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Baseline and longitudinal change in isometric muscle strength prior to radiographic progression in osteoarthritic and pre-osteoarthritic knees – data from the Osteoarthritis Initiative

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SUMMARY

Objective: To test whether cross-sectional or longitudinal measures of thigh muscle isometric strength differ between knees with and without subsequent radiographic progression of knee osteoarthritis (KOA), with particular focus on pre-osteoarthritic female knees (knees with risk factors but without definite radiographic KOA).
Methods: Of 4,796 Osteoarthritis Initiative participants, 2,835 knees with Kellgren Lawrence grade (KLG) 0-3 had central X-ray readings, annual quantitative joint space width (JSW) and isometric muscle strength measurements (Good strength chair). Separate slope analysis of covariance (ANCOVA) models were used to determine differences in strength between "progressor" and "non-progressor" knees, after adjusting for age, body mass index, and pain.
Results: 466 participant knees exceeded the smallest detectable JSW change during each of two observation intervals (year 2→4 and year 1→3) and were classified as progressors (213 women, 253 men; 128 KLG0/1, 330 KLG2/3); 946 participant knees did not exceed this threshold in either interval and were classified as non-progressors (588 women, 358 from men; 288KLG0/1, 658KLG2/3). Female progressor knees, including those with KLG0/1, tended to have lower extensor and flexor strength at year 2 and at baseline than those without progression, but the difference was not significant after adjusting for confounders. No significant difference was observed in longitudinal change of muscle strength (baseline→year 2) prior to radiographic progression. No significant differences were found for muscle strength in men, and none for change in strength concomitant with progression.
Conclusion: This study provides no strong evidence that (changes in) isometric muscle strength precedes or is associated with structural (radiographic) progression of KOA.

Introduction

Knee osteoarthritis (KOA) causes severe functional limitations and reductions in the quality of life[1] and has substantial impact on medical care expenditures[2]. Biomechanical factors and excessive joint loading are known to play an important role in the onset and progression of KOA[3–5]. Loss of thigh muscle strength, particularly the quadriceps, may adversely affect knee joint loading and biomechanics[6–13] and is an important contributor to knee pain and functional disability[14,15]. Therefore, muscle (particularly quadriceps) strengthening has been recommended for the clinical management and treatment and potential prevention of KOA[16–18]. However, it is controversial whether muscle strengthening exercise has the potential to modify structural progression in KOA[13,18,19]. It has been suggested that adequate quadriceps muscle strength may protect against incident symptomatic KOA, but not against incident radiographic KOA[13,20]. Further, conflicting evidence exists, as to whether quadriceps strength is less in KOA patients with (radiographic) progression compared with those without progression[21–25]. Thorstensson *et al.*[23] observed a relationship between reduced quadriceps strength and the onset of radiographic KOA in pre-osteoarthritic knees (knees with risk factors for, but without

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established KOA at baseline), but not with worsening of the KL grade in those with established (definite radiographic) KOA at baseline. Other studies in cohorts with KOA risk factors (but predominantly without definite radiographic KOA) also reported a relationship between muscle weakness and structural KOA progression, i.e., with femoral cartilage loss[26] and worsening of the femoro-tibial joint space narrowing (JSN) grade[25]. The latter finding was specific to women and was not evident in men[25]. Hence, it has been proposed that muscle strength may be a modifiable risk factor of KOA progression in women, but not in men, and that this may apply primarily to pre-osteoarthritic knees [Kellgren Lawrence grade (KLG) 0-1], but not to those with definite radiographic KOA (KLG $\geq$ 2).

In the current study, we used data from the Osteoarthritis Initiative (OAI) cohort, in which isometric measurement of thigh muscle strength and quantitative measurement of knee joint space width (JSW) were obtained from fixed flexion radiographs[27], to test the following primary hypotheses:

- Thigh isometric muscle strength is less in women (but not in men) with subsequent radiographic progression of KOA than in those without radiographic progression.
- Differences in thigh isometric muscle strength between progressor vs non-progressor knees are greater in female pre-osteoarthritic knees compared to female knees with definite radiographic KOA.

Secondary hypotheses were:

- Longitudinal reduction in thigh isometric muscle strength during an interval preceding radiographic progression of KOA is greater in women (but not in men) with radiographic progression than in those without.
- Differences in longitudinal reduction in thigh isometric muscle strength between progressor vs non-progressor knees are greater in female pre-osteoarthritic knees compared to those with definite radiographic KOA.

On an exploratory basis, we also studied

- whether cross-sectional differences or longitudinal reductions in thigh isometric muscle strength are stronger in pre-osteoarthritic knees of men compared to those with definite radiographic KOA,
- whether (cross-sectional) differences between progressor and non-progressor knees can be identified 2 years early to the period of radiographic progression, and
- whether longitudinal changes in thigh isometric muscle strength occur concomitant to the interval of progression.

To our knowledge, this is the first study to analyze longitudinal changes of isometric muscle strength during an interval before that of radiographic (structural) progression. This aspect is important, because in the longitudinal analysis every participant serves as his/her own control, and because a potential relationship between longitudinal change and subsequent structural progression would be more suggestive of potential benefits in modifying strength to reduce subsequent progression.

Methods

The OAI

Clinical and imaging data were obtained from the OAI, an ongoing multi-center longitudinal cohort study (http://www.oai.ucsf.edu/), designed to identify biomarkers of the onset and/or progression of KOA[28]. The 4,796 OAI participants were 45–79 years old (Table I), with or at risk of symptomatic KOA in at least one knee[28]. Both knees were studied using fixed flexion radiography at baseline, one (Y1), two (Y2), three (Y3), and 4 year (Y4) follow-up; measures of muscle strength were obtained at baseline, Y2, and Y4 in a majority of participants.

Study design and sample selection

For this prospective, longitudinal case–control study, knees were selected as following (Fig. 1):

- From the 4,796 OAI participants, we excluded 122 healthy reference subjects without risk factors of KOA[28,29]
- Of these 4,674 subjects, 1,396 were from the progression subcohort and had both frequent symptoms (most days of the month within at least one of the past 12 months) and radiographic KOA (cKLG $\geq$ 2 in the site readings) in at least one knee[28]. The remaining subjects were from the incidence subcohort and had either frequent symptoms or radiographic KOA (but not both), or neither frequent symptoms nor radiographic KOA, but risk factors of incident KOA[28].
- Of the 9,348 knees of these 4,674 participants, 8,681 had central radiographic readings (from expert readers at Boston University) at baseline for radiographic classification[28]. Please note that only knees with at least one follow-up visit and only knees with acceptable positioning, centering, tibial alignment, and radiographic exposure received central X-ray readings.
- Of these 8,681 knees, we excluded 294 with end stage radiographic KOA (KLG4) at baseline, because of a lack of a dynamic window for radiographic progression in subsequent time intervals.
- Of the remaining 8,387 knees (KLG0-3), 6,420 (77%) had measurements of isometric extensor and flexor strength at baseline (BL) and at Y2 (Fig. 1). Please note that some measurements were lacking due to equipment issues and that subjects who recently had knee replacement surgery or were not (physically) able to complete the measurement also were not included. Further, in 367 subjects, strength measurements were taken at year 1 and 3 instead of baseline and year 2, because no valid measurement was obtained at baseline (or because the participants missed the baseline strength test), and the measurement therefore had to be repeated at the next visit.
- Of the 6,420 KLG 0-3 knees with central radiographic readings and isometric strength measurement (at baseline and year 2 follow-up), 3,585 (56%) did not have complete data on JSW at Y1, Y2, Y3, and Y4 to determine/confirm radiographic progression (Fig. 1 and see below). Of these 3,585 knees, 2,720 did not get any measurement (due to limited funding), and 865 were drop outs (i.e., had some, but not all measurements). Of

Table I
Demographic data determined at year 2 follow-up, in knees with and without radiographic progression (i.e., change in medial radiographic JSW)

	Progressors		Non-progressors		Difference		*P*-value
	Mean	SD	Mean	SD	Mean	[95% CI]	
Women	***n* = 213**		***n* = 588**				
Age	62.7	8.3	62.4	9.0	0.31	[−1.07, 1.69]	0.65
BMI	30	5.4	29.1	5.0	0.96	[0.16, 1.77]	0.025*
WOMACp	3.3	3.9	2.3	2.9	1.04	[0.54, 1.54]	0.0004*
Men	***n* = 253**		***n* = 358**				
Age	61.5	9.4	61.2	9.0	0.24	[−1.24, 1.72]	0.75
BMI	29.5	4.0	28.9	3.9	0.61	[−0.03, 1.25]	0.06
WOMACp	2.2	2.8	1.7	2.2	0.43	[0.03, 0.82]	0.036*

SD = standard deviation, Diff = observed difference, CI = confidence interval (of the difference), WOMACp = 0–20; *$P < 0.05$.