Treatment of degenerative meniscal tear with intrameniscal injection of platelets rich plasma

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Short title

Treatment of degenerative meniscal tear with PRF

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Abstract

Purpose: The purpose of this retrospective study was to describe our preliminary results of intra-meniscal injections of platelet rich plasma (PRP) in patients with degenerative meniscal tears of the knee.

Material and method: Ten patients with degenerative meniscal tears according to the Stoller classification and without knee osteoarthritis were included. There were 7 men and 3 women with a mean age of 40.4 ± 13.6 [SD] years (range: 18 - 59 years). Patients were prospectively assessed at baseline and 3- and 6-months after intra meniscal PRP administration. Evaluation included the knee injury and osteoarthritis outcome score (KOOS), pain visual analog scale, and return to competition and training. MRI follow-up was performed 6 months after PRP administration. Adverse events were recorded.

Results: Volume of injected PRP was standardized to 4.0 mL. Adverse events during PRP administration was moderate pain in 8 patients. Mean KOOS total score significantly improved from 56.6 ± 15.7 (SD) to 72.7 ± 18.5 (SD) (P = 0.0007). All six patients practicing sports regularly were able to recover competition or training. In seven patients who underwent MRI follow-up at 6 months, MRI showed stability of the meniscal tears and similar Stoller grades.

Conclusion: Intra-meniscal injection of PRP under ultrasound guidnce directly into meniscal degenerative lesions is feasible and safe. Further randomized controlled studies are needed to definitely confirm the effectiveness of this procedure.

Keywords: Platelet-rich plasma (PRP); Magnetic resonance imaging (MRI); Meniscal tear; Knee joint; Visual analog scale

Introduction

The menisci, attached between the lateral and medial articular surface of the femur and tibia, are two wedge-shaped, semicircular, fibrocartilaginous structures that provide shock absorption and load transmission during dynamic movements through an innate resistance to compression, tension and shear forces [1]. Sports-related injuries are the most common causes of meniscal lesions, accounting for more than one third of all meniscal lesions [2,3]. Meniscus lesions are

thought to be clinical manifestations of early-onset osteoarthritis since they have been shown to lead to fibrocartilage loss and potential joint space narrowing [4].

Meniscal injuries can be treated using surgical approaches. Of these, arthroscopic partial meniscectomy, which consists in removing torn meniscal fragments to relieve pain-attributed symptoms, is one of the most common orthopedic procedures performed in the United State. However, this procedure failed to show efficacy compared to placebo surgery (*i.e.*, sham surgery) [5].

Thus, non-surgical and conservative management is preferred with a wide variety of possibilities including oral non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular administration of corticosteroid or hyaluronic acid. Indeed, interventional radiology techniques have a major role in pain management [6,7]. In this context, biological options have emerged to relieve pain and improve functions in these patients. Among them, platelet-rich plasma (PRP) is defined as an autologous plasma suspension of platelets, characterized by a higher platelet concentration than in physiological blood [8]. Activated platelets release growth factors (GFs) implied in reparative and regenerative processes. High levels of platelet-derived growth factors (PDGFs), transforming growth factor b1 (TGF-b1), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor 1, or fibroblast growth factor found in PRP are especially known to play a critical role in cell proliferation, chemotaxis, cell differentiation, and angiogenesis [9]. Described as an easy, fast, effective, cheap, and safe (because of its autologous origin) product, PRP has been the subject of increased clinical interest in the orthopedic field. Evidence indicates that, compared with hyaluronic acid (HA) and saline, intra-articular PRP injection may have more benefits in pain relief and functional improvement in patients with symptomatic knee osteoarthritis at 1 year post injection [10]. However, one matter of importance is the lack of prior published studies assessing the effect of PRP on meniscal healing.

The purpose of this retrospective study was to describe our preliminary results of intra-meniscal injections of PRP in patients with degenerative meniscal tears of the knee.

Materials and methods

Patients

This study was performed after the approval from the Committee for the Safety of Health Products of our university hospital to routinely use PRP for musculoskeletal disease.

Individuals with systemic disease, those who were receiving anticoagulant treatment, pregnant women, patients with severe cardiovascular disorder and patients with a bleeding disorder were not considered for inclusion.

The study cohort consisted of 10 patients with a total of 10 degenerative meniscal tears without knee osteoarthritis. There were 7 men and 3 women, with a mean age of 40.4 ± 13.6 (SD) years (range: 18 - 59 years) who underwent intrameniscal PRP injection under ultrasound guidance. Meniscal tears were grade 1 (n=2), grade 2 (n=4), grade 3 (n=4) according to the magnetic resonance imaging (MRI) Stoller classification, with internal (n=6) or external (n=4) location [11]. Patient history, characteristic of meniscal lesion and, initial pain visual analog scale (VAS) and knee injury and osteoarthritis score (KOOS) are detailed in Table 1.

PRP Preparation Method

After a four-step skin decontamination (antiseptic foaming solution, rinsing with sterile water, drying, and alcoholic dermal antiseptic), a nurse collected 18 mL of blood by venipunture using a 21-Gauge needle filling one 20-mL syringe containing 2 mL of ACD-A (Fidia, Abano). The blood was transferred into the Hy Tissue 20 device (Fidia, Abano) before centrifugation using the Omnigrafter III (Fidia, Abano) at 3200 rpm during 10 minutes. The PRP was recovered using the Push Out system and 4 mL of PRP was sampled in a 5-mL syringe. A volume of 300 µL from whole blood and each PRP preparation were sampled to determine platelets, leukocytes and red blood cells concentrations using automated hematology blood cell analyzers Sysmex XN-10 (Sysmex) and following recent guidelines [12]. Sterility was checked using 250 µL of PRP sampled in Bactec culture bottles (Peds Plus Aerobic/F and Plus Anaerobic/F culture vials, containing each 40 mL of growth medium). Bactec culture bottles were incubated at 37 °C for a total of 10 days, and automated readings were taken every 10 min. Detection of organisms resulted in an audible alarm and automatic recording of time to detection.

Intrameniscal tear PRP administration

Ultrasound-guided subcutaneous local anesthesia was performed before the procedure. Ultrasound-guided injection of PRP was performed by the same radiologist (D.G.) specialized in musculoskeletal imaging. When meniscal tear was seen on ultrasound, an intra-meniscal injection of 0.5 mL of PRP in the tear was first performed. Then 1.5m L was injected in the meniscal wall and 2 mL in the peri-meniscal space.

When meniscal tear was not seen on the ultrasound, 2 mL of PRP were injected in the meniscal wall [13] and 2 mL in the peri-meniscal space. The injection was made with a 21- or 25-Gauge needle based on thickness of the soft tissue. Pain VAS was monitored during the intra meniscal injection.

Data collection and follow-up

Safety of the procedure was graded according the CIRSE classification system [14]. Patients were prospectively assessed at baseline and at 3- and 6-months after PRP administration. After the procedure, the patients were evaluated using KOOS, pain VAS (with a 0-100 mm scale), and ability to return to competition and training. Adverse events were recorded. Follow-up MRI examinations were performed at 6 months after PRP injection using a 1.5 T MRI unit (Ingenia®, Philips Healthcare). The MRI protocol included T1-weighted images in the sagittal plane (field of view, 180 mm; slice thickness, 3.5 mm; slice number, 28), three-dimensional fat suppressed spectral attenuated inversion recovery (SPAIR) images (field of view, 180 mm; slice number, 400) with 2-mm thickness multiplanar reformatted images and fat-suppressed SPAIR images in the coronal plane (field of view, 175 mm; slice thickness, 3mm; slice number, 24) [15]. Meniscal tears were reassessed according Stoller classification and compared to initial MRI findings.

Platelets increase factors compared to whole blood corresponded to platelets or leukocytes concentration in PRP divided by platelets or leukocytes concentration in whole blood. Relative composition of PRP corresponds to the percentage of platelets, red blood cells and leukocytes within each PRP sample. A pure PRP was defined by a percentage of platelets in PRP > 90%. Responders were defined as patients presenting an improvement of at least 10 points of KOOS total score [16].

Statistical analysis

Statistical analyses were performed with SPSS statistical software, version 16.0 (SPSS, Chicago, IL). Significance was set at $P < 0.05$. Quantitative data were expressed as mean ± standard deviation (SD). All median, interquartiles ranges (Q1, Q3) and ranges were provided in corresponding table. The differences in KOOS score were analyzed by non-parametric one-way analysis of variance (ANOVA) taking into repeated measures over the time. Difference in VAS between baseline and 6 months was analyzed using a Wilcoxon matched pair test.

Results

Biological characteristics of PRP

Table 2 summarizes biological characteristics of injected PRP. The final injected volume of PRP was 4.0 mL in all patients. The mean increase in platelets and leukocytes factors compared with blood were 1.4 ± 0.4 (SD) and 0.1 ± 0.1 (SD), respectively. The percentage of platelets was 96.5 ± 1.5 (SD) % with very few contaminations of red blood cells (RBCs) (3.4 ± 1.4 %) and leukocytes (0.1 ± 0.1 %). Mean number of injected platelets was 2.0 ± 0.6 (SD) billion. Injected PRP was sterile in all patients (10/10; 100%).

Adverse events

PRP injection was performed in meniscal tear in five patients (Fig. 1) whereas for five of them, meniscal tear was not seen on ultrasound. No major complications were reported during and after the injection of PRP. Eight patients described pain at injection with a mean VAS of 50 ± 31 (SD) mm (range: 0-10 mm). Pain resolved within 10 minutes after the injection.

Effect of single PRP injection in meniscal tears

Single intra-meniscal injection of PRP was safe for all patients with only grade I adverse events with the absence of adverse events until 6 months after the procedure. Intra meniscal injection of PRP was effective in improving knee functional status with a significant increase in KOOS total score from 56.6 ± 15.7 (SD) to 72.7 ± 18.5 (SD) (P=0.0007) 6 months after the procedure. This significant difference was also observed in the stiffness and other symptoms

(*P*=0.0013), function in daily living (*P*=0.0190) and quality of life (*P*=0.0060) KOOS subscales 6 months after the procedure (Fig. 2,Table 3). This corresponded to a responder rate of 55.6% (5/9) at 3 months and 60% (6/10) at 6 months according minimal clinically important change in KOOS total score. Assessment of pain through VAS resulted in a decrease from baseline (57.0 ± 11.6 [SD] mm) compared to 6 months after the procedure (33.0 ± 29.0 [SD] mm) (*P* = 0.18) (Table 3) without reaching the significance. No significant differences were observed in KOOS total score and pain VAS between the patients injected or not in the meniscal tear. Six months after PRP administration, all patients practicing sports regularly (n=6) were able to return to competition or training activities. Seven patients underwent follow-up MRI examination at 6 month that showed stability of the meniscal tears and similar Stoller grades (Fig. 3). One patient had a parameniscal cyst which disappeared on MRI at 6 months.

Discussion

This purpose of this pilot study was to evaluate the feasibility, safety and efficiency of PRP intrameniscal injection for patient suffering from degenerative meniscal lesions. Although no radiological healing process could be observed at 6 months' follow-up, significant improvement in function scores and pain decrease in treated patients was obtained.

The management of degenerative meniscal lesions has been the subject of recent recommendations reinforcing the place of conservative treatment as a first-line therapeutic option [17]. Surgical treatment is restricted to failed medical treatment in patients with "mechanical" symptoms but the definition of an ideal conservative treatment is still debated. Some studies recommend the use of physiotherapy, which results in similar functional outcomes that surgical treatment [18–20]. Intra-articular injection of hyaluronic acid or corticosteroid is another widely used alternate option. These practices are based on evidence of the effectiveness of intra-articular injections to improve mid-term functional outcomes in patients with moderate knee arthritis but no evidence exists regarding their efficacy to relieve pain in patient suffering from degenerative meniscal lesions [21].

Recent studies have focused on the use of PRP in osteoarthritis. The effects of PRP in these studies included chondrocyte and mesenchymal stem cell proliferation increase, proteoglycan and type II collagen deposition. PRP was also found to increase chondrocytes

viability and migration chondrogenic mesenchymal stem cells differentiation or to decrease cytokines catabolic effect [22]. Cerza et al. demonstrated in a randomized controlled trial, that PRP results in a better clinical outcome than hyaluronic acid (WOMAC score, 65.1 and 36.5 in the HA and ACP groups, respectively; $P < .001$ at 24 weeks) in moderate knee arthritis (Grade < 3) [23].

Concerning the feasibility of intrameniscal injection, a previous cadaveric study evaluated the accuracy of ultrasound-guided latex injection into the body and posterior horns of medial and lateral menisci [24]. After dissection, 17 of 20 injections were accurately performed. Two of 3 inaccurate injections infiltrated the posterior horn of the medial meniscus instead of the targeted meniscal body. One inaccurate lateral meniscus injection did not contain latex despite sonographically accurate needle placement. As in our study, no neurovascular complications were observed.

In our pilot study, ultrasound-guided injections of PRP was feasible, allowing accurate and safe delivery of PRP into bodies and posterior horns of the medial and lateral menisci. However, in three patients, the degenerative lesions were not visible on ultrasound, and PRP injections were performed inside of the menisci walls. During this procedure, we only observed during the first ten minutes after injection a slight increase in patients' pain as assessed by the VAS, which confirms the acceptability of this treatment. No difference was found in terms of pain observed during the procedure or clinical outcomes during follow-up for the five patients that received an intra-meniscus tear injection.

Concerning PRP efficacy, the few published *in-vitro* studies reported contradictory results. Ishida et al. investigated whether PRP enhances meniscal tissue regeneration *in vitro* and *in vivo* [25]. They observed that PRP not only enhances proliferation of meniscal cells but also promotes glycosaminoglycan's synthesis *in vitro* [25]. To test the *in vivo* effect, PRP with gelatin hydrogel (GH) was injected into the 1.5 mm diameter full thickness meniscus defect of the rabbits. These researchers found that histologic scoring of the defect sites was significantly better in a PRP with GH treated group 12 weeks after PRP injection, suggesting that PRP enhances the healing of meniscus lesion. Another study confirmed the positive effect of FGF-2, which is one of the growth factors released from platelets [26]. This study showed that GH incorporating FGF-2 enhanced the healing of meniscus horizontal tear (4 mm in width and 2mm in length) in

rabbits [26].. At 4, 8, and 12 weeks after surgery, histologic healing scores were significantly higher in the GH with FGF-2 treated group than a GH without FGF-2 group. In another study, Shin et al. investigated the effect of leukocyte-rich PRP (L-PRP) on potential healing of the horizontal medial meniscus tears in a rabbit model [27]. A horizontal medial meniscus tear was created in both knees of nine rabbits. Left or right knees were randomly assigned to an L-PRP group, or a control group. 0.5 mL of L-PRP from 10 mL of each rabbit's whole blood was prepared and injected into the horizontal tears in L-PRP group. Nothing was applied in control group specimen's knees. The histological assessment of meniscus healing performed at two, four, and six weeks after surgery showed no significant differences of quantitative histologic scoring between two groups. But the sample size was too small and the evaluation time too short to detect differences of histologic scoring system between the two groups. Regarding *in vivo* results, to our knowledge no other studies have attempted to evaluate the efficacy of PRP in local injection for human meniscal degenerative lesions.

Although we observed a significant improvement in several functional scores, we did not observe any MRI healing of these lesions. Several hypotheses can be suggested. First, PRP does not have a healing effect on these lesions and the good functional results observed are due to an anti-inflammatory effect of PRP [28]. Second, the scar tissue obtained has a different MRI signal than healthy meniscus appearance. Third, our follow-up is too short to observe changes in MRI presentation.

Our results should be interpreted with the following limitations. First we conducted a pilot study to evaluate the feasibility of the PRP intra-meniscal injection and only 10 patients were included with no control group, which limits the interpretation of the clinical efficacy of PRP. Also, we have missing data for some scores and for 6 months MRI due to the routine care design of the study.

In conclusion, we reported here the first human clinical study to assert the feasibility of infiltration of PRP under US control directly into meniscal degenerative lesions. Although the functional results are encouraging, they will have to be confirmed by a randomized controlled study with a higher number of patients in order to affirm the effectiveness of this treatment.

Conflicts of interest

The authors have no conflict of interest to declare.

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Figure legend

Figure 1: Ultrasound-guided injection of platelet-rich plasma in the medial meniscus in a 45-year-old man. **A**, Ultrasound image of medial femoro-tibial joint shows medial meniscus (*) (F: femur; T: tibia) with meniscal tear (white arrow). **B**, Ultrasound image shows needle (arrowhead) positioned in the meniscal tear. Platelet-rich plasma can be seen to fill the meniscal tear (arrow).

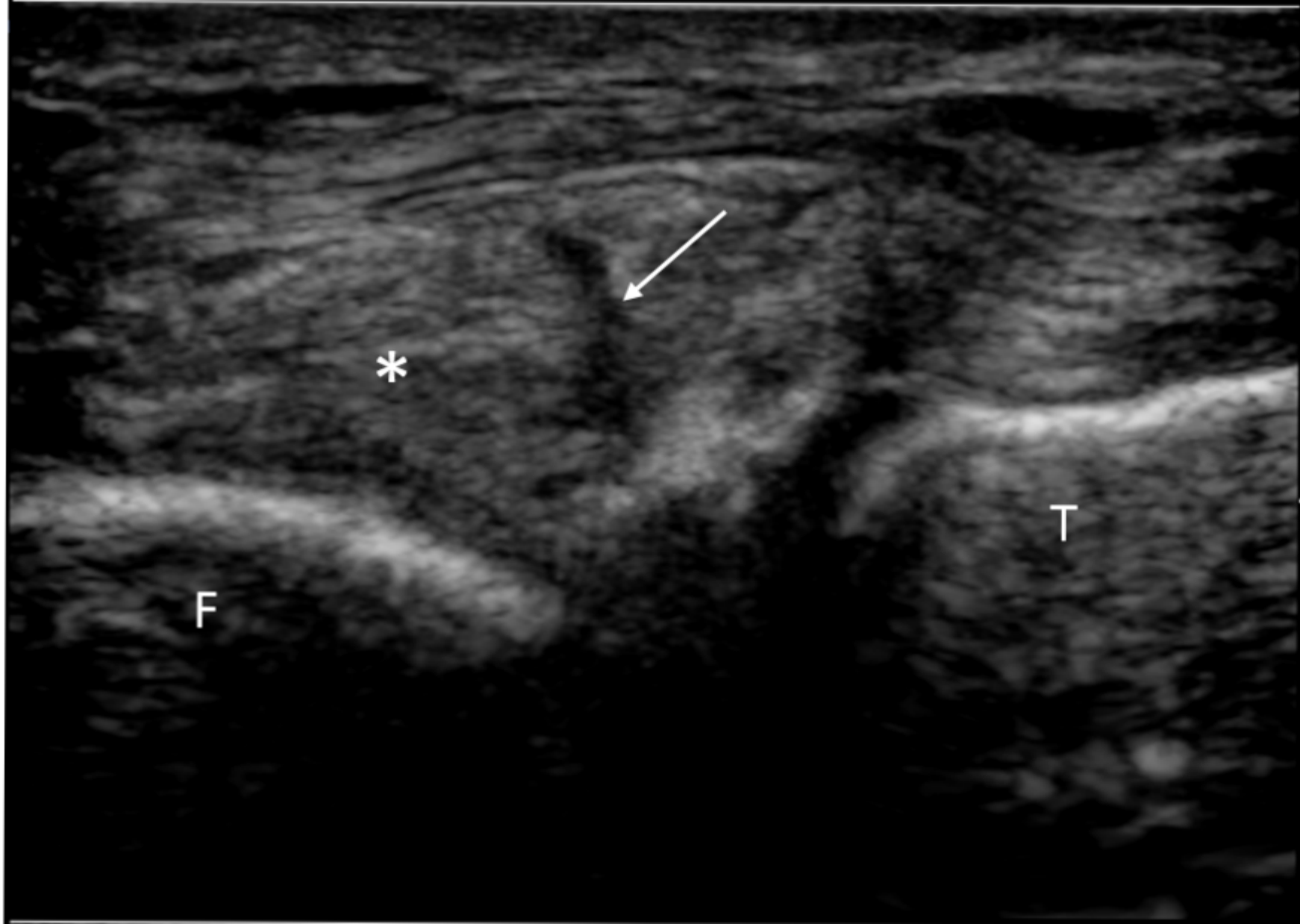
Figure 2: Graphs show changes in osteoarthritis outcome score (KOOS) scores after intra-meniscal injection of platelet-rich plasma.

Figure 3: MRI findings before platelet-rich plasma injection and at 6 months follow-up in a 35-year-old man with meniscal tear. A: Initial fat-suppressed T2-weighted MR image in the sagittal plane shows a horizontal tear of the posterior horn and meniscal body (arrow) corresponding to a grade 2 meniscal lesion according to Stoller classification. B: Fat-suppressed T2-weighted MR image 6 months after platelet-rich plasma injection shows no changes in MRI features of meniscal tear.

Table 1: Baseline characteristics of 10 patients who underwent intra meniscal injection of Platlelet Rich Plasma.

Table 2: Biological characteristics of platelet rich plasma in ten patients.

Table 3: ANOVA results from KOOS score (total and subscale) and pain VAS after intra meniscal injection of PRP.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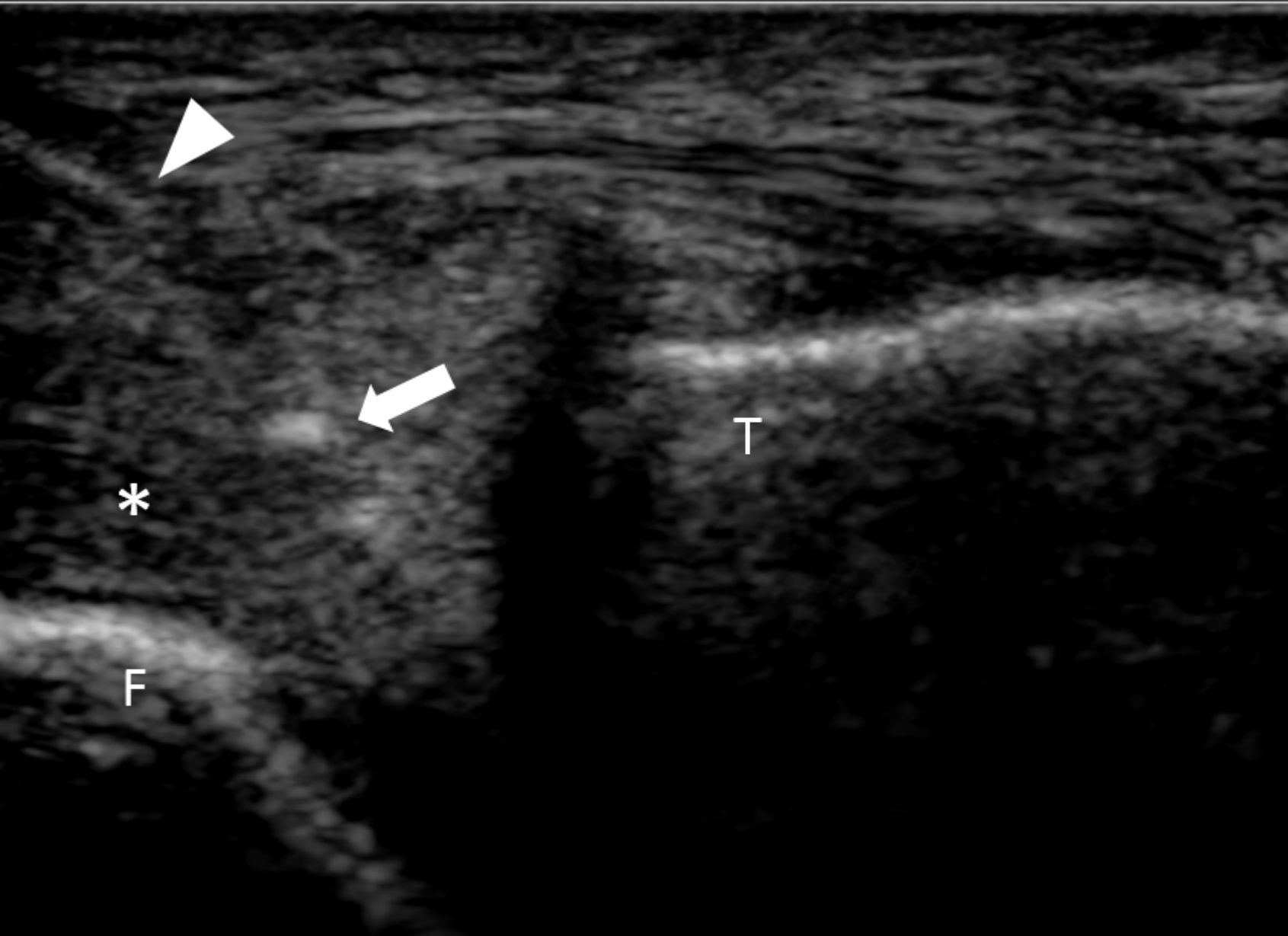
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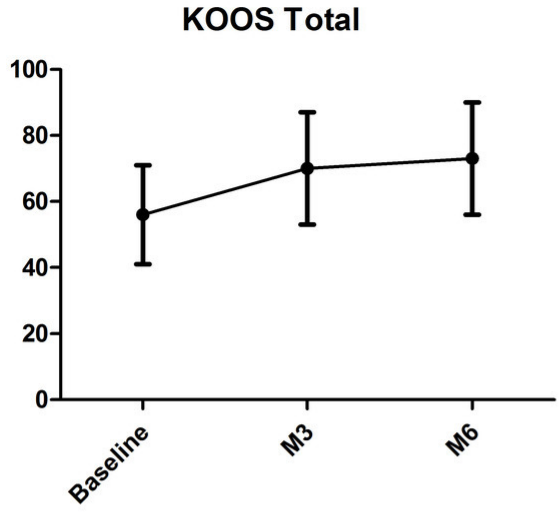
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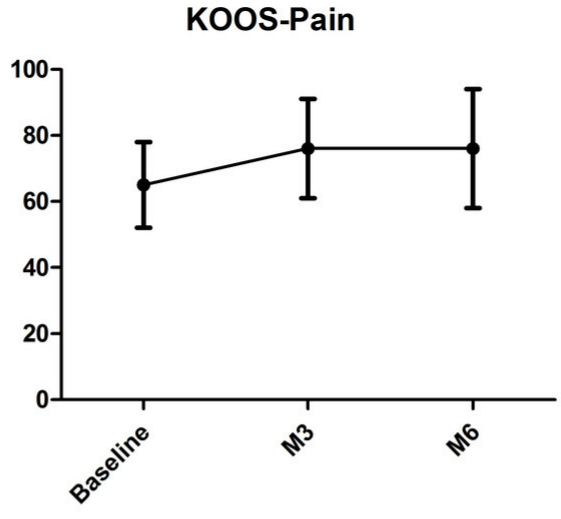
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Baseline
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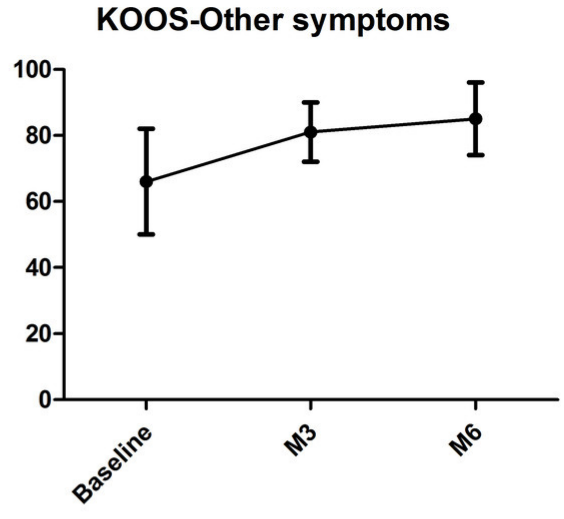
M6


KOOS-Other symptoms
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80
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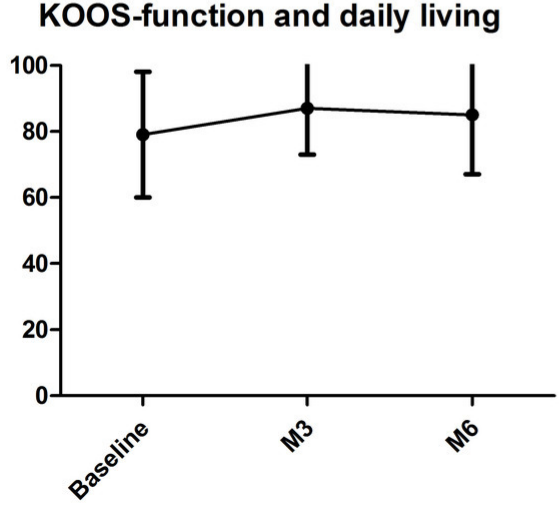
40
20
0
Baseline
M3
M6


KOOS-function and daily living
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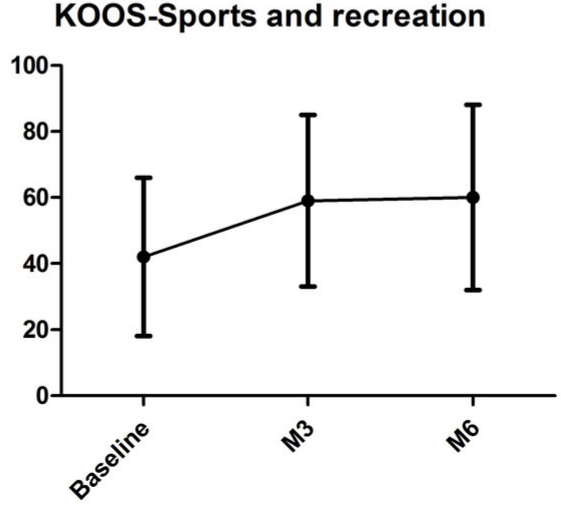
KOOS-Sports and recreation
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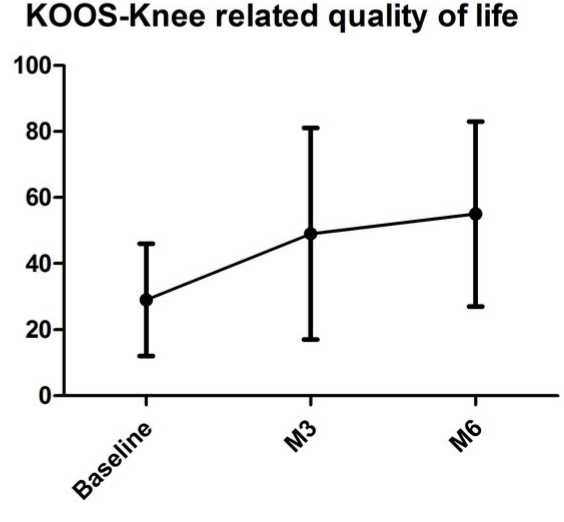
KOOS-Knee related quality of life
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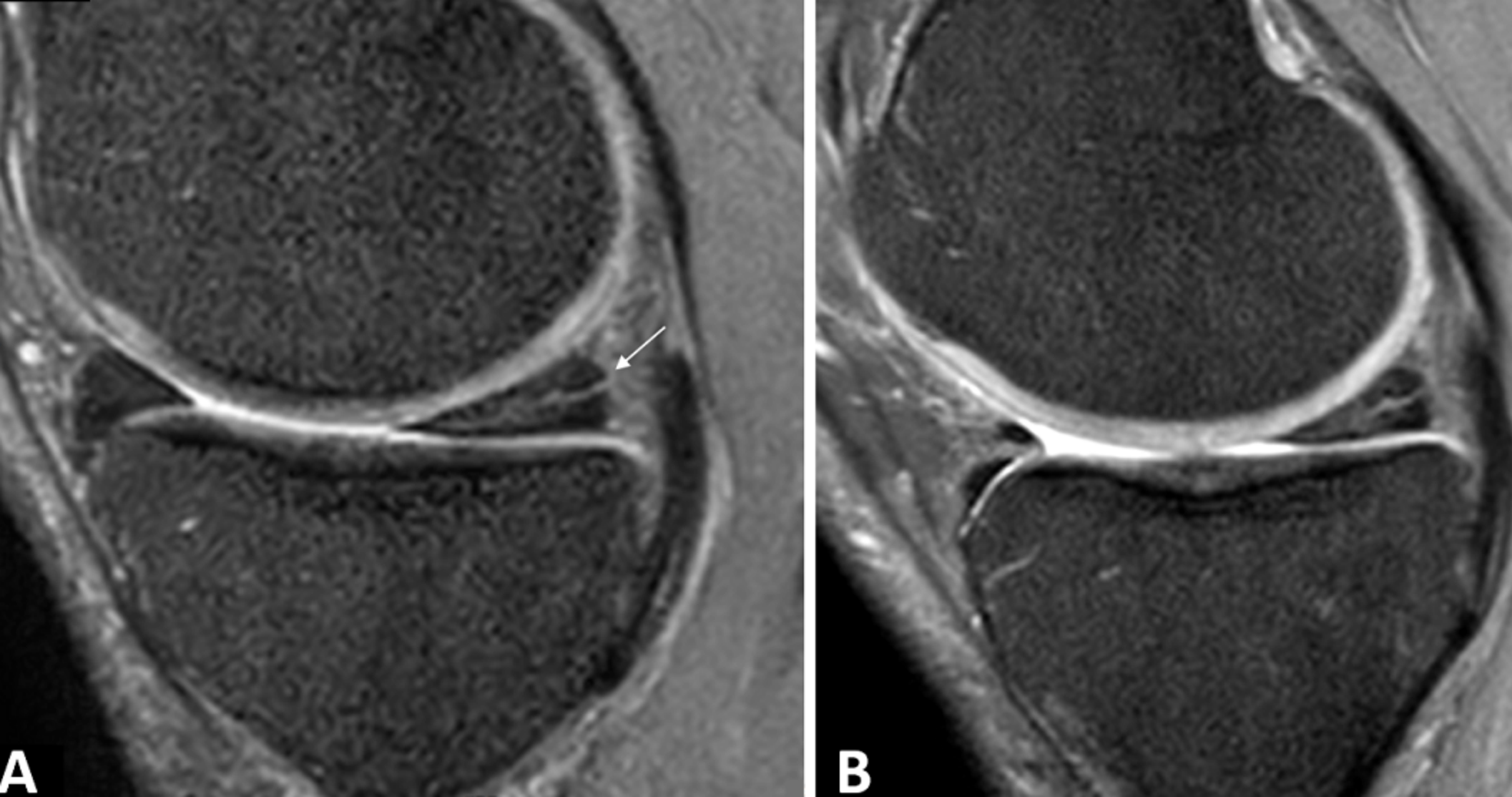
A
B

Patient #	Sex	Age	Meniscal location	Tear description	Stoller grade	Initial KOOS	Initial pain VAS
1	M	57	Right knee Internal	Horizontal Body and posterior horn	2	53	6
2	F	59	Left knee Internal	Horizontal Body and posterior horn	2	69	6
3	M	28	Right knee External	Horizontal Anterior horn	2	39	6
4	F	32	Left knee external	Complex Body	3	53	7
5	F	44	Right knee External	Horizontal Posterior horn	1	64	5
6	M	34	Left knee External	Horizontal Posterior horn	2	75	5
7	M	32	Right knee Internal	Oblique Body and posterior horn	3	59	5
8	M	18	Right knee Internal	Horizontal Posterior horn	1	65	4
9	M	47	Right knee Internal	Complex body	3	25	5
10	M	53	Right knee Internal	Complex Body and posterior horn	3	61	8

KOOS = knee injury and osteoarthritis score; VAS = visual analog scale; M = male; F = Female

Variable	Mean ± SD[range]	Median (Q1, Q3)
Blood		
Volume of whole blood collected (mL)	18.0 ± 0.0 [18-18]	-
Red blood cell concentration (T/L)	4.37 ± 0.49 [3.59-4.91]	4.63 (3.76-4.72)
Platelet concentration (G/L)	265 ± 106 [172-467]	221 (183-329)
Leukocyte concentration (G/L)	4.72 ± 1.72 [2.26-8.60]	4.91 (3.49-5.40)
PRP		
Volume of PRP injected (ml)	4.0 ± 0.0 [4-4]	-
Red blood cells concentration (T/L)	0.02 ± 0.01 [0.01-0.03]	0.015 (0.01-0.0225)
Platelets concentration (G/L)	497 ± 154 [313-756]	524.5 (339.8-623.3)
Leukocytes concentration (G/L)	0.58 ± 0.51 [0.1-1.84]	0.45 (0.28-0.785)
Quantity of injected red blood cell (millions)	70 ± 30 [34-120]	60 (39-104)
Quantity of injected red blood cells (%)	3.4 ± 1.4 [1.31-5.42]	3.08 (2.37-5.08)
Quantity of injected platelets (millions)	1999 ± 616 [1250-3023]	1999 (1357-2478)
Quantity of injected platelets (%)	96.5 ± 1.5 [94.34-98.68]	96.75 (94.83-97.54)
Quantity of injected leukocytes (millions)	2 ± 2 [0.4-7.4]	1.8 (1.1-3.1)
Quantity of injected leukocytes (%)	0.1 ± 0.1 [0.01-0.31]	0.1 (0.05-0.23)
Increase factor in platelets	2.0 ± 0.5 [1.2-3.13]	1.87 (1.79-2.07)
Increase factor in leukocytes	0.1 ± 0.1 [0.01-0.51]	0.09 (0.06-0.195)

PRP = platelet rich plasma; SD = standard deviation

		Baseline	At 3 months	At 6 months	*P*
KOOS total	mean ± SD	56.6 ± 15.7	70.2 ±16.8	72.7 ± 18.5	**0.0007**
	Median (Q1-Q3) [range]	61.0 (46.0-67.0) [25.0-75.0]	73.0 (60.5-77.0) [38.0-99.0]	74.0 (66.5-84.0) [33.0-100.0]	
KOOS other symptoms	mean ± SD	68.7 ± 15.3	81.4 ± 9.2	84.9 ± 10.5	**0.0013**
	Median (Q1-Q3) [range]	71.4 (60.7-75.0) [39.3-96.4]	78.6 (76.8-91.1) [64.3-92.9]	89.0 (75.0-92.9) [67.9-100.0]	
KOOS pain	mean ± SD	64.5 ± 14.1	75.6 ± 15.1	76.2 ± 17.6	0.0570
	Median (Q1-Q3) [range]	66.7 (59.7-76.4) [33.3-80.6]	77.8 (66.7-84.7) [47.2-100.0]	75.0 (63.9-91.7) [43.8-100.0]	
KOOS function in daily living	mean ± SD	79.2 ± 20.1	86.8 ± 14.3	85.1 ± 17.5	**0.0190**
	Median (Q1-Q3) [range]	87.5 (70.6-91.2) [32.4-97.1]	89.7 (83.8-94.9) [51.5-100]	90.0 (74.2-99.2) [46.7-100]	
KOOS sport and recreation	mean ± SD	40.1 ± 24.9	58.5 ± 25.8	60.9 ± 28.5	0.1066
	Median (Q1-Q3) [range]	50.0 (17.5-55.6) [0-70.0]	66.7 (35.0-75.0) [20.0-100.0]	58.3 (50.0-80.0) [0.0-100]	
KOOS quality of life	mean ± SD	30.6 ± 18.1	48.6 ± 32.4	56.2 ± 28.1	**0.0060**
	Median (Q1-Q3) [range]	31.3 (15.6-43.8) [0-56.3]	50.0 (21.9-75.0) [21.9-100.0]	56.3 (40.6-75.0) [0.0-100.0]	
Pain VAS	mean ± SD	57.0 ± 11.6	N.P.	36.3 ± 31.1	0.18
	Median (Q1-Q3) [range]	55.0 (50.0-62.5) [40.0-80.0]		35.0 (2.5-70.0) [0-70.0]	

KOOS = knee injury and osteoarthritis score; VAS = visual analog scale; N.P. = not performed due to >50% missing data