Tibiofemoral knee osteoarthritis progresses symmetrically by knee compartment in the GOGO cohort

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ABSTRACT

Objective: To evaluate the degree of symmetry of knee osteoarthritis (OA) structural severity and progression of participants with a mean follow-up time of 3.8 years.

Design: Participants from the Genetics of Generalized Osteoarthritis (GOGO) study (n = 705) were selected on the basis of radiographic evidence of OA in at least 1 knee, availability of radiographs at baseline and follow-up, and no history of prior knee injury or surgery. Incidence and progression of osteoarthritis were determined by radiographic Kellgren-Lawrence (KL) grade; compartmental OA progression was determined by change in joint space width of lateral and medial tibiofemoral compartments. Total OA progression was the sum of change in KL grade of both knees.

Results: Compared with left knees, right knees had more severe KL grades at baseline (p = 0.0002) and follow-up (p = 0.0002), McNemar's $\chi^2 = 34.16$ and 26.08, respectively; however, both knees progressed similarly (p = 0.121, McNemar's $\chi^2 = 10.09$). Compartmental changes were symmetric across knees: medial r = 0.287, p = 0.0002; lateral r = 0.593, p = 0.0002. Change in joint space width in the medial compartment was negatively correlated with change in the lateral compartment of the same knee (left knees: r = -0.293, p = 0.021; right knees: r = -0.195, p = 0.0002).

Conclusions: Although right knees tended to have more severe OA at both baseline and follow-up, radiographic progression did not differ by knee and compartmental progression correlated across knees. Given this trend in generalized OA, the risk of progression for both knees should be considered, even if only one knee has radiographic OA at baseline.

1. Introduction

Osteoarthritis (OA) involves multiple joints, multimorbidity, and increased risk of mortality \cite{1,2}. One study of polyarticular OA found a higher prevalence of OA in right than left knees \cite{2}. Other studies indicate that unilateral structural knee OA is associated with contralateral knee OA over time, suggesting the need for complex evaluations of OA progression in both knees \cite{3,4}. Symmetric patterns of polyarticular OA and incident knee OA have been observed \cite{2,5,6}, with moderate impact from genetic factors (Heritability:39–45\% \cite{6–8}). The goal of this
analysis was to investigate patterns of symmetry of structural knee OA and progression in the Genetics of Generalized Osteoarthritis (GOGO) cohort [9]. We hypothesized that, in the absence of prior knee injury, the distributions of radiographic OA severity and progression would be greater for right knees than left knees. Notably, this cohort of large sample size—drawn from US and UK clinics—explores distributions of knee OA in the context of polyarticular OA, expanding our understanding of knee OA severity and progression in patients with additional joints affected by OA.

2. Methods

2.1. Study participants

As described previously [9], GOGO was a collaborative study involving seven academic sites in North America and England. Participants were recruited based on clinical hand OA (bony enlargement of >3 joints distributed bilaterally, including at least one distal interphalangeal joint, and no more than three swollen metacarpophalangeal joints), self-identified white race, and at least one sibling with hand OA willing to participate. Institutional Review Board approval was obtained from all participating sites. Of note, all participants were selected independent of knee OA status. Body mass index (BMI, kg/m²) was measured at baseline. Participants were excluded based on a history of prior knee surgery (including arthroscopic), or serious knee injury (requiring use of a cane, cast, or crutch for at least 2 weeks). To evaluate the pattern of progression after OA onset in at least one knee, we evaluated a subset of participants (n = 705; Fig. 1) with knee OA in at least one knee at baseline (Kellgren-Lawrence grade ≥1) and baseline and follow-up radiographs from both knees (mean follow-up = 3.8 years; range = 1.4–6.6 years; Fig. 1).

2.2. Radiographs

Standing anteroposterior knee radiographs were scored for Kellgren-Lawrence (KL) grade [10]. Fixed-flexion knee radiographs obtained of each knee with the SynaFlexer™ positioning frame [9] were analyzed for minimum joint space width (mJSW) of medial and lateral compartments (in mm using calipers) for radiographs meeting the technical quality criterion (medial compartment tibial plateau inter-marginal distance <1.5 mm). KL grade ≥1 was defined as structural knee OA. All radiographs were read by an expert musculoskeletal radiologist (JBR) with high intra-rater reliability (weighted kappa = 0.886) [11], and read paired and blinded to timepoint.

2.3. Data analysis

All analyses were performed using R (v4.0.0). McNemar-Bowker’s test, comparing distributions of outcomes, was performed to assess whether KL grades of left and right knees were evenly distributed; the result is significant if two tested variables have dissimilar distributions of outcomes. At baseline only, analysis was impeded by the lack of participants with extreme scores (right KL = 4 vs left KL = 0 and right KL = 0 vs left KL = 4). Therefore, to enable analysis, cells with count = 0 were recoded count = 5; resulting McNemar $\chi^2$ and $p$-values were unaffected (Table S1). McNemar-Bowker’s test was used to assess whether OA progression (change in KL grade, $\Delta$KL) was evenly distributed between knees. Negative $\Delta$KL scores (n = 41 knees) were set to 0; $\Delta$KL ≥3 were grouped as an extreme change category (3+) given the limited occurrence.

At baseline, mean JSW measures of left and right knee compartments were compared by $t$-test. Change in minimum joint space width ($\Delta$mJSW) was calculated for medial and lateral compartments of each knee and compared by Pearson correlation coefficient. Participants were excluded from analyses of compartmental $\Delta$mJSW if their radiographs did not meet quality control criteria resulting in a sample of n = 458 participants. $P$-values were adjusted using Benjamini-Hochberg correction. Spearman correlation was used to evaluate whether ordinal total progression in knee OA (sum $\Delta$KL for both knees) was associated with baseline BMI, age, and/or time to follow-up.
3. Results

3.1. Cohort characteristics

This sub-study sample ($n = 705$ participants, $n = 1410$ knees; Fig. 1) was 80.8% female, with baseline mean BMI 28.8 kg/m² (SD = 6.2), and age 65.2 years (SD = 8.5). At baseline, 526 participants (74.6%) had radiographic knee OA in both knees, 123 (17.4%) had right knee only OA, and 56 (7.9%) left knee only OA (Fig. 1). At follow-up, 597 (84.7%) participants had bilateral knee OA, 65 (9.2%) had right knee only OA, and 26 (3.7%) had left knee only OA. Notably, 179 participants had bilateral knee OA, 65 (9.2%) had right knee only OA, and 56 (7.9%) left knee only OA (Fig. 1). At follow-up, 597 (84.7%) participants had radiographic knee OA in both knees, 123 (17.4%) had right knee only OA, and no change in the other; 55 (7.8%) had ΔKL = 1 in both knees; only 64 (9.1%) had ΔKL≥2 in at least one knee.

3.2. Baseline and follow-up radiographic OA more severe in right knees

Baseline KL grades of right knees were more severe than left (McNemar’s $\chi^2 = 34.16$; degrees of freedom = 10; $p = 0.0002$) (Fig. 2A); this asymmetry was especially notable in participants with unilateral OA. For instance, the combination of right KL = 2 with left KL = 0 was 2.6-fold more prevalent than right KL = 0 with left KL = 2 (Fig. 2A). Follow-up KL grades of right knees were also more severe than left knees (McNemar’s $\chi^2 = 26.08$; degrees of freedom = 10; $p = 0.004$) (Fig. 2B); this asymmetry was also notable in participants with unilateral OA. For instance, the combination of right KL = 2 with left KL = 0 was 4.3-fold more prevalent than right KL = 0 with left KL = 2 (Fig. 2B).

3.3. Knee OA progression symmetric across knees

Most participants (60.1%) had no change in either knee (Fig. 2C); when change did occur, right knees were not more likely to progress than left (McNemar’s $\chi^2 = 10.09$; degrees of freedom = 6; $p = 0.121$). Participants had small change scores: 162 (23.0%) had $\Delta$KL = 1 in one knee and no change in the other; 55 (7.8%) had $\Delta$KL = 1 in both knees; only 64 (9.1%) had $\Delta$KL≥2 in at least one knee.

3.4. Progression at a compartmental level correlated in contralateral knees

Baseline mean mJSW values (mm) were: left lateral = 5.53 ± 1.5; right lateral = 5.58 ± 1.6; left medial = 3.72 ± 1.2; right medial = 3.79 ± 1.2. Mean baseline mJSW of left and right knee medial and lateral compartments were similar ($p = 0.39$ and 0.43, respectively). Mean ΔmJSW values were: left lateral = -0.08 ± 1.1; right lateral = -0.09 ± 1.1; left medial = -0.19 ± 0.7; right medial = -0.21 ± 0.8.

We used Pearson correlation to evaluate the symmetry of quantitative ΔmJSW across knees; of note, this methodology encompassed narrowing and widening of the compartment simultaneously so was not impacted by knee alignment status. Progression (ΔmJSW) of contralateral knees was weakly to moderately positively correlated by compartment (Medial: $r = 0.287$, $p = 0.0002$; Table S2); therefore, change in one compartment was congruent with change in the corresponding compartment of the contralateral knee (Fig. 2D and E). Change in mJSW was weakly negatively correlated between ipsilateral medial and lateral tibiofemoral compartments (Right: $r = -0.195$, CI = [-0.281, -0.105], $p = 0.0002$; Left: $r = -0.293$, CI = [-0.374, -0.207], $p = 0.0002$; Table S2); narrowing of the medial compartment joint space was reciprocated by widening of the ipsilateral lateral compartment joint space, and vice-versa (Fig. 2F and G). Change in the left medial compartment was only weakly correlated with change in the right lateral compartment, while change in the right medial compartment was not associated with change in the left lateral compartment (Left Medial vs Right Lateral: $r = -0.133$, CI =

![Fig. 2. Knee KL Grades and Changes in Minimal Joint Space Width of Medial and Lateral Tibiofemoral Knee Compartments. Jitter Plots of right and left knees: A) KL Grades at Baseline; B) KL Grades at Follow-up; C) Change in KL Grades. Scatterplots displaying changes in joint space width, with Pearson correlations and significant $p$-values for: D) Left Lateral and Right Lateral compartments; E) Left Medial and Right Medial compartments; F) Left Medial and Left Lateral compartments; G) Right Medial and Right Lateral compartments.](image-url)
In summary, we analyzed participants with knee OA drawn from a unique cohort with polyarticular OA, recruited on the basis of hand OA. Knee OA progression was symmetric based on overall change in knee KL grade and correlated by knee compartment. These results suggest that knee OA progression, in the context of polyarticular OA without injury, tends to occur symmetrically across knees. Clinicians and researchers should be aware of the bilateral “joint risk” when assessing the relationship between physical function and structural disease, and in prescribing physical and other therapies. Given the trend of progression across both knees, the contralateral knee may not be an appropriate comparator for an affected knee, even if it appears healthy at baseline.

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Credit author statement

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Declaration of competing interest

The authors declare that they have no conflicts of interest related to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocarto.2022.100288.

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