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The experience of pain and emergent osteoarthritis of the knee

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Summary

Discrepancies exist between radiographic osteoarthritis of the knee (OAK) and report of knee joint pain. Little is known about how these two definitions of osteoarthritis (OA) and their correlates differ between African American (AA) and Caucasian (CA) women.

Objective: We compared the prevalence of radiographic OAK and knee joint pain in AA and CA women, and the congruency of these outcomes according to age, body size, and knee injury.

Design: A cross-sectional study of African American and Caucasian women aged 40–53 years (N=829) in Southeast Michigan used the Kellgren and Lawrence Atlas of Standard Radiographs of Arthritis to characterize radiographs of both knee joints (weight bearing) and self-report of knee pain.

Results: Current pain was a significantly more sensitive predictor of radiographic OAK among AA women (Se=0.51) compared to CA women (Se=0.35). Specificity was similar between AA women (Sp=0.77) and CA women (Sp=0.82). Positive predictive value was significantly greater for AA compared with CA women (PV+=0.40 and PV+=0.15, respectively). The odds of having radiographic OAK increased with BMI >32 kg/m^2 in both groups. Knee pain was related to BMI in CA women, but not AA women. Previous knee injury was associated with knee pain in both AA and CA women (OR=3.0 and OR=2.4).

Conclusions: Joint pain in AA women was more likely to be associated with radiographic OAK as compared with CA women. This suggests differences in these two groups in both how pain is experienced in the OAK process and in the prevalence of non-OAK related pain in knee joints.

Key words: Osteoarthritis of the knee, Pain, Race/Ethnicity, Epidemiology.

Introduction

Radiographic osteoarthritis of the knee (OAK) has been the standard case definition of OAK in epidemiologic studies; however, symptomatic OAK, typically defined by self-reported knee pain, is the most common presenting symptom of the clinical problem. In most studies, while there is an association between radiographic changes of OAK and self-reported pain, there are a considerable number of persons with discordance of these findings. Clinically, it is well recognized that individuals may have radiographic evidence of OAK without pain symptoms, and that there are those who report having knee joint pain, but do not have radiographic evidence of OAK[1–4].

There is additional evidence of a difference in the presentation of osteoarthritis (OA) according to race/ethnic groups[5–7]. Heberdens nodes are less frequently reported in African American women than in Caucasian women[7]. Hip OA is reported to be less frequent among Chinese women than among African American and Caucasian women[6]. Yet, there has been relatively little information about race/ethnic differences in populations who are in similar geographic locations with similar socioeconomic profiles.

We examined the epidemiology of self-reported knee pain and its relationship to emergent radiographically-defined OAK in a population of African American and Caucasian women in southeast Michigan. We compared the prevalence of radiographic OAK and knee joint pain in this relatively young group of African American and Caucasian women. Then, the congruency of radiographic OAK and knee joint pain was examined for their relationship to the classic risk factors for OA including age, body size and knee injury. We addressed the following questions. Do African American and Caucasian women differ with respect to radiographic OAK and reported pain, and how do the correlates related to pain and radiographic outcomes of OAK differ between African American and Caucasian women?

Materials and methods

STUDY POPULATION

The southeast Michigan population, which has been previously described[8], encompasses pre- and perimenopausal women enrolled from two population-based studies, the Michigan Bone Health Study (MBHS) and the Study of Women's Health Across the Nation (SWAN-Michigan Center). The MBHS is a population-based longitudinal

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study of musculoskeletal disease development in pre- and perimenopausal Caucasian women. The sample was derived from combining two sampling frames. The first frame was a list of pre-menopausal female offspring (aged 24–44 years in 1992) who were identified from the family records of participants in the historical Tecumseh Community Health Study organized in 1959–1960. Eighty percent of eligible women were enrolled. The second frame was a community census conducted in 1992 that identified additional women who were age-eligible pre- and perimenopausal residents and, of these, 90% were enrolled. The SWAN study at Michigan is a population-based longitudinal study of African American and Caucasian women transitioning the midlife, and includes a study of OA as a site-specific study. Enrollees in the Michigan Center of the SWAN Study were derived from a household census of two communities located within 20 miles of Detroit, Michigan. The initial census identified 24,283 households in the communities. SWAN Study personnel interviewed 2621 women between the ages of 40 and 55 (representing 65% of the eligible women). From this sample, there were 754 pre- and perimenopausal women aged 42–52 years eligible for the SWAN cohort study, and 72% of these women were enrolled (N=543). The Southeast Michigan Study includes women aged 27–52 (MBHS, N=511), and women aged 42–53 (SWAN, N=543); however, women under the age of 40 years (N=222) were eliminated from these analyses because the age range of 40–53 years comprises the at-risk group for radiographic OA[8]. From this group (N=832), one woman was eliminated due to radiographic findings consistent with rheumatoid arthritis, one was eliminated due to not having a knee X-ray and another individual did not complete an arthritis/pain questionnaire (N=829). OA measurements are undertaken in the same time frames with identical protocols.

MEASUREMENTS

Radiographic OA: Weight-bearing anteroposterior radiographs were taken of both knees. Radiographs of both knees were evaluated by at least two of the three authors (DJ, MH and MFS) using the Kellgren and Lawrence system depicted in the Atlas of Standard Radiographs of Arthritis[9]. Methods for standardization and reading of the X-rays and agreement statistics have been previously described[10].

Arthritis questionnaire: An arthritis questionnaire was administered to identify pain and clinical characteristics (yes/no), including current knee joint pain and previous knee injury. To determine whether or not a participant had current knee joint pain, participants were asked if they had any joint pain in their knees during the last month. Participants were also asked if they had ever had a serious knee injury.

Other measures: Race/ethnicity was categorized as African American or Caucasian, based on self-report. Height (cm) and weight (kg) were measured using a stadiometer and balance beam scale, respectively. Body mass index (BMI) was calculated as weight (kg) / height (m^2). Categorical variables were created for BMI to compare those who were overweight (BMI=25–31.9 kg/m^2), obese (BMI=32–39.9 kg/m^2), and severely obese (BMI>=40 kg/m^2) to those with normal weight. Smoking behavior was classified as current smoker, ever smoked, or never smoked.

DATA ANALYSIS

Women were classified as having OA if either of the knee joints had a Kellgren and Lawrence grade of 2 or greater. Prevalence of OA, observed at the 1996 clinical examination of the population, was calculated by using the number of existing cases as the numerator and number of participants in the southeast Michigan population between the ages of 40–53 years (N=829) as the denominator. This age range was used as women aged 40–53 years comprised the at-risk group for radiographic OA[8].

Univariate statistics and distributions of all continuous variables were examined for normality. Sensitivity, specificity, predictive value positive, and predictive value negative, with 95% confidence intervals were calculated to describe the predictability of current joint pain and radiographic OAK to each other, overall and within ethnic groups.

Analysis of variance (ANOVA) was used to estimate the least square means (LS means) for continuous variables in relation to OAK and pain classification groups, whereas chi-square tests were used to evaluate homogeneity of categorical variable distributions across OAK and pain groupings. Multiple variable logistic regression analyses were used to evaluate the relationships to the OAK outcomes. To assess the fit of the logistic models, the Hosmer–Lemeshow goodness of fit statistic was used to test the hypothesis that a specified model fit could have been achieved by chance alone[11]. Receiver operator characteristic (ROC) curves were constructed, and the areas under the curve were estimated to assess the predictability of these models. A receiver operator characteristics (ROC) approach was used to characterize the ability of the model to predict the binary response variable (the presence or absence of OAK). The ROC approach characterizes and quantifies area under the curve and described the predictability of the model for the binary variable (‘no OA’ vs. ‘OA’). A value of c=0.5 indicates no detectability, and reflects chance alone; in contrast, a value of c=1.0 indicates perfect detectability[12].

Results

In this population, 23.2% of African American women, aged 40–53 years, had radiographic evidence of OAK in at least one knee and 29.4% reported current joint pain in one or both knees (see Table I). OAK was present with no reported knee pain in 11.5% of African American women, and current knee pain without OAK was found in 17.7% of these women (see Table II).

Among Caucasian women aged 40–53 years, 8.5% had radiographic evidence of OAK and 19.2% reported current knee joint pain. Within Caucasian women, 5.5% of those with radiographic evidence of OAK did not report having current knee pain, and in contrast, 16.2% reported knee joint pain but had no radiographic evidence of OA.

In this relatively young population where OA is just becoming established, there was very little severe OA. None of the women in this population had a K–L grade higher than three. Most of the African American women with OA had a K–L grade of two (65/75), and most of the Caucasian women also had a K–L grade of two (38/43).

As shown in Table II, the report of current pain was a more sensitive predictor of radiographic OAK among African American women (Se=0.51, 95%, CI=0.46–0.57) as compared to Caucasian women (Se=0.35, 95%

Table I
*Characteristics related to osteoarthritis of the knee (OAK) for African American women and Caucasian women aged 40–53 years in southeast Michigan (*N*=829)**

	African American women (*N*=323)		Caucasian women (*N*=506)		
	Mean (S.D.)	*N* (%)	Mean (S.D.)	*N* (%)	*P*-value
Radiographic OAK		75 (23.2)		43 (8.5)	0.001
Current knee joint pain		95 (29.4)		97 (19.2)	0.001
Age (years)	45.5 (2.8)		44.6 (2.7)		0.0001
BMI (kg/m^2)	32.5 (8.4)		29.7 (7.5)		0.0001
BMI categories (kg/m^2)					
Normal weight (BMI<25)		61 (18.9)		164 (32.4)	0.001
Overweight (BMI 25–31.9)		106 (32.8)		166 (32.8)	0.997
Obese (BMI 32–39.9)		97 (30.0)		128 (25.3)	0.135
Severely obese (BMI >=40)		59 (18.3)		48 (9.5)	0.001
Previous knee injury		61 (18.9)		94 (18.6)	0.912
Ever smoked		158 (48.9)		149 (29.4)	0.001

*χ^2 test used for categorical variables and F-test used for continuous variables.

Table II
*Relationship between radiographically-defined OAK and report of current knee joint pain in African American and Caucasian women, aged 40–53 years (*N*=829)*

	African American women (*N*=323)*			Caucasian women (*N*=506)†		
	OA of the knee	No OA of the knee	Total	OA of the knee	No OA of the knee	Total
Reported knee pain	38 (11.8%)	57 (17.7%)	95 (29.4%)	15 (3.0%)	82 (16.2%)	97 (19.2%)
No reported knee pain	37 (11.5%)	191 (59.1%)	228 (70.6%)	28 (5.5%)	381 (75.3%)	409 (80.8%)
Total	75 (23.2%)	248 (76.8%)	323	43 (8.5%)	463 (91.5%)	506

*Sensitivity=0.51, specificity=0.77, PV+=0.40, PV−=0.83.
†Sensitivity=0.35, specificity=0.82, PV+=0.15, PV−=0.93.

Table III
Correlates of Radiographic OAK *in southeast Michigan women aged 40–53 years*

Variable*	African American women		Caucasian women	
	OR	(95% CI)	OR	(95% CI)
Age (1 year interval)	1.0	(0.9–1.1)	1.1	(0.8–1.1)
Overweight (BMI=25–31.9 kg/m^2)†	2.4	(0.6–9.1)	1.1	(0.4–3.5)
Obesity (BMI=32–39.9 kg/m^2)†	7.0	(2.0–24.7)	3.9	(1.5–10.4)
Severe obesity (BMI≥40 kg/m^2)†	29.7	(8.2–107.4)	8.8	(3.0–25.9)
Previous knee injury	1.8	(0.9–3.6)	2.2	(1.1–4.5)
Smoking behavior (ever vs never)	1.2	(0.7–2.2)	0.5	(0.2–1.1)
c statistic	0.79		0.75	

*All variables are adjusted for all other variables.
†Reference group=BMI<25 kg/m^2.

CI=0.31–0.39). Specificity (the probability of reporting no pain given no radiographic OAK) was similar between African American women (Sp=0.77, 95% CI=0.72–0.82) and Caucasian women (Sp=0.82, 95% CI=0.79–0.85). Positive predictive value (the probability of radiographic OAK given reported pain) was significantly higher for African American than for Caucasian women (PV+=0.40, and PV+=0.15, respectively).

Table III depicts the odds ratios of having selected characteristics and *radiographically defined knee OAK* in African American and Caucasian women. There was a greater odds of having radiographic OAK with a BMI>32 kg/m^2 in both groups. African American women were 7.0 times more likely and Caucasian women were 3.9 times more likely to have radiographic OAK if they were classified as obese (BMI=32–39.9 kg/m^2), adjusting for age, injury, and smoking. Further, African American women were 29.7 times more likely and Caucasian women were 8.8 times more likely to have radiographic OAK if they were classified as severely obese (BMI>=40 kg/m^2). In addition, there was a positive association between pain and previous knee injury in both Caucasian and African American women adjusting for the other covariates; however, the association was statistically significant only for the Caucasian women (OR=2.2, 95% CI=1.1–4.5; and OR=1.8, 95% CI=0.9–3.6 respectively). There is a gradation in the association between BMI categories and radiographic OAK in both African American and Caucasian women. The odds of

Table IV
Correlates of report of having current knee joint pain in southeast Michigan women aged 40–53 years

Variable*	African American women		Caucasian women	
	OR	(95% CI)	OR	(95% CI)
Age (1 year interval)	1.0	(0.9–1.1)	1.1	(0.9–1.2)
Overweight (BMI=25–31.9 kg/m^2)†	1.0	(0.5–2.1)	1.6	(0.9–3.0)
Obesity (BMI=32–39.9 kg/m^2)†	1.5	(0.7–3.1)	2.1	(1.1–4.0)
Severe obesity (BMI≥40 kg/m^2)†	1.9	(0.9–4.4)	3.1	(1.4–6.9)
Previous knee injury	3.0	(1.7–5.4)	2.4	(1.4–4.0)
Smoking behavior (ever vs never)	1.1	(0.6–1.8)	1.1	(0.7–1.9)
c statistic	0.65		0.67	

*All variables are adjusted for all other variables.
†Reference group=BMI<25 kg/m^2.

having OAK increase with increasing BMI category; however there are overlapping confidence intervals. Confidence interval widths for the relationship between OAK and BMI reflect small cell sizes for individuals who have OAK in the normal weight reference category (BMI<25).

Table IV depicts the odds ratios for *current knee joint pain* considering the role of risk factors as they present in African American and Caucasian women. Report of current knee pain was not related to body mass index in African American women. However, Caucasian women who were classified as obese were 2.2 times more likely to report current knee pain and Caucasian women who were classified as severely obese were 3.3 times more likely to report current pain, compared with Caucasian women with BMI≤25 kg/m2. Both African American women and Caucasian women with previous knee injuries were more likely to report current knee joint pain (OR=3.0, 95% CI=1.7–5.4 and OR=2.4, 95% CI=1.4–4.0, respectively).

Discussion

The incongruity between report of knee joint pain and radiographic designation of OA is well appreciated by clinicians and epidemiologists. The measures of sensitivity, specificity, and predictive values calculated in this study highlight the limitations of using either assessment of pain or radiographic assessment singly in the prediction of a clinical diagnosis of OAK or case definition of symptomatic OAK for epidemiologic studies.

There are a number of factors that can be identified that may be associated with this incongruity. It is well known that use of radiographs perpetuates an underestimate of the true prevalence of OA[13,14] in part, because the anteroposterior view from plain films allows access to only the medial and lateral compartments, but not the patellofemoral compartment. OA of the patellofemoral joint has been shown to be associated with knee pain and to be (often) present in the absence of tibiofemoral compartment[15,16]. The report of current pain has yet to be examined stratified on the disease presentation within the three knee joint compartments.

It has not been well defined how much the Kellgren and Lawrence (K–L) scoring system also contributes to the misclassification. The K–L scoring system is highly dependent upon osteophyte visualization and size, particularly at a scoring level of two, which marks the cut-off point most frequently employed to define OA and the score most frequently observed in this study of early, emergent OA. This study is underpowered to determine if the sensitivity and specificity between radiographic OA and report of pain is altered according to the individual K–L categories of three and four. This is relevant as the higher categories reflect not only osteophytes but also joint space narrowing and bone sclerosis.

It has long been recognized that the pathophysiology of pain in persons with knee OA is likely to be multifactorial and different for each individual. Periostitis associated with knee joint pain can occur at sites of osteophyte formation, synovial inflammation, joint instability, periarticular muscle spasm, subchondral bone microfractures, and ischemia[17,18].

This study evaluates emergent OAK, and explores the presentation of pain in individuals prior to, and at the early stages of the accepted K–L radiographic definition of OAK. Knee joint pain has been hypothesized to be present at an earlier stage along the continuum that will ultimately culminate in radiographically definable OAK[19]. Thus, as this longitudinal study continues, it will be important to discern if pain (and what types of pain) can be considered a precursor to the structural damage being characterized in plain films. Previous studies of pain and radiographically-defined OAK have evaluated populations dominated by elderly individuals. In the elderly, pain may be more constant, more longstanding, have origins of pain other than from the joint, and may be associated with compromised mental health status[20,21]. Certainly because of this more mixed pain presentation, it will be difficult to discern if pain actually is the precursor to either new or additional structural damage in the knee joint.

Joint pain is a characteristic difficult to consider in clinical practice because of the erratic presentation. The source of waxing and waning in joint pain has not been well characterized. Part of the erratic presentation of joint pain may be explained if the source of joint pain is related to bone marrow edema[17], a characteristic not visualized on plain films. Variable pain presentation also may be associated with localized vasodilatation characteristics and the local cytokine environment. Whereas bone marrow edema, vasodilatation and cytokine production characteristics could be transitory, the radiographic presentation of osteophytes, sclerosis and joint space narrowing would be physical landmarks that would have a substantially less transitory presentation. Thus, it may be unrealistic to expect congruency in what would be acute events as compared to a long-term structural modification.

The incongruity between report of knee joint pain and radiographic designation of OA did not present in the same manner between African American women and Caucasian women. The self-report of current knee joint pain in African

American women was more likely to be associated with radiographic OAK as compared with Caucasian women. This suggests that there could be differences in these two groups in both how pain is experienced in the OAK process and in the prevalence of non-OAK related pain in knee joints. The difference could be related to the body size in the two groups. The differences in BMI categories related to radiographic OAK outcomes suggest a difference in the intensity of the relationship between BMI and OAK between African American and Caucasian women and this more intense relationship between BMI and OAK observed in African American women may be extended to their joint pain. There is an increasing diabetes and cardiovascular literature indicating that obesity is associated with pro-inflammatory cytokines including interleukin-6 (IL-6)[22,23]. IL-6 concentrations, in turn, have been linked with report of pain in various conditions including herniated lumbar discs, ankylosing spondylitis, and juvenile rheumatoid arthritis[24–29]. Further, it is known that IL-6 concentrations are decreased after use of nonsteroidal antiinflammatory drug (NSAID) therapy to reduce pain and inflammation[30] Thus, the constellation of obesity, pain, OAK and cytokine production may be more tightly linked in the African American women than the Caucasian women. However, this difference by ethnic group is probably not explained by body size alone, because these differences have been observed following adjustment for BMI in both the models for radiographically-defined OA as well as the models for knee joint pain. Furthermore, ethnic differences in IL-6 levels have not been widely reported and need further elucidation[31,32].

Other factors might be considered when relating OAK and pain within ethnic groups. For example, smoking, which might be used as a mechanism to minimize the impact of pain, is not related to the report of pain in either African American or Caucasian women. Certainly, different cultural groups are known to have discernible differences in how they report pain in response to similar stimuli[33]. However, there is substantial controversy with respect to ethnicity which centers around trying to understand how ethnicity influences the meaning the sufferer attaches to pain and how ethnicity influences the communication of the pain experience. In clinical evaluation, this is made more complex in that the ethnicity of the health care provider may also influences report of pain.

The difference in sensitivity of pain to predict radiographically-defined knee OA among African American women and Caucasian women is not well characterized in the literature. Three reports from the National Health and Nutrition Examination Survey (NHANES-I) have examined knee pain and radiographically-defined OAK in persons aged 25–74 years. While the films from NHANES-I were scored with the K–L scale, OAK prevalence was very low, probably, in part, to the use of a non-weight bearing positioning. Furthermore, African Americans were sampled according to their frequency in the population and not over-sampled, as in our study. Thus, detection of associations may be influenced by the low statistical power, given a lower frequency of African Americans and the low frequency of OAK. Davies *et al*. could not identify that factors associated with knee pain were differentially distributed according to ethnicity in men and women[34], while Hochberg *et al*.[35], and Hannan *et al*.[36] did not expressly examine this association. In the other US population study that includes African American women (aged 45–75+), Jordon[37] reported no difference in the association of pain and OAK according to ethnicity and no greater risk for OAK among the African American women.

Resolution of the incongruency between radiographic evidence and report of pain will become more important when therapies are equally directed at pain resolution and joint structure characteristics. Current practice is primarily associated with pain resolution; however, as treatment options for OA expand, efficacious treatment will require an understanding of the full scope of characteristics being addressed. For example, the importance of adiposity to both the structural presentation of OAK and the cellular constituents of pain may be a function of the amount of obesity, distribution of adipose tissue, as well as timing with respect to onset of OA[8]. In addition, individuals have different thresholds for pain and different thresholds at which they will seek medical care for pain. This suggests that interventions and therapies of the future will need to consider multiple elements including the collagen and bone turnover processes associated with structural damage, the molecular/cellular constituents and products of adipose tissue that interface with adrenergic receptor regulation, and the behavioral response to pain. It may be impossible to rely on a single measurement of pain until measurement issues are resolved with respect to OA, and until we understand the natural history of the report of pain in OA. These concerns can be better achieved with well-developed longitudinal studies.

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