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Hyperintense signal alteration in the suprapatellar fat pad on MRI is associated with degeneration of the patellofemoral joint over 48 months: data from the Osteoarthritis Initiative

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Abstract

Objective To analyze associations of suprapatellar fat pad (SPFP) hyperintense signal alterations and mass effect with progression of patellofemoral osteoarthritis (OA) and clinical symptoms over 48 months.

Materials and methods Subjects from the Osteoarthritis Initiative ($n = 426$; 51.8 ± 3.8 years; 49.8% women) without radiographic tibiofemoral OA underwent 3T-MRI of their right knees and clinical evaluation using the Knee Injury and Osteoarthritis Outcome Score at baseline and at 48 months. Elevated SPFP signal was assessed on intermediate-weighted, fat-saturated turbo spin-echo (TSE) images. Mass effect was defined as a convex posterior contour. Patellofemoral cartilage, bone marrow lesions (BML), and subchondral cysts were assessed using the Whole-Organ Magnetic Resonance Imaging Score (WORMS). Associations of SPFP imaging findings with MRI and clinical progression were assessed using general linear models and logistic regressions.

Results Baseline SPFP signal alterations were found in 51% of the subjects ($n = 217$), of whom 11% ($n = 23$) additionally had a mass effect. Progression of cartilage lesions was significantly higher in subjects with signal alteration versus without (adjusted mean increases, 95% CI; patella: 0.29, -0.07 to 0.64

vs -0.04 , -0.40 to 0.31; $p < 0.001$; trochlea: 0.47, 0.16 to 0.77 vs 0.31, 0.01 to 0.61; $p = 0.007$). BML progression was also more likely in subjects with signal alteration (OR 1.75, 95% CI 1.09 to 2.82; $p = 0.021$). Mass effect was not associated with joint degeneration and SPFP findings were not associated with clinical worsening ($p > 0.18$ for all).

Conclusion Patellofemoral joint degeneration over 48 months was significantly increased in subjects with SPFP signal alteration, suggesting an association between SPFP abnormalities and the progression of patellofemoral OA.

Keywords Osteoarthritis · Knee · MRI · Patellofemoral · Fat pad · Suprapatellar fat pad

Introduction

The role of the three intra-capsular, extra-synovial fat pads of the knee joint in joint degeneration and the development of knee osteoarthritis (OA) is poorly understood. Most studies have focused on the infrapatellar or Hoffa's fat pad, considering it to be relevant for the progression of knee osteoarthritis [1–3]. It has been suggested to contribute to joint lubrication and to absorb loading forces [4–7]. Associations of infrapatellar fat pad imaging findings and joint degeneration have been inconsistent, with an increase in the volume of Hoffa's fat pad being associated with either accelerated [8] or slowed cartilage degeneration [9], and signal intensity alterations associated with worsening of clinical symptoms and knee OA imaged with MRI [3].

Less is known about the role of the prefemoral and the suprapatellar fat pads (SPFPs) in the evolution of joint degeneration and clinical symptoms. The latter, also known as quadriceps fat pad, is located within the joint capsule superior to the patella. It fills the gap between the quadriceps tendon, the

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retropatellar cartilage, and the suprapatellar joint recess, which separates it from the prefemoral fat pad [10–13]. Like the impingement syndrome of the infrapatellar fat pad, also known as Hoffa’s disease [4, 5, 14–16], abnormalities may also be found in the SPFPs that have typical MRI findings and may be associated with clinical symptoms [10, 11, 17, 18]. However, data on the relevance of MRI findings of the SPFPs in OA are scarce. Previous cross-sectional studies found possible correlations between SPFP enlargement and signal alterations on fluid-sensitive MRI sequences [10], interpreted as edema, in addition to meniscal tears [11] and anterior knee pain [10, 11], whereas a third study found no significant association with knee pain, patellofemoral malalignment or patellofemoral OA [17]. A fourth cross-sectional study reported an association between SPFP signal alterations and mass effect with knee pain and signal alteration and bone marrow lesions, but not degenerative changes such as cartilage defects [18]. To the best of our knowledge, associations of SPFP imaging findings with patellofemoral joint degeneration and clinical worsening have not yet been assessed in a longitudinal analysis. Therefore, the aims of this study were first, to analyze the association of MRI findings of SPFPs with progression of patellofemoral OA, as assessed by the modified Whole-Organ Magnetic Resonance Imaging Score (WORMS) [19, 20] over 48 months, and second, to evaluate associations between SPFP abnormalities and clinical outcome over 48 months.

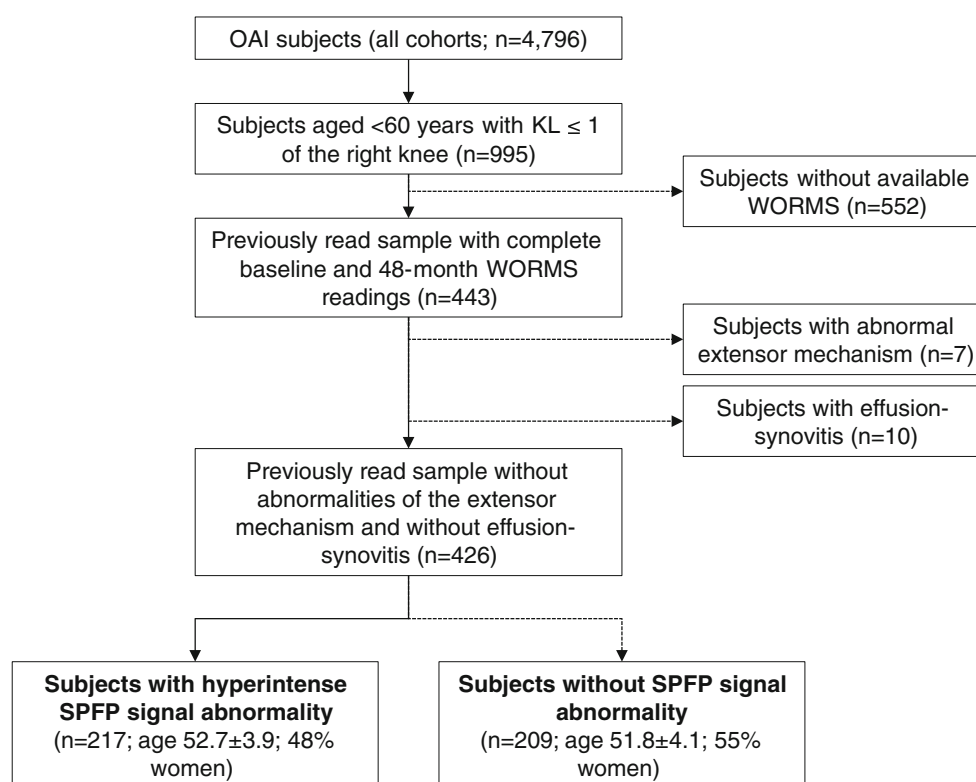
Materials and methods

Database and subjects

We included subjects from the Osteoarthritis Initiative (OAI; oai.ucsf.edu), an ongoing, longitudinal, prospective, multi-center cohort study. The OAI is sponsored by the US National Institutes of Health (NIH) for the investigation of diagnosis, treatment, and prevention of OA. For this analysis, subjects from the incidence group (with risk factors for developing symptomatic knee OA) and the normal control cohort (no knee pain or OA risk factors) were eligible. Pertinent OA risk factors were excess weight, previous knee injury or surgery, Heberden’s nodes, frequent knee bending activities, or a family history of total knee replacement.

To focus on a relatively young population with no or early degenerative changes in the tibiofemoral joint, only subjects younger than 60 years and a baseline Kellgren–Lawrence (KL) score of 0 or 1 in the right knee ($n = 995$) were eligible [21]. Complete baseline and follow-up patellofemoral WORMS readings were available for the right knees of a sample of 443 of these potentially eligible subjects previously obtained by our group for several NIH-funded studies (Fig. 1) [22–28]. To minimize any potential influence caused by abnormalities of the extensor mechanism, and especially the quadriceps tendon in addition to inflammatory processes leading to effusion-synovitis, subjects showing these findings at

Fig. 1 Flowchart illustrating patient selection from the Osteoarthritis Initiative (OAI) database. *KL* Kellgren–Lawrence scale, *WORMS* Whole-Organ Magnetic Resonance Imaging Score, *SPFP* suprapatellar fat pad



baseline (extensor mechanism, $n = 7$; effusion-synovitis, $n = 10$) were excluded.

Baseline characteristics of the remaining subjects ($n = 426$) did not differ significantly from the potentially eligible subjects ($n = 552$) in the OAI cohort who were not included in this analysis ($p > 0.10$ for all outcome variables).

Informed written consent was obtained from all subjects; the study was Health Insurance Portability and Accountability Act-compliant and approved by the local institutional review boards of all participating centers.

Magnetic resonance imaging and analysis

Magnetic resonance images were acquired using four identical 3.0-T scanners (Siemens Trio; Siemens Healthcare, Erlangen, Germany) and quadrature transmit-receive coils (USA Instruments, Aurora, OH, USA) at four sites (University of Maryland, School of Medicine, Baltimore, MD; University of Pittsburgh, Pittsburgh, PA; Memorial Hospital of Rhode Island, Pawtucket, RI; and The Ohio State University, Columbus, OH). SPFP imaging characteristics were assessed primarily in a sagittal intermediate-weighted (IW) fat-saturated 2D turbo spin-echo (TSE) sequence (for sequence parameters, see Table 1). A coronal IW 2D TSE sequence, a

sagittal T2-weighted 3D dual-echo in steady-state (DESS) sequence and its axial reformations were also used to assess morphological cartilage changes and other knee joint structures. Further details about the image acquisition are available in the MRI protocol of the OAI [29].

The UCSF-modified WORMS grading [19, 20] was used to semi-quantitatively assess articular cartilage, bone marrow lesions (BML), and subchondral cysts of the patellofemoral joint at baseline and 48-month follow-up. Cartilage was graded on an incremental scale from 0 (normal cartilage thickness and signal) to 6 (diffuse full-thickness loss in more than 75% of the region) and BML and subchondral cysts were graded on an incremental scale from 0 to 3 according to their size. A single score for each feature was assigned to the patella and the trochlea. The total patellofemoral WORMS represents the sum of all subscores for cartilage, BML, and subchondral cysts in both the patella and the trochlea. The evolution of subscores was expressed by delta values, describing the difference between values at 48 months and baseline.

To minimize any potential influence caused by abnormalities of the extensor mechanism, and especially the quadriceps tendon, all baseline MR examinations were reviewed for partial or complete tears or abnormal swellings of the tendon. Furthermore, the suprapatellar bursa was evaluated for the presence of effusion-synovitis, consisting of synovial thickening and joint effusion, as described previously [30, 31]. Subjects showing these signs were excluded from the analysis (see Database and subjects; Fig. 1).

As patellar malalignment has been shown to be associated with knee pain and patellofemoral OA progression [32], baseline MRI examinations of all subjects were also assessed for the following abnormal imaging findings by a board-certified radiologist with 4 years of experience in musculoskeletal radiology (L.F.): a patellar bisect offset of more than 65%, a patellar tilt of more than 9° [33], a patella alta expressed by a modified Insall–Salvati ratio of more than two [34], and a sulcus angle of more than 145° [35, 36].

Evaluation of SPFP signal alteration and mass effect

Findings of SPFPs at baseline and 48 months were evaluated by a board-certified radiologist with 4 years of experience in musculoskeletal radiology (J.M.W.) and a second radiologist with 4 years of experience in musculoskeletal radiology (B.J.S) independently in all MRI examinations, whereas evaluations of two time points in the same patient were separated by at least 4 weeks. In the case of disagreement, a consensus reading was performed with a third board-certified musculoskeletal radiologist (T.M.L., with 23 years of experience). Radiologists were blinded to morphological readings and SPFP findings at the other time point, and to demographic or clinical information.

Table 1 Knee MRI acquisition parameters of sequences assessed for our study according to the Osteoarthritis Initiative (OAI) study protocol (adapted from Peterfy et al. [29])

Scan	Coronal IW 2D TSE	Sagittal 3D DESS WE ^a	Coronal T1W 3D FLASH WE	Sagittal IW 2D TSE FS ^b
Plane	Coronal	Sagittal	Coronal	Sagittal
Fat suppression	No	WE	WE	FS
Matrix (phase/frequency)	307/384	307/384	512/512	313/448
Number of slices	35	160	80	37
FOV (mm)	140	140	160	160
Slice thickness/gap (mm)	3/0	0.7/0	1.5/0	3/0
Flip angle (°)	180	25	12	180
TE/TR (ms)	29/3,700	4.7/16.3	7.57/20	30/3,200
Bandwidth (Hz/pixel)	352	185	130	248
Number of excitations (averaged)	1	1	1	1
Echo-train length	7	1	1	5
Acquisition time (min)	3.4	10.6	8.6	4.7

DESS dual-echo in steady state, FLASH fast low-angle shot, FS fat suppression, TSE turbo spin-echo, FOV field of view, IW intermediate-weighted, TE echo time, TR repetition time, WE water excitation

^a Also used for axial and coronal multi-planar reformations; slice thickness, 1.5 mm each

^b Used for the assessment of suprapatellar fat pad (SPFP) imaging characteristics

Signal characteristics of SPFPs were assessed on the IW fat-saturated 2D TSE sequence in direct comparison to signal levels of the prefemoral fat pad as a standard of reference (Fig. 2), similar to the previously described method [10, 11, 18]. The signal level was considered normal if SPFP signal intensity was comparable with or lower than the prefemoral fat pad signal, and abnormal if the relative SPFP signal intensity was higher than the prefemoral fat pad. Other fatty structures, such as subcutaneous fat, were evaluated to ensure homogeneous fat saturation throughout the field of view.

The configuration of the posterior border of the SPFP was assessed in the mid-sagittal section. Mass effect was defined as the presence of a convex posterior border contour in at least two continuous slices in contrast to a normal SPFP morphology, i.e., a triangular shape with a linear or almost linear delineation of the posterior border, as previously described (Fig. 2) [10, 17, 18].

Clinical findings

Clinical knee findings at baseline and follow-up were assessed using four subscales of the Knee injury and Osteoarthritis Outcome Score (KOOS) [37], measuring knee pain, any symptoms other than pain (such as stiffness, swelling, or limited range of movement), sport and recreation function, and knee-related quality of life (QOL). Subscales range from 0 to 100, with the best value of KOOS being 100. A change in any of the subscales over 48 months was expressed as the difference between the absolute 48-month and baseline scores, with a negative value indicating clinical worsening. KOOS subscale worsening was considered to reliably represent a clinically relevant progression if the difference between the 48-month and the baseline exceeded the minimal detectable change (MDC) values, as previously described for the osteoarthritic knee [38]: pain ≥ 13 ; symptoms other than pain ≥ 16 ; sport and recreation function ≥ 20 and QOL ≥ 21 .

Statistical analysis

To compare subject characteristics, Fisher's exact tests were used for categorical data and Student's *t* tests for numerical and approximately normally distributed data. Descriptive statistics were used to assess the prevalence of MRI findings.

To assess differences in baseline WORMS subscores in the patellofemoral joint in addition to changes in these WORMS subscores over 48 months in subjects with versus without SPFP signal abnormalities, and in subjects with versus without SPFP mass effect (each as a separate independent variable in all models) at baseline, general linear models adjusted for the presence of patellofemoral malalignment parameters at baseline (as described above), age, sex, baseline BMI, and KL score, and OAI cohort affiliation were used with the baseline value or the delta of the respective WORMS subscore as the dependent variable respectively. Logistic regression models adjusted for the same parameters were used to test the association between the presence of an SPFP signal alteration or mass effect at baseline (both as separate independent variables in all models) and progression of WORMS subscores (indicating any difference between a 48-month and baseline score larger than 0) separately for each compartment.

General linear models (for baseline values and delta values for outcomes) and logistic regressions (for the presence of an MDC) were also used to assess associations between SPFP signal characteristics and KOOS subscales. Intra- and inter-reader reproducibility for WORMS subscores and the assessment of signal alteration and mass effect was assessed using intra-class correlation coefficients (ICCs).

We conducted a subgroup analysis in subjects with a normal SPFP signal at baseline to evaluate associations between incident SPFP imaging findings (between baseline and 48 months) and the progression of patellofemoral joint degeneration using the same analysis methods as in the primary analyses.

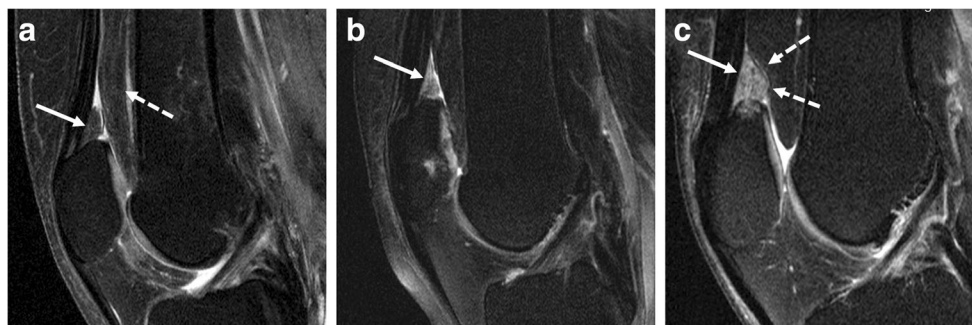


Fig. 2 Representative sagittal fat-saturated intermediate-weighted fast spin-echo sequences (field of view, 160 mm; slice thickness, 3 mm; gap, 0 mm; flip angle, 180°; echo time/repetition time, 30/3,200 ms; acquisition time, 4.7 min) of the right knee in three subjects. **a** Normal appearance of the SPFP with isointense signal of the SPFP (arrow)

compared with the posterior suprapatellar (prefemoral) fat pad (dashed arrow) and without mass effect. **b** Hyperintense signal alteration of the SPFP (arrow). **c** Hyperintense signal alteration (arrow) and mass effect with convex posterior border of the SPFP (dashed arrows)

Statistical analyses were performed using SPSS 23 (IBM, Armonk, NY, USA), using a two-sided 0.05 level of significance.

Reproducibility

Reproducibility results for WOMBS readings have been described previously by our group [39–41]. ICCs range between 0.92 and 0.99 for intrareader agreement and 0.91 and 0.98 for interreader agreement. For the grading of SPFP imaging findings, intra-observer reproducibility was calculated in 60 randomly selected baseline or 48-month studies by a single radiologist (J.M.W.), with intrareader ICCs of 0.97 for the presence of a signal abnormality and 0.88 for the presence of mass effect. Interreader ICCs, assessed in all subjects (J.M.W. and B.J.S.), were 0.94 for signal abnormality, and 0.85 for mass effect. A consensus reading was necessary in 16 of the cases (3.7%) for SPFP signal abnormality and 19 (4.3%) for mass effect.

Results

Prevalence of SPFP abnormalities and association with baseline MR imaging findings

In this sample of $n = 426$ subjects (mean age, 51.8 ± 3.8 ; BMI, 27.7 ± 4.1 ; 49.8% female; 75.0% KL score 0), the prevalence of a hyperintense signal alteration was 50.9%, ($n = 217$). Of these subjects, 10.6% ($n = 23$) showed an SPFP mass effect in addition to the signal alteration. A mass effect of the SPFP was not seen in any of the subjects without SPFP signal alteration.

Subjects with an SPFP signal alteration were significantly older than controls (52.7 ± 3.9 vs 51.8 ± 4.1 years, $p = 0.021$), whereas no other significant differences were found between the groups regarding their demographic parameters (Table 2) or KOOS subscales ($p > 0.48$ for all outcome variables; from general linear models).

At baseline, no significant differences in any of the patellofemoral WOMBS subscores were found between

subjects with and those without SPFP signal alterations (Table 3; $p > 0.06$ for all outcome variables; from general linear models). In addition, no significant differences were found between subjects with and those without SPFP mass effect ($p > 0.10$ for all outcome variables).

In total, 37 subjects (8.7%) showed one or several signs of patellar malalignment, including 6 subjects (1.4%) with patella alta, 13 (3.1%) with abnormal patellar bisect offset, 29 with abnormal patellar tilt (6.8%), and 18 (4.2%) with trochlear dysplasia. None of those findings was significantly associated with the presence of an SPFP signal alteration or mass effect ($p > 0.12$ for all).

Longitudinal change in SPFP imaging findings over 48 months

In a subgroup analysis of the 209 subjects (49.1%) with a previously normal SPFP signal, a hyperintense signal alteration at the 48-month follow-up was found in 32 subjects (15.3%; Fig. 3). When comparing subjects with versus those without newly developed SPFP signal abnormality, no significant associations with any of the baseline parameters (presence of mass effect or patellofemoral malalignment, age, sex, BMI, KL, OAI cohort affiliation; $p > 0.05$ for all outcome variables, from adjusted logistic regression) were found. The change in cartilage WOMBS of the patella was significantly higher in subjects who developed a SPFP signal alteration over 48 months compared with subjects with normal signal at both time points (adjusted mean changes, 95% CI; 0.22, -0.11 to 0.56 vs -0.01 , -0.28 to 0.25 ; $p = 0.023$ from the general linear model), whereas no significant differences were found in any of the other WOMBS subscores ($p > 0.30$ for all other outcome variables).

In 6 of the 23 patients with an SPFP mass effect at baseline, this finding resolved over 48 months, and none of the subjects showed a new mass effect (Fig. 3). In 10 of the 217 subjects (4.6%) with a signal abnormality at baseline, the SPFP showed a normal signal after 48 months, whereas 207 of these subjects (95.4%) showed identical signal characteristics compared with baseline (Fig. 3).

Table 2 Baseline characteristics of subjects with versus without SPFP signal alteration at baseline

Parameter	Subjects with SPFP signal alteration ($n = 217$)	Controls without SPFP signal alteration ($n = 209$)	p value
Female sex (n ; %)	103 (47.5%)	115 (55.0%)	0.119
Age (years; mean \pm SD)	52.7 ± 3.9	51.8 ± 4.1	0.021
BMI (kg/m^2 ; mean \pm SD)	26.4 ± 4.0	27.0 ± 4.4	0.166
Baseline KL, n (%)	0: 157 (72.4%) 1: 60 (27.6%)	0: 161 (77.0%) 1: 48 (23.0%)	0.267

KL Kellgren–Lawrence

p values ≤ 0.05 in bold

Table 3 Adjusted mean values of patellofemoral Whole-Organ Magnetic Resonance Imaging Score (WORMS) subscores at baseline and their change over 48 months and the prevalence and progression rates of structural abnormalities in subjects with versus those without SPFP signal alteration at baseline

Time point	Parameter	Subjects with SPFP signal alteration*	Controls without SPFP signal alteration*	<i>p</i> value*; OR (95% confidence intervals) from logistic regressions
Baseline	WORMS patellar cartilage, mean (95% CI)	1.99 (1.26, 2.72)	1.72 (1.08, 2.36)	0.092
	WORMS trochlea cartilage, mean (95% CI)	1.11 (0.54, 1.67)	0.98 (0.41, 1.53)	0.236
	WORMS patellar BML, mean (95% CI)	0.54 (0.09, 0.98)	0.52 (0.08, 0.97)	0.871
	WORMS trochlea BML, mean (95% CI)	0.27 (−0.07, 0.62)	0.16 (−0.19, 0.50)	0.080
	WORMS patellar subchondral cysts, mean (95% CI)	0.24 (−0.01, 0.49)	0.20 (−0.05, 0.45)	0.361
	WORMS trochlea subchondral cysts, mean (95% CI)	0.14 (−0.08, 0.35)	0.09 (−0.16, 0.34)	0.063
	WORMS patellofemoral joint ^a , mean (95% CI)	3.81 (1.69, 5.93)	3.42 (1.78, 5.05)	0.060
	Partial-thickness cartilage defect present, WORMS 2, 3, 4; <i>n</i> (% of subgroup)	114 (52.5)	97 (46.4)	0.215
	Full-thickness cartilage defect present, WORMS 2.5, 5, 6; <i>n</i> (% of subgroup)	16 (7.4)	14 (6.7)	0.795
	Change over 48 months	Delta WORMS patellar cartilage, mean (95% CI)	0.29 (−0.07, 0.64)	−0.04 (−0.40, 0.31)
Delta WORMS trochlea cartilage, mean (95% CI)		0.47 (0.16, 0.77)	0.31 (0.01, 0.61)	0.007
Delta WORMS patellar BML, mean (95% CI)		0.11 (−0.24, 0.46)	0.01 (−0.34, 0.36)	0.135
Delta WORMS trochlea BML, mean (95% CI)		0.18 (−0.11, 0.47)	0.13 (−0.15, 0.42)	0.416
Delta WORMS patellar subchondral cysts, mean (95% CI)		−0.04 (−0.29, 0.22)	−0.06 (−0.31, 0.20)	0.708
Delta WORMS trochlea subchondral cysts, mean (95% CI)		0.21 (−0.02, 0.43)	0.18 (−0.04, 0.40)	0.556
Delta total WORMS patellofemoral joint, mean (95% CI)		1.21 (0.34, 2.08)	0.53 (−0.34, 1.40)	<0.001
Progression of WORMS cartilage ^a , <i>n</i> (%)		98 (45.2)	44 (21.1)	<0.001; OR 3.71 (2.33, 5.90)
Progression of WORMS BML ^a , <i>n</i> (%)		62 (28.6)	38 (18.2)	0.021; OR 1.75 (1.09, 2.82)
Progression of total WORMS patellofemoral joint ^{a, b} , <i>n</i> (%)		121 (55.8)	64 (30.6)	<0.001; OR 3.58 (2.30, 5.56)

*Estimated marginal means for numerical outcome variables and *p* values from general linear models; odds ratios for binary outcome variables and *p* values from logistic regressions. All models adjusted for the presence of mass effect and patella malalignment parameters, age, sex, BMI, KL, and OAI cohort affiliation at baseline

^a Progression indicating any difference in WORMS subscores larger than 0 between 48 months and baseline either in the patella or trochlea, or both

^b Composed of subscores for cartilage, BML, and subchondral cysts in the patella and trochlea

p values ≤ 0.05 in bold

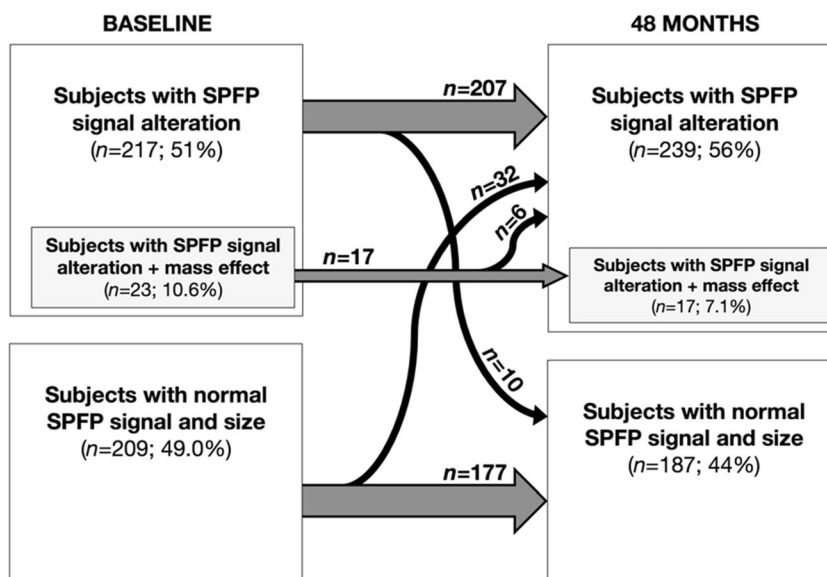
Evolution of degenerative changes and association with baseline SPFP imaging characteristics

Progression of patellofemoral cartilage degenerative disease over 48 months, as expressed by the change in WORMS subscore for cartilage, was significantly higher in subjects with an SPFP signal alteration at baseline compared with subjects with normal SPFP signal (adjusted mean changes, 95% confidence interval; patella: 0.29, −0.07 to 0.64 vs −0.04, −0.40 to 0.31; *p* < 0.001; trochlea: 0.47, 0.16 to 0.77 vs 0.31, 0.01 to 0.61; *p* = 0.007), as was the evolution of total WORMS for the patellofemoral joint (1.21, 0.34 to 2.08 vs 0.53, −0.34 to 1.40; *p* < 0.001; all from general linear models;

Table 3, Fig. 4). No significant differences in any of the WORMS subscores were found between the subjects with and those without an SPFP mass effect at baseline (*p* > 0.18 for all outcome variables).

After dichotomizing subjects in groups with versus those without progression of WORMS subscores, subjects with an SPFP signal alteration at baseline were found to be at a significantly higher risk for the progression of BML in the patella (odds ratio [OR], 95% confidence interval 1.72, 1.01 to 2.90; *p* = 0.044) and overall in the patellofemoral joint (OR 1.75, 1.09 to 2.82; *p* = 0.021; from logistic regressions). Similarly, subjects with an SPFP signal alteration were significantly more likely to show a cartilage progression (OR 3.71, 2.33

Fig. 3 Evolution of SPFP signal alterations and mass effect over time. *Gray arrows* indicate numbers of subjects with unchanging SPFP imaging findings, while *thin black arrows* indicate the number of subjects changing from one group to the other over 48 months



to 5.90 ; $p < 0.001$) and a progression of the total patellofemoral WORMS over 48 months (OR 3.58, 2.30 to 5.56; $p < 0.001$). Again, no significant associations between the presence of an SPFP mass effect at baseline and the progression of any of the WORMS subscores were found ($p > 0.05$ for all outcome variables).

Evolution of clinical scores and association with baseline and follow-up SPFP imaging characteristics

Over 48 months, subjects showed only minimal changes regarding their clinical performance, as assessed by KOOS (delta pain, mean -0.07 ± 13.02 ; delta symptoms other than pain, -0.59 ± 10.17 ; delta sport and recreation function

-0.04 ± 16.17 ; delta knee-related QOL, 2.27 ± 15.40). Evolution of any of the KOOS subscales was not significantly associated with the presence of an SPFP signal alteration at baseline ($p > 0.17$ for all outcome variables, from general linear models). Similarly, the presence of an MDC was not associated with the presence of an SPFP signal alteration at baseline for any of the KOOS subscales ($p > 0.18$ for all outcome variables, from adjusted logistic regressions).

In a subgroup analysis of subjects with a new SPFP signal alteration at follow-up ($n = 32$), no significant differences were found in the evolution of KOOS subscales compared with subjects with a normal signal at both time points ($n = 177$; $p > 0.05$ for all outcome variables, from general linear models).

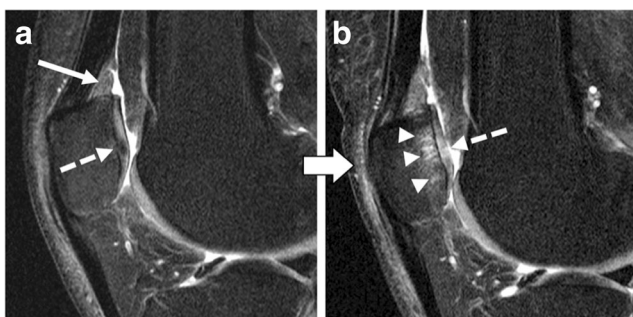


Fig. 4 Right knee of the same subject at **a** baseline and **b** after 48 months, as shown by sagittal intermediate-weighted fat-saturated turbo spin-echo sequences (FOV, 160 mm; slice thickness, 3 mm; gap, 0 mm; flip angle, 180° ; TE/TR, 30/3,200 ms; acquisition time, 4.7 min). **a** Hyperintense signal alteration of the SPFP (*arrow*) and early degenerative changes of the patellar cartilage shown as hypointense signal heterogeneity (*dashed arrow*). **b** The same subject showing patellofemoral cartilage degeneration after 48 months, including an extensive subchondral bone marrow lesion (*arrowheads*) and a full-thickness cartilage fissure in the patella (*dashed arrow*)

Discussion

In our study, the presence of a hyperintense signal alteration of the SPFP at baseline was significantly associated with increased degeneration of the patellofemoral cartilage and progression of patella BML over 48 months. Interestingly, no such associations were found between the presence of an SPFP mass effect and the degeneration of any structure in the patellofemoral joint. A SPFP signal alteration at baseline was not associated with any clinical worsening, nor was the development of a new SPFP signal alteration over 48 months.

To the best of our knowledge, this is the first longitudinal study assessing the associations of SPFP MRI findings with patellofemoral joint degeneration and clinical outcomes of subjects at risk for or with early tibiofemoral OA. Few studies have previously addressed the significance of SPFP findings cross-sectionally: Roth et al. reported a prevalence of SPFP

signal alteration of 54% and a prevalence of SPFP mass effect of 12% in 84 subjects without a history of knee surgery [10], which corresponds well with the numbers found by Wang et al. [18], Shabshin et al. [11], and Tsavalas and Karantanas [17] as well as our results, even though the prevalence of the SPFP mass effect in our population was slightly lower.

Although Wang et al. found a significant association between the presence of an SPFP signal intensity alteration as detected by 1.5-T MRI and bone marrow lesions, they did not find any associations with other MRI findings, nor between SPFP mass effect and any other MRI findings [18]. Similarly, the other available cross-sectional studies did not find any significant associations between the presence of SPFP findings and degenerative change in the knee joint such as cartilage abnormalities, either [10, 11, 17]. This corresponds with our finding that baseline WOMS subscores did not differ significantly between subjects with versus those without SPFP signal alterations.

In this context, our finding that SPFP signal alteration was associated with joint degeneration over 48 months, but not baseline pathological conditions, suggests that pathological conditions associated with signal alterations may promote structural damage in other joint structures.

The presence of an SPFP signal alteration was not associated with clinical progression as measured by the KOOS subscales. Three other cross-sectional studies did not identify an association between signal alterations or mass effect and clinical performance either [10, 11, 17]. Of note, their models did not adjust for other possible causes of pain, and questionnaires and examinations were not standardized. In contrast, cartilage loss and BML in the patellofemoral joint—which were significantly associated with SPFP signal alterations in our study—have been reported to be associated with knee pain [42]. Also, Wang et al. found the presence of SPFP signal intensity alteration to be significantly associated with knee pain in their cross-sectional analysis [18]. However, in their study, subjects were substantially older than in our study, and associations between SPFP imaging characteristics and both knee pain and bone marrow lesions were more evident in subjects with radiographic OA. In contrast, we included only subjects with a KL score of 0 or 1 to focus our analysis on a relatively healthy population and to reduce bias by other joint pathological conditions. However, this may be the reason why only minimal clinical progression over 48 months was detected, and may have reduced the sensitivity of our study for clinical worsening. Overall, SPFP signal abnormalities were associated with structural changes, i.e., cartilage loss and bone marrow lesions, which themselves may become clinically relevant at a later time point, but subjects with signal abnormalities did not suffer from significantly greater worsening of clinical symptoms. Therefore, to further assess the clinical relevance of SPFP pathological

conditions, future studies may investigate older subjects or those with more advanced clinical and/or radiographic degenerative disease.

The SPFP mass effect was found in about 11% of the subjects with SPFP signal alteration, but in none of the subjects with normal SPFP signal. Mass effect was not associated with patellofemoral joint degeneration, or any of the clinical parameters. Therefore, in our study, the relevance of a SPFP mass effect for early OA changes to the patellofemoral joint was considered negligible, and no further conclusions may be drawn regarding its relevance for knee OA.

Articular fat pads are structurally similar to subcutaneous tissue [43], and it is assumed that they contribute to joint lubrication, stability, and absorption of forces generated in the moving joint [4–7]. For the infrapatellar fat pad, it has been shown that acute or repetitive trauma or surgery can induce hemorrhage and inflammation [6, 44], subsequently leading to hypertrophy and impingement [16]. It has been shown that an increase in signal intensity on fluid-sensitive fat-saturated sequences, representing an increase in tissue fluid referred to as edema, is sensitive in the acute phase of the disease [4, 5, 45]. More recently, it has been suggested that the infrapatellar fat pad also plays a relevant role in the development of OA [1–3]. OA is a disease with multifactorial pathophysiology, including inflammatory processes, modulated by mediators, some of which ultimately accelerate cartilage degeneration [46–52]. The infrapatellar fat pad, as the other intracapsular articular fat pads, consists mostly of adipocytes, but also contains various immune cells and mesenchymal stem cells, all of which are able to interact with other joint tissues, making it likely that inflammation of the infrapatellar fat pad may accelerate degenerative changes [1, 2]. Less is known about the SPFP, but it may be assumed that pathophysiology is similar to that observed in the infrapatellar fat pad. Hence, an abnormal SPFP signal may represent ongoing inflammatory processes, eventually leading to the degeneration of other joint structures. As we focused on a relatively young and healthy population to minimize a possible bias by other advanced pathological joint conditions, it is an intrinsic limitation that no histological samples of the SPFP or other joint tissues were available.

This study has some other limitations. We only analyzed a subset of eligible subjects, those who had WOMS readings from previous studies. Our statistical evaluation showed that our sample had sufficient power to provide significant results and therefore we considered this as large enough. Note that baseline demographic characteristics of the analyzed sample and the entire sample of eligible subjects were not significantly different.

An assessment of the infrapatellar or Hoffa's fat pad was not part of our analysis, as we focused on the SPFP and assessment of knee joint structures using WOMS. Therefore, pathological conditions in the infrapatellar fat pad may

possibly have confounded our results. Also, our patient selection was based on the KL score evaluated on anteroposterior radiographs. Per OAI imaging protocol, no lateral radiographs were acquired, which reduces the sensitivity to degenerative changes in the patellofemoral joint. However, we used this parameter as a selection criterion to exclude subjects with substantial tibiofemoral OA. As a consequence, our findings apply to a range of baseline patellofemoral OA severities and not solely to early patellofemoral disease. At baseline, though, subjects had relatively mild degenerative changes in their patellofemoral cartilage and subchondral bone, and WOMBS baseline parameters did not significantly differ between subjects with and those without SPFP signal alterations.

In this study, we focused specifically on the SPFP. As stated before, the infrapatellar or Hoffa's fat pad is currently a topic of avid research with a number of recent publications [3, 8, 53]. In contrast, the SPFP fat pad has been less well studied, which is why this longitudinal analysis adds important insights into the role of fat pads in knee joint degeneration. Finally, our outcome measures for knee pain, other symptoms, and function were relatively unspecific for the patellofemoral joint.

Per OAI protocol, the Knee injury and Osteoarthritis Outcome Score (KOOS) was used as the primary clinical and functional outcome parameter [37]. The KOOS is well established as an outcome parameter both in subjects with osteoarthritis and in younger subjects with knee injuries or post-injury arthritis. However, knee pain and symptoms are only assessed globally for the whole knee joint, which diminishes its specificity for pathological patellofemoral conditions. In future prospective analyses of the clinical impact of fat pad abnormalities, a specific metric for anterior knee pain may be beneficial.

Of note, like Wang et al. [18], Shabshin et al. [11], and Roth et al. [10], we chose to use a binary parameter to confirm or reject the presence of a SPFP signal intensity alteration. Tsavalas et al. used a numeric parameter to describe the SPFP signal intensity (i.e., a relative signal intensity index equaling the mean signal intensity difference between the suprapatellar and prefemoral fat pad divided by background noise standard deviation) [17], which correlated significantly with SPFP mass effect. However, SPFP mass effect was not associated with symptoms or patellofemoral degeneration in this previous study. In addition, sagittal, spectral, selective, fat-saturated, intermediate-weighted, fast spin-echo sequences as used in our analysis do not allow for accurate quantitative measurements owing to field heterogeneities. Although a numeric parameter as used by Tsavalas et al. may suggest a quantitative measurement, a likely bias is introduced, for example, by magnetic field heterogeneities and other examination conditions.

In summary, hyperintense SPFP signal alterations—indicating SPFP edema—were a frequent finding in middle-aged subjects with and without risk factors for OA, but no

radiographic tibiofemoral OA. Our longitudinal analysis showed that subjects with SPFP signal alterations have more severe progression of patellofemoral cartilage defects and patella BML over 48 months compared with subjects with normal SPFP signal. On the other hand, SPFP mass effect was not associated with a higher patellofemoral cartilage progression, and no imaging feature was associated with clinical worsening. Overall, our findings suggest that SPFP signal abnormalities might lead to progressive degenerative changes and eventually to patellofemoral OA.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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