Patterns of progression differ between Kellgren-Lawrence 2 and 3 knees fulfilling different definitions of a cartilage-meniscus phenotype in the Foundation for National Institutes of Health Osteoarthritis Biomarkers study (FNIH)

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OBJECTIVE: Aim was to describe three definitions for an MRI-defined cartilage-meniscus phenotype and to report phenotypic progression in Kellgren-Lawrence (KL) 2 and 3 knees over 48 months.

METHODS: The study sample was a nested case-control study with knees showing either 1) radiographic and pain progression (“composite” case), 2) radiographic progression only, 3) pain progression only, and 4) no progression. MRI was performed on 3T systems. MRIs were read according to the MOAKS system. Knees were classified as having the cartilage-meniscus phenotype according to three modified ROAMES (Rapid OsteoArthritis MRI Eligibility Score) definitions (D): 1) \(D1\) \(=\) 2.2 (10–75% of the region of cartilage surface area with 10–75% affected by full thickness loss), i.e. ‘\(D1\)’ 2) \(D2\) \(=\) 2.1 (10–75% of the region of cartilage surface area with <10% affected by full thickness loss), i.e. ‘\(D2\)’ and 3) \(D3\) \(=\) 2.0 (10–75% of the region of cartilage surface area without full thickness loss), i.e. ‘\(D3\)’. The odds of being a composite case for those with vs. without each definition was determined using logistic regression.

RESULTS: 485 knees were included. 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 \(D3\).

CONCLUSION: Increased odds for progression are seen for KL2 knees for all definitions, while this was not observed for KL3 knees. KL knees exceeding the maximum damage thresholds and not fulfilling the phenotypic definitions are still likely to experience further progression.

1. Introduction

Imaging plays an important role in determining structural disease severity and potential eligibility of patients recruited to disease-modifying osteoarthritis drug (DMOAD) trials [1]. From a structural perspective, knees with established structural OA grades 2 and 3 on the Kellgren-Lawrence (K-L) scale are commonly considered eligible. In the context of personalized medicine, it has been recognized that OA is a heterogeneous disease. This heterogeneity led to the concept of defining different subtypes of OA, also known as phenotypes, that are characterized by distinct underlying pathobiological and pain mechanisms [2]. While imaging-based structural characterization into subtypes of disease

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is still in its infancy, three main MRI-defined structural phenotypes have been proposed, i.e., inflammation, cartilage-meniscus and subchondral bone [3]. Acknowledging that these subtypes may not necessarily fulfill the overarching suggested definition of OA phenotypes including clinical parameters [2], structural stratification may be relevant particularly in the context of clinical trials. Recently introduced Rapid Osteoarthritis MRI Eligibility Score (ROAMES) system allows structural classification based on abbreviated MRI assessment and thus, may potentially be applicable in screening efforts for inclusion into DMOAD trials [4]. In a recent report based on the Foundation for National Institutes of Health (FNHI) Osteoarthritis Biomarkers Consortium cohort, we found that the bone phenotype was associated with increased odds of progression, while the inflammatory and cartilage-meniscus phenotypes were not [5]. However, a drawback of that analysis was the low prevalence of the phenotype yield using the primary definitions according to ROAMES. This was the case particularly for the inflammatory and cartilage-meniscus phenotypes (prevalence <5% for both phenotypes) [4]. Concerning progression, the cartilage-meniscus phenotype is of particular relevance given the target tissue of most DMOAD approaches is cartilage concerning progression, the cartilage-meniscus phenotype is of particular relevance given the target tissue of most DMOAD approaches is cartilage.

Thus, the aim of our study was to describe frequencies for different structural thresholds regarding the definition of a modified ROAMES cartilage-meniscus phenotype and to report patterns of progression in Kellgren-Lawrence (KL) 2 and 3 knees over 48 months in a simulated clinical trial population, the FNHI cohort.

2. Methods

2.1. Sample selection

The FNHI study is a nested case-control study embedded within the larger Osteoarthritis Initiative (OAI) study [6]. In brief, the OAI is a multicenter prospective observational cohort study of knee OA (https://oai.nih.gov) that enrolled 4796 participants aged 45–79 years at four clinical centers. Details of the OAI inclusionary and exclusionary criteria have been published [7].

2.2. Case-control selection

The FNHI study sample was defined by symptomatic and structural progression outcomes over 48 months [1]. A pre-determined number of index knees was selected in the following outcome groups, for measurement of imaging biomarkers: 1) case knees had both radiographic and pain progression (i.e. “composite case”); 2) knees with radiographic but not pain progression (i.e., joint space loss - JSL case”), 3) knees with pain but not radiographic progression, and 4) knees with neither radiographic nor pain progression.

Knees with KL1 at baseline were excluded in the current analysis as these are not considered to have radiographic OA. Knees with posterior meniscal root tears at baseline were also excluded as these knees are considered at increased risk for rapid structural progression due to the effect of a subtotal meniscectomy biomechanically and increased risk for subchondral insufficiency fractures [8–11].

2.3. MRI acquisition

MRIs of both knees were acquired using 3T systems (Siemens MAGNETOM Trio, Erlangen, Germany) at the four OAI clinical sites. The sequence protocol included a coronal intermediate-weighted 2-dimensional turbo spin echo sequence, a sagittal 3-dimensional dual-echo steady-state (DESS) sequence, and a sagittal intermediate-weighted fat-suppressed turbo spin-echo sequence [12]. Two musculoskeletal radiologists, blinded to clinical data and case-control status, read the baseline MRIs according to the MRI Osteoarthritis Knee Score (MOAKS) system [13].

2.4. Phenotypic definitions

The current analysis focuses primarily on the medial compartment, which is commonly the primary outcome in clinical DMOAD trials [14–16]. 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 in any of the five medial subregions: 1) ≤2.2 (10–75% of the region of cartilage surface area with 10–75% affected by full thickness loss), i.e. ‘D1’ 2) ≤2.1 (10–75% of the region of cartilage surface area with <10% affected by full thickness loss), i.e. ‘D2’ and 3) ≤2.0 (10–75% of the region of cartilage surface area without full thickness loss), i.e. ‘D3’.

These definitions will result in the exclusion of compartments without any damage and those with severe wide-spread full thickness damage of more than 75%. In a separate analysis, we defined a combined medial and lateral cartilage phenotype based on the concomitant presence of the same criteria for both the medial and lateral compartments as described above.

2.5. Statistical analysis

For each of the three definitions, the odds of outcome (composite or JSL case) for those with vs. without the phenotype according to threshold was determined using logistic regression. Knees not fulfilling the definition were used as the referent. 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). In addition, we present the frequencies of knees using different cartilage-meniscus phenotype definitions based on medial-only or medial/lateral compartment cartilage thresholds. Further, we are presenting data on the frequencies of knees using the different cartilage-meniscus phenotype definitions based on medial cartilage thresholds and concomitant ipsilateral compartmental presence of any or severe medial meniscal damage. All analyses were conducted in SAS 9.4 (SAS Institute, Cary NC).

3. Results

After exclusion of KL 1 knees (n = 71) and knees with posterior meniscal root tears (n = 44), 485 knees were included. Excluded participants were similar to included participants with respect to baseline characteristics and case status. Mean age of the participants was 61 years (standard deviation (SD) ± 8.8), 59% of the participants were women, average body mass index was 31.0 kg/m² (SD ± 4.8). 297 knees were KL2 and 188 knees KL3.

For KL2 knees, 191 (64%) knees fulfilled D1 criteria. Of the 106 KL2 knees that did not meet the criteria, 5 (2%) exceeded the maximum damage severity threshold and 101 (34%) had no damage in any medial subregion. 183 (62%) met D2 criteria and 167 (56%) D3. For KL3 these numbers were 164 (87%) for D1, 103 (55%) for D2 and 77 (41%) for D3. Of the 24 KL3 knees that did not meet the D1 criteria, 23 (12%) exceeded the maximum damage severity threshold and 1 (1%) knee had no damage in any medial subregion. Odds for being a composite case were 2.52 (95% CI 1.40,4.54) for D1, 1.93 (95% CI 1.11,3.35) for D2 and 1.92 (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 the JSL-only outcome numbers were similar, with increased odds for KL2 knees and a protective effect for KL3 knees (Table 1). For KL2 knees, 2% (D1), 4% (D2) and 10% (D3) of the controls had too much damage, while 34% did not have any damage. For KL3 12%, 45% and 59% had too much damage, while only one (1%) knee had no damage in the medial compartment. Further details are shown in Appendix 1a.

Considering the medial and lateral compartments combined frequencies of those knees fulfilling a phenotype definition and those that did not due to either “too much” or “no” damage are presented in...
4. Discussion

Adapting the thresholds of cartilage damage and including or excluding meniscal damage for different definitions of a cartilage-meniscus phenotype leads to increased frequencies of knees fulfilling those definitions of up to 64% for KL2 knees and 87% for KL3 knees depending on the definition and considering the medial compartment only. Increased odds for being a composite or JSL case at 48 months were seen for KL2 knees for all three definitions compared to those knees not fulfilling the definition. For KL3 using the medial compartment-only definitions, a seemingly protective effect was observed particularly for using the composite case outcome. One third of knees with KL2 (vs. 1% in KL3 knees) did not show any medial cartilage damage.

Reasons for failure of DMOAD trials are complex but include radiography-based eligibility screening to define structural disease severity [17]. X-ray is only able to depict osseous changes at relatively late stages and radiography has shortcomings regarding reproducible image acquisition [18]. MRI in contrast, is an instrument that has matured over recent years and is likely able to replace X-ray-based screening efforts [4,19]. Using phenotypic definitions based on structure may help in further stratifying suitable patient populations [20]. While particularly three different structural phenotypes have been introduced, limitations include overlap of phenotypes and that more than one may be present in an individual [5]. In addition, such phenotypic definitions as in our current study are based on a priori hypotheses and whether other relevant structural phenotypic definitions may exist has not been agnostically evaluated. In a systematic meta-analysis Deveza and colleagues described significant heterogeneity across studies in the selection of participants and characteristics and methods used to investigate knee OA phenotypes [21]. Furthermore, we acknowledge that a wide range of views exist on how best to operationalize the concept of OA phenotypes. The term phenotype as used in our study does not fulfill the characteristics as suggested by others and may potentially be adapted to structural “subtype” [2].

Limitations of our study include the retrospective aspect of our work analyzing a sample that has been defined by certain outcomes. We acknowledge that the matching of cases and controls has been broken up influenced our analysis. We did not screen the image acquisition [18]. MRI in contrast, is an instrument that has matured over recent years and is likely able to replace X-ray-based screening efforts [4,19]. Using phenotypic definitions based on structure may help in further stratifying suitable patient populations [20]. While particularly three different structural phenotypes have been introduced, limitations include overlap of phenotypes and that more than one may be present in an individual [5]. In addition, such phenotypic definitions as in our current study are based on a priori hypotheses and whether other relevant structural phenotypic definitions may exist has not been agnostically evaluated. In a systematic meta-analysis Deveza and colleagues described significant heterogeneity across studies in the selection of participants and characteristics and methods used to investigate knee OA phenotypes [21]. Furthermore, we acknowledge that a wide range of views exist on how best to operationalize the concept of OA phenotypes. The term phenotype as used in our study does not fulfill the characteristics as suggested by others and may potentially be adapted to structural “subtype” [2].

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Appendix 1b The odds for being a composite case were 2.13 (95% CI 1.27, 3.59) for D1, 1.91 (95% CI 1.12, 3.26) for D2 and 1.81 (95% CI 1.03, 3.19) for the D3 definition for KL2 knees (Appendix 2). For KL3 knees odds were 1.12 (0.62, 2.02) for D1, 1.00 (0.51, 1.97) for D2 and 0.90 (0.41, 1.97) for D3. For the JSL-only outcome, increased odds for KL2 knees for definitions D1 and D2 but not D3 were observed and for KL3 knees no statistically significant results were seen (Appendix 2).

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 (Table 2a). Including any ipsocompartmental 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 2b). Associations between phenotype and progression (composite JSL + pain case, JSL-only case) were generally similar between definitions with (Appendix 3) and without (Table 1) meniscal involvement.

4. Discussion

Adapting the thresholds of cartilage damage and including or excluding meniscal damage for different definitions of a cartilage-meniscus phenotype leads to increased frequencies of knees fulfilling those definitions of up to 64% for KL2 knees and 87% for KL3 knees depending on the definition and considering the medial compartment only. Increased odds for being a composite or JSL case at 48 months were seen for KL2 knees for all three definitions compared to those knees not fulfilling the definition. For KL3 using the medial compartment-only definitions, a seemingly protective effect was observed particularly for using the composite case outcome. One third of knees with KL2 (vs. 1% in KL3 knees) did not show any medial cartilage damage.

Reasons for failure of DMOAD trials are complex but include...
Table 2a

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 (D1a) 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 (D2a) 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 (D3a) 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 (D1b) ³ - 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 (D2b) ³ - 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 (D3b) ³ - 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, 2.2, 3.2 or 3.3 according to MOAKS [3].

³ For phenotypes cartilage (D1a), (D2a), and (D3a): any medial/lateral meniscal score allowed, any cartilage score allowed in the lateral compartment.

⁴ For phenotypes cartilage (D1b), (D2b), and (D3b): any medial/lateral meniscal score allowed.

Table 2b

Frequencies of knees using different cartilage-meniscus phenotype definitions based on medial cartilage thresholds and concomitant ispocompartmental presence of any or severe medial meniscal damage.

| Presence of phenotype | KLG 2 | KLG 3 | KL 2 + 3 combined |
|-----------------------|-------|-------|------------------|
| Cartilage Medial and Meniscus Medial Phenotype (D1c) - med cartilage damage present, no more than 2.2, medial meniscus ROAMES ³ ¼
| No                    | 213 (72%) | 53 (28%) | 266 (55%) |
| Yes                   | 84 (28%)  | 115 (72%) | 219 (45%) |
| Cartilage Medial and Meniscus Medial Phenotype (D2c) - med cartilage damage present, no more than 2.1, medial meniscus ROAMES ³ ¼
| No                    | 216 (73%) | 107 (57%) | 323 (67%) |
| Yes                   | 81 (27%)  | 81 (43%)  | 162 (33%) |
| Cartilage Medial and Meniscus Medial Phenotype (D3c) - med cartilage damage present, no more than 2.0, medial meniscus ROAMES ³ ¼
| No                    | 222 (75%) | 131 (70%) | 353 (73%) |
| Yes                   | 75 (25%)  | 57 (30%)  | 132 (27%) |
| Cartilage Medial and Severe Meniscus Medial Phenotype (D1d) - med cartilage damage present, no more than 2.2, medial meniscus ROAMES ³ ¼
| No                    | 270 (91%) | 82 (44%)  | 352 (73%) |
| Yes                   | 27 (9%)   | 106 (56%) | 133 (27%) |
| Cartilage Medial and Severe Meniscus Medial Phenotype (D2d) - med cartilage damage present, no more than 2.1, medial meniscus ROAMES ³ ¼
| No                    | 271 (91%) | 125 (66%) | 396 (82%) |
| Yes                   | 26 (9%)   | 63 (34%)  | 89 (18%) |
| Cartilage Medial and Severe Meniscus Medial Phenotype (D3d) - med cartilage damage present, no more than 2.0, medial meniscus ROAMES ³ ¼
| No                    | 274 (92%) | 145 (77%) | 419 (86%) |
| Yes                   | 23 (8%)   | 43 (23%)  | 66 (14%) |

² ROAMES ³ ¼: any meniscal tear and/or any meniscal maceration.

³ ROAMES ³ ¼: any meniscal substance loss i.e. meniscal partial or complete maceration.

Authors contributions

Analysis and interpretation of the data: FWR, JEC, SD, DJH, AG. Drafting of the article: FWR, JEC, SD, DJH, AG. Provision of study materials or patients: FWR, JEC, SD, DJH, AG. Statistical expertise: JEC. Obtaining funding: FWR, DJH, AG. Collection and assembly of data: FWR, JEC, SD, DJH, AG. Responsibility for the integrity of the work as a whole, from inception to finished article, is taken by F. Roemer, MD (first author; frank.roemer@uk-erlangen.de; froemer@bu.edu).

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Declaration of competing interest

AG has received consultancies, speaking fees, and/or honoraria from Pfizer, Novartis, AstraZeneca, Merck Serono, and TissueGene and is President and shareholder of Boston Imaging Core Lab (BICL), LLC a
company providing image assessment services.

FWR is Chief Medical Officer and shareholder of BICL, LLC. and has received consultancies, speaking fees, and/or honoraria from Calibr –California Institute of Biomedical Research and Grünenthal, GmbH.

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Appendix A. Supplementary data

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