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The association of radiographic foot osteoarthritis and radiographic osteoarthritis at other sites

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Summary

Objective: To quantify the association between radiographic foot osteoarthritis (OA) and radiographic OA at four joints: second distal interphalangeal (DIP), third proximal interphalangeal (PIP), first carpometacarpal (CMC), and the knee.

Methods: Data collected for the Clearwater Osteoarthritis Study (COS) were analyzed ($N = 3436$). The study outcome was first metatarso-phalangeal joint (first MTP) OA status. The predictor variables were second DIP, third PIP, first CMC, and knee OA. The Kellgren and Lawrence scale determined OA status. The strength of the association between foot OA and other sites was further explored by unilateral and bilateral categories.

Results: For both genders, we found a significant, positive relationship between grade 2+ foot OA and second DIP, third PIP, first CMC, and knee OA. This relationship maintained its significance after adjustment for age, body mass index, and occupational history. Adjusted odds ratios ranged from 3.2 for the second DIP joint ($P < 0.0001$) to 3.7 for the knee joint ($P < 0.0001$). Relative to unilateral joint disease, co-existing bilateral disease yielded a significantly elevated risk for foot OA for all joints examined. While other studies have not specifically examined co-occurrence with foot OA, our findings are consistent with results from related studies.

Conclusions: There is a dearth of studies exploring foot OA. Our findings support the theory of a systemic etiology involved in the development of OA. Future epidemiological studies that further distinguish the relationship between OA at differing sites will provide an enhanced ability to describe the respective influences of mechanical and systemic factors in the development of this disease.

Key words: Osteoarthritis, Co-occurrence, Foot, Metatarso-phalangeal, Epidemiology.

Introduction

Osteoarthritis (OA) is a disease that has been long established to share a strong association with advancing age. It is experiencing a burgeoning of interest as millions of baby-boomers enter into their senior years. Compared with diseases of similar prevalence, many questions remain about OA including its etiology, biological pathways, and genetic and familial factors[1]. The investigation of generalized OA has received attention in the molecular research arena with a focus on biochemical markers. While some markers have demonstrated ability to discriminate for site-specific OA, how certain markers affect the development of OA remains to be elucidated[2–7]. The association between OA at differing sites (e.g., foot–hand, foot–knee) may possibly be related to selected genetic factors. Epidemiological association studies will give rise to an improved understanding of the biological pathways that may influence the risk of developing this common joint disorder[8]. While the knee joint has received due attention, information about foot OA will broaden our understanding of the relationship between OA and another weight-bearing joint. Our study quantified the association between radiographic foot OA (first metatarso-phalangeal joint (MTP)) and radiographic OA at four other joints: second distal interphalangeal (DIP), third proximal interphalangeal (PIP), first carpometacarpal (CMC), and the knee. This epidemiological investigation tested the null hypothesis, ''Among individuals with foot OA, the likelihood that they would also present with either hand or knee OA was equal to the likelihood that they would *not* also present with either hand or knee OA.''

Methods

STUDY GROUP

Data from the Clearwater Osteoarthritis Study (COS) were analyzed for this study[9,10]. Initiated by The Arthritis Research Institute of America (ARIA), the COS is an ongoing, community-based, prospective cohort study designed to identify the major risk factors for the development and progression of OA. Currently, in its seventeenth year, the 25-year longitudinal study follows individuals 40 years of age and older, collecting demographic, historical, clinical,

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and radiological data. To date, more than 3500 participants have been enrolled and examined. ARIA is located in a population where a large percentage of residents are 65 years and older (22.5%)[11]. Participants received no financial compensation. Recruitment methods varied including invitational letters, television and radio announcements, newspaper articles publicizing the COS study, articles posted in community organizations' bulletins, as well as seminars held at community clubs and organizations. In efforts to include younger subjects who are more likely to be free of OA, concerted recruitment efforts are used to encourage participation by employees of the Pinellas County School System, the City of Clearwater, and Pinellas County, Inc.

CLINICAL ASSESSMENT

At initial contact with participants, a description of study procedures is given followed by a screening questionnaire that details inclusion and exclusion criteria. After eligibility is determined and the informed consent is obtained, participants are asked to complete a 139-item, self-administered, COS history questionnaire. At the initial and all subsequent ARIA appointments, a physical exam with an emphasis on clinical and functional joint evaluation is conducted, including radiographs. The following study subjects were excluded from enrollment: individuals with self-reported rheumatoid arthritis, connective tissue disease, gout, disabling neurologic disease, and those confined to a wheelchair. Study participants are re-evaluated biennially, updating both the history questionnaire and the clinical exam data.

A licensed X-ray technician using standard exposure techniques took the X-rays. The knees and feet (both weight-bearing) and hands were anterior–posterior views. A case was defined when radiographic structural evidence of disease was found. Each radiograph was graded 0–4 for OA by the ordinal criteria of Kellgren and Lawrence: 0, absent; 1, questionable osteophytes and no joint space narrowing; 2, definite osteophytes with possible joint space narrowing; 3, definite joint space narrowing with moderate multiple osteophytes and some sclerosis; 4, severe joint space narrowing with cysts, osteophytes and sclerosis present[12]. A board-certified radiologist interpreted the radiographs[9,10]. Subjects whose radiographs were interpreted as grade 0 or 1 were considered disease-free for OA. Subjects whose radiographs were interpreted as grade 2, 3, or 4 were classified as cases. Severe radiographic OA cases were defined as grade 3 or 4. The three hand joints assessed were the right and left second DIP, third PIP, and first CMC. Although the COS study currently interprets all 10 signal hand joints (bilateral second and third DIP and PIP joints and CMC1, only six hand joints have been interpreted for the majority of the study's duration. Thus, our current reporting on hand OA is limited to these six joints. For the purpose of these analyses, we adopted the term "Hand2" by Hirsch, *et al.*, defined as OA in ≥ 2 hand joint groups (e.g., DIP and PIP)[13]. Diagnosis of foot OA was based on radiological evidence of disease in the first MTP joint.

Gender, age, body mass index (BMI), and occupational exposure were considered as potential confounders. BMI was calculated as baseline weight divided by height squared. Each of the 22 response choices for occupation was classified as either high or low risk. The categorization scheme utilized findings from published studies that assessed OA and its association with occupation[14–17].

STATISTICAL ANALYSES

Data analyses included a descriptive summary of the study sample, as well as frequency percentages of the association between foot OA and OA at other sites. Logistic regression analyses were employed to test the hypotheses of the relationship between foot OA with OA at other joint sites[18]. The exponentiated beta coefficient produced odds ratios (OR) for the associations under investigation. Radiographic evidence of foot OA was the dependent variable. The dichotomous predictor variables for each of the analyses were the OA joints (e.g., CMC1 yes/no). The reference group for each of the analyses was the absence of OA at the respective sites. The adjusted analyses kept age and BMI as continuous variables. The strength of the association between foot OA and OA at other sites was further broken down into unilateral and bilateral disease categories. Statistical Analyses Software, Version 8.02 was used (PROC LOGISTIC) for the analyses of these data[19]. Our data did not show evidence of effect modification by gender in the association between foot OA and OA at other joints. However, as subsequent studies explore foot OA and its association with risk factors, researchers must make a determination regarding which factors to assess for potential bias. OA at other sites, especially the hand, has demonstrated important gender-specific differences. Since this paper is among the first to report foot OA data, we have reported both the collapsed estimates, as well as the gender-specific findings. As the first MTP is a weight-bearing joint, we also looked at the possible interaction of BMI. The resulting associated *P*-values spanning from 0.12–0.95.

Results

Among the 3542 COS study participants, 3447 (97.4%) had a complete set of baseline radiographs. Of these 3447 individuals, 11 were missing data such as age or BMI, resulting in a final study sample size of 3436 participants. Over 69% of our study samples were females and 98% were Caucasians. The study participants varied in age between 40 and 94 years, with a mean of 62 years (SD 11 years). The mean BMI was 27, spanning from 14 to 66. Stratified by gender, Table I displays site-specific percentages of grade 2+ foot OA. Among all joints evaluated, the knee joint demonstrated the lowest prevalence (17%), while the second DIP joint showed the highest prevalence (36%). While fairly modest differences between the genders were noted, the first MTP joint revealed the largest disparity between women and men, 18% and 25%, respectively.

Table II displays the percentage of co-occurrence between grade 2+ foot OA and OA at other sites. While all individuals represented in Table II have foot OA, the percentage that also have OA at another site are represented in the table. When considering only those participants with foot OA, men consistently showed a slightly

Table I
Percentage of study sample with grade 2+ OA, by site

	All (%)	Women (%)	Men (%)
Foot	20.0	17.7	25.1
Second DIP	35.6	35.9	35.0
Third PIP	18.5	19.0	17.7
First CMC	20.8	21.3	20.0
Hand2	23.2	23.9	21.9
Knee	16.6	15.7	18.6

Table II
Percentage of co-occurrence of foot OA and OA at other sites, by gender

	Women (%)	Men (%)
Foot-DIP	11.3	14.8
Foot-PIP	7.4	8.8
Foot-CMC	8.2	9.4
Foot−Hand2	9.1	10.9
Foot−knee	6.7	9.0

higher prevalence of OA at the other sites. Figure 1 depicts the number of persons with co-occurrence of OA, among those with grade 2+ foot OA, by number of joints involved. Overall, a positive trend is suggested in the percentage of individuals with foot OA with an increasing number of affected joints ($P < 0.0001$, data not shown).

The unadjusted OR between foot OA and OA at other sites were relatively similar to each other, ranging from 4.0 to 4.5. Adjustment for age, BMI, and occupational history revealed lower, yet significant, levels of association between grade 2+ foot OA and OA at other sites (Table III). Frequently modest differences in the gender-specific OR were noted. Assessment of the association between grade 3+ foot OA and OA at other sites continued to show a statistically significant association (Table IV). However, compared with grade 2+ foot OA, the risk for grade 3+ foot OA was consistently lower for each joint examined for all persons combined. Table V shows data that examined the unilateral and bilateral disease categories and their association with grade 2+ foot OA. Our study outcome, foot OA, was always categorized by collapsing unilateral and bilateral disease. For the four joints considered, each demonstrated a significantly higher risk of foot OA if bilateral disease, as compared with unilateral disease, was present.

Discussion

We examined a group of community-dwelling men and women residing in the southeastern United States for the relationship between foot OA and OA at other sites. For both genders, we found a significant, positive relationship between grade 2+ foot OA and the presence of OA of the second DIP, third PIP, first CMC, and knee joints. This relationship maintained its statistical significance after adjustment for age, BMI, and occupational history. Thus, we were able to reject our null hypothesis of no association between foot OA and OA at the hand or knee joints. Our data demonstrated an expected finding noting a strong

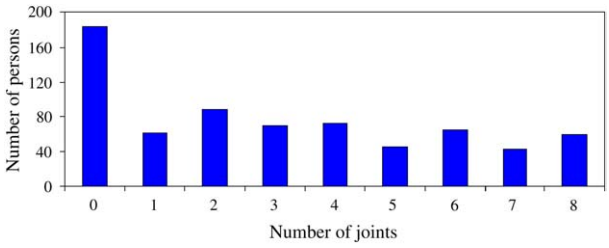

Fig. 1. Number of persons with co-occurrence of OA among those with grade 2+ foot OA (other joints include radiographic evidence of grade 2+ OA of the second DIP, third PIP, first CMC, or knee), by number of joints involved.

Table III
Adjusted OR and 95% confidence intervals (CI) for the association between grade 2+ foot OA and joint-specific OA

	OR (95% CI)		
Joint	All	Women	Men
Age adjusted			
Foot-DIP	3.2 (2.7−3.9)	3.2 (2.5−4.1)	3.5 (2.6−4.8)
Foot-PIP	3.3 (2.7−4.0)	3.3 (2.6−4.3)	3.4 (2.4−4.9)
Foot-CMC	3.5 (2.9−4.2)	3.6 (2.9−4.6)	3.3 (2.4−4.6)
Foot−Hand2	3.7 (3.0−4.4)	3.7 (2.9−4.7)	4.0 (2.9−5.6)
Foot−knee	3.8 (3.2−4.7)	4.0 (3.1−5.2)	3.5 (2.5−4.9)
Age, BMI, and occupational history adjusted			
Foot-DIP	3.2 (2.6−3.8)	3.2 (2.5−4.0)	3.5 (2.6−4.8)
Foot-PIP	3.2 (2.6−3.9)	3.3 (2.6−4.2)	3.4 (2.4−4.8)
Foot-CMC	3.4 (2.8−4.1)	3.6 (2.8−4.6)	3.4 (2.4−4.7)
Foot−Hand2	3.6 (3.0−4.4)	3.6 (2.9−4.6)	4.0 (2.9−5.6)
Foot−knee	3.7 (3.0−4.5)	4.0 (3.1−5.1)	3.4 (2.4−4.7)

All *P*-values are <0.0001.

relationship between the prevalence of foot OA and advancing age. Relative to unilateral joint disease, bilateral disease yielded a significantly elevated risk for foot OA.

While other studies have not specifically examined co-occurrence with foot OA, our findings are consistent with results from related, previous studies. A 1990 cross-sectional study identified a significant relationship between knee and hand OA among women ($P < 0.001$)[20]. However, unlike our study, this association was limited to women only. It is possible that differences in sample size may have influenced the study's ability to discern the gender-specific risks. A 1996 study investigated the patterns of joint involvement noting a tendency towards polyarticular OA among women aged 45−64 years[21]. Hirsch and colleagues reported a relationship between OA in the hand and knee joints. However, they noted that this association strengthened with increasing disease severity[13]. This is in contrast to our results describing the relationship between foot and knee OA. We noted the opposite findings with grade 2+ knee OA demonstrating a higher risk of foot OA (OR = 3.7; $P < 0.0001$) compared with grade 3+ knee OA (OR = 3.1; $P < 0.0001$). Although our study was unable to evaluate a relationship between foot OA and hip OA, an earlier investigation reported findings that support our suggestion that OA may arise from a systemic influence. A case−control study examined the association of hip OA with the presence of Heberden's nodes[22]. Their finding provided further evidence that OA of the hip can occur as part of a generalized process and does not only result from local damage to the joints.

While the role of mechanical factors in the pathogenesis of OA has compelling evidence[23], our current findings support the theory of a systemic etiology involved in the development of OA. A 2000 review of generalized OA commented that the topography of affected joints, as well as the threshold number of affected joints used in defining OA remains unidentified[24]. Mounting research has implicated genetic factors as an influential determinant of OA[25]. A possible explanation for our findings in the relationship between foot OA and OA at other sites suggests a genetic origin. Epidemiological studies exploring the relationship between genetics and OA have arisen from numerous approaches including family, twin, and genetic mapping studies. While no genetic studies have specifically addressed foot OA, results from investigations of OA at other sites implicate a genetic role in OA. Family clustering of

Table IV
Adjusted OR and 95% confidence intervals (CI) for the association between grade 3+ foot OA and joint-specific OA

	OR (95% CI)		
Joint	All	Women	Men
Age adjusted			
Foot-DIP	2.3*** (1.6–3.3)	2.5*** (1.6–3.9)	2.3** (1.3–4.1)
Foot-PIP	1.9** (2.2–2.9)	2.3** (1.3–3.9)	1.4 (0.58–3.5)
Foot-CMC	2.7*** (2.0–3.7)	2.5*** (1.7–3.9)	3.2*** (2.0–5.4)
Foot–Hand2	2.6*** (1.7–3.8)	2.6*** (1.6–4.3)	3.0** (1.5–5.8)
Foot–knee	3.0*** (2.1–4.5)	2.6** (1.5–4.4)	3.7*** (2.0–6.6)
Age, BMI, and occupational history adjusted			
Foot-DIP	2.3*** (1.6–3.3)	2.5*** (1.6–3.9)	2.3** (1.3–4.0)
Foot-PIP	1.9** (1.2–2.9)	2.3** (1.3–3.9)	1.4 (0.56–3.5)
Foot-CMC	2.7*** (2.0–3.7)	2.5*** (1.7–3.9)	3.3*** (2.0–5.4)
Foot–Hand2	2.5*** (1.7–3.8)	2.6*** (1.6–4.3)	2.9** (1.5–5.7)
Foot–knee	3.1*** (2.1–4.7)	2.7** (1.6–4.7)	3.7*** (2.0–6.9)

P-values * = <0.05; ** = <0.001; *** = <0.0001.

Table V
Adjusted[*] OR and 95% confidence intervals (CI) for the association between grade 2+ foot OA and joint-specific OA by unilateral and bilateral sites

	Unilateral[†]		Bilateral[‡]	
	OR (95% CI)	*n*[§]	OR (95% CI)	*n*[‖]
Foot-DIP	1.5** (1.2–2.0)	351	3.6*** (2.9–4.4)	871
Foot-PIP	1.6** (1.2–2.2)	243	4.2*** (3.3–5.3)	392
Foot-CMC	2.4*** (1.8–3.2)	258	3.9*** (3.1–4.9)	448
Foot–knee	2.3*** (1.7–3.1)	201	4.4*** (3.5–5.7)	356

P-values * = <0.05; ** = <0.001; *** = <0.0001.

[*]Adjusted for gender, age, BMI, and occupational history.

[†]Assesses risk of foot OA (either uni- or bilateral disease) by unilateral disease of the DIP, PIP, CMC, and knee joints.

[‡]Assesses risk of foot OA (either uni- or bilateral disease) by bilateral disease of the DIP, PIP, CMC, and knee joints.

[§]Where *n* = the sample size of subjects having unilateral disease of the DIP, PIP, CMC, or knee joints.

[‖]Where *n* = the sample size of subjects having bilateral disease of the DIP, PIP, CMC, or knee joints.

hand and knee OA have been reported[1,26,27]. Twin studies suggest that four OA sites (knee, hand, hip, and spine) are influenced by genetic factors[28–30]. The estimated heritability of radiographic OA of the hand, knee and hip ranges from 36% to 68%[31]. These, and related findings, have provided the impetus for researchers to address the systematic identification of OA susceptibility loci. Genome scanning has been employed for several rheumatic diseases[32–34], including OA[35,36]. Using affected sibling pair analysis, researchers found evidence suggestive of linkage of OA to chromosome 2q[37].

The current study contributes to a gap in OA literature by characterizing the co-occurrence of OA with OA of the first MTP, a largely unexplored site. Future epidemiological studies that further distinguish the relationship between OA at differing sites will provide an enhanced ability to describe the respective influences of mechanical and systemic factors in the development of this disease.

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