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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

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Credit author statement

Louie C Alexander Jr: Conception and design, analysis and interpretation of data, drafting the article, final approval of article for submission; Janet L Huebner, Joanne M. Jordan, Jordan B. Renner, Michael Doherty, Anthony G Wilson, Marc C Hochberg, Richard Loeser, Virginia Byers Kraus: Conception and design, acquisition of data, critical review of article, final approval of article for submission; Greg Cicconetti: Conception and design, analysis and interpretation of data, critical review of article, statistical expertise, final approval of article for submission.

Declaration of competing interest

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

Appendix A. Supplementary data

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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 = 0.0004), McNemar′s χ^2 = 34.16 and 26.08, respectively; however, both knees progressed similarly (p = 0.121, McNemar′s χ^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.

Keywords

Joint structure; Structure; Radiography; Osteoarthritis

1. Introduction

Osteoarthritis (OA) involves multiple joints, multimorbidity, and increased risk of mortality [1,2]. One study of polyarticular OA found a higher prevalence of OA in right than left knees [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 [3,4]. Symmetric patterns of polyarticular OA and incident knee OA have been observed [2,5,6], with moderate impact from genetic factors (Heritability:39–45%) [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/m^2) 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 X^2 and p-values were unaffected (Table S1). McNemar-Bowker's test was used to assess whether OA progression (change in KL grade, ΔKL) was evenly distributed between knees. Negative ΔKL scores (n = 41 knees) were set to 0; ΔKL≥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 (ΔmJSW) was calculated for medial and lateral compartments of each knee and compared by Pearson correlation coefficient. Participants were excluded from analyses of compartmental ΔmJSW 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 ΔKL 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/m^2 (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 unilateral OA at baseline, and 71 (40.0%) progressed to bilateral OA. Almost half of participants had equal KL grades in both knees at baseline and follow-up (47.4% and 50.1%, respectively; Fig. 2A and B). At follow-up, 17 (2.4%) participants had KL grades of 0/0, likely due to inherent difficulty distinguishing KL grades 0 and 1, as 15 of these had knee scores 0 and 1 at baseline. Time to follow-up was weakly associated with total knee OA progression (sum ΔKL; $r_s = 0.110$, $p = 0.003$, CI = [0.037, 0.183]). Neither baseline BMI nor age were significantly associated with total progression ($r_s = 0.043$, $p = 0.254$, CI = [−0.031, 0.117] and $r_s = 0.049$, $p = 0.192$, CI = [−0.025, 0.123], respectively).

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 ΔKL = 1 in one knee 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.

3.4. 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, CI = [0.200, 0.369], $p = 0.0002$; Lateral: r = 0.593, CI = [0.530, 0.649], $p = 0.0002$; 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: $r_s = -0.133$, CI = [−0.222, −0.042], p = 0.005; Right Medial vs Left Lateral: $r_s = -0.010$, CI = [−0.101, 0.082], p = 0.832).

4. Discussion

To our knowledge, this study is the first to observe correlations of radiographic knee OA progression by knee compartment providing new evidence that progression is similar across knees and that compartmental progression is symmetric and positively correlated contralaterally, but negatively correlated ipsilaterally. We also support findings that knee OA is more severe in right knees [2] and unilateral radiographic OA tends to progress to bilateral OA [3,4].

Notably, correlations between the ipsilateral compartments were weak (r between −0.2 and 0.3), likely due, at least in part, to the fact that 50% of knees did not progress and among progressors, the amount of progression varied. The negative correlation between medial and lateral compartments is likely due to pseudo-widening of the lateral compartment joint space—i.e. when the medial joint space narrows from cartilage degradation, the lateral compartment joint space widens in response. In contrast, lateral compartment change correlated moderately (r = 0.6) across knees, indicating that drivers of this change impact both knees with similar magnitude.

Knee OA progression was independent of BMI and baseline age, while time to follow-up was weakly correlated with progression, suggesting that more complex factors such as genetics, gait, knee alignment, and loading likely also impact progression [3,4]. Consistent with other reports [12,13], baseline age and BMI were not associated with radiographic progression. Furthermore, given that radiographic progression has been associated with high serum concentrations of hyaluronic acid and tumor necrosis factor α [13], knee OA progression is likely impacted by a confluence of morphological and biochemical factors.

A strength of this study is its large sample size and broad geographic origin—with participants from five medical centers in the USA and two in the UK. Follow-up times ranged from 1.4 to 6.6 (mean 3.8) years, allowing better assessment of progression than traditionally shorter follow-up times. Given that 65.1% of recruited participants were below BMI of 30 kg/m^2, this study furthers our knowledge of OA in non-obese participants. This cohort is notable in that it documented knee compartmental joint space width and change over time; furthermore, it provides a unique investigation of knee OA in a subset of participants from a hand OA cohort and furthers knowledge of polyarticular OA.

There were several study limitations. Given that most participants (81%) were female, we did not perform gender stratified analyses. The GOGO study was an all-white cohort for purposes of simplifying genetic analyses; therefore, findings may not be generalizable to other groups. Although participants had a broad range of time to follow-up, only 1 follow-up timepoint was obtained; frequent follow-up over a long period of time would

have allowed further discrimination of progression patterns. Compartmental mJSW could not be determined for some radiographs thereby reducing the power of compartmental level analyses of ΔmJSW. Consistent with variability of knee positioning and semi-quantitative scoring of the serial radiographs, some radiographs had negative ΔKL scores. Although not common in clinical practice, such a limitation could potentially be overcome by 3D imaging methods, such as magnetic resonance imaging (MRI), that might allow for more precise follow-up of OA changes, especially direct measurement of cartilage loss in contrast to an indirect measure as provided by radiographic JSW [14]. This study did not include assessment of radiographic progression in the patellofemoral compartment. Furthermore, we lacked knowledge of dominant leg so could not adjust for this in the model. However, it is estimated that approximately 12–24% of the population is 'left-footed' [15]; a similar proportion (20.6%) was identified in this study with more severe left KL grade than right at baseline. This suggests that the greater prevalence of more severe OA of right knees may be related to the greater prevalence of right foot dominance that in turn may relate to asymmetrical loading of the lower extremities.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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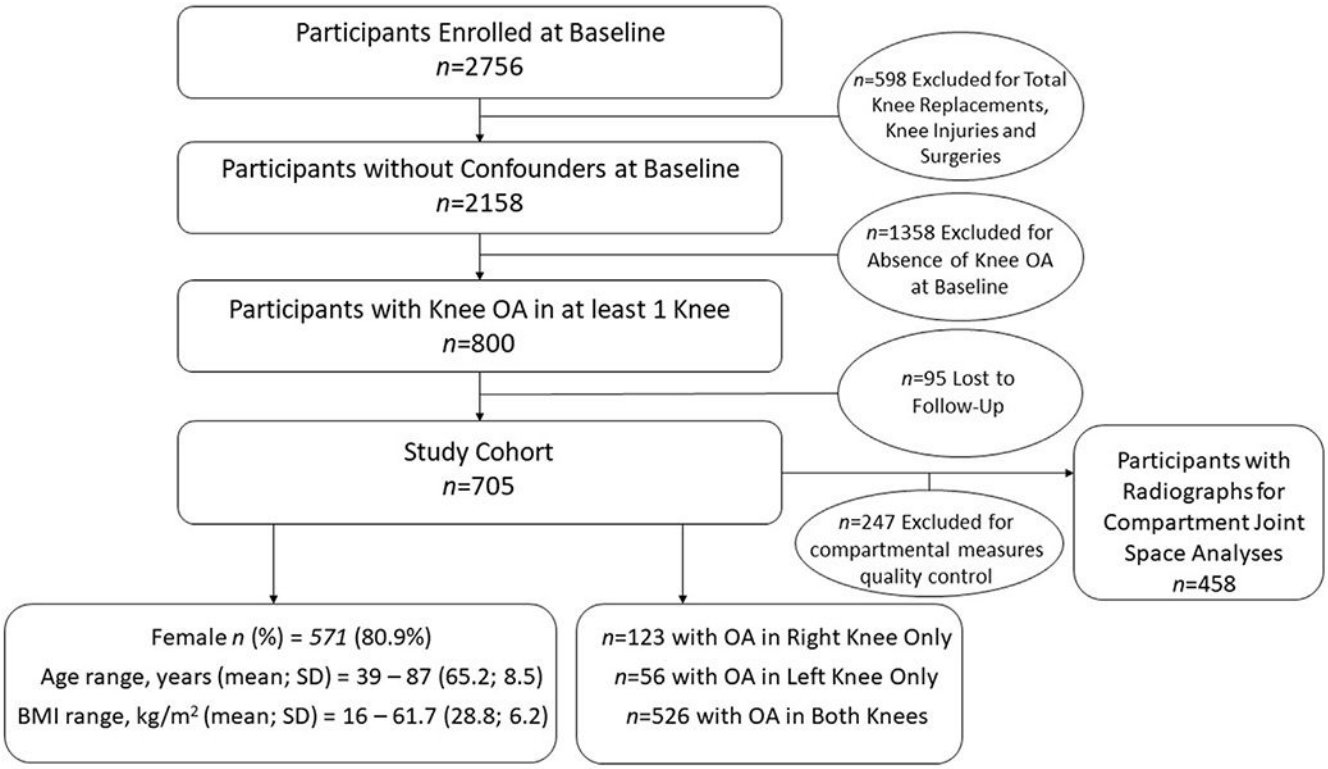

Fig. 1.

GOGO Consort Diagram. Exclusion criteria applied to Genetics of Generalized Osteoarthritis cohort prior to analyses. BMI: body mass index; OA: osteoarthritis. Total participants by site: Duke University (n = 145), University of North Carolina at Chapel Hill (n = 128), Case Western Reserve University (n = 71), Rush Medical College (n = 7), University of Maryland at Baltimore (n = 0), University of Nottingham (n = 170), and University of Sheffield (n = 184).

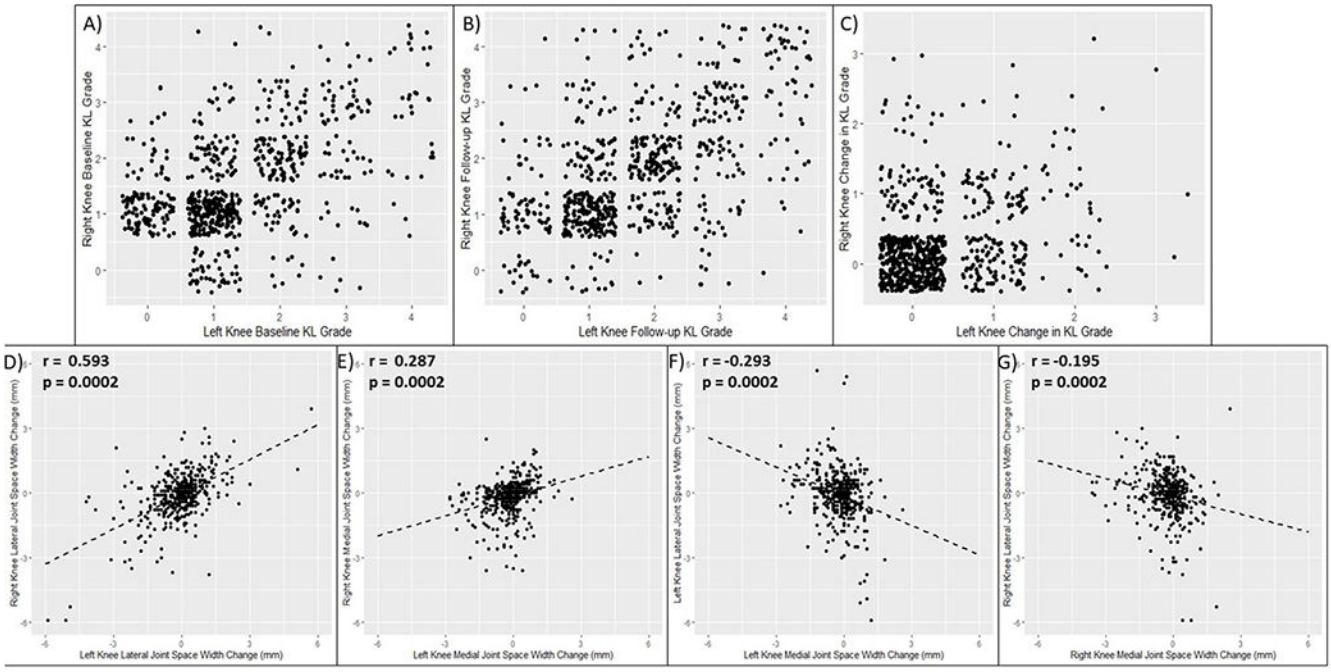

Fig. 2.

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.