Frequencies of MRI-detected structural pathology in knees without radiographic OA and worsening over three years: How relevant is contralateral radiographic osteoarthritis?

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ABSTRACT

Purpose: To test whether radiographically normal knees with contralateral radiographic knee osteoarthritis (ROA) (i.e. ‘early OA model’) exhibit MRI-defined structural tissue pathology to a greater extent and show higher rates of progression compared to knees with bilateral radiographically normal knees without risk factors (‘healthy reference’).

Methods: We included 154 knees from the Osteoarthritis Initiative without ROA (Kellgren-Lawrence = 0), but with definite ROA (Kellgren-Lawrence ≥ 2) in the contralateral knee, and 78 participants from the OAI healthy reference cohort (without any signs of radiographic OA, knee pain or risk factors in either knee). Effusion-synovitis, Hoffa-synovitis, bone marrow lesions (BMLs), cartilage lesions, meniscus morphology and - extrusion and osteophytes were assessed at year 1 (Y1) and year 4 (Y4). Frequencies of features for both groups at Y1 and rates of worsening from Y1 to Y4 were compared using Fisher’s exact test.

Results: 69% (early OA model) vs. 46% (healthy reference) had baseline Hoffa-synovitis, 26% vs. 19% effusion-synovitis, 27% vs. 13% femorotibial (FT) BMLs, 77% vs. 50% FT cartilage lesions, 36% vs. 9% meniscal damage, 51% vs. 24% meniscus extrusion, and 92% vs. 74% FT osteophytes. Apart from effusion-synovitis, all differences were statistically significant. For structural worsening, statistically significant differences were observed for FT cartilage (p = 0.03) and FT osteophytes (p = 0.01).

Conclusion: MRI structural abnormalities are substantially more frequent and more progressive in radiographically normal knees with contralateral osteoarthritis than in ‘healthy reference’ controls. Compared with published data, they also are more frequent compared to radiographically normal knees “at risk”, without contralateral knee OA.

1. Introduction

Recruitment of participants for clinical trials studying disease-modifying osteoarthritis drugs (DMOAD) is commonly based on the presence of radiographic osteoarthritis (OA) as defined by the Kellgren-Lawrence (K-L) scale. Knees with K-L grades 0 or 1 are considered not to have structural OA and are thus usually excluded from DMOAD trials, whereas knees with evidence of definite osteophytes (i.e. K-L grade 2) or joint space narrowing (i.e. K-L grade 3) are generally considered to be eligible [1,2].

However, large population-based observational studies reported presence of magnetic resonance imaging (MRI)-detected osteophytes in up to 74% of knees with apparently normal radiographs (i.e. K-L grade 0) [3]. Due to its insufficient contrast resolution, radiography not only lacks...
sensitivity for visualizing specific bony features of OA, such as osteophytes, but in particular non-bony early features of OA such as a spectrum of soft tissue changes [2]. A study on Osteoarthritis Initiative (OAI) participants without knee OA (bilateral K-L 0) but with risk factors for OA development revealed that 76% of the knees had cartilage damage, 61% bone marrow lesions (BMLs), 21% meniscal tears, and 14% meniscal extrusion [4]. In addition, it has been shown that the presence of specific structural features of MRI-detected joint damage increased the risk of incident radiographic OA [5]. These numbers suggest that radiographically ‘normal’ knees cannot necessarily be considered ‘structurally normal’, and patients with such knees could potentially be considered for inclusion in OA clinical trials, in particularly those attempting to prevent the onset of radiographic knee OA at an early stage of the disease.

Ideally, intervention and prevention of structural damage based on pharmacologic or other approaches should commence prior to the onset of radiographic change, and should aim to maintain such structurally ‘normal’ knees. As preventive treatment is unlikely to be without side effects and risks, it is important to identify patients who would be ideal candidates for preventive treatment of a radiographically normal knee in view of a positive benefit/risk ratio of the intervention [6]. It has been shown that radiographically normal (i.e K-L 0) knees carry a greater risk of developing radiographic OA and display greater rates of cartilage thickness loss and greater change in deep layer cartilage composition, when the contralateral knee has already established radiographic knee OA compared to those where contralateral knees are radiographically normal [7,8].

The aim of the current study therefore was to test whether radiographically normal knees (K-L 0) with definite contralateral radiographic knee OA (K-L 2 to 4), but without contralateral trauma history (i.e. an ‘early OA model’), exhibit greater frequency and progression of structural joint pathology as defined by MRI than those with bilateral radiographically normal knees (K-L 0) without risk factors (‘healthy reference’). In another step we compared the frequency and progression rates with those previously reported for bilateral K-L 0 knees with risk factors.

2. Methods

2.1. Study participants

The participants for this analysis were selected from the Osteoarthritis Initiative (OAI) cohort (http://www.oai.ucsf.edu/) [9]. All OAI participants provided written informed consent and this study was carried out in accordance with the IRB-approved OAI data user agreement. At baseline, the OAI cohort included 4796 participants aged 45–79 years that were recruited at one of four clinical sites [9]. At each of five subsequent annual visits the OAI collected clinical data and acquired MRI of that were recruited at one of four clinical sites [9]. At each of

2.2. MRI acquisition

MRIs of both knees were acquired at four sites on identical 3 T systems (Siemens Trio, Erlangen, Germany). The MRI pulse sequence protocol included a coronal two-dimensional intermediate-weighted (IW) turbo spin-echo (TSE), sagittal three-dimensional (3D) dual-echo at steady-state (DESS), coronal and axial multplanar reformations of the 3D DESS, and sagittal IW fat saturated (fs) TSE sequences. Details of the OAI MRI protocol have been published [11].

2.3. MRI assessment

Baseline effusion-synovitis, Hoffa-synovitis, BMLs, cartilage lesions, osteophytes, meniscus morphology and meniscus extrusion were assessed for year 1 and year 4 visits in chronological order by one experienced radiologist (FWR) using the semi-quantitative MOAKS scoring system [12]. The reason for choosing Y1 and Y4 was that readings for double K-L 0 knees without radiographic OA, but with risk factors, were available from a published study [4]. Inter- and intrarader reliability for MOAKS has been described previously for the same reader and all of the measures showed substantial (0.61–0.8) or reached almost perfect agreement (0.81–1.0) 5,12.

2.4. Analytic approach

Due to low frequencies of knee joint structural lesions at baseline and the relatively small sample size, the MOAKS subscales were dichotomized into presence or absence of specific features, the only exception being meniscus morphology where a grade 1 lesion (intrameniscal signal) was considered normal. Compartment-specific analysis differentiating the femorotibial from the femoropatellar joints was performed. Sensitivity analyses were performed for knees from the early OA model to compare the prevalence of features between age (stratified as < 60, 60–70 and > 70 years) and body mass index (BMI – stratified as normal < 25 kg/m², overweight 25–30 kg/m² and obese >30 kg/m²) strata. Comparative statistics were applied using Fisher’s exact test, to detect potential differences between the two groups. A p-value of <0.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS 24 software (IBM Corporation, Armonk, NY).

3. Results

3.1. Demographics

Participants in the early OA model group were older and had a higher BMI than subjects in the healthy reference group. Additional demographic information is presented in detail in Table 1.

3.2. Frequencies of structural damage at Y1

At year 1, the early OA model group exhibited higher rates of structural pathology in their radiographically normal (K-L 0) knee than the healthy reference group (Table 2). This applied for all features apart from effusion-synovitis, which had a similar prevalence in both groups (19.2% vs 26.0%, p = 0.33). Femorotibial cartilage damage was seen in 77.3% vs. 50%, femorotibial BMLs in 27.3% vs. 12.8% and meniscal damage in 5.2% vs. 26.0%, p = 0.33). Femorotibial cartilage damage was seen in 77.3% vs. 50%, femorotibial BMLs in 27.3% vs. 12.8% and meniscal damage in 5.2% vs. 26.0%, p = 0.33). Femorotibial cartilage damage was seen in 77.3% vs. 50%, femorotibial BMLs in 27.3% vs. 12.8% and meniscal damage in 5.2% vs. 26.0%, p = 0.33). Femorotibial cartilage damage was seen in 77.3% vs. 50%, femorotibial BMLs in 27.3% vs. 12.8% and meniscal damage in 5.2% vs. 26.0%, p = 0.33). Femorotibial cartilage damage was seen in 77.3% vs. 50%, femorotibial BMLs in 27.3% vs. 12.8% and meniscal damage in 5.2% vs. 26.0%, p = 0.33). Femorotibial cartilage damage was seen in 77.3% vs. 50%, femorotibial BMLs in 27.3% vs. 12.8% and meniscal damage in

Table 1

Demographics. Early OA model vs. healthy reference group.

| Age (Years, SD) | Early OA Model group | Healthy reference group |
|----------------|----------------------|------------------------|
| 65.1 ± 8.6     | 53.3 ± 7.2           |
| BMI (kg/m² ± SD) | 27.7 ± 4.3         | 24.4 ± 3.2           |
| Women (n (%))  | 90 (58.4%)           | 47 (60.3%)            |
| Radiographic OA’ |                      |                        |
| K-L 0          | 127 (82.5%)          | 71 (91%)              |
| K-L 1          | 12 (7.8%)            | 3 (3.9%)              |
| K-L 2          | 4 (2.6%)             | 2 (2.6%)              |
| K-L 3          | 5 (3.2%)             | 0 (0%)                |

a At year 4.
Increase of existing or incidence of new features. Studies by Sharma et al. and Kumm et al. (Appendix 2), which included literature we have included an overview of the main frequencies in the factors report markedly lower frequencies for the different features participants with K-L 0 in both knees but with risk factors. Those studies FT – femoro-tibial; FP – femoro-patellar, FT & FP – feature present in both compartments; P-values from Fisher Exact test. A P-value of <0.05 was considered statistically significant. 95% bias-corrected and accelerated bootstrap confidence intervals (CI) of percentages were calculated using bootstrapping with 1000 iterations; Worsening: Increase of existing or incidence of new features.

In order to allow better comparison with available data from the literature we have included an overview of the main frequencies in the studies by Sharma et al. and Kumm et al. (Appendix 2), which included participants with K-L 0 in both knees but with risk factors. Those studies report markedly lower frequencies for the different features – despite risk factors – compared to our early OA model.

### Tabular Data

#### Table 2

**Individual features - Healthy reference vs Early OA model.**

| Feature                        | Healthy reference (N = 78) | Early OA Model (N = 154) | P-Value |
|--------------------------------|----------------------------|--------------------------|---------|
|                                | N  | %     | 95% CI | N  | %     | 95% CI |         |
| Cartilage lesions:             |    |       |        |    |       |        |         |
| FT                             | 39 | 50.0  | 39.0   | 119 | 77.3  | 70.4   | 84.6   | <0.001a|
| FP                             | 48 | 61.5  | 50.8   | 131 | 85.1  | 78.9   | 90.8   | <0.001a|
| FT or FP                       | 61 | 78.2  | 69.0   | 151 | 98.1  | 95.2   | 100.0  | <0.001a|
| BML                            | 26 | 33.3  | 23.6   | 99  | 64.3  | 56.8   | 72.5   | <0.001a|
| FT                             | 10 | 12.8  | 6.3    | 42  | 27.3  | 19.7   | 34.8   | 0.018  |
| FP                             | 25 | 32.1  | 22.4   | 101 | 65.6  | 58.0   | 73.2   | <0.001a|
| FT or FP                       | 32 | 41.0  | 29.9   | 117 | 76.0  | 69.4   | 82.9   | <0.001a|
| Osteophytes                    |    |       |        |    |       |        |         |
| FT                             | 3  | 3.8   | 0.0    | 26  | 16.9  | 10.9   | 23.0   | 0.005a |
| FP                             | 6  | 7.7   | 2.5    | 36  | 23.4  | 15.9   | 31.5   | 0.015a |
| FT or FP                       | 12 | 15.4  | 9.9    | 15  | 9.7   | 5.5    | 14.0   | 0.01a  |
| FT and FP                      | 1  | 1.3   | 0.0    | 4   | 2.6   | 0.6    | 6.6    | 0.43   |
| Osteoarthritis                 |    |       |        |    |       |        |         |
| FT                             | 7  | 9.0   | 3.7    | 55  | 35.7  | 28.6   | 43.1   | <0.001a|
| FP                             | 5  | 6.4   | 1.4    | 16  | 10.4  | 6.1    | 15.1   | 0.47   |
| FT or FP                       | 10 | 12.8  | 6.3    | 26  | 16.9  | 11.5   | 23.3   | 0.45   |
| FT and FP                      | 13 | 16.7  | 9.0    | 44  | 28.6  | 21.0   | 37.4   | 0.05   |
| Meniscus                       |    |       |        |    |       |        |         |
| Morphology                     | 5  | 6.4   | 1.4    | 21  | 13.5  | 8.0    | 20.5   | 0.29   |
| Exudation                      | 12 | 15.4  | 8.2    | 35  | 22.1  | 15.9   | 28.7   | 0.30   |
| Synovitis                      |    |       |        |    |       |        |         |
| Hoffa                          | 4  | 5.1   | 1.2    | 14  | 9.1   | 5.0    | 13.4   | 0.44   |
| Effusion                       | 11 | 14.1  | 6.9    | 36  | 23.4  | 17.1   | 29.9   | 0.12   |
| Osteoarthritis                 |    |       |        |    |       |        |         |
| FT                             | 9  | 11.5  | 5.3    | 20  | 13.0  | 8.1    | 18.3   | 0.84   |
| FP                             | 7  | 7.7   | 2.5    | 32  | 17.9  | 9.9    | 26.4   | 0.085a |
| FT or FP                       | 14 | 17.9  | 9.9    | 25  | 16.2  | 10.7   | 22.8   | 0.32   |
| BML                            | 1  | 1.3   | 0.0    | 4   | 0.0   | 0.0    | 0.0    | 0.33   |
| FT                             | 10 | 12.8  | 6.3    | 24  | 15.6  | 10.7   | 21.7   | 0.70   |
| FP                             | 9  | 11.5  | 5.1    | 24  | 15.6  | 10.5   | 21.5   | 0.44   |
| FT or FP                       | 17 | 21.8  | 13.5   | 46  | 29.9  | 23.3   | 37.4   | 0.21   |
| Osteoarthritis                 |    |       |        |    |       |        |         |
| FT                             | 2  | 2.6   | 0.0    | 6   | 3.9   | 2.0    | 6.6    | 0.43   |
| FP                             | 6  | 7.7   | 2.5    | 16  | 10.4  | 6.1    | 15.1   | 0.47   |
| FT or FP                       | 11 | 14.1  | 6.9    | 36  | 23.4  | 17.1   | 29.9   | 0.12   |
| Meniscus                       |    |       |        |    |       |        |         |
| Morphology                     | 9  | 11.5  | 5.0    | 25  | 16.2  | 10.7   | 22.8   | 0.32   |
| Exudation                      | 2  | 2.6   | 0.0    | 4   | 1.3   | 0.0    | 3.4    | 0.60   |
| Synovitis                      | 2  | 2.6   | 0.0    | 6   | 3.9   | 2.0    | 6.6    | 1.00   |
| Effusion                       | 11 | 14.1  | 6.9    | 28  | 18.2  | 12.4   | 23.8   | 0.46   |

3.3. Progression of structural damage from Y1 to Y4

Femorotibial cartilage damage worsening was seen in 34.4% in the early OA model groups over 3 years, vs. 20.5% in the healthy reference group (p = 0.03). Other structural features also showed more frequent worsening in the early OA model, but only for osteophytes the difference attained statistical significance (Table 2). Knees in the healthy reference group showed greater increase in number of lesion types compared to the early OA model group (increase by one for 15.4% vs 8.4%, increase by two for 11.5% vs. 3.2%) (Table 3).

#### 3.4. Incidence of structural damage from Y1 to Y4

Development of new femorotibial or femoropatellar osteophytes were more commonly seen in the early OA model than in healthy reference knees (9.7% vs 1.3%, p = 0.01 and 9.7% vs 1.3%, p = 0.01) (Table 2).

#### 3.5. Impact of BMI and age

Concerning the different BMI strata in the early OA model, no differences were seen for presence of features at year 1 and only meniscal damage more frequently worsened in the obese group compared to the other two groups (31.9% vs. 23.5% vs. 7.7%, p = 0.02). Details of this sub-analysis are shown in Appendix 3. Significantly more incident cartilage damage was seen in the obese group compared to the overweight and normal subgroups (23.4% vs. 19.1% vs. 2.6%, p = 0.01). No differences were seen for presence of number of lesion types and change in number of lesion types over time (Appendix 4). Additional sensitivity
analyses, stratifying the early OA model into three different age groups (<60, 60–70, >70 years), did not reveal any statistically significant difference in the frequencies of features at year 1 or in incidence of features between year 1 and year 4 (Appendix 5).

Also no differences between age groups were seen in regard to multi-tissue involvement (i.e. number of lesions present at year 1), nor worsening over 3 years (Appendix 6). The only significant difference observed in the early OA model group was worsening of femoro-patellar bone marrow lesions from year 1 to year 4 with less worsening in the oldest age group (16.7% vs. 28.3% in the middle age group and 42.6% in the youngest age group) (Appendix 5).

4. Discussion

We found that knees without ROA (i.e. K-L 0) but with contralateral ROA more frequently presented with structural MRI pathology typical of early OA compared to a group of knees that had no signs of OA in either knee and no risk factors. The only MRI feature that appeared to not differ significantly between both groups was joint effusion-synovitis. Femoro-tibial cartilage more commonly worsened over 3 years in the early OA model group compared with healthy reference knees, which is an important finding in the context of DMOAD testing. Additionally, increased worsening of osteophytes on MRI supports the hypothesis that these knees are already in an on-going disease process compared to healthy reference knees. This is also reflected by the higher number of knees that developed early or definite ROA over the three-year observational period in the early OA model group (percentage of knees with K-L ≥ 1.3.6% vs. 6.4% in the healthy reference group). It may be argued that these findings are possibly due to the participants being older or due to higher BMI in the early OA model group, but our sensitivity analyses taking into account age and BMI do not support this explanation. Thus, one has to assume that indeed prevalent structural damage is influenced by contralateral radiographic disease severity. Whether this is mediated by clinical factors such as pain in the contralateral knee resulting in increased loading in the non-affected knee and subsequent structural lesion development remains speculative and was not the focus of our study.

The finding that MRI structural pathology as detected by MRI is frequent in radiographically normal knees has been shown by several studies [3,4,13]. The largest of these is the population-based Framingham study, in which MRI abnormalities were seen in as much as 95% of studies [3,4,13]. The striking finding of the current study is that radiographically normal knees (i.e. K-L 0) may differ largely in regard to prevalent MRI features, and knees with contralateral knee OA appear to exhibit these to a much greater extent. When compared to a group of knees with bilateral K-L 0 but with risk factors, - as we reported previously using a similar analytic approach - our early OA model still showed markedly more structural damage compared to those knees with common risk factors for disease incidence [4]. The overall frequencies in that study were 75.5% (vs. 98.1% in our early OA model) for any cartilage damage, 60.5% (vs. 76.0% in our sample) for BMLs, and 21.2% (vs. 35.7% in our sample) for meniscal damage.

We dichotomized MRI findings into presence and absence and deliberately ignored individual feature severity, which may be regarded as a limitation. This approach included also low-grade pathology but one has to assume that particularly such mild disease features may potentially be amenable to a DMOAD effect. We have previously shown that cartilage damage, BMLs and meniscal pathology were associated with prevalent frequent symptoms and also incident persistent symptoms.
suggested that such lesions are not incidental but rather represent early disease in persons at increased risk of knee OA [4]. Further, we have only differentiated the tibio-femoral from the patellofemoral joint and did not subdivide the knee joint further based on anatomical subregions or plates, which would not have been meaningful given the relatively low prevalence of features observed. This approach, however, may have limited our ability to localize where in the joint prevalent and incident joint damage is occurring.

A limitation of our study is that we did not take the development of clinical manifestations of early disease such as pain or limitations in function at year 4 into account. The aim of our study was prevalence of structural features of disease and progression over time. However, it would potentially be informative in subsequent work to assess whether structural pathology in K-L knees is predicting symptomatic OA over time. The small sample size is another short coming. However, we included all participants fulfilling our inclusion criteria and the OAI is the largest OA study with available MRI data with multiple time points. For these reasons matching for age, BMI and sex was not possible.

We have looked at three year progression over time, while commonly DMOAD trials will have shorter follow-up periods of usually 24 months, which needs to be considered when interpolating our rates of progression to other cohorts.

Commonly, changes of MRI features over time are in the focus of interest when applying semi-quantitative assessment to a given dataset in a longitudinal fashion. There has been an on-going discussion of whether reading blinded to time points of image acquisition is preferable to reading in an un-blinded fashion. Reading un-blinded to time points may result in a slight tendency to read more change in comparison to a blinded reading. However, it has been shown that scoring without knowing the chronological sequence substantially decreases sensitivity in the detection of clinically relevant changes in comparison with scoring in chronological order [14,15]. These studies showed that blinding to time point may result in misclassification and that it may compromise the assessment of the relation of that feature and its outcome, which was also translated to OA assessment [16]. However, it has to be acknowledged that to date longitudinal OA studies comparing SQ MRI assessment blinded and non-blinded to chronological order is missing.

Recent work by Kumm et al., who analyzed a younger sample from the OAI with bilateral K-L 0 knees, also confirmed a high prevalence of features particularly in knees with risk factors [13]. The prevalence of structural features was higher in our early OA model group compared to the Kumm-sample of K-L 0 knees with risk factors. Reason for this is the fact that the risk factor profile in the Kumm-sample did not include contralateral knee OA but only participants with K-L grades 0 in both knees were included. The younger age of participants in the Kumm-cohort did not appear to play role in this context. The same research group further compared two samples of bilateral K-L 0 participants from the OAI (one with risk factors and one without) [17]. Authors found that the development of structural MRI-defined or radiographic OA was surprisingly similar irrespective of the presence of OA risk factors.

In a context of DMOAD study, one may argue that participants in our early OA model already have moderate to advanced disease in one knee, and it is highly unlikely that a DMOAD may be able to reverse such pathology. However, given that structural joint pathology in the contralateral “normal” knee is already present to a greater extent than in bilateral K-L 0 knees it seems desirable to prevent progression of these features in the “healthy” knee in order to maintain function and prevent clinically manifest OA.

In summary, we found that MRI-defined structural tissue pathology is far more prevalent in an early OA model of K-L 0 knees with contralateral ROA, compared with a healthy reference sample with K-L 0 in both knees and not risk factors. This applied to all features, apart from effusion-synovitis. Regarding longitudinal change, incident cartilage damage was more commonly seen in the early OA model group, supporting the assumption that patients with a radiographically normal knee but contralateral ROA represent a suitable model for testing DMOADs in clinical trials of early, non-radiographic OA.

Authors contributions

(1) All authors were involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data.
(2) All authors contributed to drafting the article or revising it critically for important intellectual content.
(3) All authors gave their final approval of the manuscript to be submitted.

Additional contributions:

Analysis and interpretation of the data: FWR; FE; SM; GD; AG; LS, WW.
Drafting of the article: FWR; FE; SM; GD; AG; LS; WW.
Provision of study materials or patients: FWR; FE; SM; WW.
Statistical expertise: WW; FWR, FE.
Obtaining of funding: FWR; FE; SM; GD; WW.
Collection and assembly of data: FWR; FE; SM; WW.
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 Sanofi-Aventis, Merck Serono, and TissuGene and is President and shareholder of Boston Imaging Core Lab (BICL), LLC a company providing image assessment services.
FE is CEO and co-owner of Chondrometrics GmbH. He provides consulting services to MerckSerono, Synarc and Servier, and has held educational lectures for Medtronic. He has received funding support (for studies not related to the current one) from Pfizer, Eli Lilly, Stryker, Novartis, MerckSerono, Glaxo Smith Kline, Wyeth, Centocor, Abbvie, Kolon, Synarc, Ampio, and Orthotrophix.
FWR is Chief Medical Officer and shareholder of BICL, LLC.
SM is co-owner and has a part time employment with Chondrometrics GmbH. WW is co-owner and has a part time employment with Chondrometrics GmbH.

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Appendix 1. Relative risks for presence of a specific structural lesion using the healthy reference group as the referent

|                         | Healthy (N = 78) | Early OA Model (N = 154) | P-Value | Relative Risk* (95% CI) |
|-------------------------|-----------------|--------------------------|---------|------------------------|
| Cartilage damage        |                 |                          |         |                        |
| FT                      | 39              | 119                      | 0.000   | 1.55 (1.22, 1.96)      |
| FP                      | 48              | 131                      | 0.000   | 1.38 (1.15, 1.67)      |
| PT or FP                | 61              | 151                      | 0.000   | 1.25 (1.11, 1.41)      |
| PT and FP               | 26              | 99                       | 0.000   | 1.93 (1.38, 2.70)      |
| BML                     |                 |                          |         |                        |
| FT                      | 10              | 42                       | 0.013   | 2.13 (1.13, 4.01)      |
| FP                      | 25              | 101                      | 0.000   | 2.05 (1.45, 2.88)      |
| FT or FP                | 52              | 117                      | 0.000   | 1.85 (1.46, 2.45)      |
| PT and FP               | 3               | 26                       | 0.005   | 4.39 (1.37, 4.05)      |
| Osteophytes             |                 |                          |         |                        |
| FT                      | 58              | 141                      | 0.001   | 1.23 (1.07, 1.41)      |
| FP                      | 36              | 117                      | 0.000   | 1.65 (1.27, 2.13)      |
| FT or FP                | 66              | 150                      | 0.001   | 1.15 (1.04, 1.27)      |
| FT and FP               | 32              | 117                      | 0.000   | 1.85 (1.40, 2.45)      |
| Meniscus                |                 |                          |         |                        |
| Morphology              | 7               | 55                       | 0.000   | 3.98 (1.90, 8.32)      |
| Extrusion               | 19              | 78                       | 0.000   | 2.08 (1.36, 3.17)      |
| Synovitis               |                 |                          |         |                        |
| Hoffa                   | 36              | 106                      | 0.001   | 1.49 (1.15, 1.94)      |
| Effusion                | 15              | 40                       | 0.327   | 1.35 (0.80, 2.29)      |

Appendix 2. Frequencies of selected features in the studies by Kumm * and Sharma **

| Overall                  | Kumm 1 | Sharma 2 |
|--------------------------|--------|----------|
| Cartilage damage (TF or FP or both) | 240 (82) | 641 (76) |
| Bone marrow lesions (TF or FP or both) | 176 (60) | 514 (61) |
| Meniscal damage (any) 5 | 55 (19) | 180 (21) |
| Meniscal extrusion (any) | 68 (23) | 117 (14) |
| Synovitis effusion (any) | 86 (29) | not mentioned |
| Hoffa synovitis (any)   | 130 (44) | not mentioned |

*unadjusted.

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**Appendix 3. Individual features - Early OA Model stratified by BMI groups**

| Frequencies at Year 1: | Normal (N = 39) | Overweight (N = 68) | Obese (N = 47) | P-Value |
|------------------------|-----------------|---------------------|----------------|---------|
| Cartilage:             |                 |                     |                |         |
| FT                     | 31              | 79.5                | 91.6           | 0.08    |
| FP                     | 32              | 82.1                | 93.5           | 0.77    |
| FT or FP               | 38              | 97.4                | 100.0          | 0.07    |
| BML                    |                 | 25                  | 64.1           | 0.23    |
| FT                     | 12              | 30.8                | 17.5           | 0.54    |
| FP                     | 24              | 61.5                | 76.5           | 0.82    |
| FT or FP               | 29              | 74.4                | 59.4           | 0.07    |
| Osteophytes:           |                 |                     |                |         |
| FT                     | 33              | 84.6                | 72.7           | 0.09    |
| FP                     | 30              | 76.9                | 61.5           | 0.28    |
| FT or FP               | 38              | 97.4                | 99.9           | 0.09    |
| BML                    |                 | 25                  | 64.1           | 0.41    |
| FT                     | 12              | 30.8                | 17.5           | 0.54    |
| FP                     | 24              | 61.5                | 76.5           | 0.82    |
| FT or FP               | 29              | 74.4                | 59.4           | 0.07    |
| Meniscus Morphology:   |                 |                     |                |         |
| FT                     | 14              | 35.9                | 21.1           | 0.98    |
| FP                     | 23              | 59.0                | 42.4           | 0.41    |
| FT or FP               | 28              | 71.8                | 55.8           | 0.09    |
| Synovitis Hoffa:       |                 |                     |                |         |
| FT                     | 28              | 71.8                | 55.8           | 0.09    |
| FP                     | 23              | 59.0                | 42.4           | 0.41    |
| FT or FP               | 32              | 78.1                | 61.5           | 0.28    |
| Meniscus Extrusion:    |                 |                     |                |         |
| FT                     | 14              | 35.9                | 21.1           | 0.98    |
| FP                     | 23              | 59.0                | 42.4           | 0.41    |
| FT or FP               | 28              | 71.8                | 55.8           | 0.09    |
| Meniscus Synovitis:    |                 |                     |                |         |
| FT                     | 3              | 7.7                 | 0.0            | 0.02    |
| FP                     | 2              | 5.1                 | 0.0            | 0.02    |
| FT or FP               | 5              | 12.8                | 0.0            | 0.02    |
| Meniscus Effusion:     |                 |                     |                |         |
| FT                     | 2              | 5.1                 | 0.0            | 0.02    |
| FP                     | 0              | 0.0                 | 0.0            | 0.02    |
| FT or FP               | 2              | 5.1                 | 0.0            | 0.02    |
| Incidence of new features between Year 1 & Year 4: | Normal (N = 39) | Overweight (N = 68) | Obese (N = 47) | P-Value |
| Cartilage:             |                 |                     |                |         |
| FT                     | 1               | 2.6                 | 8.6            | 0.01    |
| FP                     | 0               | 0.0                 | 0.0            | 0.00    |
| FT or FP               | 1               | 2.6                 | 8.6            | 0.01    |
| BML                    |                 | 3                   | 7.7            | 0.29    |
| FT                     | 3               | 7.7                 | 17.6           | 0.29    |
| FP                     | 5               | 12.8                | 24.3           | 0.01    |
| FT or FP               | 7               | 17.9                | 31.4           | 0.12    |
| Osteophytes:           |                 |                     |                |         |
| FT                     | 1               | 2.6                 | 9.1            | 0.73    |
| FP                     | 0               | 0.0                 | 0.0            | 0.73    |
| FT or FP               | 1               | 2.6                 | 9.1            | 0.73    |
| Meniscus Morphology:   |                 |                     |                |         |
| FT                     | 1               | 2.6                 | 8.9            | 0.11    |
| FP                     | 0               | 0.0                 | 0.0            | 0.26    |
| FT or FP               | 1               | 2.6                 | 8.9            | 0.11    |
| Synovitis Hoffa:       |                 |                     |                |         |
| FT                     | 2               | 5.1                 | 12.5           | 0.28    |
| FP                     | 0               | 0.0                 | 0.0            | 0.00    |
| FT or FP               | 2               | 5.1                 | 12.5           | 0.28    |

**FT** – femoro-tibial; **FP** – femoro-patellar; FT & FP – feature present in both compartments; FT and FP; P-values from Fisher Exact test; 95% bias-corrected and accelerated bootstrap confidence intervals (CI) of percentages were calculated using bootstrapping with 1000 iterations; Worsening: Increase of existing or incidence of new features.
Appendix 4. Number of lesion types and change in number of lesion types – Early OA Model stratified by BMI groups

### Normal (N = 39)

| Number of lesion types | N % | 95% CI | N % | 95% CI | N % | 95% CI |
|------------------------|-----|--------|-----|--------|-----|--------|
| 0                      | 0.0 | 0.0    | 0.0 | 0.0    | 0.0 | 0.0    |
| 1                      | 0.0 | 0.0    | 0.0 | 0.0    | 0.0 | 0.0    |
| 2                      | 0.0 | 0.0    | 0.0 | 0.0    | 2  | 8.8    |
| 3                      | 10  | 25.6   | 40.5| 13.3   | 7  | 10.3   |
| 4                      | 16  | 41.0   | 56.6| 26.2   | 31 | 45.6   |
| 5                      | 13  | 33.3   | 47.0| 18.9   | 24 | 35.3   |

| Change in number of lesion types | N % | 95% CI | N % | 95% CI | N % | 95% CI |
|----------------------------------|-----|--------|-----|--------|-----|--------|
| 1                               | 0.0 | 0.0    | 1  | 2.1    | 0  | 1.4    |
| 2                               | 0.0 | 0.0    | 6  | 8.8    | 2  | 4.3    |
| 3                               | 10  | 25.6   | 40.5| 13.3   | 12 | 25.5   |
| 4                               | 16  | 41.0   | 56.6| 26.2   | 13 | 27.7   |
| 5                               | 13  | 33.3   | 47.0| 18.9   | 19 | 40.4   |

p = 0.07 for number of lesion types; p = 0.07 for change in number of lesion types.
P-values from Fisher Exact test; 95% bias-corrected and accelerated bootstrap confidence intervals (CI) of percentages were calculated using bootstrapping with 1000 iterations.

### Overweight (N = 68)

| Number of lesion types | N % | 95% CI | N % | 95% CI | N % | 95% CI |
|------------------------|-----|--------|-----|--------|-----|--------|
| 0                      | 0.0 | 0.0    | 0.0 | 0.0    | 0.0 | 0.0    |
| 1                      | 0.0 | 0.0    | 0.0 | 0.0    | 0.0 | 0.0    |
| 2                      | 1   | 1.4    | 1.4 | 1.4    | 0  | 0.0    |
| 3                      | 9   | 13.2   | 17.9| 8.3    | 31 | 46.5   |
| 4                      | 4   | 5.9    | 11.8| 1.4    | 4  | 8.5    |

| Change in number of lesion types | N % | 95% CI | N % | 95% CI | N % | 95% CI |
|----------------------------------|-----|--------|-----|--------|-----|--------|
| 1                               | 1   | 1.5    | 1   | 1.5    | 4  | 8.5    |
| 2                               | 2   | 5.1    | 12.5| 0.0    | 8  | 17.0   |
| 3                               | 0   | 0.0    | 0.0 | 0.0    | 0  | 0.0    |

Appendix 5. Individual features - Early OA Model stratified by Age groups

| Frequencies at Year 1: |
|------------------------|
| Cartilage lesions:     |
| FT                     | 34 | 72.3 | 57.6 | 87.3 |
| FP                     | 46 | 97.9 | 92.1 | 100.0|
| FT or FP               | 31 | 66.0 | 51.0 | 81.1 |
| BML                    | 14 | 29.8 | 17.0 | 42.7 |
| FP                     | 31 | 66.0 | 52.3 | 79.4 |
| FT and FP              | 35 | 74.5 | 61.2 | 87.0 |
| Osteophytes            |
| FT                     | 43 | 91.5 | 82.7 | 98.1 |
| FP                     | 43 | 91.5 | 83.0 | 98.3 |
| FT or FP               | 46 | 97.9 | 92.1 | 100.0|
| FT and FP              | 13 | 28.3 | 17.3 | 40.8 |

| Worsening from Year 1 to Year 4 |
|----------------------------------|
| Cartilage lesions:               |
| FT                     | 19 | 40.4 | 26.1 | 55.9 |
| FP                     | 10 | 21.3 | 10.6 | 32.7 |
| FT or FP               | 24 | 51.1 | 36.4 | 66.6 |
| FT and FP              | 7  | 14.9 | 4.5  | 25.6 |
| Osteophytes            |
| FT                     | 7  | 14.9 | 4.5  | 25.6 |
| FP                     | 1  | 2.1  | 0.0  | 6.8  |
| FT or FP               | 5  | 10.6 | 9.3  | 20.0 |
| FT and FP              | 7  | 14.9 | 4.5  | 25.6 |
| Meniscus Morphology    |
| FT                     | 7  | 14.9 | 4.5  | 25.6 |
| FP                     | 3  | 6.4  | 3.5  | 11.6 |
| FT or FP               | 13 | 23.4 | 12.2 | 36.1 |
| FT and FP              | 4  | 8.5  | 2.0  | 16.3 |

| Incidence of new features between Year 1 & Year 4 |
|----------------------------------|
| Cartilage lesions:               |
| FT                     | 7  | 14.9 | 4.5  | 25.6 |
| FP                     | 1  | 2.1  | 0.0  | 6.8  |
| FT or FP               | 10 | 5.6  | 2.3  | 10.0 |
| FT and FP              | 7  | 14.9 | 4.5  | 25.6 |
| Osteophytes            |
| FT                     | 7  | 14.9 | 4.5  | 25.6 |

(continued on next page)
Appendix 6. Number of lesion types and change in number of lesion types – Early OA Model stratified by Age groups

| Number of lesion types | <60 years (N = 47) | 60-70 years (N = 53) | ≥70 years (N = 54) |
|------------------------|--------------------|----------------------|-------------------|
|                        | N      | %      | 95% CI  | N      | %      | 95% CI  | N      | %      | 95% CI  |
| Synovitis              | 0      | 0.0    | 0.0  | 0.0  | 0      | 0.0    | 0.0  | 0     | 0.0    | 0.0  |
|                        | 1      | 0.0    | 0.0  | 0.0  | 0      | 0.0    | 0.0  | 0     | 0.0    | 0.0  |
|                        | 2      | 4.3    | 0.0  | 10.9 | 4      | 7.5    | 1.7  | 15.1  | 2      | 3.7    | 0.0  |
|                        | 3      | 9.1    | 8.8  | 29.9 | 10     | 18.9   | 8.7  | 29.8  | 10     | 18.5   | 8.7  |
|                        | 4      | 21.4   | 31.2 | 56.9 | 24     | 45.3   | 31.2 | 58.5  | 25     | 27.8   | 16.7 |
|                        | 5      | 15.1   | 19.7 | 45.3 | 15     | 28.3   | 16.9 | 40.0  | 26     | 48.1   | 33.4 |
| Change in number of lesion types | 0 | 10.6 | 2.3 | 20.5 | 2 | 3.8 | 0.0 | 9.6 | 1 | 1.9 | 0.0 | 6.3 |
|                        | 38     | 80.9   | 69.5 | 91.3 | 43     | 81.1   | 69.7 | 91.4  | 46     | 85.2   | 74.5 |
|                        | 2      | 4.3    | 0.0  | 11.1 | 7      | 13.2   | 5.3  | 22.8  | 4      | 7.4    | 1.7 |
|                        | 2      | 2.1    | 0.0  | 7.3  | 1      | 1.9    | 0.0  | 6.5   | 3      | 5.6    | 0.0 |
|                        | 3      | 2.1    | 0.0  | 7.3  | 0      | 0.0    | 0.0  | 0.0   | 0      | 0.0    | 0.0 |

p = 0.35 for number of lesion types; p = 0.28 for change in number of lesion types.

P-values from Fisher Exact test; 95% bias-corrected and accelerated bootstrap confidence intervals (CI) of percentages were calculated using bootstrapping with 1000 iterations.

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