**RESEARCH**

# MRI-based cartilage changes and clinical effectiveness of autologous intra-articular platelet-rich plasma injections in symptomatic patients with moderate osteoarthritis of the knee

Syeed Aalishan Fatima[1], Aijaz Ahmed Ganai[2], Majid Jehangir[1], Arshed Hussain Parry[1*], Sulaiman Sath[3] and Seema Qayoom[4]

## Abstract

**Background**  An autologous blood product containing a high percentage of various growth factors, cytokines, and modulating factors such as platelet-rich plasma (PRP) is thought to play a role in chondral remodeling by promoting the production of cartilage matrix molecules and repairing and regenerating articular cartilage. In symptomatic patients with moderate osteoarthritis (OA) of the knee, we aimed to investigate MRI-based cartilage changes and the clinical efficacy of autologous intra-articular PRP injections.

**Results**  Thirty-three patients with grades 2 and 3 OA of knees as per Kellgren and Lawrence OA classification underwent three consecutive PRP injections at monthly intervals. These patients were followed up monthly for the first 3 months, and then after every 3 months at 6 months, 9 months, and 12 months. There was statistically significant improvement in joint pain and functionality with the visual analogue scale (VAS) scores showing a reduction from $7 \pm 2$ at baseline to $2.76 \pm 1.34$ at 12 months and Western Ontario and McMaster Universities Osteoarthritis Index Score (WOMAC) scores declining from $77.91 \pm 1 1.6$ at baseline to $23.61 \pm 19.1$ at 12 months ($p < 0.05$). The reduction in VAS and WOMAC scores was maximum during the first 3 months after PRP therapy. MRI showed a statistically insignificant improvement in cartilage thickness [Whole Organ Magnetic Resonance Imaging Score (WORMS) $3.15 \pm 1.41$ to $3.3 \pm 0.84$) ($p > 0.05$)].

**Conclusions**  PRP had a positive effect on pain alleviation and patient functioning, but there was no significant change in articular cartilage as measured by MRI.

**Keywords**  Knee osteoarthritis, Platelet-rich plasma, Visual analog scale, Western Ontario and McMaster Universities Osteoarthritis Index Score, Whole Organ Magnetic Resonance Imaging Score

*Correspondence:
Arshed Hussain Parry
arshedparry@gmail.com
Full list of author information is available at the end of the article

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## Background

Knee osteoarthritis (OA) is a chronic, degenerative disease that affects the knee joint, with a global prevalence of 10–18% [1]. It significantly contributes to musculoskeletal and physical disability in the elderly [2]. Many medical and surgical treatments are available to treat joint pain caused by OA. Nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular injections of corticosteroids (CS) or hyaluronic acid (HA) and saline are the conservative therapies that have been used for a long time to address mild knee OA [3–5]. There are currently no approved medications that can change the course of a disease. The available conservative therapies entail substantial health risks and only yield a small to moderate benefit [6, 7]. Intra-articular platelet-rich plasma (PRP) has recently been used to treat mild to moderate OA as a disease-modifying agent [8]. PRP treatment involves injecting a patient's own platelet concentration. Transforming growth factor (TGF), insulin like growth factor (IGLF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epidermal growth factors (EGF) are abundant in platelet alpha granules [9]. These growth factors are thought to play a role in chondral remodeling by promoting the production of cartilage matrix molecules and repairing and regenerating articular cartilage [10]. However, there is necessity of robust studies to produce a substantial body of evidence in support of PRP use in OA [7].

The aim of the study was to evaluate the effectiveness of PRP in symptomatic patients with moderate OA of the knees using clinical scores and MRI-based chondral changes as assessment tools (Figs. 1, 2, 3).

## Methods

This was a multicentric prospective study conducted over a 36-month period after receiving approval from the institutional ethics committee. The study included 37 people with grades 2 and 3, as per Kellgren and Lawrence OA Classification [11]. Three of the patients declined the procedure, and one patient could not be reached for follow-up; as a result, they were excluded. Finally, 33 patients were enrolled in the study.

The Kellgren and Lawrence grading system is based on single standing limb in stance phase with antero-posterior standing X-rays, it classifies the KOA in following categories.

*Grade 0:* No radiographic features of OA are present.

*Grade I:* Doubtful joint space narrowing (JSN) and possible osteophytic lipping.

*Grade II:* Definite osteophytes and possible joint space narrowing (JSN) on anterior–posterior weight bearing radiograph.

*Grade III:* Multiple osteophytes with definite joint space narrowing (JSN), sclerosis, and bony deformity,

*Grade IV:* Multiple large osteophytes, marked (JSN), severe sclerosis, and bony deformity.
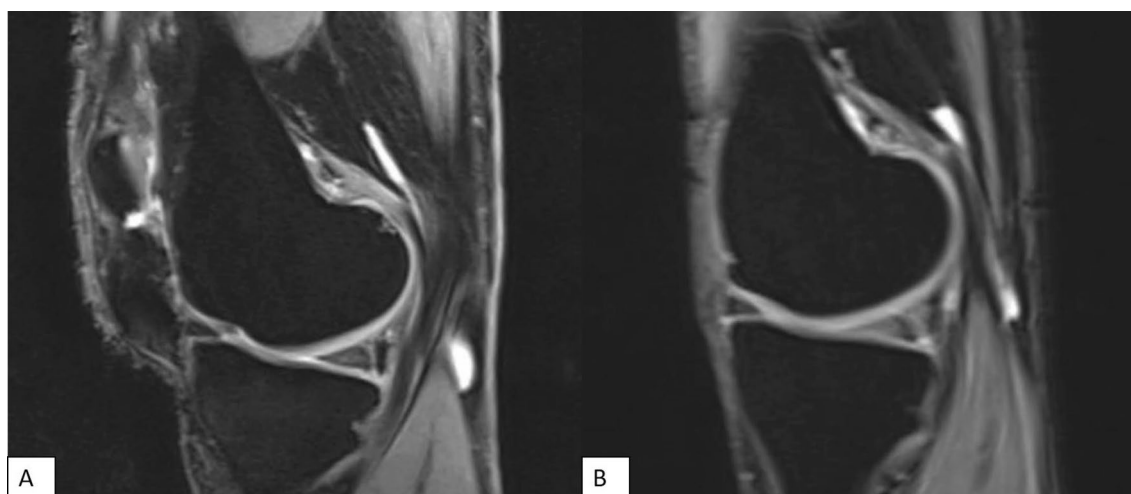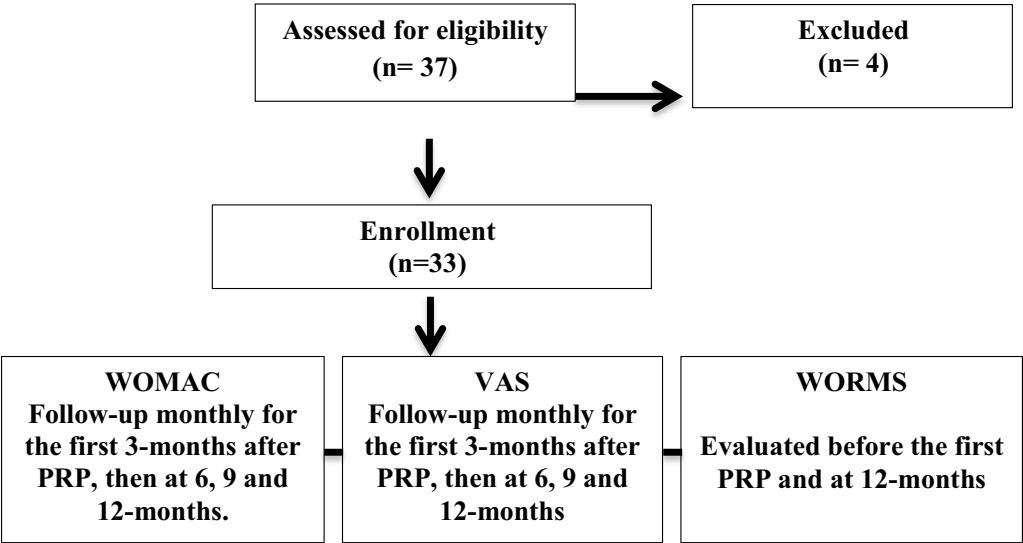


**Fig. 1** A female, aged 67 years, with complaint of pain in right knee. Sagittal three-dimensional double-echo steady-state (3D-DESS) magnetic resonance imaging of the knee at baseline and after a year of PRP therapy showing increase in WORMS cartilage score (**A**) Pre-PRP WORMS cartilage score grade 3 over lateral femoral condyle posteriorly (LFp) and lateral tibial condyle anteriorly (LTa) (**B**) Post-PRP WORMS cartilage score grade 1 over LFP and LTa
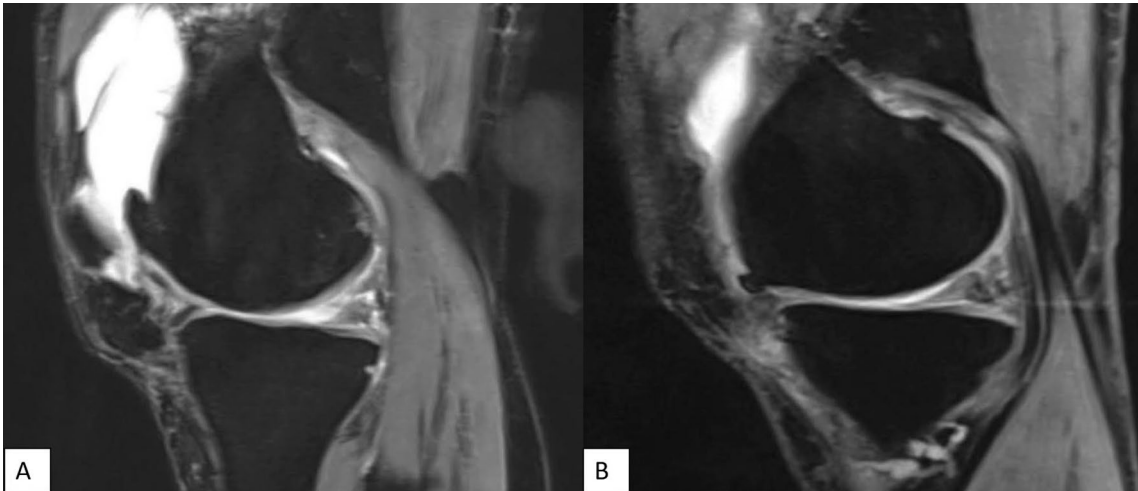
**Fig. 2** A male patient, aged 57 years, presented with history of difficult in walking upstairs. Sagittal 3D-DESS images of the knee at baseline and after a year of PRP therapy showing increase in WORMS cartilage score (**A**) Pre-PRP WORMS cartilage score grade 4 over lateral femoral condyle posteriorly (LFp) and lateral tibial condyle anteriorly (LTa) (**B**) Post-PRP WORMS cartilage score grade 2 over LFP and LTa



**Fig. 3** A female, aged 55 years, complaining of pain when getting up. Pre-PRP (**A** and **C**) radiographs of the knee with marginal osteophytes and definite osteophytes-grade 2 OA Kellgren and Lawrence OA classification. Post-PRP (**B** and **D**) after 1 year of follow-up showed no significant interval changes

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┌─────────────────────────┐          ┌─────────────────────────┐
│  Assessed for eligibility│          │       Excluded          │
│        (n= 37)          ├─────────▶│        (n= 4)           │
└───────────┬─────────────┘          └─────────────────────────┘
            │
            ▼
┌─────────────────────────┐
│      Enrollment         │
│        (n=33)           │
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| WOMAC Follow-up monthly for the first 3-months after PRP, then at 6, 9 and 12-months. | VAS Follow-up monthly for the first 3-months after PRP, then at 6, 9 and 12-months | WORMS Evaluated before the first PRP and at 12-months |

The inclusion criteria were as follows: (1) age > 50 years (in reference to American college of rheumatology (ACR) criteria for diagnosis OA knee) [12] (2) at least 6 months of knee joint OA with radiological evidence of grades 2 and 3 OA (Kellgren–Lawrence OA classification). Exclusion criteria included: Grade 1 and 4 OA (Kellgren and Lawrence OA classification), systemic disease (uncontrolled diabetes mellitus, anemia, bleeding disorder, and rheumatoid arthritis), recently operated knees, active knee infection, steroids injection in the previous 3 months, and any contraindications for MRI.

All patients had their pertinent medical histories taken, and those with OA grades 2 and 3 (Kellgren–Lawrence OA Classification) underwent a comprehensive local examination by an experienced orthopedician. The visual analogue scale (VAS), which has scores ranging from 0 (no pain) to 10 (the worst possible pain), was used to measure the intensity of the pain [13]. The Western Ontario and McMaster Universities Osteoarthritis Index Score (WOMAC), a disease-specific questionnaire that assesses pain, stiffness, and physical functioning in OA patients, with values ranging from 0 to 96 was used a clinical assessment tool [14]. There are twenty-four questions in all, including five about pain, two about stiffness, and seventeen about physical functioning that were assessed. The patients underwent routine blood tests such as complete blood counts, C-reactive protein, rheumatoid factor, random blood sugar levels, and screenings for communicable diseases (HIV, HBV, and HCV). Radiographs of the knee were performed in both the weight bearing and Rosenberg views. All patients underwent a baseline MRI of knee joint on a Siemens MAGNETOM Lumina 1.5 Tesla scanner. Patients remained supine with their fully extended knee and foot perpendicular to the MRI table, with an extremity coil around the knee. In addition to routine sequences (sagittal proton density with fat suppression (PDFS) sequence, T2W and T1W sagittal and coronal spin echo sequence, a coronal short TI inversion recovery sequence), high-resolution cartilage sequences in 3D-DESS (dual echo study state) repetition time (TR), 18 ms; echo time (TE), 3 ms; Flip

**Table 1** Worms cartilage score

| Score | MRI findings |
|---|---|
| 0 | Indicates normal cartilage |
| 1 | Increased signal with fluid sensitive intermediate-weighted sequences |
| 2 | Partial thickness defect less than 1 cm in greatest width |
| 2.5 | Full-thickness defect less than 1 cm in greatest width |
| 3 | Multiple areas of partial thickness (grade2) defects intermixed with areas of normal thickness or a partial thickness defect wider than 1 cm but less than 75% of the region |
| 4 | Diffuse (> 75% of the region) partial thickness loss |
| 5 | Multiple areas of full thickness loss (grade 2.5) or a full thickness defect wider than 1 cm but less than 75% of the region |
| 6 | Diffuse (≥ 75% of the region) full thickness loss |

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angle (FA) $25^0$, band width (BW), 130 Hz; slice thickness, 1.91 mm, number of slices 44; (to cover the entire knee with a low scan duration and a high signal-to-noise ratio (SNR), the slice thickness of 1.9 mm and slice count of 44 were chosen); acquisition time, 7 min:51 s; field of view (FOV) $150 \times 150$ mm and fat signal suppression using water-excitation pulse were taken. Articular cartilage was evaluated on MRI using Whole Organ Magnetic Resonance Imaging Score (WORMS), a semiquantitative scoring system based on cartilage thickness and the percentage of the area affected [15] (Table 1). To avoid inter-observer variability, two experienced radiologists (MJ with 32-years of experience and AP with 12-years of experience) independently read the MRI on a dedicated Syngo workstation. The WORMS cartilage score was then recorded for the section with the greatest number of cartilage changes or defects. Any disagreement between the two readers over these scores was settled in consensus. In the final consensus, the WORMS score assigned by a more experienced radiologist trained in musculoskeletal radiology was used as the final score.

### Patient preparation and intra-articular injection of PRP

Under strict aseptic conditions, 30–40 mL of whole blood was obtained from the patient's antecubital vein via venipuncture and placed in 8.5 ml of acid citrate dextrose (ACD) tubes. The blood was centrifuged for three minutes using a soft spin at a speed of 3000 rpm. After that, platelet-containing supernatant plasma was transferred into a different sterile tube (without the use of anticoagulation). The tube was then centrifuged at a higher speed (a hard spin at 4000 rpm for 15 min) to obtain a platelet concentrate. PRP, in the bottom one-third of the concentrate, was used for intra-articular injection.

An experienced orthopedic surgeon used the table in 90-degree flexion of the knee joint and an anterolateral approach to administer an intra-articular PRP injection by an 18G needle while the patient's legs were hanging from the table. This was done in an aseptic environment. Total, 3 intra-articular injections of PRP, containing 3 ml each, were given at an interval of 4-weeks. All intra-articular PRP injections were completed as day care operations, and the patient was required to remain in the facility for a 30-min observation period following the treatment. Additionally, the patients were instructed to minimize their professional or vocational activities and to apply cold packs two to three times daily for the first 48–72 h following the treatment.

### Post-PRP follow-up

A follow-up was conducted every month for the first three months following the PRP injections, and then at 6 months, 9 months, and 12 months. Each follow-up included the calculation of the WOMAC and VAS scores. Twelve months after the initial PRP injection, MRI was performed to evaluate the changes to the cartilage using the WORMS Cartilage Score.

### Statistical analysis

Statistical software, SPSS (version 20.0), and Microsoft Excel were used to carry out the statistical analysis of the data. The data were provided as mean values with standard error of the mean (SEM), and p values less than 0.05 were considered significant. The Shapiro–Wilk test was used to examine the normality of the variables VAS, WOMAC, and WORMS scores for inferential statistics. The p value of the Shapiro–Wilk test for the variables under examination was less than 0.05, indicating that the data deviated considerably from normal distribution. We employed nonparametric statistical tests to analyze the data since the variables under inquiry were not normally distributed. The Friedman test was used to evaluate the efficacy of the PRP treatments at various follow-ups for WOMAC and VAS ratings. The Wilcoxon signed rank test was used to analyze the pre- and post-interventional data.

## Results

### Physical characteristics

The current prospective study enrolled 33 patients with knee osteoarthritis grades 2 and 3 knee OA (Kellgren and Lawrence classification), consisting of 42.4% males ($n = 14$) and 57.6% females ($n = 19$), with a mean age of $52.6 \pm 8.99$ years. The demographics of patients are depicted in Table 1.

### Follow-up assessment

WOMAC: There was a decline in the WOMAC score after the PRP therapy. The 1-month ($56.48 \pm 13.87$), 2-month ($31.33 \pm 13.294$), and 3-month ($27.2 \pm 11.29$) follow-up WOMAC scores showed a statistically significant

**Table 2** Demographic characteristics and distribution of the patients

| Number of patients | n = 33 | |
|---|---|---|
| | K L II 9 | 27.3% |
| | K L III 24 | 72.7% |
| Female | 19 | 57.6% |
| Male | 14 | 42.4% |
| Mean Age (years) | 52.64 ± 8.999 | |
| Side—Right/Left | 17/16 | 51.5%/48.4% |
| BMI | 30.7 ± 4.4 | |

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**Table 3** Changes in the mean clinical scores (WOMAC and VAS) at follow-up

|  | Before first PRP | 1-month follow-up | 2-month follow-up | 3-month follow-up | 6 months | 12 months | *p* value |
|---|---|---|---|---|---|---|---|
| WOMAC Score | 77.91 ± 11.65 | 56.48 ± 13.87 | 31.33 ± 13.294 | (27.2 ± 11.29) | 24.94 ± 14.97 | 23.67 ± 19.12 | 0.000 |
| VAS Score | 7.00 ± 2.00 | 4.58 ± 1.48 | 2.18 ± 1.103 | 2.01 ± 1.2 | 2.64 ± 1.342 | 2.76 ± 1.803 | 0.000 |

**Table 4** The WORMS Cartilage score before first PRP injection and at 12-month follow-up

| Wilcoxon Signed Ranks Test | WORMS cartilage score before first PRP | WORMS cartilage score after 12 months of PRP | *p* Value |
|---|---|---|---|
| Mean ± SD | 3.15 (1.417) | 3.3 (0.847) | 0.528 |

decline from the pre-PRP score of 77.91 ± 11.6. The WOMAC score at 6 months (24.94 ± 14.9; $p = 0.15$) and 12 months (23.67 ± 19.1; $p = 0.22$) after the first PRP did not show a statistically significant decline when compared to the previous PRP scores (Table 2).

VAS: VAS showed a similar declining trend akin to the WOMAC score after the PRP therapy. The 1-month (4.58 ± 1.48), 2-month (2.18 ± 1.103), and 3-month (2.01 ± 1.2) follow-up VAS scores showed a statistically significant decline from the pre-PRP score of 7.00 ± 2.00. The VAS score at 6 months (2.64 ± 1.342; $p > 0.05$) and 12 months (2.76 ± 1.803; $p > 0.05$) did not show a statistically significant decline when compared to previous PRP scores (Table 2).

WORMS Cartilage score: Improvement in WORMS cartilage score was not significant on application of the Wilcoxon signed rank test. Analysis of the pre-interventional and post-interventional WORMS cartilage was done using the Wilcoxon Signed Rank test. The baseline WORMS cartilage score was 3.15 ± 1.417 and it increased marginally to 3.3 ± 0.847 at 12 months. The increase in cartilage score was statistically insignificant ($p = 0.528$) (Table 3). In terms of correlation, we found no significant correlation between the WORMS Cartilage score before first PRP and WOMAC score before first PRP ($p = 0.50$), and WOMAC score at 9th from first PRP and WORMS cartilage score at 12 months from first PRP ($p = 0.316$). Furthermore, no significant correlation was found between VAS score before first PRP and WORMS cartilage score before first PRP ($p = 0.42$) and VAS score at 9th from first PRP and WORMS cartilage score at 12 months from first PRP ($p = 0.39$) (Table 4).

## Discussion
Osteoarthritis is a complicated biochemical condition that changes the structure of the joint and eventually results in loss of function [16]. Along with the continuous inflammatory process in the joint, the distinctive characteristics include increasing degradation of the articular cartilage, subchondral sclerosis, and osteophyte production [17]. Knee osteoarthritis can be treated non-surgically with analgesic drugs, chondroprotective drugs, intra-articular steroid injections, viscosupplementation, physical therapy, or surgically with high tibial osteotomy, arthroscopic lavage, autologous chondrocyte implantation, and total knee replacement [18]. Furthermore, medication treatments might have negative side effects, and physical therapy does not offer long-term advantages; thus, none of these approaches aim to alter the course of disease. Intra-articular injections of glucocorticoids and hyaluronic acid offer very temporary, few-month benefits. Repeated corticosteroid injections may have a negative impact on the cartilage in the knee joint, according to recent studies [6, 7].

PRP is an autologous blood product rich in alpha granules, which serve as reservoirs for growth factors, cytokines, and other biologically active substances. These bioactive substances promote the production of cartilage matrix molecules and aid in chondral remodeling by promoting cartilage regeneration and repair (intra-articular platelet-rich plasma (PRP)) is one treatment that may be able to address the underlying biological causes of OA [10].

Several studies have demonstrated clinical benefits in osteoarthritis patients receiving platelet-rich plasma treatment, but only a small number of these studies have compared these clinical improvements with the radiological effects of PRP on joint cartilage [1, 2, 19–22].

The study demonstrates that PRP is beneficial in reducing pain and improving patient functioning. The reduction in clinical scores (VAS and WOMAC) is steepest in the first 3 months and the reduction is less after 6 and 9 months. MRI showed no significant change in the articular cartilage 12 months after the therapy. However, interestingly, we did not detect any appreciable cartilage loss after 12 months of the study.

For patients suffering from knee OA, several intra-articular injection treatment strategies have been employed including corticosteroids, hyaluronic acid, and PRP. Sanchez et al. [23] conducted the first randomized control trial to evaluate the safety and efficacy of intra-articular PRP in OA. They divided the patients in two groups of 30 each and administered intra-articular

injection of PRP in one group and hyaluronic acid (HA) in other. They recorded a 33.4% improvement in pain scores in PRP group compared to 10% in HA group, demonstrating the superiority of the PRP treatment over HA.

Joshi Jubert N et al. [24] conducted a randomized double blinded clinical trial, enrolling 75 patients of KL grade 3rd and 4th symptomatic knee OA. One group were administered a single 54 leucocyte poor PRP and second group were given intra-articular injection of corticosteroid. The study concluded that a single PRP injection is more efficacious in improving the patient's 57 symptoms and quality of life compared to corticosteroid injection.

Raeissadat SA et al. [25] conducted a blinded randomized clinical trial in patients who were having grade I, II, and III OA knee. They found a significant reduction in WOMAC, VAS scores in the patients who received intra-articular PRP compared to non-PRP group. They also reported a significant improvement in cartilage volume of patello-femoral compartment and synovitis in PRP group. Halpern et al. [26] reported that at 6 months and 1 year after baseline, pain scores decreased significantly, although functional and clinical scores increased. After one year, qualitative MRIs revealed no change in at least 73% of patients. Burchard et al. [1] used three doses of intra-articular PRP weekly in 59 patients and observed that pain and clinical severity of OA improved but they did not find a positive correlation between the degree of cartilage damage as indicated by the WORMS score and a positive clinical outcome to PRP treatment was not seen. On the other hand, Bennell et al. [27] reported no statistically significant difference in change in overall knee pain between PRP and placebo, with 95% CI excluding a clinically important difference ($p$ value $= 0.528$). A number of hypotheses have been put forth to account for the effectiveness of PRP in OA. It is believed that various growth factors like VEGF, TGF, PDGF, ILGF, EGF, and FGF, which are abundant in platelet granules, may be responsible for cartilage regeneration [18]. However, significant improvement in clinical scores like VAS and WOMAC with insignificant changes in WORMS cartilage score post-PRP therapy suggests that probably PRP exerts its clinical benefit primarily due to the anti-inflammatory action without leading to significant cartilage regeneration. The PRP has several modulatory biological activities like angiogenesis and inflammation, which may account for its pain alleviation effect [28, 29]. Proliferation of mesenchymal stem cells and autologous chondrocytes was shown in an ovine model following PRP exposure [30].

In our study, there was no significant change in the WORMS cartilage score before initial PRP and 1 year after. Additionally, in relation to the WORMS cartilage score in KL grade 2 and grade 3, the scores did not change

significantly before and after treatment ($p > 0.05$). Raeissadat SA et al. [25] measured the patello-femoral cartilage volume 8 months after treatment and found a considerable increase in cartilage volume ($p = 0.001$) in the PRP group in comparison to the control group (exercise and analgesia) ($p = 0.001$). The Guillibert et al. [31] evaluated the articular cartilage before and after PRP therapy using the MRI Osteoarthritis Knee Score Bone Marrow Lesion (MOAKS BML) and concluded that although pain and knee function improved significantly, no significant improvement in MRI parameters was observed. These findings are congruent with the findings of Buendia-Lopez et al. [2] who measured articular thickness in all knee articular compartments before and after intra-articular PRP and came to the same conclusion. There is disagreement over the impact of PRP on articular cartilage, with some showing an improvement and others reporting a reduction post-PRP therapy. Even if PRP is chondrogenic, the pace at which it regenerates the cartilage may not match the natural degradation of articular cartilage in OA, which may explain the heterogeneity reported between studies [32]. The present study supports the role of PRP in clinical and functional improvement on OA knee patients.

However, the study has some other important limitations. Since the acquisition time is short, multi-echo sequences provide a more practical method for obtaining T2 maps than other approaches (such as DESS). It has also been demonstrated that T2 relaxation time measurements are reproducible, even at 1.5 T.

Quantitative cartilage imaging is demanding for resolution, with slice thickness from 0.7 to 1.5 mm and in plane resolution from $0.3 \times 0.3$ mm to $0.5 \times 0.5$ mm necessary to reliably detect and follow small defects less than 5 mm$^2$. In the present study to cover the entire knee with a low scan duration and a high signal-to-noise ratio (SNR), the slice thickness of 1.9 mm and slice count of 44 were chosen, which could have potentially missed small cartilage defects.

A small sample size, lack of a control group and randomization, and short follow-up are some other limitations of the study due to which generalization of the study population may not be possible.

## Conclusions

Intra-articular PRP injections for knee OA have a positive effect on pain relief and patient functioning. However, there was no significant change in articular cartilage as determined by MRI, and interestingly, no significant cartilage loss was seen in the cohort one year post-PRP therapy.

**Abbreviations**

| | |
|---|---|
| OA | Knee osteoarthritis |
| PRP | Platelet-rich plasma |
| VAS | Visual analog scale |

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WOMAC    Western Ontario and McMaster Universities Osteoarthritis Index Score
WORMS    Whole Organ Magnetic Resonance Imaging Score

## Declarations

### Ethics approval and consent to participate
The study was duly approved by the Institutional Ethical Committee (IEC) of GMC, Srinagar, Jammu & Kashmir, India. A reference number was not applicable. Consent was obtained from the patients.

### Consent for publication
Not applicable.

### Competing interests
None.

### Author details
[1]Department of Radiodiagnosis, Government Medical College, Srinagar, Jammu & Kashmir 190011, India. [2]Department of Orthopaedics, Government Medical College, Anantnag, Jammu & Kashmir, India. [3]Department of Orthopaedics, Government Medical College, Srinagar, Jammu & Kashmir, India. [4]Department of Dermatology, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India.

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