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Patterns of Compartment Involvement in Tibiofemoral Osteoarthritis in Men and Women and in Caucasians and African Americans: the Multicenter Osteoarthritis Study

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Abstract

Objective—We conducted a cross-sectional study to describe the prevalence of tibiofemoral joint space narrowing (JSN) in medial and lateral compartments and assess whether it differs by gender and ethnic groups, and if it does, to what extent such a difference is accounted for by knee malalignment.

Methods—The NIH-funded Multicenter Osteoarthritis (MOST) Study is an observational study of persons age 50 to 79 years with either symptomatic knee OA or at high risk of disease. Knee radiographs were assessed for JSN in each tibiofemoral compartment. Mechanical axis angle was measured using full-limb films. We compared the proportion of knees with medial compartment JSN and with lateral JSN between men and women as well as Caucasians (CC) and African Americans (AA) using a logistic regression model adjusting for covariates (race or gender and BMI, age, education, clinic site), and used generalized estimating equations to account for correlation between two knees within a person.

Results—Of 5202 knees (2652 subjects), 1532 (29.5%) had medial JSN, and 427 (8.2%) had lateral JSN. Lateral JSN was more prevalent in women's than in men's knees (OR=1.9, 95% CI 1.5–2.4) and was also higher in knees of AA than in CC (OR=2.4, 95% CI: 1.7–3.3). Further adjustment for malalignment attenuated the OR for gender but not the OR for race.

Conclusion—Women and AA are more likely to have lateral JSN than men and Caucasians. Valgus malalignment may contribute to the higher prevalence in women.

INTRODUCTION

Knee osteoarthritis (OA) is one of the most common causes of pain and disability in the elderly (1–4). Approximately 12% of US adults 60 years of age or older experience symptomatic knee OA (5), and prevalence of knee OA is increasing due to both aging and obesity. Overall tibiofemoral knee OA is more commonly seen in the medial than lateral compartment, possibly because of heavier loading in the former (6). Joint space narrowing (JSN) is an important compartment-specific manifestation of knee osteoarthritis with demonstrated associations with important clinical outcomes including pain (7).

Numerous studies have reported that prevalence of OA in different joints and clinical manifestations vary in gender and ethnic groups. For example, the prevalence of radiographic and symptomatic OA in hands, knees, and hips was higher in women than in

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men over the age 45 (8); and African Americans (AA) were more likely to have radiographic knee OA than non-Hispanic whites (9). A few studies also found that prevalence of OA in different compartments of a specific joint differed between ethnic groups. Braga et al. reported a higher likelihood of radiographic findings of lateral sclerosis and lateral JSN in AA than in Caucasians (CC) (10, 11). Data from the Framingham and Beijing OA Studies also demonstrated that among individuals with radiographic tibiofemoral OA, the proportion of knees with lateral compartment OA was much higher in Chinese than that in CC (12). The reasons for these differences in OA prevalence between sex or racial groups are not clearly understood.

Knee malalignment is strongly associated with an increased risk of OA progression. Biomechanical evidence demonstrates that varus malalignment increases force through the medial compartment whereas valgus malalignment places a greater proportion of the force through the lateral compartment of the knee (13). If the prevalence of knee malalignment varied between sex and racial groups, it could lead to different patterns of OA in different compartments of the knee. To date, only a few studies have tested this hypothesis. The results are conflicting. Among individuals without knee OA, Harvey et al. have reported that Chinese persons have a more valgus mean distal femur alignment than Caucausans (14). Jordan and colleagues found no difference by race in knee alignment between AA and CC using anatomic angle (15, 16).

We hypothesized that there is a higher prevalence of lateral compartment JSN in women than in men and in African Americans than in Caucasians. Secondarily, we hypothesized that differences between sexes and between races in malalignment prevalence would explain part of observed differences in JSN prevalence. Using the data collected from the Multicenter Orthteoarthritis Study (MOST) we compared the prevalence of radiographic OA feature JSN in the medial and lateral knee compartments between men and women as well as between CC and AA, and examined to what extent such difference in prevalence was accounted for by prevalence of knee malalignment.

METHODS

The Multicenter Osteoarthritis Study (MOST) is an NIH-funded observational study of risk factors for individuals who either had or were at high risk of knee OA due to obesity, knee pain, aching or stiffness on most of the previous 30 days, a history of knee injury, or a history of knee surgery. 3026 subjects, age 50–79 years at enrollment were recruited from two US communities, Birmingham, Alabama and Iowa City, Iowa. A detailed description of the study population has been published previously (17).

At the clinic visit, subjects were queried about social demographic information, including age, sex, and ethnic origin. Race was assessed at baseline by the question “what is your racial background?” with potential answers being “white or Caucasian, black or African American, Asian, American Indian or Alaskan native, Hawaiian or other Pacific islander, more than one race, other, don’t know”. Information about knee injury was collected by self-report using the question “Have you ever injured your knee badly enough to limit your ability to walk for at least two days?” asked at baseline for each knee.

Participants in the MOST Study had baseline bilateral weight-bearing, fixed flexion posteroanterior (PA) and lateral radiographs collected(18). The knee radiographs were scored by two readers (one rheumatologist and one musculoskeletal radiologist). Medial and lateral tibiofemoral compartment were scored for maximal joint space narrowing (JSN) grade on a semi-quantitative scale based on the Osteoarthritis Research International Radiographic Atlas (range 0–3; i.e. 0 = normal, 1 = mild, 2 = moderate, 3 = severe) (18, 19).

The weighted kappa for inter-rater reliability for medial JSN was 0.81 on PA view and 0.78 on lateral view. The weighted kappa for inter-rater reliability for lateral JSN was 0.86 on PA view and 0.84 on lateral view.

Knees were further divided into four groups according to presence of JSN at a specific compartment: (1) isolated medial compartment JSN, where JSN>0 in the medial compartment only; (2) isolated lateral compartment JSN, where JSN>0 in the lateral compartment only; (3) mixed medial and lateral compartment JSN, where JSN>0 in both the lateral and medial compartments; and (4) no JSN, where JSN=0 in both the medial and lateral compartments. In this analysis, "lateral JSN" refers to the combination of isolated lateral compartment JSN and mixed medial and lateral JSN, whereas "medial JSN" refers to the combination of isolated medial compartment JSN and mixed medial and lateral JSN. Thus, our main analysis examines lateral JSN irrespective of medial JSN presence and medial JSN irrespective of lateral JSN presence. We also defined a group of subjects with both medial and lateral compartment JSN and referred to it as "bicompartment" JSN.

Knee malalignment was assessed using long-limb films in the MOST. A knee was defined as having valgus malalignment if its mechanical axis>181 degrees; neutral malalignment if its mechanical axis was between 179 and 181 degrees; and varus malalignment if its mechanical axis <179 degrees. The intraclass correlation coefficient for assessment of mechanical axis was 0.95 with $p<0.001$(20).

We calculated the sex-specific prevalence compartment-specific JSN (i.e., medial and lateral JSN) for CC and AA, separately. We compared prevalence of compartment-specific JSN between gender and between racial groups using a logistic regression model. Variables included in the multivariable logistic regression models were sex, race, age, body mass index (BMI), education, prior injury to knee, and clinic site. We used generalized estimating equations (GEE) to account for the correlation between knees within a person. Finally, we assessed whether differences in prevalence of lateral compartment JSN between sex and racial groups could be explained by knee mechanical axis by entering knee alignment into regression model.

RESULTS

Of 3026 participants at baseline visit, 2981 (98.5%) were either CC or AA. We excluded 850 knees which had either total knee replacement or missing data on JSN, knee alignment, history of knee injury or BMI, leaving 2652 subjects (5202 knees) in the final analysis.

The characteristics of the subjects are presented in Table 1. Compared with women, men had a higher percentage who received a college education, higher percentage of history of knee injury, and had lower prevalence of valgus alignment. Overall, CCs were older, had lower BMI, had a higher percentage who received college education, and had a lower prevalence of valgus alignment than AA.

As shown in Table 2, women had higher prevalence of lateral compartment JSN than men in both AA and CC, although the difference did not reach significance among AA. Women also had higher prevalence of medial compartment JSN than men in AA; among CC men had a higher prevalence of medial compartment JSN. AA had higher prevalence of lateral compartment JSN than did CC, in both women and men.

Adjusting for potential confounding factors other than malalignment, the prevalence of lateral JSN was significantly higher in women than in men (Table 3). However, after adding knee alignment into the regression model, the magnitude of this effect was attenuated and the association became statistically insignificant. In contrast, for medial JSN adding knee

alignment into regression model not only changed the direction of association but also made it statistically significant. The association between sex and bicompartmental JSN was insignificant irrespective of adjustment (Table 3).

As shown in Table 4, prevalence of lateral JSN in AA was much higher than CC. Further adjustment for knee malalignment did not change the magnitude of the association materially. On the other hand, no association was found between race and the prevalence of medial JSN, and adjustment for knee malaligment did not change the effect estimate at all. AA were far more likely to manifest bicompartmental JSN than CC were, and again this association was not altered by adjusting for alignment.

When we examined the distribution of malalignment among subjects without TFROA, women were more likely to have valgus malalignment than men, but no difference was observed between AA and CC. Among the knees without tibiofemoral radiographic osteoarthritis (Kellgren/Lawrence≤2; TFROA) prevalence of varus malalignment was higher in men and AA than in women and CC, respectively (Table 5).

DISCUSSION

We found that prevalence of lateral knee JSN is higher in women than in men, and higher in AA than in CC. After adjusting for alignment this difference disappeared between men and women but remained significant between CC and AA. This finding suggests that alignment may be an important factor in the etiology of lateral JSN, but that factors other than alignment may account for observed differences by race. Also, prevalence of bicompartmental disease is much higher in AA than that in CC, but no difference was observed between sexes; thus, the findings for bicompartmental disease bear similarities to the findings for lateral compartment JSN, suggesting that those relationships may be driven by the lateral JSN component of the mixed disease. It should be noted also that the group with bicompartmental disease is actually quite small, and does not drive the results for lateral JSN. In fact, bicompartmental disease may represent a later stage and more severe lateral compartment disease.

The examination of patterns of joint involvement in OA may have clinical relevance. First, understanding these patterns gives insight into the potential pathologic mechanisms which underlie the development of the condition in general. If these patterns vary by sex or by race, this affords an opportunity to begin to understand the risk factors for OA in different populations. Furthermore, exploration of these variations may enable the identification of previously neglected subsets of patients who may have different risks for functional outcomes or arthroplasty than the general population of persons with OA. Since past OA studies have primarily focused on medial compartment disease, risk factors for lateral compartment OA have been relatively understudied.

Research on the variation in compartment of JSN by sex is limited. Weidow et al reported that lateral OA of the knee was associated with a wider pelvis and shorter femoral neck(21) than in women with medial compartment disease. Although these measures are not exactly equivalent to knee alignment, it is possible that changes in the geometry of the pelvis and femoral neck may affect knee alignment. Our findings suggest that at least in women in the subgroup with lateral compartment OA, alignment may also play a role.

We found that prevalence of malalignment of the knee differs in sex and racial groups among individuals without radiographic OA. Nelson et al noted no difference in valgus knee malalignment by race in the Johnston County cohort using anatomic axis measurement, and our findings using mechanical axis confirm this (16). Our findings that prevalence of valgus malalignment is much higher in women and that adjustment for valgus malalignment

removed the difference in prevalence of lateral compartment JSN between men and women suggests that at least in some groups, valgus malalignment plays a role in lateral compartment knee OA. The presence of varus malalignment is higher among men and adjustment for malalignment revealed a significantly greater odds of medial compartment JSN in women as compared with men. This may suggest that malalignment also plays a role in medial compartment knee OA in some groups.

Sharma et al found that in the MOST cohort varus but not valgus alignment was associated with incident knee OA, and also that varus alignment was associated with risk of progression of medial OA and valgus alignment with risk of lateral progression (22). Our finding that adjusting for valgus malalignment did not reduce the difference in prevalence of lateral JSN between AA and CC is interesting in this light: the two analyses parallel along the concept that valgus malalignment does not predispose to lateral compartment OA, but may contribute to a "vicious cycle" of OA progression in the lateral compartment. If this is the case, then our finding that adjusting for malalignment makes insignificant the differences between men and women most likely represents a manifestation of this cycle, rather than a cause of the higher prevalence of lateral compartment OA in women. However, the higher prevalence of valgus malalignment in women *without* TFROA argues for an etiologic role in that group.

Mazzuca et al reported that the incident radiographic knee OA in AA were three-fold greater than CC but did not evaluate compartmental differences (23). Some potential reasons for increased prevalence of lateral JSN in AA compared with CC include differences in life activity, hormonal or neuronal differences, and bone developmental differences in the hip or knee shape. Felson et al commented that difference in compartment-specific prevalence of knee OA between Chinese and Whites may suggest "…fundamentally different etiologies [for knee OA] in different cultures"(12). In the present study, although certainly cultural differences may exist between CC and AA within the United States, these differences are likely to be very minor compared with the differences between persons living in Beijing, China and Framingham, Massachusetts. However, there may be differences by race in the type of labor done which we could not correct for directly, but which adjusting for education partly corrects.

Although our findings do not support a role for valgus malalignment in explaining differences in prevalence of lateral compartment OA by race, it is important to emphasize that these measurements are of static alignment. Dynamic alignment is by definition different in either kind or degree from static alignment in a knee. Chang et al. found that AA in the Osteoarthritis Initiative Study had significantly greater odds of valgus thrust, both in those with and in those without knee OA (24). Increased frequency of valgus thrust in AA may represent a partial explanation for the differences in lateral compartment JSN by race that we have identified in MOST. Although somewhat different in approach, the findings of Chang and the present paper are consistent, mutually supportive and reinforcing.

Several characteristics of this study are worth noting: the radiological studies in MOST are well-performed, standardized radiographs were taken and were read across all racial/ethnic strata, and the readings have excellent reliability. Mechanical axis was measured using full-limb films, rather than anatomic axis. Finally, the number of subjects in both AA and CC is large enough that findings from this study are unlikely to be due to random error.

However, this study has limitations. Misclassification of compartment JSN, especially the mixed lateral and medial compartment JSN, could occur. However, there is also likely to be misclassification due to the relative insensitivity of the ordinal JSN measure to true differences in the joint space and this may have biased our results and weakened the

observed associations. Also, these are cross-sectional not longitudinal data so the full picture of the lateral compartment JSN knee OA over time might not be demonstrated. Finally, there may also be misclassification error of race by self-report.

In summary, the prevalence of medial and lateral compartment JSN varies by sex and between AA and CC. This difference by sex is partly accounted for by a difference in prevalence of knee malalignment between comparison groups, but racial group differences are not altered by adding malalignment into the model. Longitudinal studies are needed to elucidate the role of lateral compartment disease in the development and worsening of knee OA.

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INNOVATION

- We used a large, well-characterized, multicenter OA cohort to elucidate knee joint space narrowing compartment patterns by sex and race.
- We identified differences in lateral compartment disease, a relatively understudied component of knee OA.
- We explored in detail the contribution of alignment to observed differences by sex and race in patterns in knee OA using mechanical axis measures obtained from long limb films.

SIGNIFICANCE

- Understanding variations in patterns of knee OA by gender and by race may enable the identification of previously neglected subsets of patients who may have different risks for functional outcomes or arthroplasty than the general population of persons with OA.

TABLE 1

Characteristics of subjects (n=2652 subjects).

	Men N=1066	Women N=1586	P-Value	AA N=371	CC N=2281	P-value
Age, years [mean ± SD]	62.3 ± 8.2	62.6 ± 7.9	0.327	59.5 ± 7.9	63.0 ± 7.9	<.001
BMI	30.3 ± 5.0	30.7 ± 6.2	0.154	33.0 ± 6.4	30.1 ± 5.5	<.001
Education, %						
High school or less	27.0	29.5	<.001	33.2	27.8	<.001
Some college	22.3	29.1		31.5	25.5	
College graduate or higher	50.77	41.4		35.3	46.7	
Knee injury, %	31.5	21.0	<.001	20.5	26.0	0.004
Knee alignment, % *						
Varus <179	60.0	40.3	<.001	51.1	47.8	0.016
Neutral 179–181	30.8	35.0		28.7	34.0	
Valgus >181	9.2	24.7		20.2	18.2	

* Knee alignment is a knee-based measurement, assuming two knees per person.

Table 2

Frequency (N) and prevalence (%) of compartment-specific JSN by sex and race; n=5202. P-values for comparisons are provided in the last four columns of the table.

Status of JSN	AA		CC		Among AA	Among CC	Among men	Among women
	Men	Women	Men	Women	Men vs. Women	Men vs. Women	AA vs. CC	AA vs. CC
Total Number of Knees ▸	N=256	N=466	N=1836	N=2644	p-value	p-value	p-value	p-value
JSN (n (%)) ▾								
Medial JSN (n (%))	69 (27.0%)	170 (36.5%)	572 (31.1%)	721 (27.3%)	0.043	0.024	0.295	0.001
Lateral JSN (n (%))	32 (12.5%)	78 (16.8%)	89 (4.8%)	228 (8.6%)	0.184	<.001	<.001	<.001
Bicompartment JSN (n (%))	12(4.7%)	32 (6.9%)	30 (1.6%)	45 (1.7%)	0.325	0.864	0.010	<.001
No JSN (n (%))	167 (65.2%)	250 (53.6%)	1205 (65.6%)	1740 (65.8%)	0.016	0.990	0.902	<.001

medial JSN and lateral JSN both include bicompartmental JSN.

Table 3

Association between gender and compartment-specific disease. Reference group is men.

Compartment	Crude	Age, race, BMI, injury, education, clinic site		Age, race, BMI, injury, education, clinic site, alignment	
	OR (95% CI)	OR (95% CI)	p-value	OR (95% CI)	p-value
Lateral JSN	1.8 (1.4, 2.3)	1.9 (1.5, 2.4)	<.001	1.1 (0.9, 1.5)	0.402
Medial JSN	0.9 (0.8, 1.1)	0.9 (0.8, 1.0)	0.174	1.3 (1.1, 1.5)	0.002
Bicompartment JSN	1.2 (0.8, 1.9)	1.2 (0.8, 1.9)	0.372	1.1 (0.7, 1.8)	0.622

medial JSN and lateral JSN both include bicompartmental JSN.

Table 4

Association between race and compartment-specific disease. Reference group is Caucasians.

Compartment	Crude	Age, sex, BMI, injury, education, clinic site		Age, sex, BMI, injury, education, clinic site, alignment	
	OR (95% CI)	OR (95% CI)	p-value	OR (95% CI)	p-value
Lateral JSN	2.3 (1.8, 3.1)	2.4 (1.7, 3.3)	<0.001	2.6 (1.8, 3.7)	<0.001
Medial JSN	1.2 (1.0, 1.5)	1.2 (1.0, 1.6)	0.097	1.2 (0.9, 1.5)	0.289
Bicompartment JSN	3.8 (2.4, 5.9)	3.6 (2.1, 6.0)	<0.001	3.6 (2.1, 6.0)	<0.001

medial JSN and lateral JSN both include bicompartmental JSN.

Table 5

Malalignment by sex and by race among those without TFROA.

Malalignment	**Sex**		
	Female knees (n=1990)	**Male knees (n=1372)**	**p-value**
Varus	631 (31.7%)	707 (51.5%)	<.001
Valgus	495 (24.9%)	137 (10.0%)	<.001
	Race		
	CC knees (n=2945)	AA knees (n=417)	p-value
Varus	1151 (39.1%)	187 (44.8%)	0.091
Valgus	553 (18.8%)	79 (18.9%)	0.986