CS) *p=.0004.*	NR	Δ19 (PRP), Δ6.3 (CS) *p=.0004.*	NR	NR
Filardo et al. (2015) [34]	NR	Δ+0.44 (PRP), Δ+1.8 (HA) (ns)	Δ+8.8 (PRP), Δ+11.3 (HA) (ns)	Δ+13.8 (PRP), Δ+14.6 (HA) (ns)	NR	NR	NR	NR	NR	NR	NR	Δ+0.6 (PRP), Δ-0.8 (HA), ns)	NR
Freire et al. (2020) [35]	Δ-16.57 (CS), Δ-41.14 (PRP).	NR	NR	NR	NR	NR	NR	NR	NR	NR	Δ16.96 (CS), Δ32.92 (PRP). P<0.05	NR	NR
Gaballa et al. (2019) [36]	total: Δ-26.0 (PRP) (p<0.0004), Δ-4.0 (ozone) (p<0.0002), Δ1.2 (rehab) (p<0.0001) (from baseline)	Δ-3.3 (PRP) (p<0.0003), Δ-0.7 (ozone) (p<0.0002), Δ-0.2 (rehab) (p<0.0001) (from baseline)	NR	NR	NR	NR	NR	NR	Δ48 (PRP) (p=0.001), Δ11 (ozone) (p<0.0002), Δ-1 (p=0.052) (rehab) (from baseline)	NR	NR	NR	NR
Ghai et al. (2019) [37]	total: Δ-19.4 (PRP) (p<0.001), Δ-0.2 (NS) (p=0.046) (from baseline); pain: Δ-7.15 (PRP) (p<0.001), Δ-0.15 (NS) (p=0.046) (from baseline); stiffness: Δ-2.8 (PRP) (p=0.00), Δ0 (NS) (p=1.00) (from	Δ-3.55 (PRP) (p<0.001), Δ-1.45 (NS) (p=0.017) (from baseline)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

	baseline); function: Δ-9.3 (PRP) (p=0.00), Δ0 (NS) (p=1.00) (from baseline)												
Huang et al. (2019) [38]	Total score; Δ-16.59 (IA-HA), Δ-14.4 (IA-CS), Δ-32.09 (IA-PRP), *p<.05.*	Δ-2.400 (IA-HA), Δ-2.380 (IA-CS), Δ-2.590 (IA-PRP)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Jubert et al. (2017) [39]	NR	Δ-3.69(PRP); Δ-2.87(CS), p=.568	Δ+16.88(PRP) ; Δ+3.56(CS), (p=.03)	NR	NR	Δ+4.25(PRP); Δ-4.92(CS, (p=.018)	NR	NR	NR	NR	NR	Follow -up scores NR	NR
Kesiktas et al. (2020) [40]	Pain: Δ-6 (peptide); Δ-4.4 (HA), Δ-7.1 (PRP), *p=.013;* stiffness: Δ-2.4 (peptide), Δ-1.6 (HA), Δ-2.8 (PRP), p=0.053*;* function: Δ-19.9 (peptide), Δ-14.4 (HA), Δ-24.8 (PRP), p=*.832;* total: Δ-29.7 (peptide), Δ-21.5 (HA), Δ-36.2 (PRP), *p*=0.555.	Resting pain: Δ-20.6 (peptide), Δ-9.4 (HA), Δ-18.9 (PRP), p=.018; VAS movement pain: Δ-35 (peptide), Δ-35 (HA), Δ-28.9 (PRP), p=.372.	NR	NR	NR	NR	NR	NR	NR	NR	NR	103.9 (peptide), 113.4 (HA), 108.3 (PRP).	NR
Khan et al. (2018) [41]	Pain: Δ-3 (CS), Δ-4.76 (PRP); stiffness: Δ-1.5 (CS), Δ-.94 (PRP); function: Δ-23.28 (CS), Δ-20.68 (PRP).	Δ-3.3 (CS), Δ-2.735 (PRP).	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lana et al. (2016)	Pain: Δ-188(HA), Δ-238 (PRP), Δ-200 (HA+PRP), p=0.0000 (between HA and PRP); stiffness: Δ-75 (HA), Δ-100 (PRP), Δ-88 (HA+PRP), p=0.3192; physical activity: Δ-450 (HA), Δ-775 (PRP), Δ-825 (HA+PRP), p=0.0089	Δ-2 (HA), Δ-5(PRP), Δ-5 (HA+PRP), p=0.0000 (between HA and PRP)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lin et al. (2019) [43]	Total score: Δ10.9 (PRP), Δ-3.34 (HA), Δ-1.65 (NS) p<0.05.	NR	NR	Δ14.22 (PRP), Δ2.71 (HA), Δ-0.34 (NS).	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lisi et al. (2018) [44]	total: Δ-23.5 (PRP), Δ-15 (HA) (p=0.29) (from baseline); pain: Δ-4 (PRP), Δ-4 (HA) (p=0.91) (from baseline); stiffness: Δ-2 (PRP), Δ-3 (HA) (p=0.58) (from baseline); function: Δ-18 (PRP), Δ-11 (HA) (p=0.002) (from baseline)	Δ-6 (PRP), Δ-5 (HA) (p=0.78) (from baseline)	NR	NR	NR	NR	Δ-7 (PRP), Δ-4 (HA) (p=0.04) (from baseline)	NR	NR	NR	NR	NR	NR

Louis et al. (2021) [45]	total: Δ-21.2 (microfat PRP high density) (p=0.008), Δ-15.1 (microfat PRP low density) (p=0.031), Δ-23.8 (microfat NS) (p=0.01) (from baseline); pain: Δ-6 (microfat PRP high density) (p=0.008), Δ-3 (microfat PRP low density) (p=0.031), Δ-5.1 (microfat NS) (p=0.012) (from baseline); stiffness: Δ-1.4 (microfat PRP high density) (p=0.063), Δ-2 (microfat PRP low density) (p=0.016), Δ-1.8 (microfat NS) (p=0.016) (from baseline); function: Δ-13.8 (microfat PRP high density) (p=0.002), Δ-9.7 (p=0.1), Δ-16.9 (p=0.01)	Δ-36.7 (microfat PRP high density) (p=0.004), Δ-34.4 (microfat PRP low density) (p=0.004), Δ-33.3 (microfat NS) (p=0.016) (from baseline)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Louis et al. (2018) [46]	total: Δ-10.1 (PRP), Δ-5.3 (HA) (p=0.068) (between groups at final follow-up); pain: Δ-2.3 (PRP), Δ-1.5 (HA) (p=0.463) (between groups at final follow-up); stiffness: Δ-0.95 (PRP), Δ-0.9 (HA) (p=0.896) (between groups at final follow-up); function: Δ-6.9 (PRP), Δ-2.8 (HA) (p=0.167) (between groups at final follow-up)	Δ-1.5 (PRP), Δ-1.5 (HA) (p=0.972) (between groups at final follow-up)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Montañez-Heredia et al. (2016) [47]	NR	% with 50% decrease at 6 months: 44.4% (PRP), 42.3% (HA), p=1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nabi et al. (2018) [48]	pain: Δ-36.37 (PRP), Δ-15.68 (triamcinolone) (p=0.0001); symptoms: Δ-29.76 (PRP), Δ-13.13 (triamcinolone) (p=0.0001); ADL: Δ-25.49 (PRP), Δ-5.92 (triamcinolone) (p=0.0001); sports/rec: Δ-18.79 (PRP), Δ-3.97 (triamcinolone) (p=0.0001); QOL: Δ-17.8	Δ-3.91 (PRP), Δ-2.31 (triamcinolone) (p=0.0001)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

	(PRP), Δ-4.6 (triamcinolone) (p=0.0001)												
Patel et al. (2013)	Total, % change: Δ51% (single PRP), Δ43% (double PRP), Δ-20% (NS), p<0.001 (between PRP and NS groups)	Δ-2.380 (single PRP), Δ-2.10 (double PRP), Δ+0.043 (NS), p<0.001 (only for PRP groups)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Paterson et al. (2016) [49]	NR	Δ-1.12(PRP); Δ-1.41 (CS); p value NR	Pain: Δ+11.82 (PRP); Δ+9.32 (CS); p value NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Park et al. (2021) [50]	Pain; Δ1.9 (PRP), Δ1.7 (HA), p=0.697. function; Δ4.0 (PRP), Δ4.4 (HA), p=0.802. stiffness; Δ0.5 (PRP), Δ0.4 (HA), p=0.918. total; Δ6.4 (PRP), Δ6.5 (HA), p=0.967.	Δ20.9 (PRP), Δ13.6 (HA), p=0.058.	NR	Δ11.5 (PRP), Δ6.3 (HA), p=0.29.	NR	NR	NR	NR	NR	NR	NR	NR	NR
Phul et al. (2018) [52]	NR	Δ4.83 (PRP), Δ5.73 (CS), *p<.01*.	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pishgahi et al. (2020) [53]	Δ6.4 (dextrose), Δ-14.66 (PRP), Δ-21.4 (ACS).	Δ-3.7 (dextrose), Δ-6.1 (PRP), Δ-26.25 (ACS).	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Qamar et al. (2021) [54]	NR	Δ50% pain reduction: 46/50 (92%) (PRP); 15/50 (30%) (NS); (p<0.0001)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Raeissadat et al. (2020) [55]	Pain: Δ-4.29 (PRP), Δ-2.43 (exercise), *p=.056;* stiffness: Δ-1.74 (PRP), Δ-.6 (exercise), *p=.036;* functional capacity: Δ-14.13 (PRP), Δ-8.14 (exercise), *p=.038*.	Δ-3.24 (PRP), Δ-1.28 (exercise), *p =.001*.	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Raeissadat et al. (June 2020) [56]	Pain: Δ-2.78 (PRGF), Δ-1.84 (HA), *p=.339;* stiffness: Δ-1.06 (PRGF), Δ-.97 (HA), *p=.856;* function: Δ-10.93 (PRGF), Δ-4.6 (HA), *p=.009;* total; Δ-	Δ-3.3 (PRGF), Δ-1.7 (HA), *p=.0001*.	NR	NR	NR	NR	Pain: Δ-1.4 (PRGF), Δ-.6 (HA), *p<.0001; MWD:* Δ.10 (PRGF), Δ.20 (HA), *p<.0001;*	NR	NR	NR	NR	NR	NR

	14.08 (PRGF), Δ-5.3 (HA), *p=.02*.					ADL: Δ-.9 (PRGF), Δ-.3 (HA), *p=.009;* total: Δ-2.1 (PRGF), Δ-.6 (HA), *p<.0001*.						
Raeissadat et al. (2021) [57]	Pain: Δ-4.4 (PRP), Δ-4.4 (PRGF), Δ-3.1 (HA), Δ-1.7 (ACS), *p<.001;* stiffness: Δ-1.0 (PRP), Δ-0.96 (PRGF), Δ-0.8 (HA), Δ-0.2 (ozone), p<.001; function: Δ-10.0 (PRP), Δ-10.5 (PRGF), Δ-5.8 (HA), Δ-4.4 (ozone), *p<.001;* total: Δ-15.5 (PRP), Δ-15.9 (PRGF), Δ-8.4 (HA), Δ-6.4 (ozone), *p<.001*.	Δ-3.3 (PRP), Δ-3.4 (PRFG), Δ-2.6 (HA), Δ-1.3 (ozone), *p<.001*.	NR	NR	NR	NR	Walk: Δ -.25 (PRP), Δ-.2 (PRGF), Δ-.16 (HA), Δ-.06 (ozone), *p=.13;* ADL: Δ-1.1 (PRP), Δ-1.1 (PRGF), Δ-.4 (HA), Δ.4 (ozone), *p<.001;* total: Δ-2.8 (PRP), Δ-2.6 (PRGF), Δ-1.2 (HA), Δ-.9 (ozone), *p<.001*.	NR	NR	NR	NR	NR	NR
Rahimzadeh et al. (2018) [58]	total: -28.4 (PRP), -36.5 (prolotherapy) p<0.001; pain: -6.6 (PRP), -8.6 (prolotherapy) p<0.001; stiffness: -2.2 (PRP),-2.9 (prolotherapy) p<0.001; function: -19.5 (PRP), -25 (prolotherapy) p<0.001	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Reyes-Sosa et al. (2020) [59]	All: P<0.05 (PRP > Celecoxib)	P<0.05 (PRP > Celecoxib)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Simental-Mendía et al (2016) [60]	Δ-24.0 (PRP), Δ-11.5 (acetaminophen) (p<0.05)	At week 12: Δ-3.0 (PRP), Δ-1.8 (acetaminophen) (p<0.01)	NR	NR	NR	Mean changes p<0.001, only in PRP	NR	NR	NR	NR	NR	NR	NR
Smith et al. (2016) [61]	% change from baseline: 78% (PRP); 7% (HA), (*p*≤.001)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Su et al. (2018) [62]	Total score: Δ7.19 (PRP +mfciPRP), Δ17.44 (IAPRP), 15.2 (HA). pain; Δ1.89 (PRP + mfciPRP), Δ4.34 (IAPRP), Δ3.92 (HA); stiffness: Δ0.85 (PRP + mfciPRP), Δ1.3 (IAPRP), Δ1.2 (HA); physical function: Δ5.86 (PRP + mfciPRP), Δ10.83 (IAPRP), Δ11.68 (HA).	Δ.54 (PRP + mfciPRP), Δ3.2 (IAPRP), Δ3.1 (HA).	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Sun et al. (2021) [63]	Pain: Δ-2.5 (PRP), Δ-2.5 (PRP+HA), *p=.801;* stiffness: Δ-1.2 (PRP), Δ-.7 (PRP+HA), *p=.117;* function: Δ-7.8 (PRP), Δ-8.3 (PRP+HA), *p=.998;* total: Δ-11.5 (PRP), Δ-11.5 (PRP+HA), *p=.815*.	Pain: Δ-20.4 (PRP), Δ-31.8 (PRP+HA), *p=.020*.	NR	NR	NR	NR	Δ-3.6 (PRP), Δ-3.5 (PRP+HA), *p=.750*..	Δ18.5 (PRP), Δ19.8 (PRP+HA), *p=.846*.	NR	NR	NR	NR	NR
Tavassoli et al. (2019) [64]	Pain: Δ-4.71 (PRP1), Δ-5.86 (PRP2), Δ-1.44 (HA), *p<.001;* stiffness: Δ-1.6 (PRP1), Δ-2.47 (PRP2), Δ-0.92 (HA), *p<.001;* physical function: Δ-15.04 (PRP1), Δ-17.85 (PRP2), Δ-3.67 (HA), *p<.001;* total: Δ-21.21 (PRP1), Δ-26.25 (PRP2), Δ -5.85 (HA), *p<.001*.	Δ-2.86 (PRP1), Δ-3.83 (PRP2), Δ -1.11 (HA), *p<.001*.	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Uslu et al. (2018) [65]	total: Δ-19.3 (CS), Δ-33.8 (single dose PRP), Δ-38.3 (triple dose PRP) (all p<0.001); pain: Δ-4.0 (CS), Δ-6.5 (single dose PRP), Δ-6.7 (triple dose PRP) (all p<0.001); stiffness: Δ-1.0 (CS), Δ-1.5 (single dose PRP), Δ-4.8 (triple dose PRP) (all p<0.001); function: Δ-16.0 (CS), Δ-24.7 (single dose PRP), Δ-30.6 (triple dose PRP) (all p<0.001)	rest: Δ-1.3 (CS), Δ-2.4 (single dose PRP), Δ-2.2; night: Δ-1.4 (CS), Δ-2.9 (single dose PRP), Δ-3.6 (triple dose PRP); movement: Δ-2.7 (CS), Δ-3.9 (single dose PRP), Δ-5.5 (triple dose PRP); improvements noted from baseline among PRP groups (p<0.001)	NR	NR	NR	NR	Δ-2.7 (CS), Δ-4.4 (single dose PRP), Δ-6.7 (triple dose PRP) (all p<0.05)	NR	NR	NR	NR	NR	NR
Wu et al. (2018) [66]	Pain: Δ-16.6 (PRP), Δ-9.3 (NS); stiffness: Δ-5.9 (PRP), Δ-3.6 (NS); physical function: Δ-42.9 (PRP), Δ2-8.6 (NS). total; Δ-66 (PRP), Δ-41.5 (NS). p<0.001 for all	NR	NR	NR	NR	NR	NR	NR	NR	60/sec ex, Nm: Δ17.8 (PRP), Δ13.1 (NS); 60/sec fx, Nm: Δ35.9 (PRP), Δ18.7 (NS); 180/sec ex, Nm: Δ18.4	NR	NA	NR

										(PRP), Δ11.1 (NS); 180/sec fx, Nm: Δ40.2 (PRP), Δ29.7 (NS).			
Xu et al. (2020) [67]	*P*<0.001, *PRP + HA > PRP > HA*	*P<0.001, PRP + HA > PRP/HA alone*	*NR*	*NR*	*P<0.001, PRP + HA > PRP > HA*	*NR*	*P<0.001, PRP + HA > PRP > HA*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Yu et al. (2018) [68]	Pain: Δ4.67 (PRP); Δ3.61 (HA); Δ5.58 (PRP+HA). stiffness; Δ1.19 (PRP); Δ0.49 (HA); Δ1.92 (PRP+HA). physical function; Δ9.98 (PRP); Δ6.79 (HA); Δ16.19 (PRP+HA). all p≤0.01.	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NA	NR

6MWD: 6 minute walking distance; ACS: autologous conditioned serum; CS: corticosteroid; HA: hyaluronic acid; IA: intra-articular; IKDC: International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritis Outcome Score; KSS: Knee Society Score; NS: normal saline; PRGF: plasma rich growth factors; PRP: platelet-rich plasma; PT: physical therapy; ROM: range of motion; SF-12: 12-Item Short Form Survey; SLS: single leg stand; TUGT: timed up and go test; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table 5. Patient Reported Outcome Measures using Bone Marrow Stem Cells

Study	*WOMAC*	*VAS pain*	*KOOS*	*IKDC*	*SF-12*	*LEAS*	*KSS - knee score*	*KSS - functional score*	*ROM*	*NPS*	*OKS*	*ICOAP*	*Lequesne*
Anz et al. (2020) [20]	Total: Δ-15.9 (BMSC), Δ-15.3 (PRP), p>0.05; pain: Δ-3.5 (BMSC), Δ-3.3, p>0.05; stiffness: Δ-1.5 (BMSC), Δ-1.6 (PRP), p>0.05; Function: Δ-10.1 (BMSC), Δ-10 (PRP), p>0.05	NR	NR	Δ19.3 (BMSC), Δ16.3 (PRP)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Centeno et al. (2018) [69]	NR	Δ-8.0 (exercise), Δ-12.5 (BMSC), p=.4.	NR	NR	Physical: Δ2.4 (exercise), Δ4.9 (BMSC), *p=.27*; mental: Δ-1.5 (exercise), Δ-2.4 (BMSC) p=0.68.	Δ-1.1 (exercise), Δ.8 (BMSC), p=.002.	Δ.6 (exercise), Δ12 (BMSC), p<0.001.	Δ2.3 (exercise), Δ7.5 (BMSC), p=.17	Δ2.6 (BMSC and exercise), p=.97).	NR	NR	NR	NR
Emadedin et al. (2018) [70]	Total: p=0.01; pain: p=0.001; stiffness: p=0.4; function: p=0.04.	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Estrada et al. (2020) [71]	NR	NR	NR	Δ27.4 (BMSC), Δ30.3 (ATDSC), Δ26.2 (PRP), p=0.4246	NR	NR	Δ22.9 (BMSC), Δ26.7 (ATDSC), Δ21.3 (PRP), p=0.1193	Δ23.6 (BMSC), Δ23.4 (ATDSC), Δ15.2 (PRP), p=0.8416	NR	NR	NR	NR	NR
Gupta et al. (2016) [72]	Composite score, improved most in 25 million dose group vs. HA (p=0.2651)	% decrease most pronounced in 25 million dose group versus HA (67.4% vs. 36.0%, p=0.0587)	NR	NR	NR	NR	NR	NR	NR	NR	NR	Maximum reduction in 25 million dose group vs. HA (p=0.5271)	NR

Jin et al. (2020) [73]	p=0.297	NR	NR	p=0.260	NR	NR	p=0.136	p=0.445	NR	NR	NR	NR	NR
Kon et al. (2021) [74]	NR	Δ-3.3, p<0.0005	Pain: Δ19.8, p<0.0005; Symptoms: Δ13.7, p<0.0005 ADL; Δ15.6, p<0.0005. sport Δ30.3, p<0.0005. QoL; Δ22.5, p<0.0005.	Δ22.1, p<0.0005.	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lamo-Espinosa et al. (2016) [75]	Overall: Δ-15.5 (HA), Δ-15.5 (low dose), Δ-7.5 (high dose)	Improvements in all groups but no differences between, p values NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lamo-Espinosa et al. (2020) [76]	Pain: Δ27.3% (PRP), Δ45.5% (PRP+BMSC); stiffness: Δ33.3% (PRP); Δ50% (PRP+BMSC); physical function: Δ24.4% (PRP); Δ28.6% (PRP+BMSC)	Δ0.5 (PRP); Δ1.8 (PRP+BMSC)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rodriguez-Fontan et al. (2018) [77]	Δ20.2, p<0.001	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shapiro et al. (2017) [78]	NR	Δ-1.1 (BMSC), Δ-1.3 (NS), p=0.44	NR	NR	NR	NR	NR	NR	NR	NR	NR	Constant pain: Δ-10 (BMSC), Δ-10 (NS), p=0.89; intermittent pain: Δ-17 (BMSC), Δ-21 (NS), p=0.49; total pain: Δ-14 (BMSC), Δ-11 (NS), p=0.54	NR
Shapiro et al. (2019) [79]	NR	Δ-1.4 (BMSC), Δ-1.8 (NS), p=0.23	NR	NR	NR	NR	NR	NR	NR	NR	NR	Constant pain: Δ-15 (BMSC), Δ-15 (NS), p=0.97; intermittent pain: Δ-21 (BMSC), Δ-	NR

												13 (NS), p=0.54; total pain: Δ-18 (BMSC), Δ-18 (NS), p=0.68; QOL (constant): Δ14 (BMSC), Δ11 (NS), p=0.77; QoL (intermittent): Δ15 (BMSC), Δ12 (NS), p=0.23.	
Themistocleous et al. (2018) [80]	NR	NR	NR	NR	NR	NR	NR	NR	NR	Δ-3.84, p<0.001	Δ12.09, p<0.001	NR	NR
Toan et al. (2020) [81]	NR	p<0.05	P<0.05 for knee pain, knee symptoms, daily activity, playing sport, and QoL	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Vega et al (2015) [82]	Pain: Δ-6 (HA), Δ-16 (BMSC); general: Δ-4 (HA), Δ-13 (BMSC), p values NR	Δ-1.3 (HA), Δ-2.1 (BMSC), p value NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Δ-3 (HA), Δ-9 (BMSC), p value NR

AL: anterolateral; ADL: activities of daily living; AM: anteromedial; BMSC: Bone-Marrow Stem Cell; IKDC: International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritis Outcome Score; KSS: Knee Society Score; LEAS: Levels of Emotional Awareness Scale; QoL: quality of life; ROM: range of motion; SF-12: 12-Item Short Form Survey; SL: superolateral VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table 6. Patient Reported Outcome Measures using Adipose Derived Mesenchymal Stem Cells

Study	*WOMAC*	*VAS for knee pain*	*SF-36*	*LYSHOLM score*	*KOOS*	*TEGNER*
Dallo et al. (2021) [83]	NR	Δ-1.33 (PRP + HA), Δ-1.78 (ADMSC), p=0.176	NR	NR	Symptoms: Δ5.72 (PRP + HA), Δ15.37 (ADMSC). pain; Δ1.21 (PRP + HA), Δ19.13 (ADMSC); ADL: 2.77 (PRP + HA), Δ17.33 (ADMSC); Sport: Δ7.14 (PRP + HA), Δ18.83 (ADMSC); QoL: Δ12.30 (PRP + HA), Δ25.55 (ADMSC)	Δ0.74 (PRP + HA), Δ1.23 (ADMSC), p<0.05
Ehlers et al. (2020) [84]	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05
Freitag eta al. (2019) [85]	P<0.05	NR	NR	NR	P<0.05.	NR
Garza et al. (2020) [86]	Total score: Δ-34.2 (SVF), Δ-7.4 (Non-SVF).	NR	NR	NR	NR	NR
Kuah et al. (2018) [87]	Combined ADMSC group (low and high dose) improved from baseline (p<0.014) but not significantly for HA group	Δ-1.856 (low dose ADMSC), Δ-0.722 (high dose), HA group NR but not significantly improved from baseline	NR	NR	NR	NR
Lee et al. (2019) [88]	Total score: Δ-12 (NS) p= 0.0602; Δ-35 (MSCs) p=.0001; pain score: Δ-2 (NS) p= .0635, Δ-8 (MSCs) p=.0001; stiffness score: Δ-1.1 (NS) p=.0559, Δ-3 (MSCs) p=.0007; physical function score: Δ-8 (NS) p=.0786, Δ25 (MSCs) p=.0001	Δ0 (NS) p=0.3606, Δ-3.5 p=0.0001.	NR	NR	Pain management; Δ7 (NS) p=.3923, Δ23 (MSCs) p=.0010; symptom improvement: Δ1 (NS) p=.8036, Δ19 (MSCs), p= 0.0075; ADL: Δ5 (NS) p= .1908, Δ22 (MSCs) p= .0030; sport and recreation: Δ3 (NS) p=.2070, Δ28 (MSCs) p=.0049; QoL: Δ5 (NS) p=0.0568, Δ26 (MSCs) p= .0033.	NR
Louis et al. (2021) [45]	total: Δ-21.2 (microfat PRP high density) (p=0.008), Δ-15.1 (microfat PRP low density) (p=0.031), Δ-23.8 microfat NS) (p=0.01) (from baseline); pain: Δ-6 (microfat PRP high density) (p=0.008), Δ-3 (microfat PRP low density) (p=0.031), Δ-5.1 microfat NS) (p=0.012) (from baseline); stiffness: Δ-1.4 (microfat PRP high density) (p=0.063), Δ-2 (microfat PRP low density) (p=0.016), Δ-1.8 microfat NS) (p=0.016) (from baseline); function: Δ-13.8 (microfat PRP high density) (p=0.002), Δ-9.7 (microfat PRP low density) (p=0.1), Δ-16.9 microfat NS) (p=0.01)	Δ-36.7 (microfat PRP high density) (p=0.004), Δ-34.4 (microfat PRP low density)) (p=0.004), Δ-33.3 (microfat NS) (p=0.016) (from baseline)	NR	NR	NR	NR
Lu et al. (2019) [89]	Total score; Δ28.52% (haMPC); Δ20.74% (HA), *p*=0.2177	*p=.0190* for the left knee and *p=.0178* for the right knee between the haMPC and HA groups.	Δ-9.39 (haMPC), Δ-3.91, *p*=0.0097.	NR	NR	NR

Tran et al. (2019) [90]	P<0.05	P<0.05	NR	Δ33.1 (SVF), Δ4.2 (microfracture), p<0.05.	NR	NR
Yokota et al. (2019) [91]	NR	P<0.05	NR	NR	ADL: p=0.086; Symptom: p<0.05; Pain: p=0.574; Sports: p=0.263; QoL: p=0.629;	NR
Zhao et al. (2019) [92]	p>0.05	NR	p>0.05	NR	NR	NR

ADL: activities of daily living; ADMSC: Adipose Derived Mesenchymal Stem Cell; HaMPC: human adipose-derived mesenchymal progenitor cells; HD: high dose; LD: low dose; NS: normal saline; QoL: quality of life; ROM: range of motion; SF-12; 12-Item Short Form Survey; SVF: stromal vascular fraction; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table 7. Patient Reported Outcome Measures using Amniotic Derived Mesenchymal Stem Cells

Study	*WOMAC*	*VAS*	*KOOS*	*SF-36 Physical*	*SF-36 Pain*	*EQ-5D-5L*	*SANE*	*IKDC*	*Tegner*
Castellano et al. (2019) [93]	p>0.05	NR	NR	NR	NR	NR	NR	NR	NR
Dilogo et al. (2020) [94]	Δ-9.09, p=0.071	Δ-1.62, p=0.158	NR	NR	NR	NR	NR	Δ7.17, p=0.038	NR
Farr et al. (2019) [95]	NR	Overall pain: Δ-39.56 (ASA), Δ-25.97 (HA), Δ-57.14 (NS) (p=0.0072). strenuous work pain: Δ-40.39 (ASA), Δ-27.79 (HA), Δ-62.61 (NS) (p=0.0320) sedentary work pain: Δ-12.63 (ASA), Δ-12.58 (HA), Δ-33.34 (NS) (p>0.05). normal daily living pain: Δ-28.73 (ASA), Δ-16.64 (HA), Δ-50.16 (NS) (p=0.0015).	Pain: Δ17.29 (ASA), Δ13.34 (HA), Δ21.71 (NS); symptoms: Δ11.84 (ASA), Δ3.85 (HA), Δ9.88 (NS); activities of daily living: Δ16.23 (ASA), Δ14.11 (HA), Δ19.5 (NS); sports and recreation: Δ14.8 (ASA), Δ20.35 (HA), Δ27.86 (NS); quality of life: Δ20.3 (ASA), Δ12.13 (HA), Δ29.05 (NS) All p<0.05.	NR	NR	Mobility: Δ-.6 (ASA), Δ-.7 (HA) Δ-.9 (NS); selfcare: Δ-.2 (ASA), Δ-.2 (HA), Δ-.3 (NS); activities: Δ-.7 (ASA), Δ-.5 (HA), Δ-.6. pain: Δ-.7 (ASA), Δ-.5 (HA), Δ-1 (NS); anxiety: Δ-.3 (ASA), Δ-.2 (HA), Δ-.3 (NS); health today: Δ5.85 (ASA), Δ1.72 (HA), Δ7.34 (NS); all p<0.05.	Δ25.13 (ASA), Δ23.75 (HA), Δ31.73 (NS) p<0.05.	NR	Δ-.1 (ASA), Δ-.2 (HA), Δ.4 (NS) p>0.05.
Gomoll et al. (2021) [102]	NR	Overall pain: Δ-32.9; strenuous work: Δ-38.0; sedentary work: Δ-13.7; normal daily living: Δ-27.6; all p<0.05 compared to HA and NS	Pain: Δ14.7; symptoms: Δ10.0; ADL: Δ12.6; S&R: 19.6; QoL: 20.9; all p<0.05 compared to HA and NS	NR	NR	NR	NR	NR	NR
Matas et al. (2019) [97]	Total: Δ -13.7 (HA), Δ -22.5 (MSC1), Δ -31.4 (MSC2). function: Δ-9.5 (HA), Δ-15.8 (MSC1), Δ-21.2 (MSC2), *p*=0.15*;* stiffness: Δ-1.5 (HA), Δ-1.2 (MSC1), Δ-2.2 (MSC2), *p*=0.21*;* pain: Δ-2.7 (HA), Δ-5.6 (MSC1), Δ-7.0 (MSC2), p=0.04.	Δ-16.6 (HA), Δ-31.5 (MSC1), Δ-37.0 (MSC2), *p*=0.02.	NR	p>0.05	p>0.05	NR	NR	NR	NR

ADL: activities of daily living; ASA: amniotic suspension allograft; HA: hyaluronic acid; KOOS: Knee Injury and Osteoarthritis Outcome Score; MSC: mesenchymal stem cells; NS: normal saline; QoL: quality of life; ROM: range of motion; S&R: sports and recreation; SANE: single assessment numerical evaluation; SF-36: Short Form 36; VAS: visual analog scale; WOMAC: Western Ontario and McMaster University Osteoarthritis Index; WORMS: Whole-Organ Magnetic Resonance Imaging Score

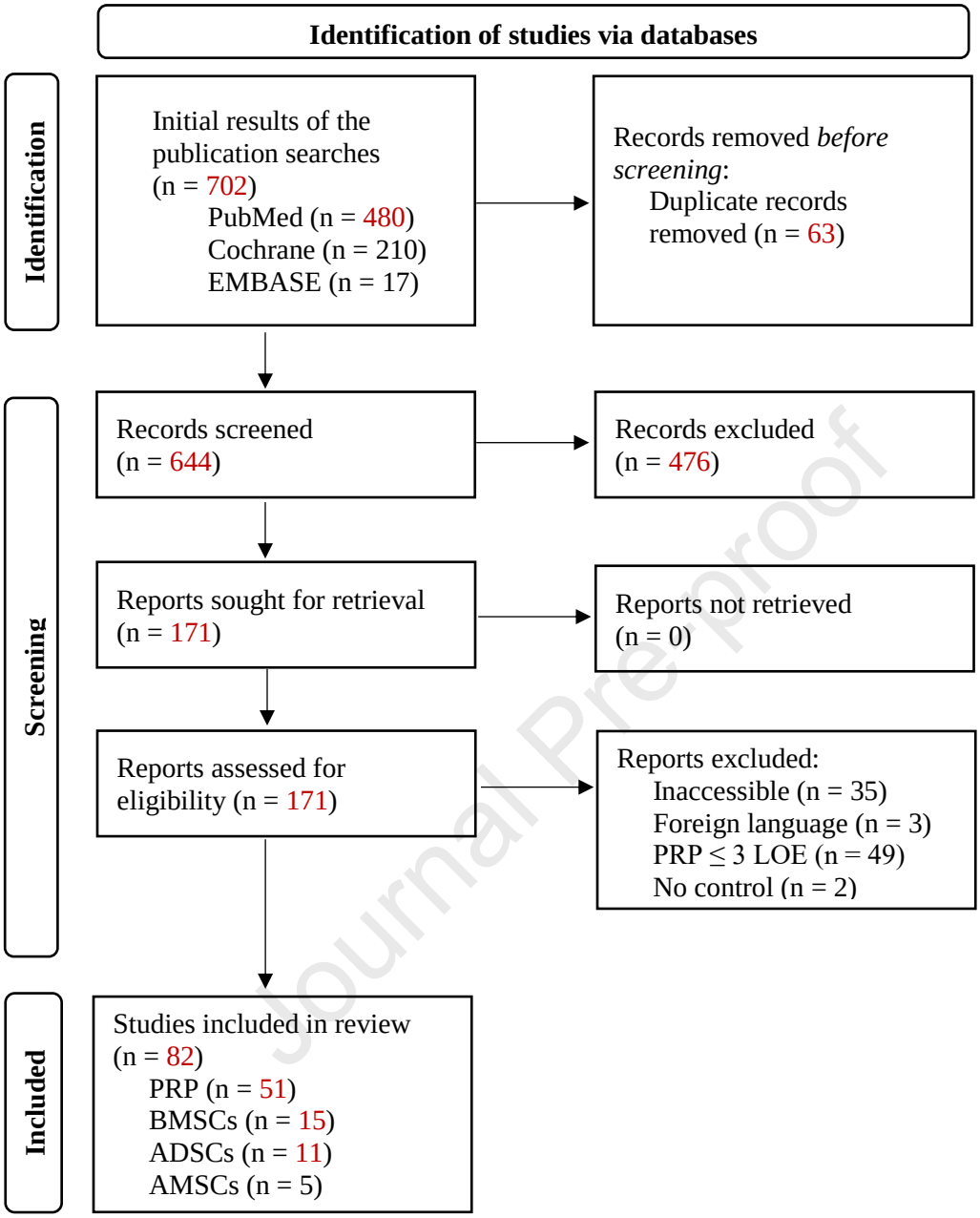

Figure 1. PRISMA Flow Diagram

Highlights

- PRP in relation to NS, HA, CS, and other comparative groups remain non-superior given low methodology scores, variable cell preparations/techniques, and inconsistent functional and structural outcomes.
- Studies assessing bone marrow, adipose, and amniotic stem cells demonstrated similar results, albeit with far fewer available studies.
- These results highlight the uncertain efficacy of biologic therapies for use in knee OA.