CHAPTER 7

RADIOGRAPHIC PROGRESSION OF KNEE OSTEOARTHRITIS IS ASSOCIATED WITH MRI ABNORMALITIES IN BOTH PATELLOFEMORAL AND TIBIOFEMORAL JOINT

de Lange-Brokaar BJE, Bijsterbosch J, Kornaat PR, Yusuf E, Ioan-Facsinay A, Zuurmond A-M, Kroon HM, Meulenbelt I, Bloem JL, Kloppenburg M

submitted

ABSTRACT

Objective: To investigate patterns of MRI abnormalities in the patellofemoral (PFJ) and tibiofemoral joint (TFJ) and their association with radiographic progression, using hypothesis free analyses.

Methods: 205 patients from the GARP study with symptomatic OA at multiple sites (mean age 60 years, 80% woman, median BMI 26 kg/m2), underwent knee MRI at baseline. Cartilage damage, osteophytes, cysts, bone marrow lesions (BMLs) and effusion/synovitis were scored according to a validated scoring method. Baseline and 6-year TFJ and PFJ radiographs were scored (0-3) for JSN and osteophytes according to OARSI and Burnett atlases, respectively; progression was defined as ≥1 point increase. Baseline patterns of MRI abnormalities derived from principal component analysis (PCA) were associated with progression using adjusted generalized estimating equations.

Results: PCA resulted in extraction of 6 components, explaining 69% of variance. In 29% and 29% of 133 patients with follow-up the TFJ progressed, whereas in 15% and 9% the PFJ progressed for osteophytes and JSN, respectively. Component 1 (cartilage damage of the PFJ and osteophytes of both joints) was statistically significant associated with TFJ JSN progression and PFJ osteophyte progression. Component 2 (all lateral PFJ abnormalities except osteophytes) was associated with JSN/osteophyte progression in the PFJ alone, whereas component 3 (all medial TFJ abnormalities except osteophytes) was associated with JSN and osteophyte progression in both PFJ and TFJ.

Conclusion: Baseline structural damage and bone turnover activity, as reflected by BMLs, seem to be involved in knee OA progression. Moreover, progression in PFJ and TFJ seems to be related.

INTRODUCTION

Knee OA is the most frequent subtype of OA. It can result in end-stage knee OA with cartilage damage and abnormalities in the subchondral bone with pain and functional loss[1,2]. In some patients rapid progression can be observed, while others progress very slowly[3]. Unfortunately, due to insufficient knowledge concerning pathophysiological mechanisms of OA, we cannot identify patients at risk for rapid progression. This lack of knowledge also limits the development of structure modifying drugs for OA.

Degenerative and repair mechanisms in cartilage, subchondral bone and synovium are involved in OA development and progression. Processes, such as increased bone turnover as assessed by bone marrow lesions (BMLs) and cysts, and inflammation as assessed by synovitis and effusion, have been shown to associate with radiographic progression represented by loss of joint space[4-6]. Radiographic progression was especially related to ipsilateral MRI abnormalities, suggesting effects of local processes[7]. But also the presence of radiographic features, such as osteophytes and joint space narrowing (JSN), are associated with radiographic progression[8]. Since all these structural abnormalities are known to be highly correlated investigation of the role of the individual abnormalities is difficult.

Knee OA comprises two joints: the patellofemoral joint (PFJ) and the tibiofemoral joint (TFJ). Although most studies investigate the TFJ, the PFJ might also be of clinical importance as the exclusive presence of PFJ OA is known to lead to functional limitation, pain and stiffness[9,10]. Several studies have observed that interaction of the TFJ and PFJ could be linked to OA development in those joints and some have suggested that PFJ OA precedes TFJ OA[11]F. Earlier studies have shown that MRI abnormalities in knee OA have a tendency to follow a medialized or lateralized pattern in both PFJ and TFJ [12], supporting that similar underlying mechanical processes play a role and that these ipsilateral compartments are part of one single joint surface. On the other hand the two joints have different weight bearing properties due to their anatomical location, which could lead to different OA phenotypes. Currently, the relationship between the TFJ and PFJ remains largely unclear.

The aim of this study is to investigate patterns of different OA tissue abnormalities as assessed with MRI of both the PFJ and TFJ by using principal component analysis allowing for an objective analysis without assumptions concerning underlying relationships. Subsequently, the association between these patterns with radiological progression over 6 years has been investigated.

PATIENTS AND METHODS

Study design

This study is part of the Genetics, Osteoarthritis, and Progression (GARP) study, an observational cohort aimed at identifying determinants of OA susceptibility and progression[13]. This study has been approved by the ethics committee of the Leiden University Medical Center (LUMC). All patients provided written informed consent.

Patients

Probands, between 40 and 70 years of age, and their siblings, both with symptomatic OA at multiple sites, were included between 2000 and 2003[14].Patients with secondary OA were excluded. Sib pairs with at least one subject with symptomatic hip or knee OA (but not in a radiographic end-stage) were eligible for the MRI sub-study[15,16]. Patients were followed for 6 years (For details see[17]).Demographics and disease characteristic were collected via standard questionnaires. 105 sibpairs with at least one subject with symptomatic hip or knee OA (but not in a radiographic end-stage) were eligible for the MRI sub-study[15,16]. In 5 out of 210 patients no MRI (claustrophobia (N=1), not fitting into the knee-coil (N=1)) or an MRI of insufficient quality (motionartefacts (n=3)) was available, leaving 205 patients with an MRI for present study. As purpose of the study was to assess progression of OA, no MR images were made of a knee that already had an end-stage (KL score 4)[18]. In 133/205(65%) patients TFJ radiographic follow-up was available and in 130/205(63%) patients for the PFJ (of 3 patients no lateral knee radiographs were available)

Radiographic scoring and definition of progression

Semi-flexed posterior-anterior and lateral knee radiographs were obtained at baseline and follow-up. Radiographic severity at baseline was assessed by a single radiologist (HMK) according to the KL atlas[13].

Progression was scored (0-3) for both osteophytes and JSN at both TFJ and PFJ according to the Osteoarthritis Research Society International (OARSI) atlas [19] and Burnett atlas [20], respectively. Radiographs were scored paired in chronological order blinded for patient characteristics by consensus opinion of two experienced readers (JB, EY). Intra-observer reproducibility was good, as reflected by the intra-class correlation coefficient (ICC, (95% CI)) (One-way random models, single measures). The ICC calculated for the sum scores based on a randomly selected sample of 48 radiographs (both baseline and 6 year follow-up) of 24 patients ranged from 0.93 (0.89-0.96) to 1.00 (1.00-1.00). The mean ICCs for TFJ and PFJ were 0.97 and 0.99, respectively.

Radiographic progression was defined as an increase of 1 point in JSN which was calculated to be the smallest detectable change (SDC). The SDC indicated changes on summarized score above the measurement error[21].

MRI acquisition and scoring

MR scanning was performed at baseline using a 1.5 T superconducting magnet (Philips Medical Systems, Best, The Netherlands) using a 8-channel dedicated knee coil as described elsewhere[18,22].

The following images were obtained: coronal proton density- and T2-weighted dual spin echo (SE) images without fat-suppression (with repetition time (TR) of 2,200; echo time (TE) of 20/80; 5 mm slice thickness; 0.5 mm intersection gap;16 cm field of view; 206 x 256 acquisition matrix); sagittal proton density- and T2-weighted dual SE images without fat-suppression(TR 2,200; TE 20/80; 4 mm slice thickness; 0.4 mm intersection gap;16 cm field of view; 205 x 256 acquisition matrix); sagittal three-dimensional (3D) T1-weighted spoiled gradient echo (GE) frequency selective fat-suppressed images (TR 46; TE 2,5; flip angle 40°; 3.0 mm slice thickness; slice overlap 1.5 mm; no gap; 18 cm field of view; 205 x 256 acquisition matrix); and axial proton density- and T2-weighted turbo spin echo (TSE) fat-suppressed images (TR 2,500; TE 7.1/40; echo train length 6,2 mm slice thickness; no gap;18 cm field of view; 205 x 256 acquisition matrix). Total acquisition time (including the initial survey sequence) was 30 min.

Cartilage damage (thinning and focal lesions), osteophytes (central and marginal), cysts, bone marrow lesions (BMLs) and effusion (reflecting a combined feature that incorporates both effusion and synovitis) were scored according the Knee Osteoarthritis Scoring System (KOSS) score for presence or absence in 9 compartments, including 5 compartments of the patellofemoral joint (PFJ) and 4 compartments of the tibiofemoral joint (TFJ)[20,22]. Cartilage defects (diffuse and focal) were scored from 0-3 for depth extent (0= absent, 1 < 50% reduction, 2 ≥ 50% reduction, 3 = (near) full-thickness cartilage loss), osteophytes were scored from 0-3 (0= no osteophyte, 1= minimal osteophytes < 3 mm from base to tip, 2= moderate osteophyte 3-5 mm, 3= severe osteophyte ≥ 5 mm), subchondral cysts (0= absent, 1 minimal < 3 mm greatest dimension measures, 2 moderate 3-5 mm, 3= severe ≥ 5 mm) and BML were defined as an ill-defined area in the subchondral bone extending from the articular surface and also graded from 0-3 (0 = absent, 1= minimal < 5 mm, 2= moderate 5-20 mm, 3= severe ≥ 20 mm). Presence of knee effusion was scored from 0-3 (0= physiological shiver of synovial fluid, 1= small amount of fluid distended one or two joint recesses, 2= >two joint recesses partially distended, 3= full distension of all joint recesses; evaluated were lateral, medial and suprapatellar joint recesses).

MRIs were scored in consensus by three readers (PK, RC, JLB) with 3, 15 and 25 years of experience in scoring MRIs (blinded to radiographic results and patient data)[16]. In an earlier study a good to very good inter- and intra-reader reproducibility was observed using Kappa, weighted kappa and intraclass correlation coefficient (ICC). Intra-observer reliability was assessed by two readers (PK,JLB) using at least a 2 week interval between the randomized readings[23]. To investigate a single joint surface, compartments were combined to create 4

locations: medial PFJ (containing patellar medial facet and trochlea medial facet), lateral PFJ (containing patellar lateral facet and trochlea lateral facet), medial TFJ (medial femoral condyle and tibia plateau) and lateral TFJ (lateral femoral condyle and tibia plateau).
We aimed to investigate local longitudinal associations, as was done before by Felson et al[24]. We therefore combined different compartments of the KOSS to create the following compartments: medial PFJ (patellar medial facet and trochlea medial facet), lateral PFJ (patellar lateral facet and trochlea lateral facet), medial TFJ (medial femoral condyle and tibia plateau) and lateral TFJ (lateral femoral condyle and tibia plateau). As the patellar crest is in continuum with both the medial and the lateral patellar facet and articulates with both medial and lateral trochlear articular facet, it cannot be medialized/lateralized and we therefore excluded the patellar crest from the analysis[15].
To create a uniform score the maximum defect score was used to create a score for all variables from 0-3 (0=absent;1=minimal;2=moderate;3=severe). For cartilagedefects a maximum depth of either diffuse or focal cartilagedefect was used. For example if an osteophyte of medial femoral condyle had a score of 2 and the osteophyte at the tibia plateau was scored a 3, the score for medial TFJ osteophyte was a 3.

Statistics

Normal distributed variables are displayed as mean (SD), otherwise median (range) is given. To investigate whether patients with complete follow-up differed from the total study population the following tests were used: Students-t test (age), Mann-Witney-U test (BMI), Chi-squared test (gender) and Kruskal-Wallis test (KL grade). Principal component analysis (PCA) was used to investigate patterns of MRI features (osteophytes, cartilage defects, subchondral cysts, bone marrow lesions and effusion) in the different joint sites. PCA is a statistical method that determines groups or patterns (named components) based on correlation of features with each other. This method allows for an objective analysis taking in account all variables, without inclusion of assumptions related to possible mechanisms or anatomical sites, and interrelationships can be investigated. For PCA analysis ordinal variables were used and all medial and lateral MRI features of both the PFJ and TFJ (0-3) were subjected to PCA.
Prior to performing PCA, suitability of data was assessed. For this purpose the correlation matrix was inspected and revealed the presence of correlation coefficients of 0.3 and above. Furthermore, the Kaiser-Meyer-Oklin value was 0.728, which exceeded the recommended value of 0.6[25,26]. Finally, the Barlett's Test of Sphericity [27] was calculated, which turned out to be significant ($p < 0.001$), supporting the factorability of the correlation matrix. Using Eigen values >1, the number of components was determined. A Varimax rotation with Kaiser Normalization was done to help with the interpretation of the results. In the present study all variables were said to load significantly on a component if the factor loading was at least 0.4[28].

To investigate the association between components and radiologic progression at follow-up, regression factor scores that represented location on a factor for each patient, were calculated for all components[29]. Subsequently, the association of patterns of MRI abnormalities with radiographic progression (outcome, 0 = no progression, 1 = progression) was calculated using logistic regression analysis with generalized estimating equations (GEE) to correct for possible family effects, since observations were obtained from probands and their siblings. The results were presented as odds ratio (OR) with 95% confidence intervals (CI). The GEE was performed with adjustment for age, gender and BMI. Statistics were calculated using SPSS 20.0 (Amonk, NY: IBM Corp.).

RESULTS

Patients

In the present study 205 patients (mean age (SD) 60 (7) years, 79.5% woman, median BMI (range) 26 (20-40), median (range) KL score 1 (0-3) were included. Patients with KL 0, 1, 2 and 3 were included in the present study. In this study 68% (139/205) of the patients had a Kellgren-Lawrence (KL) score ≥1 in their imaged knee at baseline (32% had a KL score of 0). More than half (55%) of patients had a JSN score ≥ 1 and 47% osteophyte score ≥ 1 in PFJ or TFJ.

The prevalence of MRI abnormalities at baseline is displayed in Table 1. Cartilage damage and osteophytes were the most frequent MRI abnormalities, both in the PFJ and TFJ.

Principal component analysis of MRI features

PCA of all 205 patients resulted in extraction of six components (Eigen value > 1), explaining 69% of the variance (table 1). Component 1 was characterized by medial and lateral cartilage damage and osteophytes of the PFJ and medial and lateral osteophytes of the TFJ; hence included both abnormalities of the PFJ and of the TFJ. The other five components included either abnormalities of the PFJ or of the TFJ. In all compartments, except for the lateral TFJ, cartilage damage was incorporated in the same component as BMLs and cysts. Interestingly effusion/synovitis was not incorporated in any of the components.

Table 1. Loading table of MRI abnormalities of the knee in 205 patients with osteoarthritis at multiple sites; only loadings ≥ 0.4 are displayed.

		Component					
MRI feature	**Prevalence of MRI feature (%)**	**1**	**2**	**3**	**4**	**5**	**6**
PFJ medial cartilage damage	61	0.723			0.414		
PFJ medial OP	48	0.755					
PFJ medial cyst	15				0.869		
PFJ medial BML	19				0.838		
PFJ lateral cartilage damage	44	0.577	0.500				
PFJ lateral OP	46	0.761					
PFJ lateral cyst	16		0.902				
PFJ lateral BML	17		0.909				
TFJ medial cartilage damage	59			0.546			0.407
TFJ medial OP	81	0.585					0.401
TFJ medial cyst	16			0.738			
TFJ medial BML	13			0.792			
TFJ lateral cartilage damage	42						0.830
TFJ lateral OP	61	0.454					0.536
TFJ lateral cyst	4					0.827	
TFJ lateral BML	5					0.787	
Effusion joint	55						
Explained variance 68.6%		*16.9*	*11.9*	*11.2*	*10.0*	*9.3*	*9.1*

Abbreviations: PFJ=patellofemoral joint, TFJ= tibiofemoral joint, OP=osteophytes, BML=bone marrow lesion. For description of variables see Patients and Methods.

Correlation of patterns of MRI abnormalities with radiographic progression

The demographic characteristics and KL scores of the patients available for follow-up (n=133) did not differ statistically significant from the total study population (data not shown). Progression of JSN and osteophytes in the TFJ were seen in 38/133 (28.6%) and 39/133 (29.3%) of patients, respectively. Progression of JSN and osteophytes in the PFJ were less frequently being observed in 12/130 (9.2%) and 20/130 (15.4%) of patients, respectively.

Radiographic JSN or osteophyte progression in the PFJ and TFJ were not related; the Spearman rank correlation was 0.095 (p-value 0.296) for JSN and 0.136 (p-value 0.133) for osteophytes.

The associations of the components with radiographic progression in JSN are shown in Table 2. JSN progression in the PFJ was associated with component 2 (incorporating cartilage damage, BML and cysts of the lateral PFJ); the OR (95%CI) of this association was 2.0 (1.2-3.2). JSN progression was also associated with component 3 (incorporating cartilage damage, BML and cysts of the medial TF); OR (95%CI) 2.9 (1.5-5.7)). All associations were adjusted for age, sex and BMI. No independent associations were seen with component 1, 4, 5 and 6. JSN progression in the TFJ was associated with component 1 (incorporating cartilage damage

of the PFJ and osteophytes of both PFJ and TFJ), with an OR (95%CI) of 1.6 (1.1-2.5), and with component 3 (incorporating cartilage damage, BML and cysts of the medial TF with an OR (95%CI) of 1.4 (1.002-2.0), all after adjustment for age, sex and BMI. No association were seen with components 2, 4, 5 and 6.

Associations of the components with osteophyte progression are depicted in Table 3. Osteophyte progression in both the PFJ and TFJ was associated with component 3 (incorporating cartilage damage, BMLs and cysts of the medial TFJ). The OR (95%CI) for PFJ was 1.9 (1.3-2.9), whereas the OR (95%CI) for TFJ was 1.8 (1.2-2.6). In addition, associations were observed between osteophyte progression in the PFJ and component 1 (incorporating cartilage damage of the PFJ and osteophytes of both PFJ and TFJ) with an OR (95%CI) of 1.7 (1.039-2.9), and component 2 (incorporating cartilage damage, BMLs and cysts of the lateral PFJ) with an OR (95%CI) of 1.6 (1.031-2.4).

Table 2. Association of components with radiographic joint space narrowing progression over 6 years, analysed for all patients.

		Joint space narrowing PFJ (n=130)		Joint space narrowing TFJ (n =133)	
Component		Crude OR (95%CI)	Adjusted* OR (95%CI)	Crude OR (95%CI)	Adjusted* OR (95%CI)
1	Cart/OP med/lat PFJ,OP med/lat TFJ	**1.8 (1.01-3.2)**	1.6 (0.8-3.2)	**1.8 (1.2-2.7)**	**1.6 (1.1-2.5)**
2	Cart, cyst, BML lat PFJ	**1.5 (1.03-2.3)**	**2.0 (1.2-3.2)**	0.8 (0.6-1.2)	0.8 (0.5-1.3)
3	Cart, cyst, BML med TFJ	**2.1 (1.3-3.1)**	**2.9 (1.5-5.7)**	1.3 (0.9-1.8)	**1.4 (1.002-2.0)**
4	Cart, cyst, BML med PFJ	0.9 (0.5-1.7)	1.0 (0.5-2.2)	0.9 (0.6-1.3)	0.9 (0.6-1.3)
5	Cyst, BML lat TFJ	1.1 (0.6-1.9)	1.0 (0.5-1.7)	1.0 (0.6-1.5)	1.0 (0.6-1.6)
6	Cart/OP med/lat TFJ	1.4 (0.8-2.3)	1.6 (0.8-2.9)	1.2 (0.8-1.7)	1.2 (0.9-1.7)

**Adjusted OR: GEE model adjusted for age, gender, BMI and family effect. Outcome is progression in joint space narrowing (0 = no, 1 = yes). Abbreviations: Cart =cartilage damage, OP = osteophytes, PFJ = patellofemoral joint, med =medial, lat = lateral, TFJ =tibiofemoral joint, cyst = subchondral cyst, BML = bone marrow lesion, OR =odds ratio*

Table 3. Association of components with radiographic osteophyte progression over 6 years, analysed for all patients.

		OP PFJ (n =130)		OP TFJ (n = 133)	
Component		Crude OR (95%CI)	Adjusted* OR (95%CI)	Crude OR (95%CI)	Adjusted* OR (95%CI)
1	Cart/OP med/lat PFJ, OP med/lat TFJ	**1.8 (1.1-3.0)**	**1.7 (1.04-2.9)**	1.4 (0.9-2.0)	1.4 (0.9-2.1)
2	Cart, cyst, BML lat PFJ	1.4 (0.9-1.9)	**1.6 (1.03-2.4)**	0.8 (0.5-1.2)	0.8 (0.5-1.2)
3	Cart, cyst, BML med TFJ	**1.8 (1.2-2.6)**	**1.9 (1.3-2.9)**	**1.7 (1.2-2.4)**	**1.8 (1.2-2.6)**
4	Cart, cyst, BML med PFJ	1.1 (0.7-1.6)	1.2 (0.7-1.9)	0.8 (0.5-1.2)	0.8 (0.5-1.3)
5	Cyst, BML lat TFJ	1.1 (0.6-1.7)	1.0 (0.7-1.5)	1.4 (0.9-2.1)	1.4 (0.98-1.9)
6	Cart/OP med/lat TFJ	1.4 (0.9-2.1)	1.6 (0.9-2.6)	1.4 (0.97-2.0)	1.5 (0.97-2.2)

** Adjusted OR: GEE model adjusted for age, gender, BMI and family effect. Outcome is progression in joint space narrowing (0 = no, 1 = yes). Abbreviations: Cart =cartilage damage, OP = osteophytes, PFJ = patellofemoral joint, med =medial, lat = lateral, TFJ =tibiofemoral joint, cyst = subchondral cyst, BML = bone marrow lesion, OR =odds ratio*

Associations of components at baseline with both medial and lateral progression of radiographic osteophytes and JSN of the TFJ are depicted in Table 4. Component 1 (incorporating cartilage damage of the PFJ and osteophytes of both PFJ and TFJ) was associated with JSN at the medial TFJ with an OR (95%CI) of 1.9 (1.2-2.9). Component 3 (including cartilage, cysts and BML of the medial TFJ) was associated with medial JSN progression with an OR (95%CI) of 1.6 (1.1-2.3), with medial osteophyte progression with an OR (95%CI) of 2.2 (1.4-3.4) and interestingly also with lateral osteophyte progression with an OR (95%CI) of 1.7 (1.2-2.5). Furthermore, a statistical significant association between lateral osteophyte progression with both component 5 (including lateral MRI features of the TFJ) with an OR (95%CI) of 1.4 (1.01-2.0) and component 6 (including both cartilage and osteophyte features of the TFJ) with an OR (95%CI) of 1.6 (1.1-2.5) was observed.

Table 4. Association of components with radiographic joint space narrowing and osteophyte progression over 6 years, analysed for all patients.

		JSN progression		OP progression	
		JSN TFJ med	JSN TFJ lat	OP TFJ med	OP TFJ lat
Component		Adjusted* OR (95%CI)	Adjusted* OR (95%CI)	Adjusted* OR (95%CI)	Adjusted* OR (95%CI)
All patients, N = 133					
1	Cart/OP med/lat PFJ, OP med/lat TFJ	**1.9 (1.2-2.9)**	**0.9 (0.4-2.0)**	1.4 (0.9-2.3)	1.1 (0.7-1.8)
2	Cart, cyst, BML lat PFJ	0.6 (0.3-1.2)	1.0 (0.7-1.7)	0.6 (0.2-1.6)	0.8 (0.5-1.2)
3	Cart, cyst, BML med TFJ	**1.6 (1.1-2.3)**	2.1 (0.01-448,3)	**2.2 (1.4-3.4)**	**1.7 (1.2-2.5)**
4	Cart, cyst, BML med PFJ	0.9 (0.6-1.4)	1.1 (0.7-1.7)	0.7 (0.4-1.2)	0.9 (0.5-1.4)
5	Cyst, BML lat TFJ	0.6 (0.3-1.5)	1.4 (0.9-2.4)	0.9 (0.6-1.5)	**1.4 (1.01-2.0)**
6	Cart/OP med/lat TFJ	1.2 (0.9-1.8)	1.2 (0.7-2.0)	0.9 (0.6-1.6)	**1.6 (1.1-2.5)**

** Adjusted OR: GEE model adjusted for age, gender, BMI and family effect. Outcome is progression in osteophyte or joint space narrowing in the tibiofemoral joint (0 = no, 1 = yes). Abbreviations: Cart =cartilage damage, OP = osteophytes, PFJ = patellofemoral joint, med =medial, lat = lateral, TFJ =tibiofemoral joint, cyst = subchondral cyst, BML = bone marrow lesion, OR =odds ratio*

DISCUSSION

To our best knowledge this is the first study that investigates MRI abnormalities and their association with radiographic knee OA progression without inclusion of assumptions related to possible mechanisms or anatomical sites. Clustering in MRI abnormalities of the PFJ and TFJ were observed at baseline, since the component that explained most of the variance incorporated both abnormalities seen in the PFJ and the TFJ. Interestingly, in some components cartilage damage clustered with osteophytes, whereas in other components clustering of cartilage damage with BMLs and cysts was seen.

Longitudinal analyses showed that radiological progression over 6 years in the PFJ was associated with components including MRI abnormalities of both the TFJ and the PFJ. Likewise, radiological progression in the TFJ was associated with components including MRI abnormalities of both the PFJ and TFJ. These results suggest that underlying processes in PFJ and TFJ as visualized on MRI at baseline are related with respect to radiological progression. Furthermore, radiographic progression was associated with components including cartilage damage and osteophytes, or with components including cartilage damage and BMLs and cysts in the medial TFJ or lateral PFJ. These observations suggest that not only osteoarthritic structural damage enhance further progression, but that also processes reflecting increased bone turnover result in progression.

The component incorporating medial and lateral cartilage damage and osteophytes of the PFJ and medial and lateral osteophytes of the TFJ (no.1) was significantly associated with JSN progression of the TFJ and osteophyte progression in the PFJ. This component explains the largest proportion of variance (26.3% unrotated and 17% after rotation) and probably reflects the largest proportion of people in our population. This observation suggests that patients with evident OA involvement of both compartments of the knee are at risk for ongoing OA progression, as a vicious circle, which involves the whole joint. An alternative explanation could be the presence of effusion. Since we set our cut-off value for significant loading to 0.4 [28], effusion was not incorporated in any of the components, although effusion was loaded on both component 1 (loading 0.326) and 3 (loading 0.350). Component 1 and 3 both were associated with radiographic progression. Several studies in the past have found that effusion significantly correlates with cartilage damage over time, which are in accordance with our results[4].

The role of osteophytes in OA is much debated as some argue that osteophytes are related to normal aging rather than to the presence of OA[30]. This argument is supported by studies that have found that osteophytes do not always relate to cartilage damage[31,32]. However, in the present study using PCA osteophytes, which were highly prevalent, clustered with cartilage damage, supporting that osteophytes are part of the OA process, for instance as compensatory mechanism to stabilize the joint[33]. Although osteophytes did not cluster with BMLs and cysts cross-sectionally, component 3 (including cartilage damage, cysts and BMLs in the medial TFJ) is associated with osteophyte progression, which further supports that osteophytes are a result of the OA process. In the present study osteophytes did cluster with local cartilage damage, but also with osteophytes at other locations, suggesting also a non-location specific mechanism for formation osteophytes. The association between component 3 and osteophyte progression in the lateral TFJ suggest additional systemic mechanism in the formation of osteophytes. These findings encourage further studies looking into inflammatory and metabolic factors in the formation of osteophytes and development and progression of OA[34].

The present study, using PCA to investigate association with MRI abnormalities in an unbiased way, reveals that BMLs and cysts were associated with cartilage damage in almost all compartments. Furthermore, two of the three components that were associated with radiographic progression in longitudinal analyses incorporated BMLs and cysts. These observations are in line with earlier studies that showed that BMLs are associated with cartilage damage cross-sectionally and predict cartilage loss over time[4,6,35,35,36,36].

The nature of BMLs is not fully elucidated, but seems to represent local regions of trabecular remodelling or compression[37,38]. Both osteoblasts as well as increased expression of insulin-like growth factor 1 (IGF-1) and transforming growth factor - β (TGF-β) by subchondral bone

are thought to play a role in the abnormal bone remodelling in OA[39 40,41]. In line with potential local processes we report an associated between BMLs and cysts medially with JSN and OP progression medially in the TFJ, and BMLs and cysts laterally with OP progression laterally in the TFJ. In addition we also found BMLs and cysts in the medial TFJ to be associated with OP progression in the lateral TFJ, suggestion a reflection of a systemic effect. The latter effect encourages further study.

The most extensive component for radiographic progression in the knee joint appeared to be component 3. BMLs and cysts together with cartilage damage located at the medial TFJ were associated positively with progression of JSN and osteophytes in both joints. This could be explained by varus malalignment, which has a significant influence on the biomechanical properties of both the TFJ and the PFJ. Varus malalignment has been shown to be a risk factor for the development of BMLs in the medial TFJ[35,42,43] and leads to progression of OA in the medial compartment[43,44]. Furthermore, in patients with a varus malalignment the q-angle of the patella increases resulting in an increasing medial patellar force and increased load on the medial compartment of the patella and subsequently in PFJ progression[45-47]. Unfortunately, only lateral view, not skyline view, radiographs were available in the present study and therefore we could not confirm that medial TFJ abnormalities lead to medial PFJ JSN progression.

The majority of scientific literature suggests that PFJ OA is more common in the lateral patella compared to the medial patella in OA patients, due to a naturally occurring lateral reaction force vector[46,47]. Our study does not support this notion, as at baseline medial PFJ MRI abnormalities were more common. This is in concordance with a study by Gross et al. that found a higher prevalence of medial PFJ OA compared to lateral PFJ OA[48]. However, our longitudinal data suggest that lateral PFJ processes are of higher impact than medial PFJ processes since radiological progression in PFJ is especially associated with lateral PFJ involvement.

The present study has some limitations. First, the study population is relatively small and PFJ progression was seen only in a limited number of patients. Therefore, findings should be interpreted with caution and should be replicated in larger samples. Second, our results suggest that MRI abnormalities in the TFJ can influence progression of the PFJ. Since knees with a KL score of 4 were excluded the role of severe structural damage of the TFJ on progression in the PFJ could not be studied. Third, our study did not include synovitis in PCA. Since synovitis has been implicated in radiographic progression, inclusion of synovitis in the PCA would have been preferable. Yet, we did include effusion in our analysis, which can be considered as surrogate of synovial inflammation. Fourth, only lateral view radiographs

were available for scoring PFJ progression, not skyline view. Therefore we were unable to investigate medial and lateral PFJ progression, which could have led to an underestimation of PFJ progression. Finally, in present study we only included depth of cartilage defect (either diffuse or focal) in our analysis, while the KOSS scoring system scores the surface of the defect. Therefore small full-thickness cartilage defects were treated the same as large full-thickness cartilage defects and could have biased our results. Furthermore, the patellar crest was excluded from our analysis as it could not be medialized or lateralized. This could have biased our results.

In conclusion our findings, showing that both osteophytes as well as BMLs and subchondral cysts are clustered with cartilage defects and are associated with radiographic progression, in a localized way, but also in the whole knee joint, suggest that the OA process and progression is a complicated interplay between different underlying pathogenetic processes, where likely biomechanics, but also systemic factors play a role. Therefore these factors should be investigated as a whole.

Author contributions

Authors made substantial contributions to the following: (1a) conception and design of the study: BDL, JLB, MK; (1b) acquisition of data: JB, PK, EY, MK; (1c) interpretation of data BDL, JB, PK, EY, AIF, AMZ, HK, IM, JLB, MK; (2) drafting or critical revision of manuscript: BDL, JB, PK, EY, AIF, AMZ, HK, IM, JLB, MK; (3) final approval of manuscript BDL, JB, PK, EY, AIF, AMZ, HK, IM, JLB, MK

Role of funding source

Financial support was obtained from the Dutch Arthritis Association and Pfizer Groton Inc.. However they did not contribute to design, interpretation of data, drafting and final approval of the manuscript.

Conflict of interests: none

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