Title
Variation of radius of curvature around the femoral head and its associations with gender and incident radiographic hip osteoarthritis: Data from the Osteoarthritis Initiative

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(*continued*)

	Group	Progression	OR	95% CI	aOR**	95% CI
	Gainers	25/85 (29%)	1.59	0.89 − 2.84	1.55	0.87 − 2.76
	Losers	18/88 (20%)	1.00	0.54 −1.84	1.39	0.76 − 2.55
Progression cartilage defects						
TFJ	Steadies	67/514 (13%)	1	Reference	1	Reference
	Gainers	10/85 (12%)	0.89	0.45–1.74	0.83	0.43 −1.60
	Losers	10/88 (11%)	0.90	0.45–1.80	0.75	0.37–1.52
PFJ	Steadies	117/514 (23%)	1	Reference	1	Reference
	Gainers	26/85 (31%)	1.48	0.89 − 2.47	1.49	0.89 − 2.49
	Losers	15/88 (17%)	0.73	0.43–1.25	0.75	0.43 −1.30
Progression osteophytes						
TFJ	Steadies	66/514 (13%)	1	Reference	1	Reference
	Gainers	13/85 (15%)	1.22	0.64–2.36	1.07	0.56 − 2.04
	Losers	15/88 (17%)	1.41	0.64 − 3.11	1.32	0.60–2.94
PFJ	Steadies	34/514 (7%)	1	Reference	1	Reference
	Gainers	9/85 (11%)	1.65	0.68–4.02	1.56	0.67–3.65
	Losers	10/88 (11%)	1.81	0.78–4.20	1.62	0.67 − 3.91
Progression meniscal abnormalities						
Medial and/ or lateral	Steadies	142/514 (28%)	1	Reference	1	Reference
	Gainers	25/85 (29%)	1.08	0.61 −1.89	1.05	0.58 −1.88
	Losers	25/88 (28%)	1.09	0.61–1.97	1.02	0.55–1.88
Progression meniscal extrusions						
Medial and/ or lateral	Steadies	87/514 (17%)	1	Reference	1	Reference
	Gainers	16/85 (19%)	1.13	0.61 − 2.11	0.97	0.52 −1.82
	Losers	11/88 (13%)	0.72	0.36–1.44	0.79	0.38 −1.64

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PROGNOSTIC CHARACTERISTICS OF MR FEATURES ASSOCIATED WITH RADIOGRAPHIC OA DEVELOPMENT IN PARTICIPANTS WITH KNEE PAIN SUSPECTED FOR EARLY KNEE OA

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Purpose: To investigate the associations of Magnetic Resonance (MR) features with development of radiographic knee OA and to determine their prognostic values, in participants with knee pain suspected for early knee OA.

Methods: Participants from Cohort Hip & Cohort Knee (CHECK) were eligible, a study in 45–65 year olds with knee or hip symptoms for which they had consulted their general practitioner never or not longer than 6 months ago. In the present study participants were included with knee pain, a Kellgren and Lawrence (KL) score of $\leq$1 and a knee MRI available at baseline; the knee with most complaints was studied. Development of radiographic knee OA was defined after 5 years by a KL score $\geq$2 or receipt of a total arthroplasty. Baseline knee MRIs were semi-quantitatively scored according to KOSS. Categorical features were cartilage defects, osteophytes, bone marrow lesions (BMLs), Baker's cysts and effusion. Furthermore we scored presence of meniscal pathology, defined as a tear and/or extrusion and assessed femorotibial joint OA, according to the proposed criteria by Hunter et al. These criteria consist of a definite osteophyte and full thickness cartilage loss or one of these features combined with 2 or more other OA related MR features.

We determined the association of these MR features with development of radiographic OA using binary logistic regression analyses by calculating odds ratios (OR) with 95% confidence intervals (95%CI). Adjustments were made for age, sex and BMI. The provided ORs are for 1 unit increase in score. Furthermore, sensitivity, specificity and predictive values were calculated for (dichotomized) statistically significant associated MR features. Finally, we calculated the area under the curve (AUC) of the receiver operating characteristic curve, to test the discriminative ability of associated MR features. The discriminative ability is reasonable with an AUC above 0.7, and strong above 0.8.

Results: Data of 148 participants were analyzed with a mean age of 56 years and 78% women. At baseline most patients (60%) had a KL score of 1; 28% developed radiographic OA. 16 patients (11%) had completely normal MR images. In 89 knees (60%) we assessed any form of cartilage loss, 81 knees (55%) had at least one osteophyte and 25 knees (17%) had a BML. A Baker's cyst was present in 38 knees (26%) and effusion was seen in 54 knees (36%). 80 knees (54%) showed meniscal pathology. Femorotibial OA on MR images was seen in 14 knees (9%) according to Hunter's proposed criteria. Statistically significant associations with radiographic OA after five years were: cartilage defects (OR 1.7 (95%CI 1.1, 2.6) and AUC 0.593), osteophytes (OR 3.1 (1.7, 5.7) and AUC 0.663), BMLs (OR 2.0 (1.2, 3.4) and AUC 0.573), effusion (OR 2.1 (1.2, 3.5) and AUC 0.621), meniscal pathology (OR 2.8 (1.3, 6.3) and AUC 0.615) and femorotibial OA at baseline (OR 9.7 (2.6, 35.6) and AUC 0.603). No associations were seen for Baker's cysts. Sensitivity was highest for cartilage defects (any), osteophytes (any) and presence of meniscal pathology, however not higher than 71%, with specificities ranging from 40 to 50%. Specificity above 90% was seen for higher graded MR features being osteophytes grade $\geq$2, BMLs grade $\geq$2, moderate to large effusion and femorotibial OA, although with a low sensitivity ranging from 22 to 27%. For osteophytes grade $\geq$2, effusion grade $\geq$2 and femorotibial OA on MR the pretest probability of development of radiographic OA in 5 years at least doubled from 28% to positive predictive values above 60%.

Conclusions: In early knee OA, MR depicts OA associated pathology in cartilage, bone and menisci, where the radiograph fails to detect these changes. Although MR imaging has potential in identifying patients at risk for developing radiographic knee OA, the MR features had insufficient sensitivity and specificity with AUCs below 0.7 to be used as diagnostic biomarkers in early knee OA.

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VARIATION OF RADIUS OF CURVATURE AROUND THE FEMORAL HEAD AND ITS ASSOCIATIONS WITH GENDER AND INCIDENT RADIOGRAPHIC HIP OSTEOARTHRITIS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

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Purpose: To examine whether the shape of the femoral head is associated with gender or incidence of hip osteoarthritis.

Methods: Participants from the Osteoarthritis Initiative were eligible for this study if they did not have definite radiographic hip osteoarthritis (RHOA) in at least one hip on their baseline visit pelvis x-ray. Cases of incident RHOA were hips which developed definite RHOA by 48-month follow-up. Control hips were randomly selected, frequency matched by contralateral RHOA status, from hips which had not developed RHOA by 48-month follow-up. The femoral head outline on the baseline x-ray was recorded using a semi-automated method with 60 evenly spaced points placed from the inferior point of the narrowest part of the femoral neck around the femoral head to the superior point of the narrowest part of the femoral neck. The angle of the femoral neck was defined as the angle to the horizontal of a line through the centre point of the femoral neck to the centre point of the femoral head. Over each 10 degree arc around the femoral head, the local radius of curvature was calculated using a least squares fit, and was normalized to the radius of curvature fitted to all points within 90 degrees of the neck-head axis direction, to give a relative curvature, which was plotted as a function of the angle at which the point was relative to the femoral head centre. The angular position of the inflection point on the superior side of the head neck junction at which the outline of the femoral head switched from concave to convex was also recorded (see Figure 1).

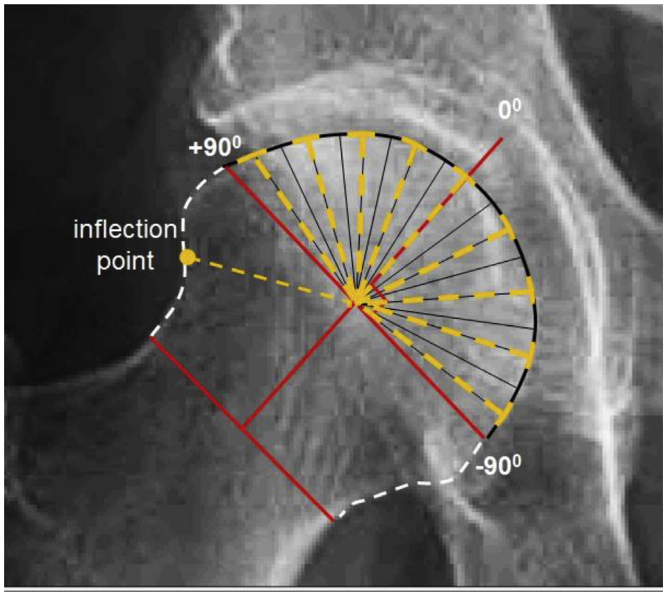

Figure 1. Showing position of the inflection point and the +/−90 degree arc over which relative curvature was measured.

This gave 19 values of relative curvature, along with the inflection point angle which described the shape of the femoral head. Gender differences in relative curvature values and inflection point angle were examined using ANOVA with correction for multiple comparisons. Associations of relative curvature values and inflection point angle with incident RHOA were examined in the following two step process (1) In a univariate analysis, each of the 19 values of relative curvature, along with the inflection point angle was examined as a predictor of incident RHOA using binary logistic regression (with GEE to allow for more than one hip per person in the analysis), with models corrected for covariates of age and body mass index and contralateral RHOA status, (2) Predictors (significant at $p<0.05$) were then entered into a multivariate model to determine which independently predicted RHOA.

Results: 678 hips (452 participants) were analysed (265 women, 187 men). In women, there were 68 hips with incident RHOA and 343 control hips. In men, there were 41 hips with incident RHOA and 226 control hips. In hips with no RHOA, inflection point angle was significantly larger in men than women, relative curvature was significantly higher at the supero-lateral (+90 degree) and a more medial position (+40 degrees) in men than women (see Table 1).

Table 1. Gender differences in femoral head shape measurements in normal hips

	Men		Women		p<
	Mean	95% CI	Mean	95% CI	
inflection angle (degrees)	123.2	122.2–124.2	117.2	116.3–118.0	0.0001**
relative curvature (+40 degrees)	0.974	0.995–1.004	0.885	0.848–0.992	0.0007**
relative curvature (+90 degrees)	0.982	0.925–1.000	1.291	1.224–1.359	0.0001**

** of the 20 measurements, only those remaining significant after correcting for multiple comparisons are shown

In the multivariate analysis of the association between femoral head shape and incident RHOA, only 2 relative curvature values (at +80 degrees – supero-medial, and +40 degrees - more medially), along with the inflection point angle were significantly associated with incident RHOA, and all three image based measurements predicted incident RHOA with similar odds ratios (see Table 2).

Table 2. Showing independent predictors of incident RHOA

Predictor		Adjusted OR*	95% CI	p<
inflection angle	per +1 SD	1.33	1.07–1.65	0.009
relative curvature (+80 degrees)	per -1 SD	1.43	1.14–1.79	0.002
relative curvature (+40 degrees)	per -1 SD	1.26	1.04–1.52	0.018

* models were adjusted for age, sex, BMI and contralateral RHOA status. ORs for relative curvature are per -1SD (ie: flattening)

Conclusions: Larger inflection angles were associated with increased odds of developing incident RHOA, and larger values existed in normal hips of men compared to women. Flattening of the femoral head supero-laterally (+80 degrees) and more medially (+40 degrees) were also independently associated with increased odds of incident RHOA. These two positions were also ones in which gender differences occurred in normal hips. Increased inflection angle may be a measure of pistol grip deformity, known to be associated with RHOA, but this study showed that flattening of the supero-lateral portion of the femoral head (seen more frequently in men) and flattening of the more medial portion of the femoral head (seen more frequently in women) are both independent predictors of incident RHOA. The mechanisms by which these are associated with gender and incident RHOA, perhaps partly related to incongruence with the acetabulum, need further investigation.

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LONGITUDINAL CHANGE IN FEMOROTIBIAL CARTILAGE THICKNESS ARE CONTINGENT ON MALALIGNMENT, BUT NOT ON ITS SEVERITY, DIRECTION, OR THE BODY MASS INDEX

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Purpose: The interaction of alignment and body mass index (BMI) as risk factors for osteoarthritis (OA) progression is controversial and has not yet been studied using quantitative MRI-based outcomes of cartilage thickness loss. The objective of this study was thus to determine the relative and interactive contributions of frontal plane alignment and BMI on quantitative measures of cartilage thickness over 2-years in patients with radiographic knee OA. Specifically, this study aimed to investigate how quantitative cartilage thickness measures change as a function of: the severity of malalignment (neutral, mild or severe), the direction of malalignment (varus or valgus), and the interaction between malalignment and BMI.

Methods: Femortibial cartilage thickness change between baseline and 2-years was available from sagittal DESS MRI measurements in 558 knees from the Osteoarthritis Initiative (OAI) with radiographic OA at baseline (KLG2-4 in central radiographic readings). Measures of location-specific cartilage thickness loss in the central weight-bearing medial (cMFTC) and lateral (cLFTC) femorotibial compartments, and location-independent subregional cartilage thinning scores (CTNS) as well as ordered values 1 (OV1 = the subregion with the greatest cartilage loss) were compared between categories of malalignment and between knees with low vs. high BMI. The femorotibial angle (FTA) was available as a measure of lower limb alignment from the OAI database and neutral alignment was defined as ±0–2°. Using the median for varus (-) and valgus (+) knees (±3.5°), mild and severe malalignment were defined as ±2–3.5°, and >±3.5°, respectively. First, measures of cartilage thickness change were compared between knees with any malalignment (mild or severe) vs. neutral alignment, independent of direction, and in a second step, they were compared between all alignment categories: severe varus (n=127), mild varus (n=111), mild valgus (n=43) and severe valgus (n=39) vs. neutral (n=238). Then, cartilage thickness change was compared between knees with mild varus vs. mild valgus malalignment, and severe varus vs. severe valgus malalignment. Finally, knees with a BMI above and below the median (29.8kg/m2) were compared across strata defined by severity and/or direction of malalignment. Analyses were performed using Kruskal-Wallis and Mann-Whitney U tests, adjusting for multiple comparisons.

Results: CTNS, OV1 and cMFTC were significantly larger in malaligned knees (mild or severe) compared to neutral knees ($p\leq0.005$). CTNS and OV1 were also significantly larger in mild malalignment vs. neutral, and severe malalignment vs. neutral, when varus and valgus knees were