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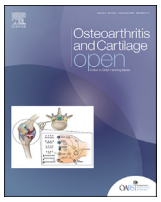

The role of Platelet-Rich Plasma (PRP) intraarticular injections in restoring articular cartilage of osteoarthritic knees. A systematic review and meta-analysis

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ABSTRACT

Objective: To assess the effect of PRP on knee articular cartilage content (thickness/volume) and examine the correlation between cartilage changes and clinical outcomes in patients with knee OA.
Method: A systematic literature search was performed using the Cochrane methodology in four online databases. Studies were included if they reported on cartilage content with cross-sectional imaging pre- and post-injection. A random-effects model meta-analysis was performed. Correlation with clinical outcomes was evaluated.
Results: 14 studies (n = 1099 patients) from 1452 records met the inclusion criteria: seven RCTs (n = 688), one prospective (n = 50), one retrospective (n = 68), and four case-series (n = 224). The PRP preparation process and treatment protocol varied widely (follow-up 6–12 months). In meta-analysis, PRP treatment was not associated with a significant increase in cartilage thickness (4 studies, n = 187, standardized mean difference: Hedges g: 0.079; 95%CI: 0.358 - 0.516; p = 0.723). Meta-analysis of 3 RCTs (n = 112) showed no significant difference in the change of overall knee cartilage content with PRP injections compared with no PRP (Hedges' g: 0.217; 95%CI: 0.177 – 0.611; P = 0.281).
Conclusion: The current literature does not support the PRP as chondrogenic in treatment of knee OA. However, there is substantial heterogeneity in the evaluated studies which limits the robustness of any conclusion. An adequately powered RCT, with a standardized PRP regime and standardized high-resolution MRI is needed to definitely define any effect of PRP on knee cartilage content and its relation to clinical outcomes. Until such high-quality evidence becomes available, we recommend that PRP is not administered with the intention of promoting chondrogenesis.

1. Introduction

Osteoarthritis (OA) is a leading cause of disability and reduced quality of life with the knee joint being the most common site of OA [1]. Treatments for knee OA are primarily aimed at improving patient symptoms, ranging from simple analgesia to surgery as part of the treatment management ladder [2]. Among the non-invasive treatment options, intra-articular (IA) therapies are considered the mainstay of management [3].

Different types of IA injectables exist e.g. corticosteroids, platelet-rich-plasma (PRP), bone marrow aspirate concentrate (BMAC), adipose-derived stem cells (ASCs), and hyaluronic acid (HA). Among these IA therapies, PRP has been increasingly used in recent years as it has been shown to improve knee OA symptoms and clinical outcomes [4–6]. Furthermore, considering the potential of activated platelets to release growth factors and cytokines stimulating cartilage growth, PRP has been increasingly used in clinical practice to promote tissue repair and regeneration [7,8], with a suggestion that it may change the cartilage content possibly slowing or reversing OA [9,10]. However, the level of evidence is low and controversial with no review or meta-analysis to

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assess the effect of PRP on knee articular cartilage [11].

The primary aim of the systematic review was to assess the effect of PRP on knee articular cartilage content and structure in patients with symptomatic knee OA. The secondary aim was to identify if there is any correlation of the changes in articular cartilage with clinical outcomes.

2. Methods

A systematic review was performed following the Cochrane methodology for systematic reviews [12]. The predefined protocol for the review was registered with the PROSPERO database (CRD42022325560). A systematic search of the literature was undertaken (ADP) in four electronic bibliographic databases in July 2022 without a limit on the publication year: MEDLINE (Interface: EBSCOhost); EMBASE (Interface: OvidSP); CINAHL (Interface: EBSCOhost); CENTRAL (Interface: Cochrane Library). Further searches of the reference lists of included studies and any identified systematic reviews were also carried out. Only studies available in English language were included. The search in all databases was performed with a combination of key-words, including wildcards (*). The search was developed using the following set of key-words combined with the Boolean operator AND: [PRP OR platelet-rich-plasma OR platelet rich plasma OR platelet*] AND [osteoarthriti* OR arthriti* OR OA] AND [cartilag* OR chondral OR MRI OR imag* OR map*].

2.1. Inclusion/exclusion criteria

- *Study designs:* Study designs included were RCTs, prospective and retrospective cohort studies, case-control studies and case series with minimum 3-month follow-up, as the highest clinical effect sizes of other injectables have been reported between 5 and 14 weeks [13]. Case reports, reviews, editorials, commentaries, personal opinions, surveys were excluded.
- *Population*: Adults with knee OA.
- *Intervention/Comparators:* Adults with knee OA having treatment with intraarticular injection with PRP. Studies which compared PRP with other injectables with regards to the effect on articular cartilage were included. Studies which looked at the effect of PRP on articular cartilage but did not compare it with other injectables were included in the systematic review and narrative presentation and synthesis of the results, but not in the meta-analysis.
- *Outcomes:* Articular cartilage volume and structure measured and/or mapped using cross-sectional imaging.

Two reviewers (ADP, EM) independently screened the titles and abstracts of all retrieved studies for inclusion. Duplicates were removed. Full texts of studies considered eligible were retrieved and reviewed independently. Disagreements for inclusion were discussed between reviewers and if still unresolved with the senior author.

2.2. Data extraction

One reviewer (ADP) extracted relevant data from the included studies using a standardized data extraction form and input onto an Excel spreadsheet. Data extracted were study characteristics, patient demographics, OA severity and grade, PRP preparation and treatment protocol, cartilage measurements in cross-sectional imaging (thickness or volume or mapping values), clinical outcomes, and follow-up period.

2.3. Data analysis – statistical analysis

An initial descriptive analysis and synthesis of the characteristics and the study results was undertaken. The primary outcome was the change in cartilage thickness and/or the change in cartilage mapping values post-injection. For each study, cartilage thickness/volume or cartilage mapping values on MRI or US were reported in absolute numbers and rates and any significant difference post-injection was established ($p < 0.05$). For studies reporting on cartilage thickness, pre- and post-injection differences in means and 95% confidence intervals (CIs) were calculated and combined in a random-effects model meta-analysis [14]. When combining studies that reported on cartilage thickness or volume, the Hedges g and 95% CI were calculated and combined in a random-effects model meta-analysis [15]. Heterogeneity was assessed using tau [2], I^2, Q and P values. Data were analyzed with Comprehensive Meta-analysis version 2 (Biostat).

2.4. Assessment of methodological quality of studies and quality of evidence

The methodological quality of the studies was assessed as per study design. The Cochrane Risk of Bias Tool was used for RCTs [16], the Newcastle-Ottawa scale for prospective cohort studies [17]; and the revised and validated version of Methodological Index for Non-Randomised Studies (MINORS) for retrospective studies [15]. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of evidence of the review [18].

3. Results

3.1. Findings of the database searches

The search identified 1452 records by title, 14 of which met the inclusion criteria and were included for the analysis [10,11,19–28]. Fig. 1 shows the Preferred Reporting Items for Systematic reviews and meta-analyses (PRISMA) flow diagram [29].

3.2. Characteristics of included studies

Table 1 summarises the characteristics of the 14 included studies [10,11,19–28]. The methodology of the non-randomised studies was classified according to Mathes and Pieper (2017) [30]. Our analysis included seven RCTs (n = 688) [10,11,19,22,26,31,32]; two prospective (n = 119) [24,25]; one retrospective cohort (n = 68) [21]; and 4 case-series (n = 244) [20,23,27,28]. The total number of participants included was 1119 (1,169TKAs).

HA was used for the control group in three RCTs [19,24,31], a placebo (Normal saline) was used in one RCT [32], and conservative management with an exercise program was used in other two RCTs [10,22]. One RCT, being a cross-sectional randomized trial which injected PRP in all patients, did not have a control group [25]. In the prospective comparative study 5 ml of 1% mesocaine was used [24], whilst in the retrospective comparative study [21], conservative management with an exercise program was used for the control group. Four case-series did not have any control group [20,23,27,28].

Patient demographics (Table 1): Age range was 18–88 years. The mean BMI in all the studies was less than 30 kg/m^2. Nine used the Kellgren-Lawrence (K-L) scale [10,11,19,20,23,25,28,31,32], while three used the Outerbridge scale to grade the OA severity [21,24,26].

3.3. Characteristics of PRP used (supplementary material: Table 1)

The PRP preparation process varied widely. Six studies used a commercial kit/method [10,11,20,23,27,32], with the rest using independent methods [19,21,22,24–26,28,31]. Nine studies used double-spin [10,19,20,22,23,25,28,31,32], and four used single spin centrifugation [11,24,26,27]. There was no consistency in the PRP volume injected in the studies, with three injecting < 4 ml [20,25,28], seven injecting 4–6 ml [10,11,22,24,26,27,31,32], and three injecting ≥8 ml [19,21,23]. Platelet concentration ranged from 1.4 to 10 times the blood concentration. Interestingly one RCT injected one dose of 10 billion platelets in 8 ml volume of PRP showing sustained therapeutic benefit in 1 year [19].

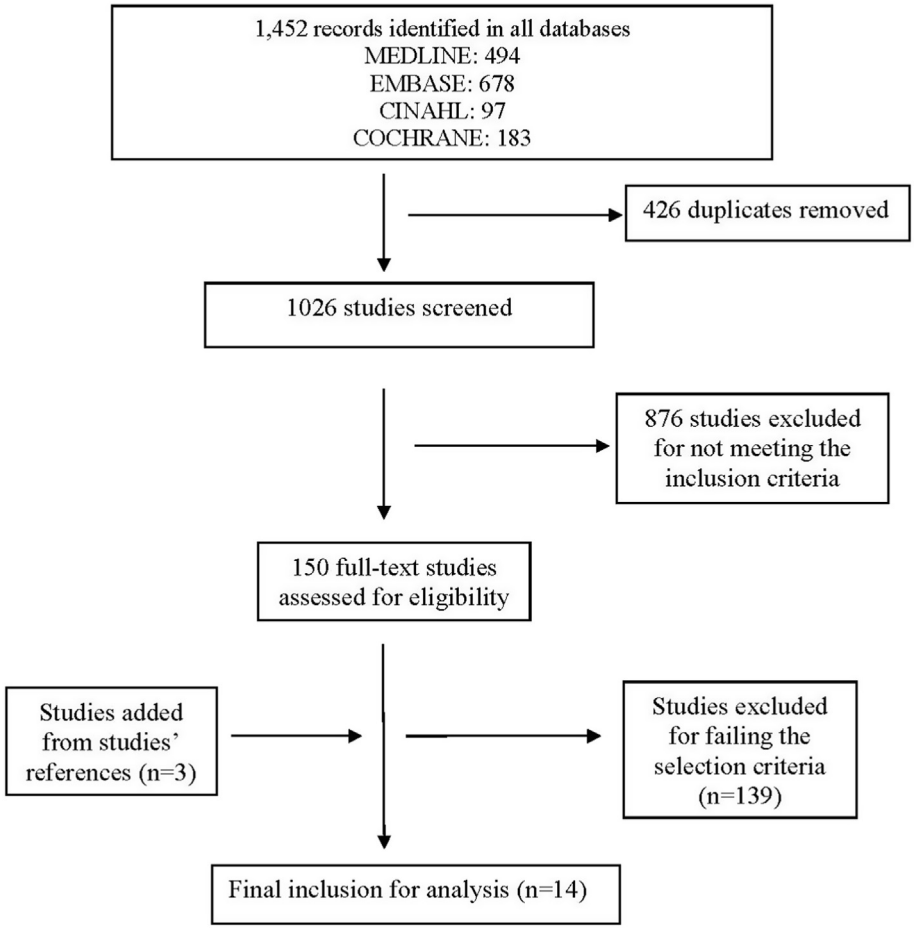

Fig. 1. Methodology of identification and selection of studies (PRISMA flow chart) [29].

The number of PRP injections and the time interval between injections varied significantly [22,24–26]. Most studies used an anticoagulant, with six using a Citrate Dextrose solution [10,20,23,24,26,27], and 4 using Calcium Chloride [21,22,31,32]. Classifying the PRPs according to the Dohan Ehrenfest classification for platelet concentrates into Leukocyte Rich-PRP (LR-PRP), Leukocyte Poor PRP (LP-PRP) or Pure-PRP (P-PRP) [33], five studies used LR-PRP [10,18,22,25,28,32], four used LP-PRP [11,21,26,31], and three using P-PRP. Two studies did not clarify if their PRP concentrate contained WBC [20,27].

3.4. Outcomes: cartilage thickness/volume (Table 2)

The cartilage thickness was evaluated with either high-resolution US or MRI before treatment and at follow-up. Nine used MRI [10,11,19,21,23–26,31], and five high-resolution US [20,22,27,28,32]. Among the studies that used MRI, three used a 3.0 T scanner [11,21,25], and six used a 1.5 T scanner [10,19,23,24,26,31]. Usually, the MRI slice thickness was 3 mm (0.5 mm intersection gap). Most studies did measurements in the medial (MFC) and lateral femoral condyle (LFC), medial (MTP) and lateral tibial plateau (LTP) [19–24,26–28,31,32]. The follow-up ranged from 6 to 12 months.

Among the nine studies that used MRI to evaluate cartilage thickness [10,11,19,21,23–26,31], three reported significant improvement post-PRP injections [10,21,25]. One study evaluated the patellofemoral cartilage volume (as the sum of cartilage area in all images multiplied by thickness of the slide) 8 months post-treatment showing significant increase in cartilage volume ($p = 0.001$), with the improvement in cartilage volume for the PRP group being significantly better as compared to the control group (exercise and analgesia) ($p = 0.001$) [10]. The second study used the MRI Osteoarthritis Knee Score Bone Marrow Lesion (MOAKS BML) [34] to assess articular cartilage before and after treatment [25]. It showed significant improvement 6 months post-PRP injection ($p = 0.007$). The third study used T2 mapping evaluation to assess cartilage thickness [21]. It used the modified whole-organ MRI score (WORMS) for quantitative analysis [35]. For quantitative analysis it recorded the T2 relaxation times in 3–5 regions in medial and lateral patella and femoral condyle (normal range was considered: 28.3–41.2 ms). It showed a significant improvement in T2 relaxation times in all regions ($p < 0.001$) and better modified WORMS score post-PRP injection ($p < 0.001$). A recent RCT (RESTORE) of 288 patients compared treatment with PRP injections with a placebo, and measured the medial tibia cartilage volume before and after treatment [11]. It showed a decrease in cartilage volume following both PRP treatment and placebo treatment (-1.4 ± 7.2 and -1.2 ± 6.8 respectively), with the difference between two groups being not significant ($p = 0.81$). A recent RCT comparing a single injection of inactivated PRP high-concentration in platelets (10 billion) with high-molecular-weight HA showed that there was no increase in cartilage thickness on MRI in either group [19]. Another RCT, comparing PRP with HA and NSAIDs and using the MOAKS BML to assess cartilage, showed that the MOAKS BML was reduced and not improved post-treatment in all groups with no significant difference between groups without reporting on the actual post-treatment values [31].

Among the five studies that used US to evaluate cartilage thickness

Table 1
Characteristics of all included studies in the systematic review.

Lead author (Year)	Study design (Level of evidence, Country)	No. of patients (knees)	Diagnosis Stage of OA	Age (years)	Gender (M:F)	BMI (kg/m^2)	Treatment received (knees)
Bansal (2021) [19]	RCT (I, USA)	132 (132)	Knee OA K-L grades I-III	PRP: 64.4 (52–74) Control: 65.8 (54–73)	PRP: 39:25 Control: 42:26	NR	PRP: 64 Control (HA): 68
Bennell (2021) [11]	RCT (I, Australia)	288 (288)	Knee OA K-L grades II, III	PRP: 62.2 ± 6.3 Control: 30.1 ± 4 NSD	PRP: 59:85 Control: 60:84 NSD	PRP: 29 ± 3.7 Control: 29.6 ± 4.5 NSD	PRP: 144 Control (placebo): 144
Raeissadat (2020) [10]	RCT (I, Iran)	42 (42)	Knee OA K-L grades I-III	57.57 ± 5.9	All females	28.49 ± 3.24	PRP: 21 Control (exercise): 21
Elik (2020) [32]	RCT (I, Turkey)	57 (57)	Knee OA K-L grades I-III	60.77 ± 7.36 (50–75)	4:53 PRP: 1:29 Control: 3:24	PRP: 30.37 ± 4.47 Control: 30.70 ± 3.97	PRP: 30 Control: 27
Buendía-López (2019) [31]	RCT (I, Spain)	99 (99)	Knee OA K-L grades I-II	56.82 (50–63)	PRP: 16:17 HA: 15:17 NSAID: 17:16	25.1 (23.8–26.1)	PRP: 33 Control groups: HA: 32 NSAID: 33
Elnemr (2019) [22]	RCT (I, Egypt)	30 (30)	Knee OA (post-meniscal repair) No classification	Range: 18-55 PRP: 27.7 ± 2.9 Control: 30.1 ± 4 P = 0.068	PRP: 14:1 Control: 13:2 NSD	PRP:27.2 ± 4.3 Control: 25.5 ± 3.3 P = 0.23	PRP: 15 Control (exercise): 15
Hart (2017) [26]	RCT (I, Czech Republic)	40 (40)	Knee PFJ OA (chondromalacia) Outerbridge II, III	Mean: 52.2 Range: 31-69	17:23	Mean: 29.3 Range: 18.8–34.9	PRP: 20 Control (HA): 20
Kenmochi (2020) [25]	Prospective, cross-sectional (II, Japan)	44 (55)	Knee OA K-L grades I-IV	Mean: 67.2 ± 9.6 Range: 36-84	6:38	Mean: 25.3 Range: 19.6–33.8	PRP No control group
Hart (2013) [24]	Prospective cohort (II, Czech Republic)	75 (75)	Knee PFJ OA (chondromalacia) Outerbridge II, III	PRP: 58.1 (31–75) Control: 58.4 (36–74)	PRP: 29:21 Control: 13:12	PRP: 28.1 (20.1–33.7) Control: 27.8 (19.6–34.7)	PRP: 50 Control (1% mesocain): 25
Cobianchi (2021) [21]	Retrospective cohort (III, Italy)	68 (68)	Knee OA Outerbridge II, III, IV	PRP: 41.8 ± 8.9 Range: 22-54 Control: Matched	PRP: 22:12 Control: Matched	NR	PRP: 34 Control: 34
Sen (2020) [28]	Case series (IV, Turkey)	71 (109)	Knee OA K-L grades II, III	Mean: 47.4 ± 10.4 Range: 35-65	24:46	Mean: 29.2 ± 4.9	No control group
Guillibert (2019) [23]	Case series (IV, France)	57 (57)	Knee OA K-L grades II, III	Mean: 63.3 ± 9.6	24:33	Mean: 25.4 ± 3.9	No control group
Calis (2015) [20]	Case series (IV, Turkey)	82 (103)	Knee OA K-L grades III, IV	Mean: 63.5 ± 9.3 Range:40-88	13:69	Mean: 33.5 ± 4.6	No control group
Sampson (2010) [27]	Case series (IV, USA)	14 (14)	Knee OA No grade reported	Mean: 51.8 Range: 18-87	12:2	Mean: 25 Range: 20.9–32.5	No control group

RCT: Randomised Clinical Trial, **USA:** United States of America, **OA:** osteoarthritis, **K-L:** Kellgren-Lawrence, **PFJ:** Patellofemoral, **PRP:** Platelet-rich plasma, **HA:** hyaluronic acid, **M:** males, **F:** females, **BMI:** Body Mass Index, **NR:** not reported, **NSD:** no significant difference, **p<0.05:** significant

[20,22,27,28,32], one case series (n = 103) reported significant improvement in cartilage thickness on the MFC six months following three PRP injections [20]. In two other case-series (n = 123) [27,28], measurement of cartilage thickness 6 months post-PRP injections was not significantly different. However, 6 of the 14 patients in one study had increased femoral articular cartilage [27]. One RCT (n = 30) showed no significant difference in change of cartilage thickness between two groups (follow-up 12 months), one group having six PRP injections and the other having none [22]. Interestingly, cartilage thickness was decreased in all areas measured with the percentage of degeneration being worse 12 months post-treatment. Similarly, another RCT (n = 57) showed no significant difference in cartilage thickness post-treatment between two groups (follow-up 6 months), one group having three PRP injections and the other having placebo injections, but did not report the actual values in mm [32].

4. Meta-analysis

4.1. Differences in mean articular cartilage thickness/volume following PRP treatment (Table 3)

Five studies (n = 313) measured the cartilage thickness in MFC pre- and post-PRP treatment [20,22,23,27,28], and meta-analysis did not show a significant increase in cartilage thickness post-PRP treatment (Fig. 2: estimated difference in means: 0.068; 95%CI: 0.050 - 0.185; p = 0.259). Four studies (n = 210) measured the cartilage thickness in LFC [22,23,27,28], and meta-analysis did not show a significant increase in cartilage thickness post-PRP treatment (Fig. 3: estimated difference in means: 0.064; 95%CI: 0.02 – 0.148; P = 0.136).

Meta-analysis of two studies (n = 87) [22,23], measuring the cartilage thickness in MTP and LTP, showed a decrease in cartilage thickness

Table 2
Cartilage thickness reported in all studies before and after treatment.

Lead author (Year)	Control group	Imaging modality	Compartments evaluated	Follow-up (months)	Cartilage evaluation pre-treatment (PRP)	Cartilage evaluation post-treatment (PRP)	Cartilage evaluation pre-treatment (Control)	Cartilage evaluation post-treatment (Control)	Statistical analysis
Bansal (2021) [19]	HA 4 ml (Monovisc®)	MRI 1.5T	Cartilage thickness (mm) MFC	12	4.48–4.98	53 (82.8%) unchanged 11 (17.1%) reduced	4.34–5.00	42 (61.7%) unchanged 16 (23.5%) reduced	PRP vs Control: Unchanged $p < 0.05$ Reduced $p > 0.05$
Bennell (2021) [11]	Placebo (5 ml Normal Saline)	MRI T1 FS 3T	Medial tibia cartilage volume (mm^3)	12	1337 ± 488	−1.4 ± 7.2	1309 ± 479	−1.2 ± 6.8	Difference in change: −0.2 (95%CI: 1.9 to 1.5) P = 0.81
Raeissadat (2020) [10]	Exercise and 500 mg Paracetamol	MRI FS PD 1.5T	Patellofemoral cartilage volume (mm^3)	8	1041.47 ± 323.01 K-L I: 26.3% K-L II: 52.6% K-L III: 21.1%	1336.88 ± 295.83	1012.68 ± 259.24 K-L I: 26.3% K-L II: 52.6% K-L III: 21.1%	1105.1 ± 262.62	PRP: **P = 0.001** Control: P = 0.05 PRP vs Control: **p = 0.001**
Elik (2020) [32]	Placebo (4 ml Normal Saline)	US (high-resolution)	Cartilage thickness (mm) MFC, LFC, intercondylar femur	6	No numbers reported	NSD	No numbers reported	NSD	NR
Buendía-López (2019) [31]	HA 2 ml (60mg/2 ml Durolane®) NDAID for 52 weeks (60 mg etoricoxib Acoxxel®)	MRI T2 FS PD 1.5T slice 3 mm 1 mm intersection gap	MOAKS BML (distal femur, proximal tibia)	12	Femur: Central: 1.73 ± 0.4 Tibia: Central: 1.82 ± 0.4 Anterior: 1.42 ± 0.26 Posterior: 1.28 ± 0.2	Reduced No increase	Femur: Central: 1.73 ± 0.4 Tibia: Central: 1.82 ± 0.4 Anterior: 1.42 ± 0.26 Posterior: 1.28 ± 0.2	Reduced No increase	PRP vs HA vs NSAID: NSD
Elnemr (2019) [22]	No PRP	US (high-resolution)	Cartilage thickness (mm) MFC, LFC, MTC, LTC	12	MFC: 2.5 ± 0.5 LFC: 2.1 ± 0.4 MTC: 2.6 ± 0.5 LTC: 3 ± 0.5 Total: 10.12 ± 1.76	MFC: 2.2 ± 0.5 LFC: 2 ± 0.4 MTC: 2.4 ± 0.5 LTC: 2.9 ± 0.5 Total: 9.51 ± 1.80 % degeneration: ↓6.16 ± 3.33	MFC: 2.4 ± 0.5 LFC: 2.2 ± 0.4 MTC: 2.6 ± 0.4 LTC: 2.7 ± 0.5 Total: 9.87 ± 1.62	MFC: 2.1 ± 0.4 LFC: 2.1 ± 0.4 MTC: 2.2 ± 0.5 LTC: 2.6 ± 0.5 Total: 8.99 ± 1.56 % degeneration: ↓ 9.07 ± 3.66	PRP vs Control: MFC: P = 0.366 LFC: P = 0.562 MTC: P = 0.338 LTC: P = 0.122 % degeneration: **P = 0.031**
Hart (2017) [26]	HA 2 ml (Erectus® Medicom International, Czech Republic)	MRI T1+T2 1.5T slice 3 mm 0.5 mm intersection gap	Cartilage thickness (mm) MFC, LFC, MTC, LTC	12	1.51 ± 0.463 Grade II: 12 Grade III: 8	1.35 ± 0.668 Increased in 1 patient Grade II: 13 Grade III: 7 Grade improved (III-II): 1/20	1.52 ± 0.472 Grade II: 11 Grade III: 9	1.37 ± 0.715 Grade II: 12 Grade III: 8 Grade improved (III-II): 1/20	PRP: P = 0.941 Control: P = 0.929
Kenmochi (2020) [25]	No control	MRI 3T	MOAKS BML (15 regions: 2 patellar, 6 femoral, 7 tibial)	6	MOAKS BML 7.44	MOAKS BML 6.6	NA	NA	**P = 0.007**
Hart (2013) [24]	5 ml 1% Mesocain	MRI T1+T2 1.5T slice 3 mm 0.5 mm intersection gap	Cartilage thickness (mm) MFC, LFC, MTC, LTC	12	2.15 ± 0.75 (1.00–4.30) Grade II: 21 (42%) Grade III: 29 (58%)	2.22 ± 0.93 (0.50–4.30)	Not measured Grade II: 9 (36%) Grade III: 16 (64%)	Not measured	PRP: P = 0.23 Control: N/A
Cobianchi (2021) [21]	No PRP	MRI T1+T2 3T slice 4 mm 0.4 mm intersection gap	T2 cartilage mapping (ms) Patellofemoral (medial + lateral patellar, MFC, LFC)	6.4 ± 1.9 (4–12)	T2 relaxation times Medial patellar: 40.4 ± 3.8 Latellar patellar: 40.1 ± 5.1	T2 relaxation times Medial patellar: 37.6 ± 4.3 Latellar patellar: 40.1 ± 5.1 MFC: 44.7 ± 3.7 LFC: 45.7 ± 2.9	T2 relaxation times Medial patellar: 42.5 ± 1.5 Lateral patellar:	T2 relaxation times Medial patellar: 42.2 ± 3.9 Lateral patellar: 41.1 ± 4.5 MFC: 45.9 ± 3.9 LFC: 36.1 ± 3.1	PRP: Medial Patellar: **P<0.001** Lateral Patellar: **P<0.001** MFC: **P<0.001**

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Table 2 (*continued*)

Lead author (Year)	Control group	Imaging modality	Compartments evaluated	Follow-up (months)	Cartilage evaluation pre-treatment (PRP)	Cartilage evaluation post-treatment (PRP)	Cartilage evaluation pre-treatment (Control)	Cartilage evaluation post-treatment (Control)	Statistical analysis
					MFC: 48.5 ± 3.1 LFC: 47.6 ± 3.7 Global: 44.2 ± 2.5 Modified WORMS: 14 ± 3.4 (10.5–18) Grades: Grade II: 4 Grade III: 18 Grade IV: 4	Global: 41.5 ± 2.5 Modified WORMS: 12.5 ± 2.4 (10–15) Improvement: 10.5% (mean) Grades: Grade II: 4 Grade III: 22 Grade IV: 0 Grade improvement: 4 (11%)	41.2 ± 5.5 MFC: 46.1 ± 3.5 LFC: 46.6 ± 3.9 Global: 43.2 ± 1.8 Modified WORMS: 15 ± 2.9 (11.6–19) Grades: Grade II: 5 Grade III: 15 Grade IV: 5	Global: 43.1 ± 2.1 Modified WORMS: 15.5 ± 2.6 (11–17) Improvement: 3.3% (mean) Grade II: 5 Grade III: 14 Grade IV: 6 Grade improvement: 1 (3%) worsening	LFC: **P<0.001** Global: **P<0.001** Modified WORMS: **P<0.001** Control: Medial patellar: P > 0.05 Lateral Patellar: P > 0.05 MFC: P > 0.05 LFC: P > 0.05 Global: P = 0.121 Modified WORMS: P = 0.132
Sen (2020) [28]	No control	US (high-resolution)	Cartilage thickness (mm) MFC, LFC, ICA	6	MFC: 1.8 ± 0.2 LFC: 1.9 ± 0.2 ICA: 2.1 ± 0.2	MFC: 1.9 ± 0.2 LFC: 2.0 ± 0.2 ICA: 2.2 ± 0.2	NA	NA	MFC: P = 0.108 LFC: P = 0.063 ICA: P = 0.684
Guillibert (2019) [23]	No control	MRI 1.5T	Cartilage thickness (mm) MFC MTP LFC LTP MPF LPF	6	MFC: 1.16 ± 0.72, MTP: 1.67 ± 0.85, LFC: 1.6 ± 0.6, LTP: 2.08 ± 0.91, MPF: 2.27 ± 0.75, LPF: 2.61 ± 1.03	MFC: 1.14 ± 0.77, MTP: 1.64 ± 0.89, LFC: 1.62 ± 0.6, LTP: 2.14 ± 1.01, MPF: 2.33 ± 0.77, LPF: 2.68 ± 1.06	NA	NA	MFC: P = 0.72 MTP: P = 0.82 LFC: P = 0.75 LTP: P = 0.26 MPF: P = 0.22 LPF: P = 0.22
Calis (2015) [20]	No control	US (high-resolution)	Cartilage thickness (mm) MFC	6	0.6 ± 0.2	0.8 ± 0.2	NA	NA	**P<0.05**
Sampson (2010) [27]	No control	US (high-resolution)	Cartilage thickness (mm) MFC, LFC, ICA	6	MFC: 2.53 ± 0.64 LFC: 2.50 ± 0.97 ICA: 3.32 ± 1.00	MFC: 2.53 ± 0.95 LFC: 2.73 ± 0.81 ICA: 3.38 ± 1.06	NA	NA	MFC: P = 0.22 LFC: P = 0.46 ICA: P > 0.05

PRP: Platelet-rich plasma, **MRI:** Magnetic Resonance Imaging, **T:** Tesla, **US:** Ultrasound scan, **K-L:** Kellgren-Lawrence, **MFC:** medial femoral condyle, **LFC:** lateral femoral condyle, **ICA:** intercondylar area, **MTC:** medial tibial condyle, **LTC:** lateral tibial condyle, **MPF:** medial patellofemoral, **LPF:** lateral patellofemoral, **WORMS:** Whole-organ MRI score, **MOAKS BML**: MRI Osteoarthritis Knee Score Bone Marrow Lesion, **p<0.05**: significant.

Table 3
Estimated differences in mean articular cartilage thickness in different intraarticular areas post-PRP treatment (as compared with cartilage thickness pre-treatment).

Areas of measurement	No. of studies (knees)	Estimated difference in means (95%CI)	Heterogeneity			
			τ^2	I^2	Q value	P value
MFC	5 (313) [20,22,23,27,28]	0.068 (−0.05 - 0.185), p = 0.259	0.01	86.284	29.163	<0.001
LFC	4 (210) [22,23,27,28]	0.064 (−0.02 - 0.148), p = 0.136	0.002	24.568	3.977	0.264
MTP	2 (87) [22,23]	−0.105 (−0.290 - 0.079), p = 0.263	<0.001	<0.001	0.804	0.370
LTP	2 (87) [22,23]	−0.019 (−0.214 – 0.176), p = 0.848	<0.001	<0.001	0.648	0.421
Overall (MFC, LFC, MTP, LTP)	3 (145) [22,24,26]	−0.075 (−0.300 – 0.150), p = 0.513	0.017	44.705	3.617	0.164

PRP: Platelet-Rich Plasma, **CI:** Confidence Interval, **MFC:** medial femoral condyle, **LFC:** lateral femoral condyle.
MTP: medial tibial plateau, **LTP:** lateral tibial plateau, **p<0.05:** significant.

post-PRP treatment which was not significant (estimated difference in means respectively: 0.105; 95%CI: 0290 – 0.079; P = 0.263. −0.019; 95%CI: 0.214 – 0.176; P = 0.848). Meta-analysis of three studies (n = 145) which reported difference in overall cartilage thickness in four areas (MFC, LFC, MTP, LTP) [22,24,26], showed a non-significant decrease (estimated difference in means: 0.075; 95%CI: 0.300 – 0.150; P = 0.513). Meta-analysis of four studies (n = 187) confirmed difference of cartilage thickness overall [10,22,24,26], including one study showing non-significant increase in cartilage content (thickness/volume) (Hedges' g: 0.079; 95%CI: 0.358 – 0.516; P = 0.723) [10].

Table 4
Clinical outcomes (pre- and post-PRP treatment) in the studies of the systematic review reporting on clinical outcomes.

Lead author (Year)	Effect of PRP on cartilage (MRI/US)	WOMAC	KOOS	IKDC	VAS	SF-36	Lysholm	Tegner
Bansal (2021) [19]	Thickness (MRI) 82.8% unchanged 17.1% reduced	WOMAC total Pre: 55 (48–66) Post: 52 (47–60) NSD	NR	Pre: 53.6 Post: 62.8 **P<0.01**	NR	NR	NR	NR
Bennell (2021) [11]	Volume (MRI) Decreased NSD	NR	KOOS pain Pre: 52.9 ± 115.2 Post: 68 ± 18.2 **P<0.05** KOOS other: Pre: 53.9 ± 15.9 Post: 67.2 ± 18.9 **P<0.05** KOOS Knee-QoL: Pre: 33.8 ± 15.8 Post: 51.1 ± 20.1 **P<0.05**	NR	NR	NR	NR	NR
Raeissadat (2020) [10]	Volume (MRI) Decreased (MRI) NSD	WOMAC pain Pre: 8.14 ± 4.56 Post: 3.85 ± 1 3.4 **P = 0.001** WOMAC stiffness Pre: 1.5 ± 2.2 Post: 0.76 ± 0.88 **P = 0.001** WOMAC functional Pre: 24.28 ± 10.95 Post: 10.15 ± 8.3 **P = 0.001**	NR	NR	Pre: 6 ± 2.07 Post: 2.76 ± 2.07 **P = 0.001**	NR	NR	NR
Elik (2020) [32]	Thickness (US) NSD	WOMAC pain Pre: 11.13 ± 4.27 Post: 4.73 ± 3.58 P < 0.001 WOMAC total Pre: 56.40 ± 18.71 Post: 24.87 ± 18.79	NR	NR	Rest: Pre: 3.87 ± 2.14 Post: 1.20 ± 1.56 P < 0.001 Movement: Pre: 7.10 ± 2.52 Post: 2.80 ± 2.32 P < 0.001	Components: Physical: **p<0.001** Mental: **p = 0.003**	NR	NR
Buendía-López (2019) [31]	MOAKS BML (MRI) Decreased	WOMAC pain: Pre: 6.09 ± 1.4 Post: 4.84 ± 0.7 WOMAC total Pre: 42.57 ± 7.3 Post: 34.51 ± 1.2	NR	NR	Pre: 6.15 ± 1.1 Post: 5.03 ± 1.7	NR	NR	NR
Elnemr (2019) [22]	Thickness (US) Decreased NSD	NR	Pre: 62 ± 9.8 Post: 86.2 ± 4 **P = 0.014**	NR	Pre: 9 (7–10) Post: 1 (1–3) **P = 0.001**	NR	NR	NR
Hart (2017) [26]	Thickness (MRI) Decreased NSD	WOMAC total Pre: 37.1 ± 12.9 Post: 13.5 ± 13.7 **P = 0.0005**	NR	Pre: 48.6 ± 15.5 Post: 73.7 ± 13.5 **P = 0.0005**	NR	NR	Pre: 58.5 ± 17.4 Post: 82.2 ± 9.6 **P = 0.0002**	Pre: 3.6 ± 1.2 Post: 6.1 ± 1.1 **P = 0.00001**
Kenmochi (2020) [25]	MOAKS BML (MRI) Improved **P = 0.007**	NR	Pre: 56.2 Post: 69.1 **P<0.01**	NR	Pre: 5.8 Post: 3.1 **P<0.05**	NR	NR	NR

(*continued on next page*)

Table 4 (*continued*)

Lead author (Year)	Effect of PRP on cartilage (MRI/US)	WOMAC	KOOS	IKDC	VAS	SF-36	Lysholm	Tegner
Cobianchi (2021) [21]	T2 relaxation times (MRI) Improved **P<0.001**	WOMAC pain Pre: 18.3 ± 4.5 Post: 7.3 ± 3.2 **P<0.05**	NR	NR	Pre: 7 Post: 2 **P<0.05**	NR	NR	NR
Sen (2020) [28]	Thickness (US) Increased NSD	WOMAC pain **P<0.001** WOMAC stiffness **P<0.001** WOMAC functional **P<0.001**	NR	NR	VAS resting pain Pre: 2.0 ± 2.3 Post: 0.7 ± 1.2 **P<0.001** VAS activity pain Pre: 4.8 ± 2.1 Post: 2.3 ± 1.9 **P<0.001**	Components: Physical: **P<0.05** Mental: NSD	NR	NR
Guillibert (2019) [23]	Thickness (MRI) Decreased NSD	NR	Pre: 43.5 ± 14.3 Post: 66.4 ± 21.7 **P<0.001**	NR	NR	Components: Physical: **P<0.001** Mental: NSD	NR	NR
Calis (2015) [20]	Thickness (US) Increased **P<0.05**	WOMAC total Pre: 81.5 ± 14.5 Post: 62.2 ± 18.5 **P = 0.001** WOMAC stiffness Pre: 5.8 ± 2.4 Post: 4.6 ± 2 **P = 0.001** WOMAC functional Pre: 58.9 ± 11 Post: 45.1 ± 13.5 **P = 0.001**	NR	NR	Pre: 8.1 ± 2.1 Post: 4.4 ± 2.9 **P<0.001**	NR	NR	NR
Sampson (2010) [27]	Thickness (US) Increased NSD	NR	KOOS pain Pre: 35.3 ± 4.96 Post: 48.1 ± 4.96 **P = 0.0295** KOOS other: Pre: 31.6 ± 4.84 Post: 43.9 ± 4.84 **P = 0.0437** KOOS Knee-QoL: Pre: 1.0 ± 6.68 Post: 13.4 ± 6.18 P = 0.1048	NR	VAS resting pain Pre: 2.5 (0–6) Post: 0.8 (0–3) **P = 0.0011** VAS activity pain Pre: 4.6 (1–9) Post: 2.5 (0–7) **P = 0.0003**	NR	NR	NR

PRP: Platelet-rich plasma, **MRI:** Magnetic Resonance Imaging, **US:** Ultrasound scan, **WOMAC:** Western Ontario and McMaster Universities Arthritis Index, **KOOS:** Knee Injury and Osteoarthritis Outcome Score, **IKDC:** International Knee Documentation Committee, **VAS:** Visual Analogue Scale, **SF-36:** Short Form Health Survey, **NSD:** no significant difference, **p<0.05**: significant.

4.2. Comparison with control group

Three RCTs (n = 112) compared PRP treatment with a control [10,22,26]. One (n = 40) compared PRP with HA [26], whilst the other two compared PRP with exercise program [10,22]. Meta-analysis showed no significant difference in cartilage thickness and/or volume with PRP (Fig. 4: Hedges' g: 0.217; 95%CI: 0.177 – 0.611; P = 0.281; heterogeneity: $\tau^2 = 0.039$; $I^2 = 31.548$; Q = 2.922; P = 0.232).

4.3. Effect of PRP on cartilage and clinical outcomes (Table 4)

Thirteen studies reported on various clinical outcomes such as WOMAC, KOOS, IKDC, VAS, SF-36, Lysholm and Tegner score. Clinical outcomes significantly improved in all studies irrespective of the effect on cartilage. Interestingly, even in studies where cartilage thickness or volume decreased (non-significant) [10,11,22,23,26], clinical outcomes were significantly improved at follow-up as compared with their baseline.

5. Assessment of methodological quality of studies and quality of evidence

RCTs – Cochrane Risk of Bias Tool [16] (Supplementary material: Table 2): Five RCTs were assessed as low risk of bias [11,19,26,31,32], two as unclear risk of bias having insufficient information for at least one domain [10,22], and one as high risk [25].

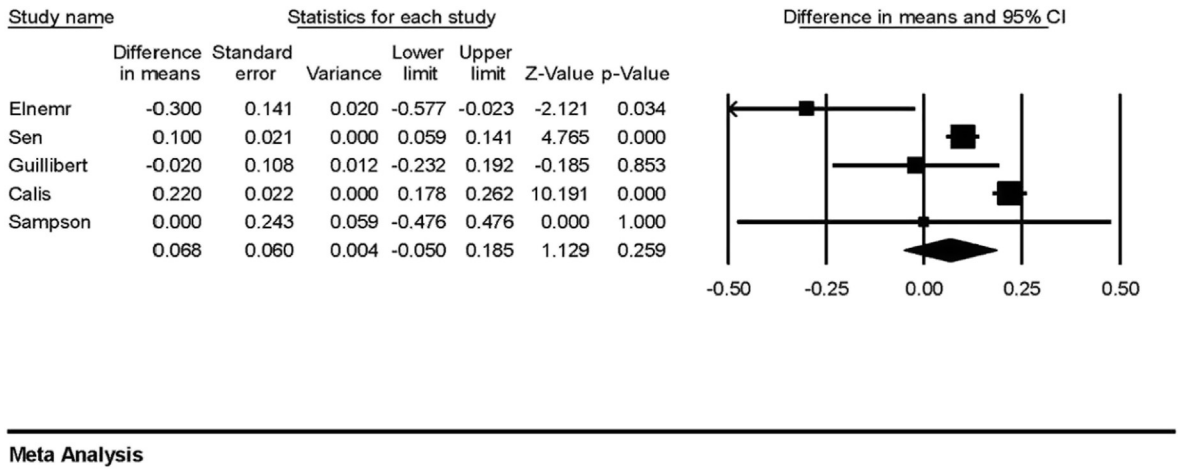

Fig. 2. Forest plot for the estimated differences in mean cartilage thickness of medial femoral condyle post-PRP treatment showing no significant increase in cartilage thickness.

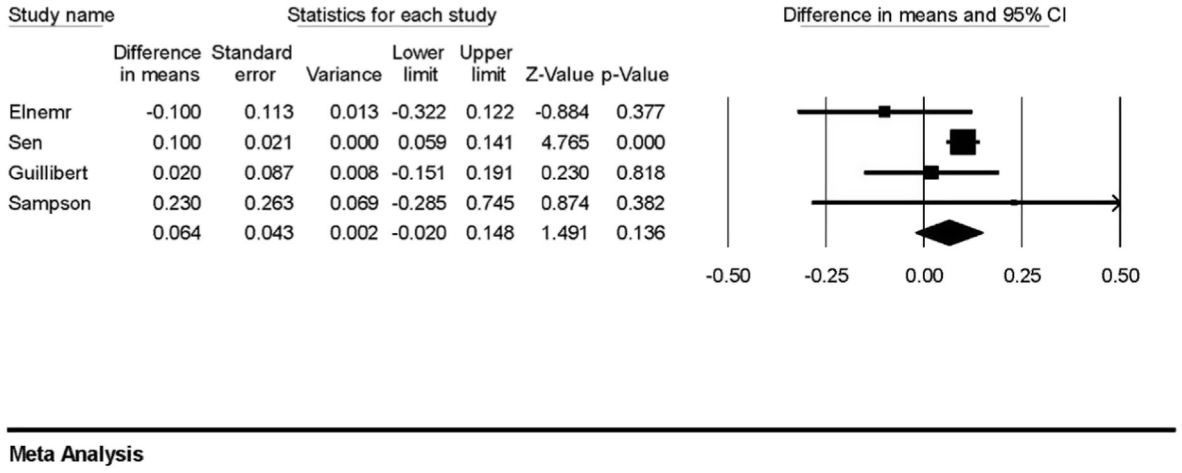

Fig. 3. Forest plot for the estimated differences in mean cartilage thickness of lateral femoral condyle post-PRP treatment showing no significant increase in cartilage thickness.

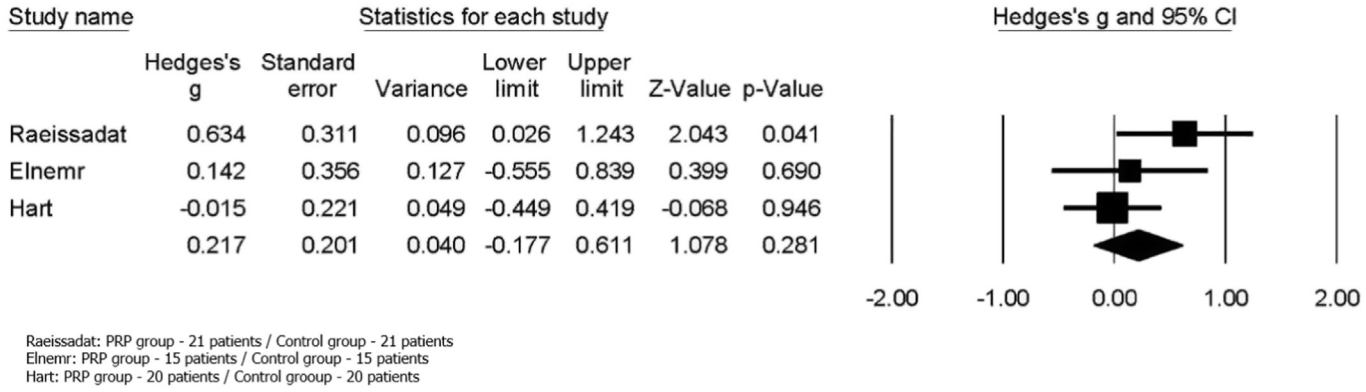

Fig. 4. Forest plot for the differences in mean cartilage thickness/volume comparing PRP with a control group showing no significant difference in cartilage thickness and/or volume with PRP.

Prospective cohort studies – Newcastle Ottawa Scale [17] (Supplementary material: Table 3): One prospective cohort study was rated as "good quality" scoring high in the NOS scale.

Retrospective cohort studies – MINORS criteria [15] (Supplementary material: Table 4): Two studies scored 18 out of 24 points [20,21], while the other three scored 15 out of 24 points [23,27,28].

Quality of evidence: The GRADE approach was used to assess the overall quality of evidence which was "low" [18]. The review included five RCTs, and six non-randomised studies. There was some inconsistency with methodological and clinical heterogeneity, but there was no significant variability in the reported results.

6. Discussion

This systematic review and meta-analysis concluded that treatment of knee OA with PRP is not associated with a significant increase in articular cartilage content and any change in cartilage content was not correlated to clinical outcomes. These findings held both by examining studies that reported pre and post treatment cartilage content as well as studies that compared PRP to a control group.

Hong et al. [4], in a recent systematic review and meta-analysis assessed the safety and efficacy of PRP injections versus placebo (or other conservative management) and showed that PRP is more effective in relieving symptoms (follow-up 6 months). There was no difference between triple versus single PRP injection with regards to their curative effect in short-term. However, they only looked at the clinical outcomes and did not assess the effect of injections on articular cartilage. Another systematic review compared the safety and efficacy of PRP versus HA injections for knee OA [36]. It showed that PRP injections improved clinical outcomes as compared with HA. Moreover, they reported that LP-PRP may be a superior treatment for knee OA as compared with LR-PRP, although admitting that further studies are needed to compare the effect of PRP's leukocyte content on outcomes. However, The American Academy of Orthopaedic Surgeons (AAOS) in its most recent guidelines from August 2021 concluded that PRP may reduce pain and improve function in patients with symptomatic OA of the knee, but downgraded two levels the strength of recommendation to limited due to inconsistent evidence [37]. In line with this, The National Institute for Health and Care Excellence in United Kingdom (UK) in its 2019 guidelines regarding PRP injections for knee OA in adults, suggested that current evidence shows no major safety concerns for PRP injections for knee OA, but with regards to efficacy, evidence is limited and low quality [38].

In addition to any clinical effect, there has been widespread interest as to whether PRP may influence cartilage content, to slow or reverse the process of OA. Such an effect could revolutionize the management of arthritic knees. This was based on encouraging in-vitro and in-vivo studies showing the positive biological effects of platelet-rich products on osteoarthritic chondrocytes and cartilage [39–42], and it was also supported by clinical studies which reported that PRP can improve grade of knee OA on MRI [43,44]. One RCT ($n = 58$) showed that nearly 50% of patients who had LP-PRP injections had more than one grade OA improvement 6 months post-injections, as compared to only 8% with HA injections ($p < 0.003$) [44]. Another series of 15 patients with knee OA having PRP injection and MRI follow-up one year post-treatment, reported no significant worsening of the OA (Outerbridge grading) in the patellofemoral joint in 80% of patients, and no change in the medial and lateral compartments in 73% [43]. A recent RCT showed that an absolute count of near 10 billion platelets in the injected PRP is needed to have long-term chondroprotective effect up to one year in patients with moderate knee OA [19]. Another important factor seems to be the proteomic analysis of the injected PRP and identification of proteins which contribute more to tissue healing. PRPs containing high concentration of platelets contain high quantity of bioactive proteins (such as growth factors and cytokines) which can promote tissue healing and regeneration and this has been and still is extensively researched [45,46].

The above findings led to MRI studies which aimed to more accurately evaluate the cartilage content of arthritic knees in relation to PRP injection. MRI is generally considered a reliable and sensitive tool to assess cartilage status and chondral lesion progression especially in osteoarthritic knees [47]. One technique is to measure the cartilage thickness or volume in a lot of areas inside the knee (MFC, LFC, MTP, LTP) which most studies did. Another more detailed technique, which only one study did [21], is to measure T2 relaxation times (T2 mapping) across the knee joint. It has been shown that T2 relaxation time measurements in the knee are sensitive to early cartilage degeneration and reflect the histological changes inside the cartilage matrix [48,49]. Moreover, some recent studies based on large cohorts showed the predictive and prognostic role of T2 mapping in detection of progression of radiological degenerative changes and morphological lesions in osteoarthritic knees, even when radiographic changes are not apparent [50,51]. The most reliable and reproducible methods to assess articular cartilage morphology and repair is with the use of objective assessment tools, such as the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) [52], or the WORMS score [35], or the MOAKS BML [34]. Unfortunately, only two studies in our review used such tools.

Our study has shown that the available evidence does not support a chondrogenic role for PRP. There is inconsistency in the included studies with variable effect on cartilage content, with some reporting an increase and some reporting a decrease following PRP treatment, and the meta-analysis confirmed that. If OA has a natural history of deterioration, even if PRP is chondrogenic, it may not match the rate of cartilage degeneration, and that may explain the variability seen between studies, and this may also depend on which stage of OA the patient is at the time of treatment.

However, our findings must be considered in the light of the limitations of the available literature. All available and eligible studies were small and differed in their protocols in multiple ways which makes it difficult to draw meaningful conclusions. There is lack of standardization in PRP treatment protocol for knee OA in terms of preparation, administration and dosing. The substantial variability in treatment protocols included multiple different preparation techniques, different centrifugation protocols, various administration protocols with different number of injections (1–6), different time intervals between injections (1–4 weeks), different volumes of PRP injections (2–10 ml), different platelet concentrations (1.4–10 times blood concentration), different WBC concentration (from none to LR-PRP), and use of a different activator. A standardized PRP preparation needs to be defined by further review of the scientific evidence as to the efficacy of different PRP preparations in improving clinical outcomes and a consensus approach amongst clinical experts. The quality of evidence is limited by the inclusion of non-randomised studies. We have included seven RCTs with a control group, but a meta-analysis with only Level I studies was not possible due to the significant heterogeneity and the small number of studies. The meta-analysis entailed an overlap of prospective and retrospective studies, but in all included studies data were reliably and prospectively collected. The method of imaging to assess articular cartilage was also not unified in all studies. This is acknowledged and a relevant recommendation is made, but overall the majority of the studies described in detail how they assessed cartilage with these methods and data were reliably reported by experienced radiologists (sometimes more than one). Lastly, there was not enough studies using objective assessment tools to do a sub-group analysis of their results which would strengthen our results and conclusions.

In conclusion, the current literature does not support the PRP as chondrogenic in treatment of knee OA. There is substantial heterogeneity in the evaluated studies which limits the robustness of any conclusion. Given the limitations of the available literature, further research is needed to draw a definite conclusion. A multi-centre adequately powered RCT with a standardized PRP preparation and treatment protocol and standardized high-resolution MRI along with a quality assessment to ensure a reproducible composition of the injectate is needed to definitely

define any effect of PRP in knee cartilage content and its relation to clinical outcomes. Until such high-quality evidence becomes available, we recommend that PRP is not administered with the intention of promoting chondrogenesis.

Author contributions

Conception and design: All authors. Analysis and interpretation of data: ADP, CPC, RV, HP. Drafting of the article: All authors. Critical revision of the article: ADP, CPC, RV, HP. Final approval of the article: All authors. Statistical analysis: ADP, CPC. Collection and assembly of data: ADP, EM.

Responsibility for the integrity of the work as a whole is taken by Apostolos D. Prodromidis, MD, MSc (first author: apostolos.prodromidis@nhs.net).

Competing interests

No conflicts of interest to declare.

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Authorship

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. By signing below each author also verifies that he (she) confirms that neither this manuscript, nor one with substantially similar content, has been submitted, accepted or published elsewhere (except as an abstract). Each manuscript must be accompanied by a declaration of contributions relating to sections (1), (2) and (3) above. This declaration should also name one or more authors who take responsibility for the integrity of the work as a whole, from inception to finished article. These declarations will be included in the published manuscript.

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Declaration of competing interest

At the end of the text, under a subheading "Conflict of interest statement" all authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and research grants or other funding.

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Appendix A. Supplementary data

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