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The Associations Between Finger Length Pattern, Osteoarthritis, and Knee Injury – Data from the Framingham Community Cohort

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Abstract

Objective—To investigate the associations between index-to-ring finger ratio (2D:4D) and radiographic knee/hand osteoarthritis (OA), previous knee injury, and meniscal lesions in the general population.

Methods—We measured the length of the right 2nd and 4th phalangeal and metacarpal bones on hand radiographs from 1020 subjects (aged 51–92 years) who were randomly recruited from Framingham, Massachusetts. Subjects also had knee radiographs and knee MRI. We divided women and men into tertiles according to their phalangeal and metacarpal 2D:4D. We assessed the odds ratios (OR) and 95% confidence intervals (CI) for radiographic knee OA, severe symptomatic knee OA, radiographic hand OA, previous knee injury, and MRI-defined meniscal lesion using logistic regression adjusted for age and body mass index. Because hand OA may affect the phalangeal 2D:4D, we performed sensitivity analyses in subjects without joint space narrowing in the 2nd and 4th interphalangeal joints.

Results—We found no significant associations between 2D:4D and radiographic knee OA, severe symptomatic knee OA, or meniscal lesions. Low phalangeal 2D:4D was associated with hand OA in women (OR 1.80, 95% CI 1.11–2.93), but in the sensitivity analysis the association was attenuated (OR 1.35, 95% CI 0.79–2.32). Low phalangeal 2D:4D was associated with knee injury in men (OR 1.78, 95% CI 1.02–3.10). We found no significant associations for metacarpal 2D:4D.

Conclusion—Low phalangeal 2D:4D in men is associated with knee injury, but we did not find any significant association with knee OA. Low 2D:4D may be the consequence rather than the cause of hand OA in women.

Keywords

osteoarthritis; epidemiology; hand; knee; finger length

Osteoarthritis (OA) is one of our most frequent musculoskeletal diseases, but we still have limited knowledge about the pathogenesis. Epidemiological studies have identified risk factors, such as female sex, obesity, genetic factors, previous joint injury/surgery, and possibly estrogen deficiency (1).

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The index-to-ring finger ratio (2D:4D) may serve as a marker for prenatal testosterone levels (2). Men typically have shorter index finger (2D) compared with the ring finger (4D), while the fingers have more equal length in women (3). Two recent case-control studies have reported that low 2D:4D is associated with radiographic knee OA (4–5). Identification of a consistent association between 2D:4D and knee OA could possibly increase our understanding of the disease pathogenesis and possibly provide prevention opportunities. The observed association may be due to a direct effect of testosterone on cartilage through receptors on the surface of human chondrocytes (6), or an indirect effect mediated through other risk factors for knee OA. Previous studies have also suggested that low 2D:4D is associated with more aggressive and risk-taking behavior (7) and better athletic skills (8), which may contribute to development of OA due to higher risk of joint trauma.

Using a large community-based dataset, the aim of this study was first, to confirm whether low 2D:4D is associated with radiographic knee OA or not. Second, to examine the associations between 2D:4D and radiographic hand OA, self-reported knee injury, and meniscal lesions, of which the latter two outcomes may serve as indicators of possible risk taking behavior and represent strong risk factors for knee OA.

METHODS

Subjects

In total, 1039 members of the Framingham community cohort (aged 50–92 years) were examined in 2002–05 after application of exclusion criteria as described elsewhere (9). We excluded 19 subjects (n=11: missing hand radiographs, n=6: assessment of finger length not possible due to malalignment/fractures/amputations bilaterally, n=2: radiographic psoriatic arthritis), leaving 1020 participants (aged 51–92 years) for analyses.

The Boston University Medical Center Institutional Review Board approved the study, and we obtained written informed consent from all participants.

Radiographic assessment

The participants underwent bilateral posteroanterior hand radiographs (analogue films). One investigator (IKH) measured the lengths of the index and ring finger (right hand) and read the radiographs for presence of hand OA (both hands) unaware of the clinical data (including radiographic and magnetic resonance imaging (MRI) findings in the knee).

The length (mm) from the midpoint of the base of the proximal phalanx to the tip of the distal phalanx, and the length (mm) from the midpoint of the base of the metacarpal bone to the tip of the metacarpal bone were measured with use of a manual caliper (0.5 mm precision). If measurement of the right hand was not possible (e.g. large malalignment/ fractures/amputations; n=33), the left hand was measured. We calculated the phalangeal 2D: 4D as the length of the 2nd phalanx divided by the length of the 4th phalanx. We similarly calculated the metacarpal 2D:4D. Twenty hands were measured twice by the same reader, and intraclass correlation coefficient (ICC) for phalangeal and metacarpal 2D:4D was 0.91 and 0.71, respectively.

The bilateral 2nd–5th distal interphalangeal (DIP), 2st–5th proximal interphalangeal (PIP), 1st–5th metacarpophalangeal (MCP), thumb interphalangeal (IP), thumb base (carpometacarpal/scaphotrapezial joint) and wrist joints were graded for hand OA with use of a modified Kellgren-Lawrence (KL) scale as previously described (10) and joint space narrowing (JSN) according to the OARSI atlas (11).

Bilateral weight-bearing posteroanterior knee radiographs (fixed-flexion) were available in 1006 participants. Of those, 6 had data from only one knee due to missing radiographs or knee replacement. One musculoskeletal radiologist (PA) graded all radiographs for tibiofemoral OA according to the KL scale unaware of clinical data (including hand radiographs and knee MRI findings) (9).

MRI

Using 1.5T proton-density–weighted (sagittal/coronal) and T1-weighted (sagittal) MRI, one investigator (ME) read medial and lateral meniscal integrity of the right knee in 966 of the subjects with available hand radiographs as detailed previously (9). The reader was unaware of clinical data (including 2D:4D and radiographic findings). We classified the presence of a meniscal tear, maceration/destruction and/or resection in either the anterior horn, body, and/or posterior horn as a meniscal lesion.

Questionnaire

At the clinic visit, 997 participants completed a questionnaire regarding previous knee injury (inability to walk for at least 3 days or requiring the use of crutches/cane). Of those with knee radiographs, 985 had data regarding frequent knee pain (pain/aching/stiffness on most days) of the right and left knee.

Statistics

We categorized men and women separately into tertiles according to their phalangeal and metacarpal ratios, respectively. The relationship between the phalangeal and metacarpal 2D:4D was assessed by Pearson correlation (continuous variables) and Cohen's kappa (tertiles).

We assessed the odds ratios (OR) with 95% confidence intervals (CI) for radiographic knee OA (≥1 knee(s) with KL grade (KLG)≥2), severe symptomatic knee OA (≥1 knee with KLG≥3 and frequent pain in the affected knee), radiographic hand OA (≥1 hand joint with KLG≥2), self-reported knee injury, and right knee meniscal lesion in those with low phalangeal 2D:4D (tertile 1) and intermediate 2D:4D (tertile 2) compared to those with high 2D:4D (tertile 3) using logistic regression. We evaluated the metacarpal 2D:4D in the same manner. We also evaluated 2D:4D as a continuous variable. The analyses were performed unadjusted (crude) and adjusted for age and body mass index (BMI). In addition, due to concerns of hand OA possibly affecting the phalangeal 2D:4D, we evaluated phalangeal 2D:4D in participants without radiographic JSN in the DIP and/or PIP joints of the index and ring finger. We evaluated the trend from high to low 2D:4D tertiles using a general linear model, and considered a two-tailed $p<0.05$ to be statistically significant (PASW version 17).

RESULTS

Men had lower phalangeal and metacarpal 2D:4D compared with women ($p<0.001$ and $p=0.06$, respectively) (table 1). We found a significant, but rather weak correlation between phalangeal and metacarpal 2D:4D in both men (Pearson correlation coefficient (r)=0.14, $p=0.004$) and women ($r=0.16$; $p<0.001$). However, the agreement between phalangeal and metacarpal 2D:4D tertiles was poor in both men (kappa=0.03) and women (kappa=0.11).

Phalangeal 2D:4D

We found no significant association between phalangeal 2D:4D and radiographic knee OA. However, women with low phalangeal 2D:4D tended to have more severe symptomatic knee OA. We found a significant association between low phalangeal 2D:4D and radiographic hand OA in women and knee injury in men (table 2). The analyses using 2D:4D as a continuous predictor variable yielded essentially the same results (data not shown).

In the sensitivity analyses of women without JSN in the 2nd and 4th DIP and PIP joints (n=431, 73.8%), the association between low phalangeal 2D:4D and hand OA was attenuated (adjusted OR 1.35, 95% CI 0.79–2.32; p for trend=0.26). Low 2D:4D in women tended to become inversely associated with knee OA (adjusted OR 0.41, 95% CI 0.21–0.81; p for trend=0.01), while the tendency for an association with severe symptomatic knee OA disappeared (adjusted OR 1.05, 95% CI 0.40–2.74; p for trend=0.93). The lack of association with meniscal lesions and knee injury in women remained (data not shown).

In the corresponding sensitivity analyses of men (n=367, 84.2%), the association between low 2D:4D and knee OA and severe symptomatic knee OA remained statistically non-significant (adjusted OR 1.76, 95% CI 0.87–3.57; p for trend=0.11 and OR 1.42, 95% CI 0.48–4.20; p for trend=0.46, respectively). The remaining sensitivity analyses yielded similar estimates of association as the primary analyses, i.e. the association between low phalangeal 2D:4D and knee injury remained essentially the same (adjusted OR 1.84, 95% CI 1.00–3.37; p for trend=0.07).

Metacarpal 2D:4D

All analyses with metacarpal 2D:4D showed no statistically significant associations. However, we found a tendency for an association between low 2D:4D and knee injury in women, but an inverse association in men (table 3).

DISCUSSION

In this large population-based cohort, we did not confirm the previously reported association between phalangeal 2D:4D and knee OA. We did find that low phalangeal 2D:4D was associated with knee injury in men. However, we found no similar association for metacarpal 2D:4D. We also found an association between low 2D:4D and radiographic hand OA in women, but this may be due to cartilage loss in the DIP and/or PIP joints and collapse of the joint plate as part of OA in the hand.

Two recent case-control studies have suggested that low 2D:4D is associated with knee OA (4–5). Our study failed to replicate these finding, and the reason(s) may be a high proportion of post-traumatic OA or residual confounding by hand OA in the former studies. Further, Zhang et al selected cases with symptomatic knee/hip OA from the orthopedic surgery list and the rheumatology clinic, while the controls had undergone intravenous urography (5). Hence, the controls may not have been representative of the population that gave rise to the cases, which may have introduced bias.

Ferraro et al performed a nested case-control study with a random selection of knee OA cases and controls from a population-based cohort (4). Still, the observed association between low phalangeal 2D:4D and knee OA may be confounded by hand OA, which is often considered as a marker of generalized OA (12). We have previously shown that the index finger is more frequently affected by OA than the ring finger (10), which may contribute to lower phalangeal 2D:4D due to JSN, bone attrition, and/or malalignment/deformity. In this study, we indeed found a significant association between low phalangeal (not metacarpal) 2D:4D and hand OA in women. Further, the association was not significant in those women without JSN in 2nd and 4th DIP and PIP joints. These findings suggest that low phalangeal 2D:4D, at least partly, is the consequence rather than the cause of hand OA, hence need to be accounted for in analyses. In this study, we performed sensitivity analyses in subjects without JSN in the 2nd and 4th DIP and PIP joints, in order to limit the problem of low 2D:4D as a consequence of OA. However, in future studies of middle-aged and elderly persons, we recommend measurement of each of the phalanges separately, which would avoid the problem with OA affecting the finger lengths. Robertson et al

recommended using the metacarpal rather than the phalangeal 2D:4D, as this ratio is less affected by hand OA (13). Zhang et al reported a significant association between metacarpal 2D:4D and knee OA in their case-control study (5). However, this finding was not reproduced in neither the Ferraro case-control study nor our study of the Framingham cohort (4). In fact our results show that the correlation and the agreement (tertiles) between phalangeal and metacarpal 2D:4D was weak, suggesting that these ratios represent two separate entities.

We also classified the individuals according to the visual index (type 1, 2, and 3) (13) and found no association with knee OA or severe symptomatic knee OA (data not shown). We decided not to present these data due to the high risk of misclassification due to varying degree of ulnar deviation of the hand affecting the visual 2D:4D.

It has been hypothesized that those with low 2D:4D are at higher risk for knee OA due to better sporting abilities and/or aggressive behavior (7–8), and therefore more prone to knee injuries. In men, we found a significant association with self-reported knee injury, but not for meniscal lesions. However, the vast majority of meniscal lesions in middle-aged and elderly are predominantly of degenerative character, hence often not due to acute knee trauma (9). Still, we failed to detect any significant association between 2D:4D and radiographic knee OA, but this could be due to low proportion of post-traumatic knee OA in this community-based sample.

Some limitations are noteworthy. First, the finger lengths were only measured in the right hand. However, the right 2D:4D has been suggested to be a better indicator of prenatal androgenization than the left (3). Hand OA and finger length was measured by the same investigator, which may have introduced bias (i.e. overestimation of the association). Last, the cross-sectional study design does not allow any conclusions about causality.

In summary, this study of the Framingham community cohort, with middle-aged and elderly subjects randomly recruited from the general population, showed no significant association between 2D:4D and radiographic knee OA or meniscal lesions. We did find that low phalangeal 2D:4D was associated with self-reported knee injury in men and hand OA in women. However, low phalangeal 2D:4D may often be the consequence rather than the cause of hand OA, hence the association seems largely to be explained by reverse causation.

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Table 1

Demographic and clinical characteristics

	Men (n=436)	**Women (n=584)**
Age, mean (SD) years	64.0 (9.0)	63.2 (8.9)
Body mass index, mean (SD) kg/m^2	28.6 (4.6)	28.6 (6.4)
Caucasians, n (%)	404 (92.7)	544 (93.2)
Index-to-ring finger ratio (2D:4D), mean (SD) - Phalangeal 2D:4D - Metacarpal 2D:4D	0.910 (0.024) 1.168 (0.032)	0.926 (0.026) 1.173 (0.042)
Radiographic OA, n (%) - Hand - Knee - Severe symptomatic knee OA	288 (66.1) 88 (20.4) 35 (8.4)	378 (64.7) 136 (23.7) 50 (8.8)
Knee injury, n (%)	120 (28.4)	130 (22.6)
Meniscal lesion, n (%)	171 (41.2)	165 (29.9)

SD=standard deviation, OA=osteoarthritis

Table 2

The association between phalangeal 2D:4D and radiographic osteoarthritis (OA), self-reported knee injury, and MRI-defined meniscal lesions. High phalangeal 2D:4D is the reference category.

	Intermediate phalangeal 2D:4D		Low phalangeal 2D:4D		
	Crude OR	**Adj. OR* (95% CI)**	**Crude OR**	**Adj. OR* (95% CI)**	**P for trend***
Women					
Knee OA	0.82	0.79 (0.47–1.33)	1.01	0.74 (0.44–1.25)	0.27
Severe sympt. knee OA	0.71	0.72 (0.29–1.78)	2.05	1.80 (0.85–3.81)	0.07
Hand OA	1.32	1.39 (0.87–2.22)	2.12	**1.80 (1.11–2.93)**	**0.02**
Knee injury	0.94	0.97 (0.59–1.58)	1.18	1.19 (0.73–1.93)	0.47
Meniscal lesion	1.19	1.15 (0.71–1.85)	1.25	1.03 (0.64–1.66)	0.95
Men					
Knee OA	1.20	1.05 (0.56–1.97)	1.65	1.43 (0.78–2.61)	0.23
Severe sympt. knee OA	0.80	0.62 (0.24–1.62)	1.40	1.11 (0.48–2.60)	0.75
Hand OA	0.83	0.80 (0.48–1.33)	1.41	1.30 (0.76–2.21)	0.36
Knee injury	1.99	**1.91 (1.10–3.30)**	1.70	**1.78 (1.02–3.10)**	**0.05**
Meniscal lesion	0.78	0.75 (0.46–1.24)	1.10	1.01 (0.62–1.66)	0.96

OR=odds ratio; 95% CI=95% confidence interval;

*Adjusted for age and body mass index

Table 3

The association between metacarpal 2D:4D and radiographic osteoarthritis (OA), self-reported knee injury, and MRI-defined meniscal lesions. High metacarpal 2D:4D is the reference category.

	Intermediate metacarpal 2D:4D		Low metacarpal 2D:4D		
	Crude OR	Adj. OR* (95% CI)	Crude OR	Adj. OR* (95% CI)	P for trend*
Women					
Knee OA	0.96	1.01 (0.60–1.70)	0.95	0.91 (0.54-1.53)	0.72
Severe sympt. knee OA	1.15	1.17 (0.52–2.60)	1.47	1.37 (0.63-2.97)	0.43
Hand OA	1.31	1.37 (0.85–2.22)	1.24	1.26 (0.78-2.04)	0.34
Knee injury	1.41	1.49 (0.91–2.45)	1.42	1.48 (0.90-2.43)	0.13
Meniscal lesion	0.97	0.99 (0.62–1.60)	1.14	1.11 (0.69-1.79)	0.66
Men					
Knee OA	0.89	0.82 (0.44–1.50)	1.06	1.14 (0.63-2.05)	0.73
Severe sympt. knee OA	0.99	0.90 (0.38–2.14)	0.90	0.93 (0.38-2.28)	0.86
Hand OA	1.19	1.13 (0.67–1.89)	1.05	1.10 (0.66-1.83)	0.71
Knee injury	0.64	0.64 (0.38–1.08)	0.64	0.66 (0.39-1.12)	0.10
Meniscal lesion	0.93	0.88 (0.54–1.43)	0.97	0.94 (0.57-1.54)	0.77

OR=odds ratio; 95% CI=95% confidence interval;

*Adjusted for age and body mass index