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## **Association of Patella Alignment with Cartilage Relaxation Times and Self-Reported Symptoms in Individuals with Patellofemoral Degeneration**

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## **Abstract**

To determine the cross-sectional and longitudinal associations of patella alignment with cartilage relaxation and patients' self-reported symptoms. Thirty participants with isolated patellofemoral joint (PFJ) degeneration (6 males,  $53.7 \pm 9.3$  years) and 24 controls (12 males,  $47.6 \pm 10.7$  years) were included. Magnetic resonance assessment was performed to provide grading of structural abnormalities, cartilage relaxation times, and patella alignment. Self-reported symptoms were assessed using the self-administrated Knee Injury and Osteoarthritis Outcome Score (KOOS). All participants were examined at baseline and 3 years. Statistical parametric mapping and Pearson partial correlation were used to evaluate the associations between patella alignment with cartilage relaxation times and self-reported symptoms, respectively. The analyses were performed between baseline (cross-sectional) as well as baseline against 3 years (longitudinal). Results indicated that patella height and patella flexion were associated with  $T_{1\rho}$  and  $T_2$  relaxation times at baseline (percentages of voxels showing significant correlation [PSV] = 10.1 to 24.8%; mean correlations  $[R] = 0.34$  to 0.36; mean p values = 0.015 to 0.026). Further, greater patella lateral alignment, lateral tilt, and lateral spin were associated with longer  $T_2$  times at 3 years (PSV = 11.0 to 14.4%,  $R = 0.39$  to 0.44,  $p = 0.017$  to 0.028). Last, a higher patella was associated with a lower KOOS at baseline and at 3 years ( $R = -0.33$  to  $-0.35$ ). The study suggests that patella malalignment as a risk factor for worsening cartilage health, informing clinicians with a better rehabilitation program that targets PFJ degeneration.

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Liao contributed to drafting the manuscript, while Souza revised it critically. Liao, Pedoia, Link, Majumdar, and Souza contributed to the acquisition, analysis, or interpretation of the data. Finally, all authors contributed to the approval of the submitted and final versions.

#### **Keywords**

cartilage relaxation; osteoarthritis; patellofemoral; patella alignment; patient outcome

#### **Introduction**

Knee osteoarthritis (OA) is a major health concern worldwide and a leading cause of disability in adults. Knee OA can affect both the tibiofemoral joint (TFJ) and patellofemoral joint (PFJ), where PFJ OA is highly prevalent but under recognized. Interestingly, some studies reported that PFJ OA is perhaps more prevalent than TFJ OA.<sup>1–3</sup> A radiographic study showed that the distribution of compartmental OA in adults aged 50 year and above with knee pain was 24% for isolated PFJ, 4% for isolated TFJ, and 40% for both joints combined.<sup>2</sup> Often, clinical OA is a late-stage condition where disease-modifying opportunities are limited; therefore, defining OA in its earlier stage might enable a better understanding and characterizing the disease process.

Early stages of OA include chondrocyte dysfunction and reduced synthesis of extracellular matrix components, proteoglycans, and collagen; thus, leading to reduced elasticity and reduction in water content.<sup>4</sup> Quantitative magnetic resonance imaging (MRI) offers tools to probe the biochemical composition of articular cartilage. For instance,  $T_{10}$  and  $T_2$  cartilage relaxation times are related to the proteoglycan content and collagen orientation of the cartilage and thus, can provide information on the state of cartilage health.<sup>5</sup> In particular, Teng et al. have shown elevated  $T_{1\rho}$  and  $T_2$  relaxation times in individuals with PFJ OA when compared to controls, supporting their potential as biomarker for early cartilage degeneration.<sup>6</sup>

In addition to assessing biochemistry features of early OA, patients' self-reported symptoms are another measure to analyze disease burden of OA. The Knee injury and Osteoarthritis Outcome Score (KOOS) is a valid and reliable self-administered knee questionnaire for assessing short-term and long-term outcomes of several types of knee injury including OA.<sup>7</sup> Even though clinical symptoms are often not associated with imaging findings,  $8-11$ examining structural and compositional changes from MRI as well as patient-reported symptoms in knee OA may provide clinicians with a more accurate information on disease status and representation.

Patella malalignment has been commonly reported as a mechanism towards PFJ-related pathologies, such as patellofemoral pain and chondromalacia patella.<sup>12, 13</sup> While little is known about the relationship between patella alignment and PFJ OA, there is suggestion that patella malalignment may be a risk factor to the development and progression of PFJ OA.<sup>14, 15</sup> Biomechanically speaking, patella malalignment may lead to decreased PFJ contact area and elevated contact forces, $16$  where excessive joint loading is related to the pathogenesis of joint pain and degeneration. Indeed, studies have demonstrated associations between patella tilt, translation, and patella alta with presence of cartilage lesions and bone marrow edema-like lesions (BMELs).<sup>14, 15</sup> While these findings are promising, it is unknown if early OA outcomes (i.e. cartilage health) and patients' self-reported symptoms are associated with patella alignment measures.

As such, the purpose of this study was to determine the associations between patella alignment with cartilage health  $(T_{1\rho}$  and  $T_2$  relaxation times) and self-reported symptoms cross-sectionally and at 3 years. The participants consisted of individuals with and without isolated PFJ degeneration as defined by the presence of morphological abnormalities of the joint seen on MRI.<sup>17, 18</sup>

#### **Methods**

#### **Participants**

A subgroup of participants from a longitudinal cohort on knee OA was included in this study. Participants above 35 years with and without knee OA symptoms were recruited from the community. Participants were excluded if any of the following criteria were present: (i) history of lower extremity or spine surgery, (ii) self-reported inflammatory arthritis, and (iii) contraindications to MRI. All participants underwent a weight-bearing, posteroanterior, fixed-flexion radiograph of the TFJ. The knee with the higher Kellgren-Lawrence (KL) grade was chosen for the following assessments. In addition, all participants underwent a knee MRI to determine if degenerative changes associated with OA existed in the PFJ and/or TFJ.

Presence of PFJ degeneration was defined as cartilage lesions and/or BMELs identified either at the patella, trochlea, or both, using an MRI-based semi-quantitative morphological grading system (the whole-organ MRI score [WORMS]), $^{17, 18}$  which is described in detail below. Participants were excluded from this current analysis if presence of TFJ degeneration was identified through the WORMS grading. Participants were stratified into the control group if no PFJ and TFJ degeneration were present on the MRI. Participants were stratified based on their morphological MRI findings but regardless of their pain or symptoms. Nevertheless, self-reported symptoms through KOOS questionnaire were obtained. This resulted in a total of 30 participants with isolated PFJ degeneration (sex, 6 males; age, 53.7  $\pm$  9.3 years; body mass index, 24.0  $\pm$  3.4 kg/m<sup>2</sup>) and 24 controls (12 males, 47.6  $\pm$  10.7 years,  $24.0 \pm 3.0 \text{ kg/m}^2$ ) included in the current study. It should be noted that even for participants with a KL grade equaled or larger than one, they might not exhibit TFJ cartilage degeneration as abnormal KL grade can be attributed to joint space narrowing, cartilage lesions, and/or meniscus lesions; 19 therefore they were included in the analysis. The study was approved by the Committee of Human Research at the University of California, San Francisco (UCSF) and prior to data collection, all participants signed a written informed consent. All participants received baseline imaging and clinical assessment as well as follow-up at 3 years. The level of evidence of the current study was Level 3.

#### **Self-reported symptoms**

All participants were required to complete the self-administrated KOOS at baseline and 3-year follow-up. The KOOS questionnaire consists of five subscales: pain, other symptoms, function in daily living, function in sport and recreation, and knee related quality of life.<sup>7</sup> A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) was calculated for each subscale.

#### **MRI Assessment**

All participants underwent unilateral knee MRI using a 3.0T GE MR 750w scanner (GE Healthcare, Milwaukee, WI, USA) with an 8-channel transmit-receive knee coil (Invivo, Inc., Gainesville, FL). Participants arrived at the imaging center and were unloaded (seated in a chair) for a 45 min period, after which the participants were positioned in a supine position in the MRI bore with the knee in neutral rotation and full extension. To reduce motion artifacts, the foot of the participant was secured in place, the study knee was stabilized with padding, and a belt was secured across the patient's waist. The following sequences were acquired: (i) sagittal thin section intermediate-weighted 3D fast-spin echo (FSE) sequence (Cube, GE Healthcare) was later reconstructed into axial and coronal planes for grading of knee structural abnormalities and cartilage segmentation (repetition time (TR)/echo time (TE) = 1500/26.69 ms, field of view (FOV) = 16 cm, matrix = 384  $\times$ 384, slice thickness = 0.5 mm, echo train length = 32, bandwidth = 37.5 kHz, number of excitations = 0.5, acquisition time = 10.5 min), (ii)  $T_{1\rho}$  relaxation time sequence (TR/TE  $= 9/2.6$  ms, time of recovery = 1500 ms, FOV = 14 cm, matrix = 256  $\times$  128, slice thickness = 4 mm, bandwidth =  $62.5$  kHz, time of spin-lock (TSL) =  $0/2/4/8/12/20/40/80$ ms, frequency of spin-lock = 500 Hz, acquisition time = 11 min), (iii) the  $T_2$  relaxation time sequence (same as the  $T_{10}$  quantification except for magnetization preparation TE = 1.8/3.67.3/14.5/29.1/43.6/58.2, acquisition time = 11 min), and (iv) sagittal fat-saturated intermediate-weighted FSE images for bone segmentation (TR/TE =  $4000/49.3$ ms, FOV = 16 cm, matrix =  $512 \times 512$ , slice thickness = 1.5 mm, echo train length = 9, acquisition time  $= 2.5$  min). The last sequence was carried out under both knee extension and 30 $^{\circ}$  of knee flexion with a custom loading device with 25% of the participant's weight.

#### **MRI-Based Morphological Grading**

Cartilage and bone marrow morphological abnormalities of the patella and trochlea were graded by an experienced board-certified radiologist on the 3D FSE sequences using the WORMS grading, <sup>17, 18</sup> which was previously shown to provide high intra- and inter-reader agreements (intra: 95.1%, inter: 95.3%).20 Cartilage lesions were graded using a 8-point scale:  $0 =$  normal thickness,  $1 =$  normal thickness, increased signal intensity,  $2 =$  partial thickness focal lesion less than 1 cm of greatest width, 2.5 = full thickness focal lesion less than 1 cm of greatest width,  $3 =$  multiple areas partial lesion less than 1 cm of greatest width, or grade 2 lesion wider than 1 cm but less than 75% of the region,  $4 =$  diffuse partial thickness loss greater than 75% of the region,  $5 =$  multiple areas of full thickness lesion greater than 1 cm but less than  $75\%$  of the region, and  $6 =$  diffuse full thickness loss greater than 75% of the region. The BMELs were graded using a 4-point scale:  $0 = none$ ,  $1 = \langle 25\% \rangle$ of the subregion,  $2 = 25 \times 50\%$  of the subregion,  $3 = 50\%$  of the subregion. Presence of PFJ degeneration at baseline was defined if the patella and/or trochlea demonstrated WORMS for cartilage lesions greater or equal to 2 and/or BMELs greater or equal to 1.

#### **Voxel-Based Relaxometry**

Image post-processing for obtaining voxel-based relaxometry was performed in MATLAB integrated with Elastix registration toolbox for non-rigid image registration.<sup>21, 22</sup> The voxel-based relaxometry approach has been previously reported to be consistent with the

traditional region-of-interest approach with the coefficient of variation of  $3.83\%$ <sup>23</sup>. The details of the process have been previously described.<sup>23</sup> Briefly, a single reference image was identified through an iterative process aimed to minimize the global image deformation. All images were then non-rigidly registered and aligned to the single reference image. Relaxation maps were computed in a voxel-by-voxel basis by fitting the morphed images from different TSLs or TEs, for  $T_{10}$  or  $T_2$  respectively, employing Levenberg-Marquardt mono-exponentials applied to each voxel (S(TSL)  $\alpha$  exp(-TSL/ T<sub>1p</sub>)).

#### **Patella Alignment**

In order to estimate patella alignment, bone segmentation and anatomical axes were obtained for the femur and patella. All image post-processing was performed with inhouse programs written in MATLAB (MathWorks, Natick, MA) and Python (Python Software Foundation, <https://www.python.org/>). Femur and patella bones were automatic segmented on the sagittal intermediate-weighted FSE images in both knee-extended and -flexed positions using a deep learning model (V-Net encoder-decoder convolutional neural network).<sup>24</sup> First, the model was trained from a manually segmented dataset (40 extended and 40 flexed position scans). The dataset was split into 25, 10, and 5 scans for the training, holdout test, and validation sets, respectively. Dice coefficients were used as a validation metric to optimize and test the model. A separate model was performed for the knee-extended and -flexed position scans. The model performance was excellent with mean Dice coefficients of 0.93 and 0.92 for knee-extended and -flexed positions, respectively. Bone segmentation was later used for the quantification of patella alignment. As a validation, patella alignment measures were compared between manual and automatic bone segmentations. Again, patella alignment measures estimated from manual and automatic segmentations showed high correlations ( $R = 0.95$  to 0.98). Other regions of interest including femoral condyles, femoral axis, and patella axis were semi-automatically identified on the images.

These regions of interest were then used to estimate patella alignment using a previously developed software program with good intraclass correlation coefficient  $(> 0.84)$  for intraand inter-user reliability.25 First, the patella and femur coordinate systems were defined anatomically as previously described.25 The segmented femoral bone in the knee-flexed position was then rigidly registered to that in the fully extended position by the use of an iterative closest-point shape-matching algorithm. Thus, the femur was held fixed to allow calculation of patella alignment relative to the femoral coordinate system in each knee-extended and -flexed position. Patella alignment was quantified in both translational and rotational planes, resulting in total 6 degrees of freedom including medio-lateral, anterior-posterior, and superior-inferior alignment as well as flexion (rotation about the medio-lateral axis), spin (rotation about the anterior-posterior axis), and tilt (rotation about the superior-inferior axis) (Figure 1). For instance, patella flexion refers to the anteriorly rotated patella position in respect to a fixed femur on the medio-lateral axis.

#### **Statistical Analysis**

Chi-square and independent t tests were used to compare demographics and KL grade between the PFJ degeneration and control groups at baseline. Mann-Whitney U test was

used to perform group comparison for KOOS as the distribution of KOOS was skewed. Statistical parametric mapping was used to evaluate the cross-sectional and longitudinal associations between patella alignment and absolute cartilage relaxation times. Pearson partial correlation was used to evaluate the same associations between patella alignment and KOOS. All analyses were carried out with the covariates of sex, age, body mass index. In addition, the longitudinal assessment of statistical parametric mapping included cartilage relaxation times at baseline as covariates. The alpha value was set at 0.05.

Statistical parametric mapping was used to perform VBR analyses. That is, Pearson partial correlations were used to evaluate the associations of patella alignment and cartilage relaxation times on a voxel-by-voxel basis. Percentage of voxels showing significant correlation (PSV), average correlation coefficient (R) of voxels showing significant correlation, and average p values of voxels showing significant correlation were reported from the statistical parametric mapping. Only results with PSV more than 10% of the voxels were considered to provide more clinically significant patterns, therefore further reported.<sup>26</sup> Since associations were examined voxels by voxels resulting in multiple comparisons, Random Field Theory correction was used to take into account possible false positives.27 For visualization, an in-house developed program was used to construct threedimensional bone mesh segmented from the MRI. The patella and trochlear compartments were interpolated from the two-dimensional sagittal images, creating a color map of the desired statistical parameter, correlation coefficient in this case, and then overlaid on the three-dimensional bone mesh.

### **Results**

Participant characteristics are presented in Table 1. Significant group differences were found for sex ( $p = 0.040$ ) and age ( $p = 0.031$ ) between the PFJ degeneration and control groups. No group differences were found for BMI, KL grade, and self-reported symptoms (KOOS) at baseline. Distribution of WORMS grading in the PFJ degeneration group at baseline is presented in Figure 2. Of all the 30 participants that exhibited PFJ morphological lesions at baseline, only one participant exhibited isolated BMELs, while the remaining participants exhibited cartilage lesions in isolation or in combination with BMELs. Additionally, lesions at the patella appeared to be more prevalent than at the trochlea.

Cross-sectionally, results of the statistical parametric mapping revealed that a lower patella superior alignment (PSV = 19.5 to 24.8%; R =  $-0.34$  to  $-0.36$ ; p = 0.015 to 0.019) and greater patella flexion (PSV = 10.1 to 23.5%; R = 0.33 to 0.36; p = 0.018 to 0.026) were associated with longer  $T_{1\rho}$  and  $T_2$  relaxation times in the knee-extended position. On the contrary, a higher patella was associated with longer  $T_{1\rho}$  and  $T_2$  relaxation times (PSV  $= 11.9$  to 13.5%; R = 0.35 to 0.36; p = 0.018) in the knee-flexed position (Table S1 & S2). When examining the associations longitudinally, the results revealed that greater patella lateral alignment (PSV = 11.8%;  $R = 0.39$ ;  $p = 0.028$ ), greater lateral tilt (PSV = 14.4%; R  $= 0.41$ ; p = 0.022), and greater lateral spin (PSV = 11.0%; R = 0.44; p = 0.017) at baseline were associated with longer  $T_2$  times at 3 years (Table S3 & S4). These findings were found exclusively in the knee-flexed position. The associations were mainly distributed in the central trochlea, except the association with lateral spin was distributed in the peripheral

trochlea (Figure 3). Last, when examining the associations of patella alignment with KOOS cross-sectionally, a higher patella in the knee-extended position was associated with a lower KOOS subscale of sports at baseline  $(R = -0.35; p = 0.012)$  (Table S4). Similar associations were found when examining longitudinally, a higher patella in the knee-extended position was associated with a lower KOOS subscale of pain  $(R = -0.34; p = 0.019)$  and quality of life (R =  $-0.33$ ; p = 0.023) (Table S5).

### **Discussion**

The purpose of this current study was to determine if patella alignment was associated with cartilage health and patients' self-reported symptoms in individuals with and without isolated PFJ degeneration, cross-sectionally and longitudinally. Our results revealed that  $T_{10}$ and  $T_2$  times were sensitive to patella vertical position cross-sectionally. Longitudinally, greater patella lateral alignment, lateral tilt, and lateral spin were associated with longer  $T<sub>2</sub>$ times at 3 years. Self-reported symptoms, on the other hand, showed weaker associations with patella alignment with only KOOS subscale of sports negatively correlated with patella vertical position cross-sectionally. Using statistical parametric mapping in the current study provides the benefit of analyzing the relationship on a voxel-by-voxel basis as compared to the traditional regions of interest that are mostly arbitrarily designated. It allows us to view the strength of associations by its percentage of significance and visually inspect the distribution of results.

The current study demonstrated that longer  $T_{10}$  and  $T_2$  relaxation times were associated with a lower patella in the knee-extended position. Interestingly, when the knee was in the flexed position, longer relaxation times were then associated with a higher patella. These results looked surprising at first glance as a higher patella (patella alta) has known to be associated with PFJ degeneration but not a low-riding patella.<sup>28, 29</sup> When considering the kinematics of PFJ, it is known that patella moves inferiorly when the knee bends from extension to flexion. Therefore, a lower patella during knee extension and a higher patella during knee flexion implies less vertical patella excursion when the knee bends. This was supported from our post-hoc analysis that found significant associations between less superior-inferior patella excursion and longer T<sub>1o</sub> and T<sub>2</sub> times (PSV = 24.0 to 30.9%; R = -0.35 to -0.37; p = 0.015 to 0.018). A less patella excursion may decrease the extent of PFJ contact during knee motion, therefore joint loads are concentrated to a limited area as well as the wear and tear of the cartilage.

When similar analysis was performed on the longitudinal data, other patella alignment measures were found to be predictors of cartilage relaxation times at 3 years, which the results were distinct from the cross-sectional analysis. Results revealed that greater patella lateral alignment, lateral tilt, and lateral spin in knee-flexed position were associated with longer  $T_2$  times. Our results were consistent with a systematic review that reported greater patella lateral position and greater lateral tilt were associated with more severe PFJ OA features,<sup>30</sup> although there were a few contradicting studies that suggested greater medial patella position as a risk factor,  $14, 15$  or both excessive patella lateralization and medialization contribute to PFJ degeneration.<sup>15</sup> Our study is one of the few that examined patella alignment in all planes and in 6 degrees of freedom. This 3D method provides

a better understanding of patella position relative to the trochlea as compared to the traditionally used 2D alignment indexes such as patella tilt angle and bisect offset index. That being said, patella spin has been less commonly discussed and associated with PFJ OA. Our results indicated that greater patella lateral spin (patella apex pointing laterally) was associated with longer  $T_2$  times.

From a biomechanical standpoint, patella lateralization decreases the utilized PFJ contact area, and can further lead to elevated stress, exposing the joint to an unhealthy environment. Although we did not measure PFJ stress directly, it is possible that patella lateralization contributes to longer  $T_2$  times with elevated PFJ stress as a mediator. It is noteworthy that patella malalignment features were associated with  $T<sub>2</sub>$  times under knee-flexed condition but not knee-extended condition. One possible explanation is that PFJ stress is higher under knee flexion as compared to extension as the forces acting on the joint are higher under greater knee flexion; since joint overloading is one of the mechanisms leading to joint degeneration, it is not surprising to see patella malalignment together with a high stress environment are associated with a longer cartilage  $T_2$  over time. Taken together, it may also explain why the associations were found mostly in the central trochlea as the contact point of the PFJ shifts from lateral to slightly medial throughout knee extension to knee flexion.

No distinct associations were found in patella alignment and self-reported symptoms other than a fair association between a higher patella vertical position and lower KOOS scores. Given the weak association here, it is uncertain if patella malalignment plays a clinically significant role in the patients' self-reported knee symptoms. Past studies have reported associations of patella alignment and KOOS, with greater patella lateralization associated with worse KOOS in individuals following total knee arthroplasty or anterior cruciate ligament reconstruction.31, 32 The self-reported KOOS may be more specific and sensitive in those surgical knees but not in our participants who represent the general population with and without PFJ cartilage degeneration.

It is also interesting to note that KOOS was not significantly different between the two groups in our cohort, namely the PFJ degeneration and control groups. Nevertheless, we observed the distribution of KOOS subscales ranging from 81.2 to 100 in our control subjects (Table 1), which is comparable to the expected KOOS in the given age group and BMI (range 75.8 to 92.1).<sup>33</sup> That is to say, even though the control subjects did not report excellent scores on KOOS, it did not indicate that these individuals exhibited knee pain or symptoms. It is worth noting that participants were stratified into the PFJ degeneration group if the patella and/or trochlea exhibited cartilage lesions and/or BMELs as shown on MRI. The definition is distinct from the OA classification which is determined based on the presence or size of osteophytes and degree of joint space narrowing on radiographs.<sup>19</sup> As such, participants in the degeneration group may not be true OA patients and therefore their KOOS were comparable to healthy controls. These data further support the established disconnection between classical morphological features of OA and the patient experience. Nevertheless, the statistical analyses in the current study were carried out with both groups combined, providing a varying degree of participant characteristics with regard to knee health status.

In light of the findings in the current study, there are several limitations that need to be addressed. First, the study has relatively small sample size of 54 participants, and that there was an uneven sex distribution (18 males vs. 36 females). This was due to the gender biased in the natural prevalence of PFJ OA as females tend to have a higher prevalence rate, and that the participants were selected based on the presence of PFJ degeneration, excluding those with TFJ degeneration. We acknowledged the bias and considered sex as a covariate in all our statistical models to minimize the effect. Second, with the design of the study, multiple comparisons were performed among various variables. Unfortunately, this may lead to increase chances of type I error. Caution should be made when interpretating the results, such that the fair associations between patella alignment and patients' self-reported symptoms may not be clinically relevant. Nevertheless, Random Field Theory correction was used in the statistical parametric mapping to account for possible false positives.<sup>27</sup> Third, patella alignment was quantified under a nonphysiological loading condition. The participants were instructed to lie supine in the MRI bore while the test foot was loaded with a weightbearing device at 25% body weight. Other research methods, such as dual fluoroscopy, may better help to estimate patella alignment under functional activities. Lastly, KOOS may not be a sensitive tool to detect PFJ OA symptoms since it is designed for general knee pain. Recently, a modified KOOS specifically designed for individuals with patellofemoral pain and PFJ OA has been developed (KOOS-PF), which may potentially be a more sensitive tool to identify symptomatic PFJ OA progression.34 Unfortunately, in our cohort we did not obtain data regarding KOOS-PF.

In summary, the results of the current study suggest that patella malalignment plays a role towards the progression of cartilage matrix degeneration, but the same relationship is not seen in self-reported functional outcome. Furthermore, greater knee flexion with patella malalignment appears to aggravate cartilage degeneration as both conditions are biomechanical factors towards greater PFJ stress. More research is warranted to confirm these associations as identifying the risk factors contributing to PFJ degeneration informs clinicians with better rehabilitation programs that target at deferring the development of PFJ OA.

#### **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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#### **References**

- 1. McAlindon TE, Snow S, Cooper C, Dieppe PA. Radiographic patterns of osteoarthritis of the knee joint in the community: the importance of the patellofemoral joint. Ann Rheum Dis. 1992;51:844– 849. [PubMed: 1632657]
- 2. Duncan RC, Hay EM, Saklatvala J, Croft PR. Prevalence of radiographic osteoarthritis--it all depends on your point of view. Rheumatology (Oxford). 2006;45:757–760. [PubMed: 16418199]
- 3. Szebenyi B, Hollander AP, Dieppe P, et al. Associations between pain, function, and radiographic features in osteoarthritis of the knee. Arthritis Rheum. 2006;54:230–235. [PubMed: 16385522]

- 4. Cucchiarini M, de Girolamo L, Filardo G, et al. Basic science of osteoarthritis. J Exp Orthop. 2016;3:22. [PubMed: 27624438]
- 5. Regatte RR, Akella SV, Lonner JH, Kneeland JB, Reddy R. T1rho relaxation mapping in human osteoarthritis (OA) cartilage: comparison of T1rho with T2. J Magn Reson Imaging. 2006;23:547– 553. [PubMed: 16523468]
- 6. Teng HL, Pedoia V, Link TM, Majumdar S, Souza RB. Local associations between knee cartilage T1rho and T2 relaxation times and patellofemoral joint stress during walking: A voxel-based relaxometry analysis. Knee. 2018;25:406–416. [PubMed: 29681528]
- 7. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes. 2003;1:64–64. [PubMed: 14613558]
- 8. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis. 2011;70:60– 67. [PubMed: 20829200]
- 9. Barker K, Lamb SE, Toye F, Jackson S, Barrington S. Association between radiographic joint space narrowing, function, pain and muscle power in severe osteoarthritis of the knee. Clin Rehabil. 2004;18:793–800. [PubMed: 15573836]
- 10. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord. 2008;9:116. [PubMed: 18764949]
- 11. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol. 2000;27:1513–1517. [PubMed: 10852280]
- 12. Stefanik JJ, Zhu Y, Zumwalt AC, et al. Association between patella alta and the prevalence and worsening of structural features of patellofemoral joint osteoarthritis: the multicenter osteoarthritis study. Arthritis Care Res (Hoboken). 2010;62:1258–1265. [PubMed: 20506169]
- 13. Song CY, Lin JJ, Jan MH, Lin YF. The role of patellar alignment and tracking in vivo: the potential mechanism of patellofemoral pain syndrome. Phys Ther Sport. 2011;12:140–147. [PubMed: 21802041]
- 14. Eijkenboom JFA, van der Heijden RA, de Kanter JLM, Oei EH, Bierma-Zeinstra SMA, van Middelkoop M. Patellofemoral alignment and geometry and early signs of osteoarthritis are associated in patellofemoral pain population. Scand J Med Sci Sports. 2020;30:885–893. [PubMed: 32096249]
- 15. Macri EM, Felson DT, Zhang Y, et al. Patellofemoral morphology and alignment: reference values and dose-response patterns for the relation to MRI features of patellofemoral osteoarthritis. Osteoarthritis Cartilage. 2017;25:1690–1697. [PubMed: 28648740]
- 16. Salsich GB, Perman WH. Patellofemoral joint contact area is influenced by tibiofemoral rotation alignment in individuals who have patellofemoral pain. J Orthop Sports Phys Ther. 2007;37:521– 528. [PubMed: 17939611]
- 17. Peterfy CG, Guermazi A, Zaim S, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage. 2004;12:177–190. [PubMed: 14972335]
- 18. Stefanik JJ, Niu J, Gross KD, Roemer FW, Guermazi A, Felson DT. Using magnetic resonance imaging to determine the compartmental prevalence of knee joint structural damage. Osteoarthritis Cartilage. 2013;21:695–699. [PubMed: 23428598]
- 19. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16:494–502. [PubMed: 13498604]
- 20. Stehling C, Liebl H, Krug R, et al. Patellar cartilage: T2 values and morphologic abnormalities at 3.0-T MR imaging in relation to physical activity in asymptomatic subjects from the osteoarthritis initiative. Radiology. 2010;254:509–520. [PubMed: 20019141]
- 21. Shamonin D, Bron E, Lelieveldt B, Smits M, Klein S, Staring M. Fast parallel image registration on CPU and GPU for diagnostic classification of Alzheimer's disease. Front Neuroinform. 2014;7:50. [PubMed: 24474917]
- 22. Klein S, Staring M, Murphy K, Viergever MA, Pluim JPW. elastix: A toolbox for intensity-based medical image registration. IEEE Trans Med Imaging. 2010;29:196–205. [PubMed: 19923044]

- 23. Pedoia V, Li X, Su F, Calixto N, Majumdar S. Fully automatic analysis of the knee articular cartilage T1rho relaxation time using voxel-based relaxometry. J Magn Reson Imaging. 2016;43:970–980. [PubMed: 26443990]
- 24. Milletari F, Navab N, Ahmadi S-A. V-Net: Fully convolutional neural networks for volumetric medical image segmentation. 2016 Fourth International Conference on 3D Vision (3DV). 2016:565–571.
- 25. Lau BC, Thuillier DU, Pedoia V, et al. Inter- and intra-rater reliability of patellofemoral kinematic and contact area quantification by fast spin echo MRI and correlation with cartilage health by quantitative T1rho MRI. Knee. 2016;23:13–19. [PubMed: 26746045]
- 26. Pedoia V, Gallo MC, Souza RB, Majumdar S. Longitudinal study using voxel-based relaxometry: Association between cartilage  $T(1\rho)$  and  $T(2)$  and patient reported outcome changes in hip osteoarthritis. J Magn Reson Imaging. 2017;45:1523–1533. [PubMed: 27626787]
- 27. Marchini J, Presanis A. Comparing methods of analyzing fMRI statistical parametric maps. Neuroimage. 2004;22:1203–1213. [PubMed: 15219592]
- 28. Stefanik JJ, Zhu Y, Zumwalt AC, et al. Association between patella alta and the prevalence and worsening of structural features of patellofemoral joint osteoarthritis: the multicenter osteoarthritis study. Arthritis Care Res (Hoboken). 2010;62:1258–1265. [PubMed: 20506169]
- 29. Haj-Mirzaian A, Guermazi A, Pishgar F, et al. Association of patella alta with worsening of patellofemoral osteoarthritis-related structural damage: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2019;27:278–285. [PubMed: 30445221]
- 30. Macri EM, Stefanik JJ, Khan KK, Crossley KM. Is tibiofemoral or patellofemoral alignment or trochlear morphology associated with patellofemoral osteoarthritis? A systematic review. Arthritis Care Res (Hoboken). 2016;68:1453–1470. [PubMed: 26814979]
- 31. Narkbunnam R, Electricwala AJ, Huddleston JI 3rd, Maloney WJ, Goodman SB, Amanatullah DF. Suboptimal patellofemoral alignment is associated with poor clinical outcome scores after primary total knee arthroplasty. Arch Orthop Trauma Surg. 2019;139:249–254. [PubMed: 30483917]
- 32. Macri EM, Patterson BE, Crossley KM, et al. Does patellar alignment or trochlear morphology predict worsening of patellofemoral disease within the first 5 years after anterior cruciate ligament reconstruction? Eur J Radiol. 2019;113:32–38. [PubMed: 30927957]
- 33. Marot V, Murgier J, Carrozzo A, et al. Determination of normal KOOS and WOMAC values in a healthy population. Knee Surg Sports Traumatol Arthrosc. 2019;27:541–548. [PubMed: 30251101]
- 34. Crossley KM, Macri EM, Cowan SM, Collins NJ, Roos EM. The patellofemoral pain and osteoarthritis subscale of the KOOS (KOOS-PF): development and validation using the COSMIN checklist. Br J Sports Med 2018;52:1130–1136. [PubMed: 28258176]



#### **Figure 1.**

Patellar alignment in 6 degrees of freedom. x-axis, medial-lateral; y-axis, anterior-posterior; z-axis, superior-inferior.

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#### **Figure 2.**

Distribution of the morphological grading of the cartilage and bone marrow edema-like lesions (BMELs) at baseline using the whole organ magnetic resonance imaging score (WORMS). Only participants who were classified in the patellofemoral joint degeneration group are shown here (number of participants  $[n] = 30$ ).



#### **Figure 3.**

Three-dimensional visualization of the correlation maps between baseline patella alignment measures and  $3$ -year  $T_2$  relaxation times. Statistical parametric mapping revealed moderate but significant positive associations of patella lateral alignment, lateral spin, and lateral tilt with 3-year  $T_2$  relaxation times (R = 0.39 to 0.44; p = 0.017 to 0.028). Data are presented as color maps, which show the spatial relationship and strength of the correlation (red indicates stronger association).

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Demographics of the PFJ degeneration and control participants at baseline. Demographics of the PFJ degeneration and control participants at baseline.



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each grade, KOOS presented as median (IQR). Abbreviations: KL grade, Kellgren-Lawrence grade; Age and body mass index presented as mean ± SD, KL grade presented as the number of participants in each grade, KOOS presented as median (IQR). Abbreviations: KL grade, Kellgren-Lawrence grade; KOOS, Knee Injury and Osteoarthritis Outcome Score. KOOS, Knee Injury and Osteoarthritis Outcome Score.

 $\dot{'}$  <br>Indicates chi-square analysis Indicates chi-square analysis

 $\stackrel{\star}{\tau}$  indicates Mann-Whitney U test.  $\ddot{t}$  indicates Mann-Whitney U test.