VARYING PATTERNS OF PROGRESSION ARE OBSERVED IN KELLGREN-LAWRENCE 2 AND 3 KNEES FULFILLING DIFFERENT DEFINITIONS OF A CARTILAGE-MENISCUS PHENOTYPE IN THE FOUNDATION FOR NATIONAL INSTITUTES OF HEALTH OSTEOARTHRITIS BIOMARKERS CONSORTIUM STUDY (FNIH)

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BACKGROUND AND PURPOSE

- No DMOAD approved to date [1]
- One reason is structural heterogeneity of included patients stratified by radiographic Kellgren-Lawrence (K-L) grading (K-L 2 and 3)
- OA has multiple phenotypic faces and joints progress at different rates [2]
- Three main structural phenotypes in knee OA based on MRI have been proposed, i.e., inflammation, cartilage-meniscus and subchondral bone [3]
- Recently, Rapid OsteoArthritis MRI Eligibility Score (ROAMES [4]) system has been introduced that allows structural phenotypic stratification based on abbreviated MRI assessment
- The cartilage-meniscus phenotype is likely to benefit most from pharmacological intervention focusing on cartilage restoration
- However, cartilage damage that is too severe may be of negative impact
- Original ROAMES definition includes severe cartilage damage (incl. full thickness loss) and bilateral meniscal damage: only 5% of FNIH knees fulfilled that definition (**Figure 1**)
- Aim was (1) to describe frequencies for different structural thresholds regarding the definition of a modified ROAMES cartilage-meniscus phenotype and (2) to report patterns of progression in KL 2 and 3 knees over 48 months in the Foundation for National Institutes of Health (FNIH) Osteoarthritis Biomarkers Consortium cohort, a sample comparable to a clinical trial population

METHODS

- The study sample was the FNIH project, as a nested case-control study with knees showing either 1) radiographic and pain progression (i.e., "composite" cases), 2) radiographic progression only (joint space loss – JSL), 3) pain progression only, and 4) neither radiographic nor pain progression at 48 months
- MRI performed on 3T systems
- Knees stratified into different cartilage-meniscus phenotypes based on baseline MOAKS readings using established subregional and compartmental definitions (**Figure 2**)
- Focus on the medial compartment, which is commonly the primary outcome in clinical DMOAD trials
- Three different phenotypes were defined according to the maximum severity of cartilage damage in the medial compartment. To be classified in a phenotype knees had to have damage in at least one subregion (score >0) but maximum damage not exceeding the following thresholds:
  - 1) D1: ≤ 2.2 (10-75% of region of cartilage surface area with 10-75% affected by full thickness loss) in any of 5 subregions
  - 2) D2: ≤ 2.1 (10-75% of region of cartilage surface area with <10% affected by full thickness loss)
  - 3) D3: ≤ 2.0 (10-75% of region of cartilage surface area without full thickness loss)
- Definitions will result in the exclusion of compartments without any damage and those with severe wide-spread full thickness damage of more than 75% (i.e. MOAKS 3.0 - 3.3)
- Odds of outcome (composite or JSL case) for those with vs. without each phenotype was determined using logistic regression
- Sensitivity analyses focused on the reference knees not fulfilling these phenotypic definitions to understand proportions of knees with either "too much" (i.e., max severity greater than threshold) or "no" damage (i.e., no subregions with score >0)

RESULTS

- After exclusion of KL1 knees and those with meniscal root tears (that would not be included in a clinical DMOAD trial), 485 knees included in study
- Mean age 61 years (SD ± 8.8), 59 % women, average BMI 31.0 kg/m^2 (SD ± 4.8)
- 297 knees were KL2 and 188 knees KL3
- Regarding frequencies of the different meniscus-cartilage phenotypes, for KL2 and 3 knees combined, numbers increased from 5% using the original ROAMES definition [4] and 21% using the modified published definition [5] to 73%, 59% and 50% for medial cartilage damage only
- Including any ipsicompartmental meniscal damage to the definitions of a cartilage-meniscus phenotype defined by changes in the medial compartment only, these numbers changed to 45%, 33% and 27% (**Table 1**)
- For KL2 knees 191(64%) knees fulfilled D1 criteria, 183 (62%) D2 and 167 (56%) D3. For KL3 these numbers were 164 (87%), 103 (55%) and 77 (41%). Odds for being a composite case for KL2 knees were 2.52 (95% CI 1.40,4.54) for D1, 1.93 (95% CI 1.11,3.35) for D2 and 1.92 (95% CI 1.13,3.28) for D3. For KL3 knees odds were 0.32 (95% CI 0.13,0.78) for D1, 0.56 (95% CI 0.31,1.01) for D2 and 0.49 (95% CI 0.26,0.91) for D3
- For KL2 knees, 2% (D1), 4% (D2) and 10% (D3) of the controls had too much damage to meet the phenotype definition, while 34% did not have any damage. For KL3 12%, 45% and 59% had too much damage to meet the phenotype definition, while only one (1%) knee had no damage in the medial compartment. Details are shown in **Table 2**

Table 1. Frequencies of knees using different cartilage/meniscus phenotype definitions based on compartmental cartilage thresholds

Presence of phenotype	KLG 2	KLG 3	KL 2+3 combined
Cartilage/meniscus Phenotype (Original ROAMES) [1]			
No	291 (98%)	172 (91%)	463 (95%)
Yes	6 (2%)	16 (9%)	22 (5%)
Cartilage/meniscus Phenotype (secondary published definition modified ROAMES) [2]			
No	282 (95%)	99 (53%)	381 (79%)
Yes	15 (5%)	89 (47%)	104 (21%)
Cartilage Medial Phenotype (1a) [3]- med cartilage damage present, no more than 2.2			
No	106 (36%)	24 (13%)	130 (27%)
Yes	191 (64%)	164 (87%)	355 (73%)
Cartilage Medial Phenotype (2a) [3]- med cartilage damage present, no more than 2.1			
No	114 (38%)	85 (45%)	199 (41%)
Yes	183 (62%)	103 (55%)	286 (59%)
Cartilage Medial Phenotype (3a) [3]- med cartilage damage present, no more than 2.0			
No	130 (44%)	111 (59%)	241 (50%)
Yes	167 (56%)	77 (41%)	244 (50%)
Cartilage Medial and Lateral Phenotype (1b) [4] - med and lat cartilage damage present, no more than 2.2			
No	192 (65%)	105 (56%)	297 (61%)
Yes	105 (35%)	83 (44%)	188 (39%)
Cartilage Medial and Lateral Phenotype (2b) [4] - med and lat cartilage damage present, no more than 2.1			
No	209 (70%)	141 (75%)	350 (72%)
Yes	88 (30%)	47 (25%)	135 (28%)
Cartilage Medial and Lateral Phenotype (3b) [4] - med and lat cartilage damage present, no more than 2.0			
No	225 (76%)	155 (82%)	380 (78%)
Yes	72 (24%)	33 (18%)	105 (22%)

[1] Presence of a meniscus score of at least ROAMES grade 3 (i.e., any type of meniscal substance loss/ maceration) in the medial and/or lateral compartment and at least ROAMES grade 1 (any type of tear) in the other compartment, respectively, and presence of cartilage damage grades 2.1, 2.2, 3.2 or 3.3 according to MOAKS (3)
[2] any type of meniscal substance loss/maceration regardless of other compartment AND presence of ipsi-compartmental cartilage damage grades ≥ 2.1 (4)
[3] For phenotypes cartilage (1a), (2a), and (3a): any medial/lateral meniscal score allowed, any cartilage score allowed in the lateral compartment
[4] For phenotypes cartilage (1b), (2b), and (3b): any medial/lateral meniscal score allowed

Table 2. Different cartilage-meniscus phenotype definitions considering **the medial compartment only**, and odds for being a case knee in the FNIH cohort

Phenotype	Composite JSL + Pain Case (KL2 and 3)		KL 2	Odds for being a composite JSL + Pain case [1] (95% confidence interval)	Odds for being a JSL-only case [2] (95% confidence interval)	KL 3	Odds for being a composite JSL + Pain case [1] (95% confidence interval)	Odds for being a JSL-only case [2] (95% confidence interval)
	No	Yes						
Cartilage-meniscus Phenotype Group (1a) - medial cartilage damage present, no more than MOAKS 2.2 [3]								
Has phenotype	233 (66%)	122 (34%)	191 (64%)	2.52 (1.40,4.54)	4.17 (2.44, 7.14)	164 (87%)	0.32 (0.13, 0.78)	0.48 (0.19, 1.21)
Does not have phenotype – damage > max	12 (43%)	16 (57%)	5 (2%)	Reference		23 (12%)	Reference	
Does not have phenotype - no damage	85 (83%)	17 (17%)	101 (34%)			1 (1%)		
Cartilage–meniscus phenotype Group (2a) - medial cartilage damage present, no more than MOAKS 2.1 [3]								
Has phenotype	193 (67%)	93 (33%)	183 (62%)	1.93 (1.11,3.35)	3.30 (1.99, 5.49)	103 (55%)	0.56 (0.31, 1.01)	0.39 (0.21, 0.71)
Does not have phenotype - damage > max	52 (54%)	45 (46%)	13 (4%)	Reference		84 (45%)	Reference	
Does not have phenotype - no damage	85 (83%)	17 (17%)	101 (34%)			1 (1%)		
Cartilage Medial Phenotype Group (3a) - medial cartilage damage present, no more than MOAKS 2.0 [3]								
Has phenotype	166 (68%)	78 (32%)	167 (56%)	1.92 (1.13,3.28)	2.73 (1.68, 4.42)	77 (41%)	0.49 (0.26, 0.91)	1.15 (0.65, 2.06)
Does not have phenotype - damage > max	79 (57%)	60 (43%)	29 (10%)	Reference		110 (59%)	Reference	
Does not have phenotype - no damage	85 (83%)	17 (17%)	101 (34%)			1 (1%)		

[1] Composite JSL + Pain case definition: radiographic and pain progression; [2] JSL- joint space loss, i.e. radiographic progression only; [3] any lateral cartilage and any meniscal status allowed

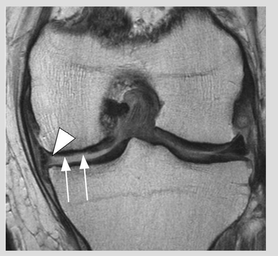

Figure 1. Original ROAMES Definition cartilage-meniscus phenotype:

Presence of a meniscus score of at least ROAMES grade 3 (i.e., **any type of meniscal substance loss/maceration**) in the medial and/or lateral compartment and at least grade 1 (**any type of tear**) in the **other compartment**, respectively, and presence of cartilage damage grades **2.1, 2.2, 3.2 or 3.3** according to MOAKS
(arrowhead points to medial meniscal substance loss, arrows show full-thickness cartilage damage 2.2. in the central medial femur)

Figure 2. Subregional division in MOAKS of femur and tibia into anterior, central and posterior subregions. In the coronal plane the femur is subdivided into a medial and lateral subregion. S designates the subspinous region of the tibia

CONCLUSION

- Phenotypic stratification of the cartilage-meniscus phenotype in different subtypes is feasible and may help in defining trial cohorts at screening
- Increased odds for progression are seen for KL2 knees and all definitions, while a seemingly protective effect is seen for KL3 knees
- The latter can be explained by the fact that KL3 knees exceeding the maximum damage thresholds were still likely to experience progression
- One-third of knees with KL2 do not have medial cartilage damage, which is an important finding and needs to be considered when selecting patients for clinical trials based on X-ray assessment only

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