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ORIGINAL PAPER

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Abstract

Purpose Cartilage lesions are usually accompanied by subchondral bone alterations or bone marrow lesions (BMLs). BML associated with joint degeneration and cartilage lesions are considered to be predictors of rapidly progressing OA. Currently no existing treatment can fully halt OA progression. One of the approaches is an autologous, biological treatment based on the use of platelet rich plasma (PRP) injections. The purpose of this study is to assess the short-term effectiveness of intraosseous PRP injections, within the BML of individuals affected by OA, in ameliorating pain and improving knee functionality.

Materials and methods The study involved 17 patients with an average age of 41.7 ± 14.3 years old. OA stage was determined using the Kellgren-Lawrence grading system by performing radiographic scanning of the knee joint before surgical intervention. Patients with K–L grade 3 knee joint OA prevailed. Patient OA history varied between one and nine years (average 5.2 ± 4.5 years). Clinical and functional state of the knee were assessed by pain visual analogue scale (VAS) score, the Western Ontario and McMaster Universities Score (WOMAC), and the Knee Injury and Osteoarthritis Outcome Score (KOOS) which were filled out by patients previous to the surgical procedure at one, three, six and 12 months post-operatively. Before surgery, in addition to standard blood tests, serum cartilage oligomeric matrix protein (COMP) levels were tested for all patients.

Results Evaluation of preliminary results revealed a statistically significant reduction of pain based on the VAS score. A significant improvement was also observed in the patients' WOMAC score and in the overall KOOS score. Serum marker levels were initially elevated in our experimental patient group compared to the same marker in healthy control respondents, and continued to rise one month and three months following surgery, at six and 12 month the level was similar as at three months.

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Conclusions In our opinion, first COMP increasing can be caused by injection of platelet rich plasma. It is not adequate to interpret this growth in COMP levels as increased osteochondral degeneration. One year follow-up period showed good quality of life improvement, significant pain reduction, and essential MRI changes. The long-term observation of these cohort of patients combined with an analysis of MRI images is still ongoing.

Keywords Osteoarthritis · Bone marrow lesions · Joint degeneration · Cartilage lesions · Platelet reach plasma · Biological treatment · Subchondral bone · Intraosseous injections

Introduction

Currently, osteoarthritis (OA) is commonly regarded as a chronic disease which is associated to damage and loss of articular cartilage, with simultaneous involvement and progressive destruction of intra-articular structures, leading to a loss of joint function and a reduced quality of life (QoL) [1].

Cartilage lesions are usually accompanied by subchondral bone alterations or bone marrow lesions (BMLs), conditions which are diagnosed using magnetic resonance imaging (MRI) with high signal on fluid-sensitive sequences [T2/proton density with fat suppression and short tau inversion recovery (STIR)] with or without low T1WI signal, and are considered as a classic feature of OA. This signal can be observed throughout different stages of OA [2–4]. Histologically, these MRI findings manifest themselves as an increased thickness and mineral density of the subarticular trabeculae, which are responsible for inducing early OA. Other typically observed processes include microcracks, micro-oedema, microbleeding, and bone cyst formation within the subchondral region [2, 4]. BMLs are typically found in the sclerosis zone of the subchondral bone and are usually accompanied by a growing volume of bone tissue and a thickening trabecular layer [5]. It has also been shown that cartilage lesions are often present in immediate proximity to the BMLs and that the degree of cartilage tissue degradation positively correlates with MRI signal intensity, pain intensity, and loss of function [6, 7]. Indeed, using MRI, Sowers M. F. et al. detected a significantly higher frequency of BMLs larger than 1 cm^2 in OA patients who reported severe pain in the affected joint, compared to those in which joint pain was not as pronounced [8]. Nevertheless, although BML presence has been strongly associated to OA pathogenesis and to pain in knee OA, the correlation between BMLs and pain is still under discussion [4, 9, 10, 11–13].

BML associated with joint degeneration and cartilage lesions are predictors of rapidly progressing OA [14]. This was confirmed in a study by Felson et al. who analyzed MRI scans performed on 223 patients with knee OA over a period of 2.5 years [9]. BMLs can, therefore, be considered a predictor of the onset of cartilage degradation and the emergence of pain even before the manifestation of the typical clinical signs of OA, such as pain, stiffness, and locomotor restriction [15]. At the same time, BMLs can be associated not only with OA but also with avascular necrosis (AVN) (traumatic, non-traumatic, or secondary to a systemic disease), firstly described by Ahlback et al. [4, 16–18]. Other authors suppose that at the origin of BML there are so-called subchondral insufficiency fractures (SIFK) which can progress to osteonecrosis (SONK).

Despite the fact that a lot of attention has been recently invested to the study of BMLs and their influence on the OA progression, a unanimously accepted opinion on the role of BMLs has not yet been achieved. Specifically, many unanswered questions remain regarding the potential influence of BMLs on subsequent pathological subchondral changes [19, 20].

Currently no existing treatment can fully halt OA progression. Since the underlying cause of OA pathogenesis is not yet known, research efforts are being devoted to the development of new OA treatments, whose approaches are focused on altering the disease's evolution [1, 21]. One of these approaches is an autologous, biological treatment based on the use of platelet rich plasma (PRP) injections. For patients with advanced OA of the knee, PRP is a substantial source of active therapeutic biomolecules which, thanks to their chondroprotective, anabolic, anti-inflammatory, and immunomodulatory effects, can positively influence joint homeostasis, while also substantially ameliorating pain and improving joint function [1, 6–8, 14, 16, 22–25].

Following this rationale, the attempts to create OA treatment methods based on PRP injections into BMLs appear to be quite promising. Indeed, since intra-articular infiltrations of PRP cannot penetrate into the subchondral bone, intraosseous injections can provide a more comprehensive treatment effect [21]. Such a procedure, in combination with early diagnosis, timely treatment, and proper monitoring of therapy effectiveness, will allow doctors to delay invasive surgery such as arthroplasty, while significantly improving the patients' quality of life. This would be particularly beneficial for athletes and other OA patients with an active lifestyle.

Until now, the gold standard for diagnosing degenerative OA changes has been a combination of radiographs and MRI. However, due to the importance of early diagnosis (which not only allows quick assessment of therapy effectiveness but also the introduction of necessary adjustments in a timely manner), new diagnostic procedures can be crucial in improving OA treatment.

One method of early diagnosis involves the observation of cartilage and bone metabolism markers in patient plasma. One of the most frequently employed markers used for this purpose is cartilage oligomeric matrix protein (COMP). COMP, also known as thrombospondin 5 (TSP 5), is a non-collagen glycoprotein belonging to the extracellular protein family of thrombospondins. It has been suggested that COMP molecules play an important role in maintaining the properties and integrity of the collagen network. For joint disease diagnostics, the serum level of this protein provides important information about the metabolic changes occurring in the cartilage matrix and is considered an early and promising marker for the remodeling of articular cartilage [26]. It is also reported that protein level significantly increases at severe stages of OA [6, 23].

The **purpose** of this study is to assess the short-term effectiveness of intraosseous PRP injections, within the BML of individuals affected by OA, in ameliorating pain and improving knee functionality.

Materials and methods

The study involved 17 patients with an average age of 41.7 ± 14.3 years old. OA stage was determined using the Kellgren–Lawrence grading system [27] by performing radiographic scanning of the knee joint before surgical intervention. Patients with K–L grade 3 knee joint OA prevailed. Patient OA history varied between one and nine years (average 5.2 ± 4.5 years). The OA diagnosis was established on the basis of complaints, anamneses, and clinical examinations (Table 1).

As for BMLs, they were minimally present in two patients, moderate in seven patients, and severe in eight patients. BMLs were assessed by MRI and analyzed by Whole-Organ Magnetic Resonance Imaging Score (WORMS) following this point-based scale:

0 points – no BML
1 point – minimally expressed BML (Ø < 5 mm)
2 points – moderate BML (5 mm ≤ Ø ≤ 20 mm)
3 points – severe BML (Ø > 20 mm) [25]

Patient inclusion criteria

1. Male and female individuals aged 30–70 years old
2. Kellgren–Lawrence grade 2–4 of knee OA
3. Ineffective previous conservative treatment, lasting at least 3 months (NSAIDs, physical therapy intra-articular injections of hyaluronic acid or PRP injections, glucocorticoids)
4. Patients able and willing to actively participate to the necessary rehabilitation protocol and clinical and radiological procedures
5. Signed an ethics committee reviewed and approved informed consent form

Patient exclusion criteria

1. Patients unwilling to participate to the study
2. Patients suffering from malignant neoplasms
3. Patients suffering from rheumatic diseases
4. Patients suffering from metabolic disorders
5. Known drug or alcohol dependence within the last year
6. Patients with deformation of the axis of the lower extremity exceeding 10°
7. Body mass index < 18 or > 35;
8. Patients who previously underwent knee joint surgery within six months of the study's surgical procedure
9. Knee joint instability

In order to assess the clinical and functional state of the knee, the pain visual analogue scale (VAS) score, the Western Ontario and McMaster Universities Score (WOMAC), and the Knee Injury and Osteoarthritis Outcome Score (KOOS) were filled out by patients previous to the surgical procedure and one and three months postoperatively [28].

Table 1 Characteristics of the patients who participated in the study

		Observation group	Control group
Sex (number of patients)	Female	10 (58.8%)	10 (58.8%)
	Male	7 (41.2%)	7 (41.2%)
Average age (y.o.)		41.7 ± 14.3	40,3 ± 12,1
Duration of knee joint impairment (years)		5.2 ± 4.5	–
Kellgren-Lawrence grade of knee OA	I	0	12 (70,6%)
	II	5 (29.4%)	5 (29.4%)
	III	10 (58.8%)	–
	IV	2 (11.8%)	–
Whole-Organ Magnetic Resonance Imaging Score	0	0	–
	1	2 (11,7%)	–
	2	7 (41,2%)	–
	3	8 (47,1%)	–

Before surgery, in addition to standard blood tests, serum cartilage oligomeric matrix protein (*COMP) levels* were tested for all patients. Blood withdrawals were also repeated at one, three, six and 12 months following surgery. All blood serum samples collected were frozen at − 70°C. The level of COMP in blood serum was measured by means of polarization fluoroimmunoassay with the use of a standard set of reagents (Human Cartilage Oligomeric Matrix Protein ELISA, BioVendor, Germany) according to the vendor's guidelines. The results were compared with data obtained from a control group of 17 healthy respondents with an average age of 40.3 ± 12.1 years old, ten (58.8%) female, and seven (41.2%) male. Patients with K–L grade I knee joint OA prevailed, without any clinical signs of OA or BMLs (volunteers, Table 1).

PRP preparation and method description

To obtain the necessary PRP product, the Regenlab (REGENACR) method was used. 30 ml of each patient's venous blood was divided into three tubes: two blue REGEN BCT tubes (20 ml) and one red REGENATS tube (10 ml). All tubes were then centrifuged for five minutes at a speed of 3100 rotations/minutes. The resulting PRP product was subsequently drawn up from the blue tubes using syringes under sterile conditions, and the autologous platelet serum was drawn from the red tubes.

Intraosseous injection of the PRP product, within the BML area, was performed under fluoroscope control by placing a trocar (13 mm (BOHR)) 1 cm close to the subchondral bone. Manipulations were conducted in the standard position of the patient lying on his/her back on the operating table under spinal or intravenous anaesthesia. Introduction of the trocar was controlled with the use of an image intensifier. Upon reaching the area affected by the relevant pathological changes with the needle, 5 ml of the previously obtained PRP products were slowly introduced into the tissue without prior mixing (Fig. 1).

Fig. 1 Introducing the medication into the femoral condyle

Statistical data processing

For the statistical analysis of results, Statistica 10.0 for Windows (StatSoft Inc., USA) was used. Quantitative variables were described using standard variation statistical methods, for which the arithmetic mean (M), standard deviation (δ), 25th and 75th percentiles, and median patient number were calculated. The average values were presented as M ± δ. The qualitative variables were described as absolute and relative frequency ratios (percentages). Differences were considered significant at $p < 0.05$. To evaluate results, the statistical analysis methods used was included: Student's *t*-test and non-parametric tests for variable samplings were inconsistent with the normal distribution law (Mann–Whitney test, the Wilcoxon test, the Chi-square test). Different activity scores were compared with the use of contingency table analysis.

Results

Evaluation of preliminary results revealed a statistically significant reduction of pain based on the VAS score. Before the treatment, patients assessed their pain level as "severe" (51.4 ± 6.9 mm). One month following surgery, it decreased by 36.4 mm, now falling into the "insignificant pain" range (15.0 ± 8.3 points, $p < 0.05$); at three months after the surgery, the score was at 18.3 ± 11.6 points, at six and 12; at three months after the surgery, the score was at 15.8 ± 10.6 and points 11.1 ± 9.3 respectively, $p < 0.05$ (Fig. 2).

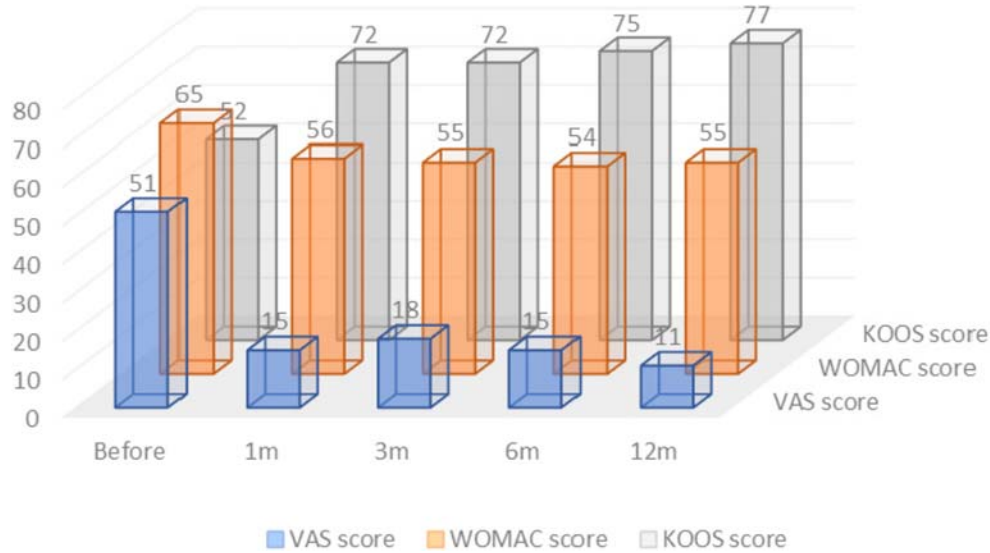
A significant improvement was also observed in the patients' WOMAC score. The average total score before surgery was 65.1 ± 6.42, while one month following surgery, it decreased significantly to 56.45 ± 5.91, $p < 0.05$. Three, six and 12 months following the surgery, no ulterior significant improvement was observed, yet the positive result was maintained at 55.33 ± 8.41, 54.23 ± 7.38, and 55.38 ± 12.85 points, respectively, $p > 0.05$.

Similarly, a significant improvement was observed in the overall KOOS score. At admission the average patient score was of 52.78 ± 13.38. One month following surgery, the score rose to 72.00 ± 7.35, $p < 0.05$; three, six and 12 months after injection, the value remained at 72.13 ± 8.50, 75.12 ± 7.50, and 77.03 ± 7.48, respectively, $p > 0.05$.

Since the KOOS scale consists of five sections evaluating individual aspects of the condition of the knee joint condition, evaluating each subscale separately was also of interest (Fig. 3).

In the symptoms subscale, the average score at admission was of 62.85 ± 10.28; one month after the intraosseous injection, it was of 74.28 ± 10.53, $p < 0.05$; three, six and 12 months

Fig. 2 Scores dynamics at Time-Points



following surgery, a slight, statistically insignificant decrease was observed, with the scores remaining at 71.43 ± 6.18, 69.43 ± 7.18, 66.48 ± 7.02 points, respectively, $p > 0.05$.

Regarding the Pain subscale, the mean score on admission was of 53.70 ± 7.18. One month after the injection, it was 74.40 ± 11.87 (an improvement of 20.70 points), $p < 0.05$; three, six and 12 months after that it decreased to 70.36 ± 12.52, 71.48 ± 9.52, 69,1 ± 13.4 points, $p < 0.05$.

Regarding the function in daily living subscale, on admission the average score was of 53.36 ± 15.41. One month after the injection, it rose to 73.04 ± 10.21, $p < 0.05$; three, six and 12 months after the injection, it rose again from 74.51 ± 4.24 points (which is 21.15 points higher than before treatment) to 76.51 ± 5.2 and 78.41 ± 4.23, respectively, $p < 0.05$.

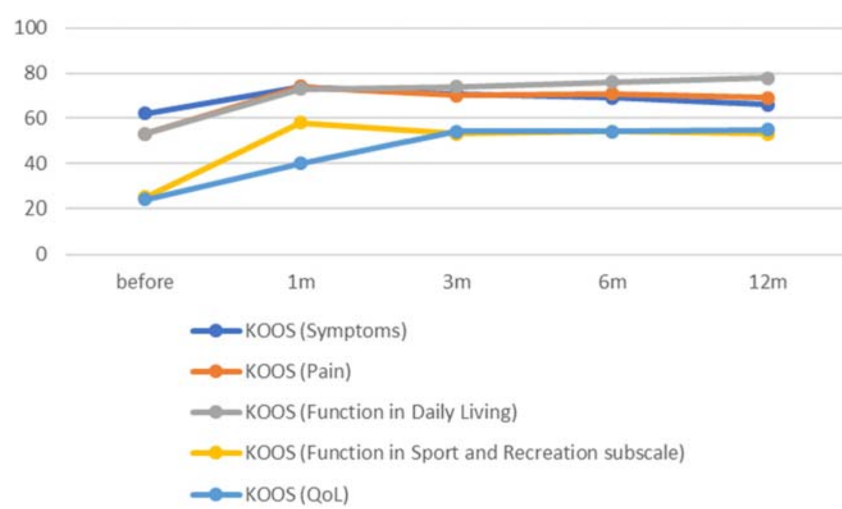
In the function in sport and recreation subscale, the mean score before treatment was of 25.83 ± 21.31, $p < 0.05$. One month after treatment, it was 58.33 ± 19.66 (32.5 points improvement), $p < 0.05$; three, six and 12 months after the injection, it decreased to 53.33 ± 28.86, 54.32 ± 27.16, and 53.73 ± 27.6 points, respectively, $p < 0.05$.

Positive results were also reported in the KOOS QoL section, where the average score before surgery was 24.08 ± 18.39 points. One month after surgery, it rose to 40.62 ± 23.30 points, $p < 0.05$; three months after surgery, it significantly rose again to 54.18 ± 21.48 points (that is 30.10 points better than before treatment started), $p < 0.05$. At six and 12 months, there were no significant changes: 54.48 ± 20.12 and 55.1 ± 22.1, $p > 0.05$.

It should be noted that the most pronounced improvements were registered in the sport and recreation and QoL sections, which appeared to be attributed, to some extent at least, to the emotional response of the patients who experienced and appreciated the positive effects of the treatment.

It is important to note that in the majority of the KOOS sections, as well as in those of WOMAC and VAS, the best scores were observed one and three months after the treatment. Indeed, statistically significant improvements at three

Fig. 3 Index improvements of KOOS subsections throughout the study period (absolute values in points)



months compared to one month following surgery were registered in the QoL subscale. Conversely, in the pain and sports and recreation subscales, the daily living and symptoms, a statistically significant decrease in average scores was observed at three, six and 12 months compared to one month following surgery.

COMP dynamics evaluation

When evaluating the changes in serum COMP levels, a consistent statistically significant increase was observed over time: from 1108 ± 439 before surgery to 1402 ± 596 points one month after surgery, $p < 0.05$, and further to 1632 ± 684 three months after surgery, $p < 0.05$; it is also noteworthy that (prior to surgery) the marker's serum levels were significantly higher in the study population than in the control group: 1108 ± 439 and 490.0 ± 77.6, respectively ($p < 0.05$) (Table 2). At six and 12 months after surgery, statistically significant changes, compared with previous data (1173 ± 410 and 1158 ± 414, respectively ($p > 0.05$)), were not found.

MRI dynamics evaluation

In all cases, within 12 months after the surgery, according to MRI, were found, and the signs of improvement assessed by WORMS classification at point 1 (Fig. 4).

Discussion

The purpose of our study was to assess effectiveness of intraosseous PRP injections, within the BML of individuals affected by OA, in ameliorating pain and improving knee functionality.

In addition to using multiple standardized OA scoring scales, we analyzed serum levels of the cartilage metabolism marker COMP, which, according to numerous studies, is an informative marker reflecting metabolic intra-articular changes [6, 23, 26].

The role of the subchondral bone, in terms of OA etiology, development, and treatment is still broadly discussed. At present, it has been demonstrated that the subchondral bone remodeling is an important process in OA pathogenesis, and changes to this tissue layer can occur due to various circumstances, both as a cause and as a result of joint degeneration. It is also recognized that the presence of these changes is of clinical significance, causing pain and inflammation that can contribute to the development of arthropathy [16, 17].

Various ways of treating BMLs have been developed and have been shown elicit beneficial structural changes in subchondral bone. Non-operative treatment, usually employed in the treatment of small BMLs (< 3.5 cm2) without clear signs of osteonecrosis, consists of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, prostacyclin, bisphosphonates (acting on different bone targets), protected weight bearing for three to eight months, physiotherapy, and close patient symptom and radiological monitoring [4, 29]. While the search for the most tropic and effective method continues, the use of PRP is gaining increased recognition and validation in clinical practice. This autologous product is harvested from the patient's blood and consists of growth factors (profuse in the plasma), which when administered into damaged tissue increase the concentration of M2 phenotype macrophages, which stimulate the reparative process [30]. Additionally, PRP influences oxidative stress mechanisms which play a substantial role in catabolic processes within subchondral bone [31]. Specifically, PRP activates the antioxidant response element (ARE) present in osteoblasts, which protects cells from reactive oxygen species (ROS) and oxidative stress [32], while also stimulating beneficial subchondral bone remodeling. These promising results on the use of PRP lead us to theorize that administering the product directly to the BML area could have a significant and rapid impact on the cells of the subchondral bone and the (structurally closely related) overlying articular cartilage.

Various intraosseous injections methods have been described in literature. One such method is subchondroplasty, a method designed to treat joint osteochondral pathology of osteoarthritic joints by injecting calcium phosphate into the affected subchondral bone, under arthroscopic control, with good results in pain reduction and a small risk of complications [33, 34]. It is important to note that in cases in which insufficiency fractures lead to bone structural collapse, subchondral support techniques are inadequate, and thus, the treatment of choice should be bone grafting of the injured and deficient bone, followed by osteochondral restoration [35].

The data obtained in our study also attests to the positive effect of intraosseous injections in treating OA. This can be clearly seen by the significant decrease in pain intensity and increase in joint function (based on WOMAC and KOOS) as observed throughout the study. Particularly remarkable is the fact that the positive results were maintained for several months following the surgical procedure. It is also important

Table 2 COMP Dynamics

	Prior to surgery	1 month after surgery	3 months after surgery	6 months after surgery	12 months after surgery	Healthy controls
COMP, ng/ml	1108 ± 439	1402 ± 596*	1632 ± 684*	1173 ± 410*	1158 ± 414*	490.0 ± 77.6*

*Statistically significant difference, $p < 0.05$

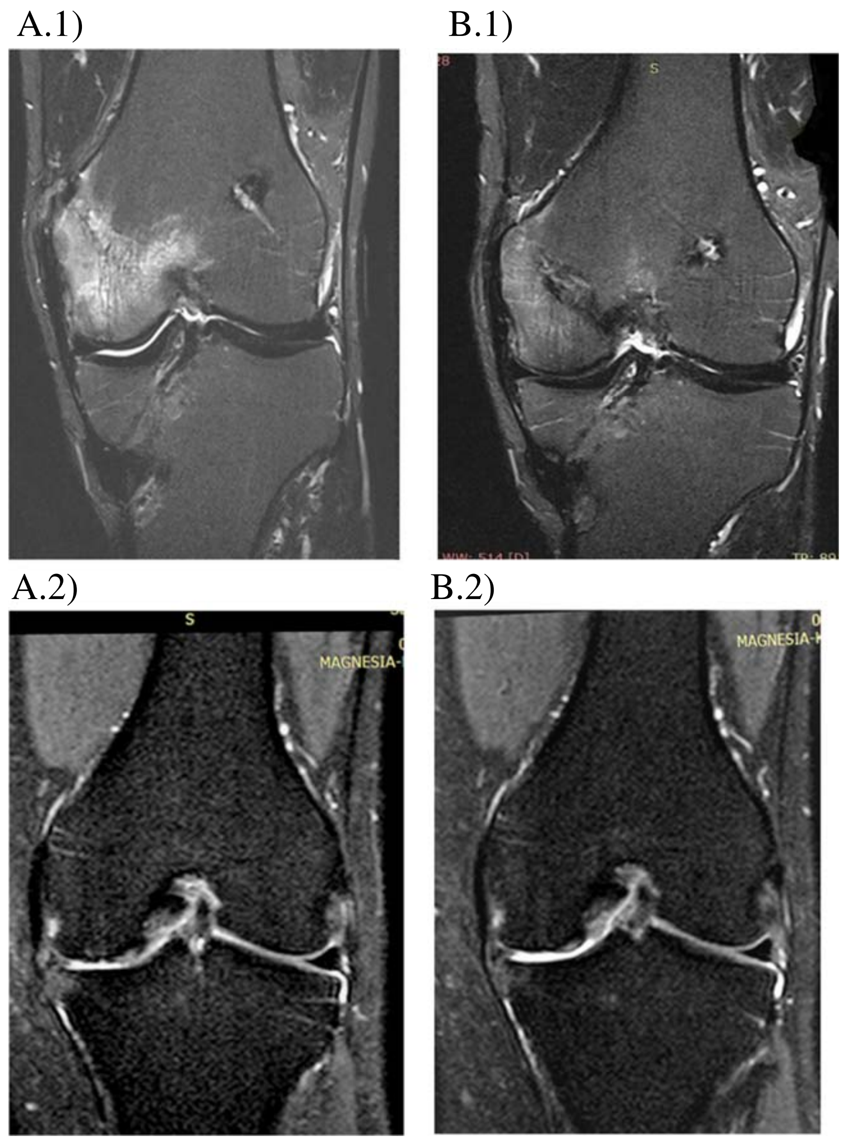


Fig. 4 MRI dynamics (A.1; A.2-before surgery; B.1; B.2–12 months after)

to note that such positive results were obtained despite the prevalence of patients with K–L grade 3 OA, a stage at which joint replacement (i.e., arthroplasty) is routinely recommended. Therefore, these positive results suggest that the technique described in this study can also be used in treating later stage OA, including cases in which there are contraindications to major surgical procedures associated to a high risk of post-operative complications.

Regarding COMP analysis, the interpretation of this marker's serum levels remains controversial [36]. Data referenced in relevant studies reveal a positive correlation between COMP and the stage of OA. Standardized values of the index, however, are still not established and can vary depending on the gender. Indeed, other studies found no correlation between serum COMP and OA presence at all [36, 37]. In our study, serum marker levels were initially elevated in our experimental patient group compared to the same marker in healthy control respondents, and continued to rise one month and three months following surgery. By the sixth and 12th month after the injection, any dynamics was not found.

Although one year of observation prevents the establishment of strong conclusions, given the significant improvement in the patients' clinical and functional state, it is not adequate to interpret the first three months of growth in COMP levels as increased osteochondral degeneration. We instead assume that increases in serum COMP levels cannot only reflect the progression of joint destruction but also the occurrence of positive cartilage turnover.

Conclusions

The role of subchondral bone in the aetiology and progression of OA is still widely discussed. Intraosseous injections within the area of BMLs can provide an additional approach for the comprehensive treatment of knee OA. In this study, injection of autologous PRP within patient BMLs substantially improved their conditions as seen by a significant reduction in pain, and a significant increase in joint function up to three months following the surgical procedure. The observed increase in COMP serum concentrations following the operation cannot be definitively interpreted, and further monitoring and research on this blood marker must be performed.

Nonetheless, this study has important limitations, including a small experimental sample size. Nevertheless, the pronounced positive improvements observed allows us to make assumptions about the effectiveness of this technique. The long-term observation of these cohort of patients combined with an analysis of MRI images is still ongoing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration ant its later amendments or comparable ethical standards.

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