Title

Clinical And Imaging Factors Associated With Incident Radiographic Osteoarthritis Over 8 Years In Individuals Age 65 And Over

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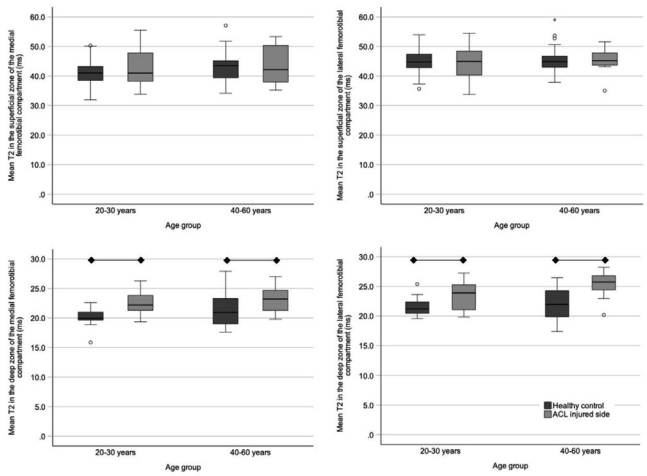

Fig. 1. Boxplot of mean T2 relaxation time in the superficial (top) and deep (bottom) zone of the medial (left) and lateral (right) femorotibial compartments for the injured knee in young and older patients 2 to 10 years after ACL injury and the left knee in healthy controls. Horizontal bars indicate significant differences (P<0.05)

Results: To date, 24 young healthy (12 female, 26.6±3.0years; 22.9±2.0kg/m^2), 24 older healthy (12 female, 49.0±6.1years; 24.7±4.3kg/m^2), 22 young ACL (14 female, 26.2±3.2years; 23.5±2.6kg/m^2), and 11 older ACL (7 female, 50.8±5.1years; 24.6±2.4kg/m^2) participated. Cartilage thickness in the medial and lateral femorotibial compartments did not differ between the injured and uninjured contralateral knee in patients after ACL injury, between the injured knee in patients after ACL injury and healthy persons, or between age groups. T2 time in the deep zone was greater in the injured than the uninjured knee for both age groups in the medial compartment (22.6±1.9 vs. 20.5±1.4 ms; 23.1±2.3 vs. 22.7±4.2 ms; P=0.013) and in the lateral compartment (23.2±2.2 vs. 21.1±1.6 ms; 25.3±2.3 vs. 22.8±3.3 ms; P<0.001) and greater in patients after ACL injury than healthy controls in the same age group in the medial and lateral compartment (P<0.001 for all) without an age effect (Fig. 1). T2 time in the superficial zone did not differ between the injured and the uninjured contralateral knee for both age groups for either compartment or between groups. None of the T2 time parameters differed between the uninjured knee in patients after ACL injury and healthy controls.

Conclusions: The lack of differences in cartilage thickness between knees of patients after ACL injury and between groups suggests that the macro structure of the articular cartilage was still intact in these participants. Differences in T2 times in the deep zone but not in the superficial zone indicates that early osteoarthritic changes are initiated here. Differences in T2 times between knees after ACL injury and knees of healthy controls in the same age group and the lack of an injury x age interaction suggests that ACL injury is equally detrimental in both age groups. The lack of an exacerbating effect of the combination of ACL injury and age and the longer remaining lifetime in younger patients emphasize the need for diagnostics of early OA and development of adequate treatment methods. Interestingly, the variability in T2 times appeared to be greater in patients after ACL injury and in the older control group suggesting that the individual status may be important but cannot be elucidated in a group analysis as presented here. It is possible that other factors such as tissue metabolism or regular physical activity level play a role in the person-specific articular cartilage health status.

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CLINICAL AND IMAGING FACTORS ASSOCIATED WITH INCIDENT RADIOGRAPHIC OSTEOARTHRITIS OVER 8 YEARS IN INDIVIDUALS AGE 65 AND OVER

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Purpose: While risk factors for osteoarthritis (OA) are well known, it is not well understood why certain individuals maintain high mobility and joint health throughout their life while others demonstrate cartilage breakdown and OA at middle-late ages. MR imaging allowed for a more comprehensive understanding of structural OA and recent studies revealed associations between T_2 relaxation times and incident cartilage lesions. To date, however, there is a limited number of studies investigating risk factors for OA in individuals age 65 and above. In this study, we therefore aim to compare demographic, clinical factors and MRI quantitative and semi-quantitative parameters of a cohort of participants from the Osteoarthritis Initiative cohort (OAI) above the age of 65 who develop radiographic OA with participants who maintain healthy knees over 8 years, to allow for a better understanding of predictive factors of OA in the elderly.

Methods: This study is based on data from the OAI, including clinical information and knee MRIs at baseline (BL) as well as radiographs at BL, 12-, 24-, 36-, 48- 72- and 96-month follow-up. Only right knees of participants at the age of 65 years or above at BL were included. Further selection criteria are illustrated in Figure 1. Participants without OA at BL (KL<2) were subdivided in an incidence cohort (n=115; participants with KL>1 at any follow-up visit) and a control cohort (n=391; participants with a 96-month follow-up visit with KL<2). Based on previous literature, and in order to decrease the probability of error due to multiple testing, the predictors in this study were subdivided into primary (Table 1) and secondary (Table 2) predictors including demographics (gender, age, BMI, and race), the clinical scoring systems "Western Ontario and McMaster Universities Osteoarthritis" (WOMAC), the "Knee injury and Osteoarthritis Outcome Score" (KOOS) with its respective subscales and the Physical Activity Scale for the Elderly (PASE) score as well as mean T_2 and cartilage thickness values in 5 regions of the knee (latera/medial femur, lateral/medial tibia, patella) and Whole-Organ Magnetic Resonance Imaging Score (WORMS) readings (Note, that WORMS readings were available in a subset of 78 participants of the incidence cohort and 130 controls without incident OA). Associations between these predictor-variables and incident OA (cases with incident radiographic OA vs controls without incident radiographic OA) were assessed using logistic regression models. Standardized odds ratios (=OR of an increase by one standard deviation) for incidence OA during a 96-month follow-up period were reported.

Results: WORMS readings were available in 208 participants. OR and p-values of primary predictors are reported in Table 1. Obesity (BMI $\geq$ 30 kg/m^2) significantly increased the odds of OA in this cohort of participants aged >= 65. The total WOMAC pain score as well as the average cartilage T2 values and the sum score for focal cartilage lesions also significantly increased the odds for OA, whereas the average cartilage thickness did not show any significant association with onset of OA.OR and p-values of secondary predictors are reported in Table 2. All subscales of WOMAC and the KOOS significantly increased the odds of OA whereas PASE scoring did not show a significant association with onset of OA. Higher T_2relaxation times in the lateral compartment and the medial femur were significantly associated with onset of OA. Interestingly, higher patellar cartilage thickness at BL significantly decreased the odds of developing OA, whereas the cartilage thickness in the further four regions of the knee did not show any significant results. Lesions of the lateral meniscus were significantly associated with the

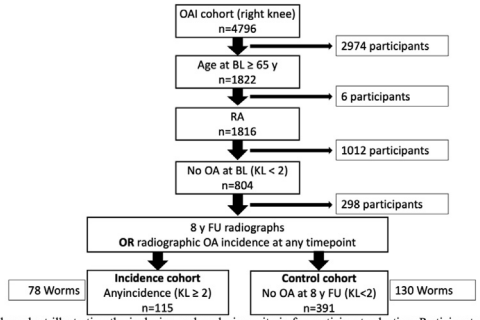

Figure 1: Flow chart illustrating the inclusion and exclusion criteria for participant selection. Participants needed either an 8 year follow up visit without radiographic OA or radiographic incidence of OA at any other TP (then 8 year follow up radiograph was not required as OA is assumed to be irreversible). BL=Baseline; FU=Follow up; KL=Kellgren Lawrence; n=Number; OAI=Osteoarthritis Initiative; WORMS=Whole-Organ Magnetic Resonance Imaging Score; y=years

Parameter	s OR	s 95%-CI	p
BMI ≥ 30	**2.31**	**1.26-4.25**	**0.007****
WOMAC Pain	**1.44**	**1.18-1.76**	**<0.001****
Average T2	**1.39**	**1.12-1.72**	**0.003****
Average thickness	0.91	0.73-1.14	0.429
Cart. all sum	**1.62**	**1.22-2.17**	**0.001****

Osteoarthritis and Cartilage

Table 1: Standardized odds ratios of primary predictors on developing radiographic osteoarthritis.

Parameter	sOR†(1/sOR)	95%-CI	p
Gender	1.39	0.91-2.14	0.136
Age	0.94	0.76-1.16	0.581
WOMAC Total	**1.47**	**1.21-1.80**	**0.001****
WOMAC Stiffness	**1.36**	**1.11-1.67**	**0.003****
WOMAC ADL	**1.44**	**1.19-1.76**	**<0.001****
KOOS Pain†	**1.49**	**1.23-1.83**	**<0.001****
KOOS Symptoms†	**1.40**	**1.15-1.71**	**<0.001****
KOOS Function†	**1.46**	**1.16-1.86**	**0.002****
KOOS QoL†	**1.55**	**1.25-1.93**	**<0.001****
Both menisci sum	**1.54**	**1.17-2.07**	**0.003****
Lat. Menisc. sum	**1.64**	**1.23-2.23**	**0.001****
Med. Menisc. sum	1.15	0.87-1.52	0.324
Cart. lat. comp. sum	1.17	0.90-1.54	0.244
Cart. med. comp. sum	**1.40**	**1.07-1.86**	**0.016***

Osteoarthritis and Cartilage

Table 2/1:Standardized odds ratios of secondary predictors on developing radiographic osteoarthritis

Cart. pat-fem. sum	1.49	1.13-1.98	0.005**
Cysts sum	1.01	0.76-1.34	0.927
Effusion	0.91	0.66-1.23	0.55
T2 lat. Tibia	**1.31**	**1.06-1.62**	**0.014****
T2 lat. Femur	**1.43**	**1.16-1.78**	**0.001****
T2 med. Tibia	1.22	0.99-1.51	0.069
T2 med. Femur	**1.48**	**1.19-1.85**	**0.001***
T2 Patella	1.04	0.84-1.27	0.734
Thickness lat. Tibia	0.83	0.66-1.04	0.105
Thickness lat. Femur	1.01	0.81-1.26	0.914
Thickness med. Tibia	1.06	0.85-1.31	0.604
Thickness med. Femur	1.08	0.86-1.34	0.522
Thickness Patella	**0.80**	**0.65-0.99**	**0.044***

Osteoarthritis and Cartilage

Table 2/2:Standardized odds ratios of secondary predictors on developing radiographic osteoarthritis

onset of OA, whereas the medial meniscus did not show a significant association. For cartilage lesions on the other hand, the sum score of the medial and the patellofemoral compartment significantly increased the odds for OA, whereas the lateral compartment did not show any significant results. Additionally, presence of BMELs significantly increased the odds for OA.

Conclusions: Overall, this study provides a more comprehensive understanding of characteristics of knee joints in older individuals who develop radiographic OA over 8 years and gives an overview over specific predictors of OA in this patient population. Although, comparing to current literature, the primary predictive parameters seem to be similar in the elderly as compared to general cohorts, the results of our exploratory secondary predictors suggest, that some parameters may be different in the elderly, especially regarding thickness and T2-values of the patella cartilage. This region may be of particular interest for further investigations directly comparing risk factors for OA between different age groups.

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3-D RELATIONSHIPS BETWEEN JOINT SPACE NARROWING AND BONE STRUCTURE AT THE KNEE AS UNCOVERED BY WEIGHT BEARING COMPUTED TOMOGRAPHY

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Purpose: Weight bearing computed tomography (WBCT) has been increasingly used in the imaging of knee osteoarthritis in recent years because of its ability to assess the weight bearing joint space. However, relatively little is known regarding the extent to which this cone beam technology can provide useful information on peri-articular bone. The purpose of this study was to explore the relationships between quantitative WBCT-derived 3-D bone parameters at the distal femur with concurrent joint space narrowing phenotypes as a platform for developing new bone-based biomarkers in knee osteoarthritis.

Methods: WBCT imaging was obtained ancillary to the Multicenter Osteoarthritis Study at the 144-month visit. After semi-automatic segmentation, femoral cortical thickness (fCT) and trabecular attenuation (fTA) maps were created for each of 663 available distal femurs using cortical bone mapping. A template distal femur was registered to each individual distal femur, a 3-D statistical shape model created, followed by transfer of fCT and fTA parameter maps onto the template. A statistical parametric mapping (SPM) general linear model adjusted for age, sex, BMI, and the first 5 joint space shape modes (controlling for effects of systematic misregistration) was used to test the dependence of fCT and fTA in turn on the experimental variables of concurrent radiographic medial and lateral OARSI joint space narrowing (JSN) grade. One knee from each participant was selected for inclusion, taking the side with worse compartmental baseline JSN grade or averaging data from sides if equal.

Results: 16 knees were excluded due to limited field of view capture of the distal femur meaning that registration could not be achieved. The final study set included 386 individual knees: 219 were female, mean ± SD age was 63.6 ± 9.6 yrs, mass 82.3 ± 17.7 kg, height 169 ± 9 cm, and BMI 28.5 ± 5.0 kg/m^2. Regions of significant relationships as tested by SPM are shown according to baseline JSN phenotype: medial JSN and fCT (figure 1); medial JSN and fTA (figure 2); lateral JSN and fCT (figure 3); lateral JSN and fTA (figure 4).

SPM revealed significantly greater fCT by up to ~0.1mm and fTA by up to ~40 attenuation units (AU) for each increment in baseline JSN grade along the outer margin of the respective compartments (unmasked blue zones in each figure). Significantly greater fCT by up to ~0.1mm for each increment in medial JSN grade was also seen across the anterior aspect of the medial femoral condyle (unmasked blue zone with * in figure 1) suggesting a wider regional relationship away from the articular surfaces. A small patch of significantly lower fTA by ~25 AU for