Sex differences in the relationship between individual systemic markers of inflammation and pain in knee osteoarthritis

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SUMMARY

Objective: There are suggestions that the relationship between inflammation and pain in osteoarthritis (OA) may differ by sex, yet studies have been limited. We investigated whether the relationship between knee-specific OA pain and systemic inflammatory markers differs by sex.

Design: 196 patients scheduled for knee arthroplasty for OA were included. Questionnaires were completed and blood samples drawn pre-surgery. Questionnaire data: knee pain (WOMAC), sex, age, height, weight, comorbidities, depressive symptoms, and symptomatic joint count. Systemic inflammatory markers (cytokines IL-6, IL-8, IL-10, IL-1β and TNF-α) were measured by multiplex ELISA. A series of regression models with interaction terms between sex and ln-transformed inflammatory markers were estimated with pain score as the outcome. The adjusted relationship between pain and inflammatory markers, by sex, were presented graphically.

Results: Mean age was 64 years (range 43–89); females comprised 58.7% of the sample. In adjusted analyses, similar relationships between knee pain and lnIL-10 (negative: β = −1.28, 95%CI (−1.97, −0.58)) and lnTNF-α (positive: β = 0.92, 95%CI (0.11, 1.76)) were found for females and males. In contrast, relationships between knee pain and lnIL-1β, lnIL-6 and lnIL-8 differed in direction for females and males. Specifically, for lnIL-1β and lnIL-8 they were positive for males, negative for females. The opposite was found with lnIL-6, negative for males, positive for females.

Conclusion: These findings provide some evidence of sex-specific relationships between individual inflammatory markers and knee OA pain. They expose a need for further exploration of sex-differences in this context, with potential future implications for treatment or drug development in OA.

1. Introduction

Pain in osteoarthritis (OA) is the cardinal symptom and a driver of functional limitations, reduced quality of life, and healthcare use. Despite concerted efforts, significant challenges remain in mitigating OA pain. Treatments that relieve OA pain and delay the need for OA surgery are a high priority in clinical practice and in public health and policy [1]. Pharmacological approaches for OA pain are largely based on use of over-the-counter and prescription oral anti-inflammatory drugs and analgesics. Sex differences in OA prevalence and frequency and severity of pain reports are well recognized [2,3], and psychosocial factors, including depression, implicated in contributing to the pain experience, only partially account for observed sex differences [4–6]. Furthermore, there is evidence that treatment response to non-steroidal
anti-inflammatory drugs (NSAIDs) for OA pain may differ by sex, which is unlikely to be fully explained by psychosocial factors [7–9].

Inflammatory markers (i.e. cytokines) have been reported to contribute to OA symptoms. For instance, biochemical and biomechanical factors can trigger proinflammatory responses that ultimately lead to articular cartilage destruction in OA [10]. While local inflammation contributes to OA joint pathologies, systemic inflammatory markers are also increased in OA, particularly in the presence of symptoms including pain [11,12]. While recognized as a driver of general pain, inflammation has shown inconsistent relationships with OA pain [13,14]. This inconsistency may be related, in part, to evidence suggesting that relationships may differ between males and females [15,16]. Further, these differences may be obscured by typical approaches that only report average effects from sex-adjusted analyses. There has been remarkably little work focused on elucidating whether there are differences by sex in the relationship between OA pain and markers of systemic inflammation. Such differences may contribute to sex differences in treatment responses [7,17], and have implications for treatment approaches.

In this study, we focused specifically on investigating whether there are fundamental differences in the relationship between circulating inflammatory markers and knee OA pain between females and males.

2. Methods

Individuals with late-stage knee OA scheduled for total knee arthroplasty for OA were recruited from the Arthritis Program, Toronto Western Hospital, Toronto, Canada, and gave written informed consent for this study. Eligibility criteria included individuals ≥35 years of age and English fluency for consent and questionnaire completion. Exclusion criteria included acute trauma/injury, prior surgical interventions for OA, or inflammatory arthritides (e.g. rheumatoid arthritis, psoriatic arthritis). Health questionnaires were completed and blood samples drawn in-clinic within the 3 weeks prior to surgery.

The study was approved by University Health Network Research Ethics Board, in accordance with the Helsinki Declaration of 1975, as revised in 2000.

2.1. Blood samples

Plasma was isolated in K2-EDTA blood collection tubes (BD Biosciences) followed by centrifugation at 3220 × g for 10 min at 4 °C. Plasma was flash frozen in liquid nitrogen prior to storage at −80 °C. Inflammatory cytokines interleukins (IL)-6, IL-8, IL-10, IL-1ß and TNF-α were measured by Eve Technologies (Calgary, Alberta, Canada) using Lumex bead-based multiplex ELISA assays obtained from EMD-Millipore (Miliplex MAP Assay catalogue number HSTCMAG-28SK) according to manufacturers’ instructions. Assays were read on a Bio-Plex 200 bead analyzer and cytokine levels determined using Bio-plex Manager Software v6.2 (Bio-rad).

2.2. Self-report health questionnaire

Knee pain was assessed using the Western Ontario McMaster University Osteoarthritis Index (WOMAC) pain subscale [18], the most often used patient-reported lower extremity pain measure in OA. The 5-item measure has documented reliability and validity [18,19]. Scores range from 0 to 20; higher indicates greater pain.

Participants recorded their sex and age, and research staff measured height and weight from which body mass index (BMI; kg/m²) was calculated.

Participants indicated the presence of chronic conditions from a list of 15 conditions using the reliable and valid AAOS-Comorbidity Scale [20]. These were summed to derive comorbidity count.

Depressive symptoms were assessed with the Hospital Anxiety & Depression Scale’s depression subscale, covering the state of loss of interest and diminished pleasure response. This measure has been widely used in patient and general populations [21]. Scores range from 0 to 21; higher indicates greater depressive symptoms.

Participants marked all symptomatic joints (“pain, stiffness or swelling most days of the month”) on a homunculus diagram (neck; back; and right and left shoulder, elbow, wrist, hand, hip, knee, ankle, foot). A total symptomatic joint count was derived, excluding the surgical joint, and categorized as <4 and ≥4 [22].

Participants were asked to indicate current ‘Over-the-counter medication’ or ‘Prescription non-steroidal anti-inflammatory medication’ use for joint pain as ‘never’, ‘sometimes’ or ‘daily’. Pain medication use was dichotomized as ‘yes’ (sometimes/daily) or ‘no’ (never).

2.3. Analyses

Two linear regression models were estimated to investigate the relationship between specific factors and knee pain score. The ‘initial’ model considered patient-reported health questionnaire data (sex, age, BMI, comorbidity count, depressive symptom score and symptomatic joint count) and systemic inflammatory markers (cytokines IL-6, IL-8, IL-10, IL-1ß and TNF-α (all ln-transformed)). In the next step, to investigate possible differences by sex, interaction terms between sex and each of the variables were tested in turn. Interaction terms with p-values < 0.20 were deemed suggestive of possible sex differences and carried forward to a final ‘interaction’ model. Residual plots by inflammatory markers were inspected to determine whether any non-linear associations were missed. Results from the final interaction model were used to generate individual predicted knee pain scores with increasing concentration of each inflammatory marker (within observed ranges only), holding all other model variables at their observed values. Graphical displays of mean pain scores against transformed marker concentrations were produced by sex.

A sensitivity analysis was undertaken re-estimating the interaction model in an analytical sample limited to individuals aged 55+, used as an age-based proxy for post-menopausal status for females.

3. Results

Of the 231 patients participating in the study, 196 (85%) had complete data; these comprised the analytical sample. A description of patients, overall and by sex, is provided in Table 1. The mean age of patients was 64 years, ranging from 43 to 89 years, with females comprising 58.7% of the sample. Females had higher comorbidity and symptomatic joint counts and worse depressive symptom and knee pain scores compared to males. Intra-plate coefficients of variation were < 5.0% for all assays, and inter-plate coefficients were < 5% for IL-6, IL-10, and IL-1ß, 8.8% for IL-8, and 10.4% for TNF-α. Minimal to no sex differences were observed in age, BMI or pain medication use. Median TNF-α levels were higher in males than females (8.3 vs. 6.8 pg/ml).

For the linear regression analyses, residuals were normally distributed with inflammatory marker concentrations transformed using the natural logarithm. Residual plots by transformed individual biomarkers did not suggest any non-linear associations were missed. Transformed values were retained. Results from the initial and final interaction linear regression analyses are presented in Table 2. From the initial model, females, younger individuals and those with higher depressive symptom scores had worse knee pain scores, and a positive relationship was also found between symptomatic joint count and knee pain scores ($β = 0.94, 95%CI (0.05, 1.83)$). Only two of the five inflammatory markers were significantly related to knee pain scores in this initial model: higher InIL-10 concentrations were associated with lower knee pain scores ($β = −1.13, 95%CI (−1.86, −0.40)$) whereas higher InTNF-α concentrations were associated with worse knee pain scores ($β = 0.93, 95%CI (0.08, 1.78)$).

Results from the intervening analyses suggested that the associations of InIL-6, InIL-8, and InIL-1ß, and BMI, with pain scores potentially differed by sex; these factors were brought forward to a final ‘interaction’ model using interaction terms. The coefficients for the biomarker
variables in this model represent the effects of a unit increase on the log scale of the marker on pain. In the interaction model the coefficient for the main effect of sex increased in magnitude. The relationships between knee pain score and IL-6, IL-8, IL-1β, and BMI differed for females and males, while the relationship with IL-10 (negative relationship) and TNF-α (positive relationship) were found to be similar for females and males (Table 2, interaction model). The relationships between the inflammatory markers and pain are graphically displayed in Fig. 1, for the overall sex-adjusted association (using results from the initial model) and stratified by sex (using results from the interaction model). The relationships between IL-1p and IL-8 and pain were positive for males and negative for females. The relationship between IL-6 and pain was negative for males and positive for females.

Findings with the age-restricted sample (ages 55+) were consistent with those from the primary analyses (Supplementary Data, Table S1).

4. Discussion

In a sample of patients with advanced knee OA, we identified possible relationships between knee OA pain and three out of five systemic markers of inflammation, specifically IL-6, IL-8, and IL-1p that differed in directionality by sex. A further two markers, IL-10 and TNF-α, each had a similar relationship with pain for both males and females. Such findings are important as differences by sex in the direction of the relationship between inflammatory markers and pain in OA may aid in explaining reported sex differences in treatment responses to NSAIDs, and could provide clues to the apparent lack of relative efficacy of newer, cytokine-targeted, drugs in OA [23–25].

The analytic methodology in our study differs from most studies of the relationship between factors of inflammation and pain, and other factors between more generally, where the approach often is simply to adjust the analyses by sex, with the implicit assumption that the ‘averaged’ associations reported are equally applicable to males and females. When we used this approach (our initial model) only two of the markers considered in the current study (IL-10 and TNF-α) were related to knee pain. However, when we included interactions with sex, an additional three markers (IL-6, IL-8 and IL-1p) were found to be related with knee pain, but differently so for females and males. ‘Differently’ here refers not to differences in the strength of a similarly oriented relationship, but rather a different direction of relationship altogether (positive vs. negative). Others have noted that while a uniform approach is traditionally assumed for males and females in biomedical research, sex may influence both pathophysiology and efficacy of therapeutics [26–28]. A lack of sex-specific investigation may miss important underlying relationships; our results confirm this possibility.

IL-1p along with its endogenous antagonist IL-1Ra play an important role in inflammatory responses, and have been implicated in OA pain [10,29,30]. Contradictory results have emerged around the influence of IL-1 cytokines from a number of studies examining genetic susceptibility to hip and knee OA [31,32]. Bessler et al. reported sex-dependent differences in an IL-1Ra gene polymorphism and suggested that this may affect both IL-1 and IL-1ra levels, and that this diversity might be one of the causes for differences in immune response observed in autoimmune diseases and pain perception between males and females [33]. These findings may help explain the differences we found by sex; increasing systemic levels of IL-1p were associated with worse knee pain scores in males but not females.

IL-6 is largely characterized as pro-inflammatory in OA pathophysiology, and a number of cytokines active in OA can directly stimulate its production [16]. Elevated systemic levels are reported in OA [34,35]. However, its exact role is debated, likely stemming from inconsistent findings in the literature with respect to associations with OA symptoms and additionally to findings that IL-6 also has anti-inflammatory properties [10,30,36,37]. We did not find a relationship between IL-6 and pain in our overall sample. However, this was likely due to an underlying relationship that was found to be negative in males and slightly positive
in females. This parallels findings reported by Azim et al. studying patients scheduled for knee arthroplasty (41 males, 57 females), in that a positive correlation between disability pain scores and systemic IL-6 was found in females but not males [38]. As in our sample, Azim et al. found no differences in median IL-6 levels between males and females. Furthermore, the authors measured IL-6 and TNF-α levels within the 72 h following surgery, and reported different patterns for IL-6 for females and males, but similar changes in TNF-α for both sexes.

There have been inconsistent results reported in the OA literature with respect to systemic IL-8 [39–41]. We found a positive relationship between IL-8 and knee pain scores in males but not in females. Solheim et al. examined inflammatory markers related to acute pain in synovial fluid and their relationship with pain intensity following knee arthroscopic procedures for OA (28 females, 37 males) [42]. Among those reporting moderate/severe pain, three markers, including IL-8, were higher in males, with differences of >1 normalized protein expression; none were overexpressed to this degree in females. Furthermore, in this moderate/severe pain group where just over half were female, the relationship between IL-8 and pain (visual analog scale) was moderately negative, while among those with less than moderate pain, 75% of whom were male, the association was moderately positive. Together with our results, these findings suggest that inconsistencies in the literature in regards to the association between IL-8 and OA pain may in part be explained by differences in relationship by sex.

In both females and males we found higher systemic levels of TNF-α were associated with worse pain. Available literature supports that TNF-α is a prominent pro-inflammatory cytokine in OA. TNF-α has been shown to contribute to OA progression, with elevated systemic levels being identified in patients with OA symptoms [10,43,44]. Similarly, in both females and males we found higher IL-10 was associated with lower pain scores. This finding is in keeping with available research that identifies IL-10 as having potent anti-inflammatory properties [30,37]. Further, it has been suggested that low systemic levels of IL-10 could be key to chronic pain, with other work finding that low IL-10 was present in patients with chronic widespread pain compared to patients without [45].

Sex differences may also relate to hormones. Hormonal effects on inflammation represent an important and complex pathway whereby sex hormones can influence pain responses. While some researchers have hypothesized that the observed increase in OA incidence at menopause may be due to estrogen loss unmasking OA symptoms by enhancing pain sensitivity, findings in relation to menopausal status and pain have been inconsistent [46,47]. Data on sex hormone levels were not available for the current study. Our sensitivity analyses that restricted the sample to those aged >55 years, used as a proxy for post-menopausal status, had unchanged results. We acknowledge this is a crude proxy and further work will need to include plasma levels of sex hormones. In addition, further study is needed to investigate whether there are fundamental underlying sex differences in OA phenotypes that may contribute to the differences we observed in the relationships between systemic inflammatory markers and pain.

This study was limited to individuals with late-stage disease and this precludes generalizability to individuals earlier in the disease course, and perhaps younger ages. However, Kisand et al. examined relationships between cytokine and growth factor profiles in early-stage knee OA (25 males, 35 females) [48], and while different cytokines than those
considered presently were evaluated, they also demonstrated significant sex-dependent differences in cytokine profiles, including with opposing directionality for males and females. As in our case, the authors noted that when patients were pooled (i.e. no sex differentiation), relationships were weakened or unobserved.

We included only 5 inflammatory markers in the current study. Further work will need to examine a wider range. Local inflammatory markers were also not considered in this study. It will be important in future work to assess synovial inflammatory marker levels and determine whether independent/synergistic associations are present that may also be sex-specific. Furthermore, it is possible that systemic markers could originate from other tissues, including other affected joints [16,49]. Consequently, the number of other symptomatic joints was explicitly considered in the current analyses. ‘Symptomatic’ was defined as “pain, stiffness or swelling most days of the month”; a definitive radiographic-based OA diagnosis was not available for all individual joints. OA pain is heterogeneous in nature (e.g. nociceptive, neuropathic) and relationships with inflammatory markers may vary by type [50]. Additional work is needed to determine whether sex-specific relationships are consistent across types of pain. The overwhelming majority of patients in this study took pain killers, but data on specific drugs were not available. Further work will need to explicitly consider use of over-the-counter and prescription NSAID drugs, as well as other pain medications.

Our findings provide some evidence of possible sex-specific relationships between individual inflammatory markers and knee OA pain. While they do not have immediate clinical implication, as further validation of the results in larger samples is needed, the findings suggest that future development of novel approaches to treat OA may ultimately need to vary by sex depending on therapeutic targets. The study provides a basis for further investigation in this area, with findings suggesting that sex considerations may potentially be key to a more comprehensive understanding of OA pathophysiology.

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Contributions

Conception and design: AVP, EMB, JDP, MC, RG, YRR.
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Analysis/Interpretation of the data: EMB, JDP, MC, MK, JR, VC, RG, NNM, JDR, KS, CV, YRR.
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Conflicts of interest

VC reports grants and personal fees from Abbvie, personal fees from Amgen, Celgene, BMS, Janssen, Novartis, Pfizer, and UCB, and personal fees and other from Eli Lilly, outside the submitted work. YRR reports personal fees from Medtronic, outside the submitted work. All other authors report no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2019.100004.

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