Osteoarthritis and Cartilage

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Examining sex differences in knee pain: the Multicenter Osteoarthritis Study

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SUMMARY

Objective: To determine whether women experience greater knee pain severity than men at equivalent levels of radiographic knee osteoarthritis (OA).

Design and methods: A cross-sectional analysis of 2712 individuals (60% women) without knee replacement or a recent steroid injection. Sex differences in pain severity at each Kellgren—Lawrence (KL) grade were assessed by knee using visual analog scale (VAS) scale and Western Ontario and McMaster Universities Arthritis Index (WOMAC) with and without adjustment for age, analgesic use, Body mass index (BMI), clinic site, comorbid conditions, depression score, education, race, and widespread pain (WSP) using generalized estimating equations. Effect sizes (Cohen's d) were also calculated. Analyses were repeated in those with and without patellofemoral OA (PFOA).

Results: Women reported higher VAS pain at all KL grades in unadjusted analyses ($d = 0.21-0.31$, $P < 0.0001-0.0038$) and in analyses adjusted for all covariates except WSP ($d = 0.16-0.22$, $P < 0.0001-0.0472$). Pain severity differences further decreased with adjustment for WSP ($d = 0.10-0.18$) and were significant for KL grade ≤ 2 ($P = 0.0015$) and 2 ($P = 0.0200$). Presence compared with absence of WSP was associated with significantly greater knee pain at all KL grades ($d = 0.32-0.52$, $P < 0.0001-0.0008$). In knees with PFOA, VAS pain severity sex differences were greater at each KL grade ($d = 0.45-0.62$, $P = 0.0006-0.0030$) and remained significant for all KL grades in adjusted analyses ($d = 0.31-0.57$, $P = 0.0013-0.0361$). Results using WOMAC were similar.

Conclusions: Women reported greater knee pain than men regardless of KL grade, though effect sizes were generally small. These differences increased in the presence of PFOA. The strong contribution of WSP to sex differences in knee pain suggests that central sensitivity plays a role in these differences.

Introduction

Women are at greater risk for developing knee osteoarthritis (OA)[1,2] compared with men, particularly those over 50 years of age[2]. Women with OA have also been found to have greater levels of knee pain and lower function[3–6]. However, a greater prevalence of radiographic knee OA in women[7,8] could account for sex differences in knee pain and function[3,4]. Few studies have examined the degree to which the symptoms of knee OA differ between men and women after accounting for the degree of radiographic severity.

In addition to OA, several chronic musculoskeletal pain conditions are overrepresented in women such as temporomandibular disorders, headaches, and fibromyalgia[9], all of which are generally thought to involve central sensitization. Indeed, the term, "central sensitivity syndromes"[10] has been coined to represent a number of these frequently comorbid chronic pain conditions that may share altered central pain processing[11]. The predominance of women with central sensitivity syndrome diseases might suggest that women are at greater risk for enhanced pain related to central sensitization than men.

Experimental pain studies of sex differences in pain sensitivity in healthy subjects, however, have produced somewhat inconclusive results. A meta-analysis found generally greater pain sensitivity in women than men for pain threshold and tolerance to a

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variety of noxious stimuli, with mean effect sizes ranging from $d = 0.09$ to 0.82[12]. In contrast, a recent review of the literature concluded little additional evidence is available to support clear sex differences in acute pain sensitivity[9]. Others have suggested women may be more susceptible to centrally-mediated pain than men, since they show greater temporal summation to heat pain[13] and greater referred pain in response to intramuscular experimental pain[14], and less conditioned pain modulation[15]. However, clinical studies of knee OA have been lacking in their explicit examination of sex differences in pain sensitivity, likely in part due to the inherently confounding issue of disease severity.

Thus, the primary purpose of this study was to examine whether women exhibit greater pain than men despite similar levels of radiographic knee OA, using a large epidemiological study of adults with or at risk for knee OA. Our secondary aim was to define the role of widespread pain (WSP) in men and women, as an indication of the presence of heightened "central sensitivity".

Methods

Study sample

For this cross-sectional analysis, data from the baseline examination of the Multicenter Osteoarthritis Study (MOST) were utilized. MOST is an observational study that enrolled 3026 community-dwelling adults aged 50–79 years with knee OA or known risk factors for knee OA including age, female sex, overweight, and history of knee symptoms, knee injury and/or surgery. Participants were from Iowa City, IA, and Birmingham, AL or the surrounding communities. The study design and participant eligibility has been described previously[16]. Participants who had a steroid injection in the past year or with a history of total knee replacement were excluded from this study ([Fig. 1](#)). The MOST study was approved by the institutional review boards at the University of Iowa; University of Alabama, Birmingham; University of

California, San Francisco; and Boston University Medical Center. All participants provided written, informed consent.

Assessments

Analgesic use

Participants provided information on analgesic medication (salicylate, non-steroidal anti-inflammatory drug (NSAID), opioid and "other" analgesic that included acetaminophen and other analgesics and antipyretics) use through an interviewer-administered questionnaire at the clinic visit. Participants were asked whether medications were used on an intermittent or regular basis. Analyses controlled for regular use of analgesic medications.

Anthropometric measures

Body mass index (BMI, kg/m^2) was calculated from weight in kilograms divided by the square of the height in meters (Stadiometer, Holtain, Wales, UK), as measured by trained and certified staff at the clinic visit.

Comorbid conditions

Participants completed the Charlson Comorbidity Index, a validated classification system of comorbid conditions[17]. Responses were categorized as none, one, and two or more comorbid conditions.

Depressive symptoms score

The Center for Epidemiologic Studies Depression Scale (CES-D)[18] was utilized as an indicator of depressive symptoms. The instrument includes 20 items which query participants' feelings over the past 7 days. A score of 16 or greater has been used as an indicator of depression[19].

Education

Participants provided information on the highest grade or year of school completed. Responses were categorized into one of three categories: less than high school education, completion of high school and at least some college.

Knee radiographs

Weight-bearing, fixed-flexion posteroanterior and lateral radiographs of the knees were obtained at baseline according to the MOST radiograph protocol as previously described[20]. Each participant's radiographs were scored by two independent readers (an experienced academically-based musculoskeletal radiologist and a rheumatologist experienced in study reading) according to Kellgren–Lawrence (KL) scale at the tibiofemoral joint. Participants who attended both the baseline MOST visit and a follow-up visit had their baseline radiographs evaluated for the presence of patellofemoral (PF) OA. Their PFOA status was indicated as present if there was an osteophyte grade ≥ 2 or if there was an osteophyte grade ≥ 1 plus presence of PF joint space narrowing (JSN) ≥ 2 or sclerosis ≥ 2 or cysts ≥ 2[21].

Pain

We used two assessments to characterize knee-specific pain. Average knee pain over the past 30 days was assessed on a 0–100 mm visual analog scale (VAS), with anchors of 0 indicating 'no pain' and 100 indicating 'pain as bad as it could be' for each knee. Pain during activities (i.e., walking, standing, stairs) was assessed using a subset of questions from the Western Ontario and McMaster Universities Arthritis Index (WOMAC pain) for each knee. This subscale comprises five items with responses that range from no (0) to extreme (4) pain with a possible total score of 20. Higher scores on the WOMAC indicate greater pain. WOMAC scores were
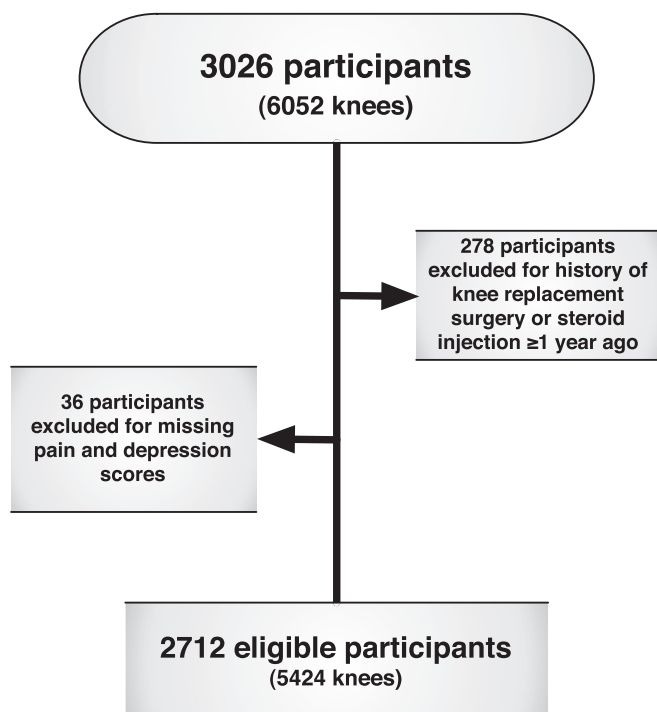

Fig. 1. Participant inclusion diagram.