Title

Association of Intermittent and Constant Knee Pain Patterns With Knee Pain Severity and With Radiographic Knee Osteoarthritis Duration and Severity

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Association of intermittent and constant knee pain patterns with knee pain severity, radiographic knee osteoarthritis duration and severity.

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Abstract

Objectives: To examine the relation of knee pain patterns to pain severity, and to radiographic osteoarthritis (OA) severity and duration.

Methods: The Multicenter Osteoarthritis Study is a longitudinal cohort of older adults with or at risk of knee OA. Participants' Intermittent and Constant OA Pain (ICOAP) scores were characterized as 1) no intermittent or constant pain; 2) intermittent pain only; 3) constant pain only; and 4) a combination of constant and intermittent pain. Knee pain severity was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale and the Visual Analog Scale (VAS). Radiographic knee OA (ROA) severity was defined as Kellgren Lawrence grade ≥ 2, and ROA duration was defined according to the clinic visit at which ROA was first noted. We assessed the relation of ICOAP pain patterns to knee pain severity, ROA severity, and ROA duration using regression models with generalized estimating equations.

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Results: There were 2322 participants (mean age 68.8, BMI 31.0 kg/m2, 60% female). Higher ICOAP pain patterns, i.e., a mix of constant and intermittent pain were associated with greater WOMAC pain severity compared with those without either pain pattern, OR 43.2 (95%CI 26.4–61.3). Results were similar for the VAS OR 71.2 (45.7–110.9). Those with more severe and longer duration of ROA were more likely to have a mix of constant and intermittent pain compared with those without either pain OR 3.7 (3.1– 4.6) and OR 2.9 (2.5–3.5), respectively.

Conclusions: Knee pain patterns are associated with radiographic disease stage and duration, as well as pain severity, highlighting that pain patterns are important for understanding symptomatic disease progression.

Keywords

ICOAP; pain severity; intermittent and constant pain

Introduction

Knee osteoarthritis (OA) is a progressive disease whereby the frequency and severity of pain typically increases with worsening disease(1). Qualitative research has identified that three specific patterns of pain in knee OA vary depending on the stage of the disease(2). These three patterns are reflected by the frequency of pain as being intermittent, constant or a mix of constant with intermittent, whereby people experience intermittent activity-related pain, then constant pain as the disease progresses, and finally the late stage of disease is demarcated by constant pain overlaid by more severe, often unpredictable, intermittent pain. Based on this understanding, a new measure, the Intermittent and Constant Osteoarthritis Pain (ICOAP) scale was developed to capture these pain patterns thus allowing for improved understanding of pain in the different phases of disease(3).

The psychometric properties of the ICOAP measure were initially assessed (items, subscale and total scores) showing significant correlations with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale and the Knee Injury and OA Outcomes symptom scale in a relatively small sample(3). The scale has subsequently been validated with measures of self-reported function, physical performance and physical activity using accelerometry(4, 5). However these studies have not evaluated the relation of the three different pain patterns (i.e., intermittent, constant or constant +/− intermittent) that appear to reflect different disease stages, regardless of pain severity, to established symptom severity assessment instruments. In addition, there has not been a specific evaluation regarding the original premise of ICOAP pain patterns reflecting stage of disease in OA, typically defined radiographically, to date. That is, are mild radiographic findings or early stage disease associated with intermittent pain, intermediate radiographic stages with constant pain, and late disease with both.

Therefore, the objectives of this study were to examine the relation of ICOAP-defined pain patterns to knee pain severity, radiographic disease severity and duration.

Methods

The Multicenter Osteoarthritis (MOST) Study is a NIH-funded longitudinal cohort of community dwelling adults between the ages of 50–79 years who had or were at risk of developing knee OA at baseline. Subjects were recruited from Birmingham, Alabama and Iowa City, Iowa. Details of the cohort have been published elsewhere(6). The study was approved by the institutional review boards at the University of Iowa, University of Alabama at Birmingham, University of California at San Francisco, and Boston University Medical Center that were in compliance with the Helsinki Declaration. The current sample comprised participants who attended the 60-month visit (baseline for this study) since it was the first time the ICOAP measure was obtained.

Pain measures

The ICOAP is an 11-item measure consisting of items for each of two subscales, Intermittent and Constant. Items include pain intensity, pain frequency (for the Intermittent subscale), effect on sleep and quality of life, and the extent to which the pain ‘upsets or worries’ and ‘frustrates or annoys’. Initial psychometric testing of the scale demonstrated good validity and reliability(3). At the 60-month visit, participants who reported at least some knee pain in the prior 30 days were asked to complete ICOAP. ICOAP was obtained in a knee-specific manner, inquiring about symptoms over the prior 7 days. ICOAP pain patterns were defined according to responses to each respective subscale item on severity ranging from none to extremely on a 5 point scale as follows: 1) no intermittent or constant pain; 2) intermittent pain only (of at least ‘mild’ severity and with a frequency of at least ‘sometimes’); 3) constant pain only (of at least ‘mild’ severity); and 4) a combination of constant and intermittent pain, as defined above. Pain severity was measured using a knee-specific WOMAC (Likert version) pain subscale (0–20 range) inquiring about pain during the past 30 days(6). Scores were categorized as none, mild/moderate or severe/extreme(7, 8). Higher scores on the WOMAC indicate greater pain. A knee-specific visual analog scale measured average pain severity (0–10) in the past 30 days, and was categorized as 0, 1–4 and >4 (out of 10)(9).

Radiographic analysis - duration and severity

Bilateral weight-bearing fixed-flexion posteroanterior radiographs of the knee were obtained at each study visit (0, 30 and 60 months). Radiographic severity in the tibiofemoral joint was graded by two experienced readers blinded to clinical data according to Kellgren and Lawrence (KL) criteria (0–4)(10). Any disagreements between readers were adjudicated by a third reader along with the first 2 readers to reach consensus. The inter-rater reliability weighted kappa for the KL grade was 0.80. Radiographic knee OA (ROA) was defined as KL > 2. OA duration was defined according to the clinic visit at which ROA was first noted (i.e., longest duration was for those who had ROA at baseline; shortest duration was for those whose ROA was identified at the 60-month visit).

Potential confounders and relevant covariates

Variables included age, sex, body mass index (BMI), widespread pain (WSP), depressive symptoms, pain catastrophizing, study site, race and Kellgren and Lawrence grade (for the

pain severity analyses) at the 60-month visit. As per previous studies, WSP was operationalized using a validated standard homunculus(11). The Center for Epidemiologic Studies Depression Scale (CES-D) score of 16 or greater was utilized to define depressive symptoms(12). Pain catastrophizing was measured using one item from the Coping Strategies Questionnaire, which has been shown to be valid and reliable (13). Race was categorized as Caucasian vs other.

Analyses

We first evaluated the mean WOMAC pain and mean VAS pain (outcomes) for each ICOAP pain category (none, intermittent only, constant pain only, both constant and intermittent pain) (exposure), and the relation of ICOAP pain patterns (exposure) to likelihood of having greater pain severity with generalized estimating equations (GEE) to account for two knees within an individual. We also hypothesized that those with greater pain severity would be more likely to have constant pain. We therefore evaluated the relation of knee pain severity categories (WOMAC and VAS, separately) (exposures) to ICOAP pain patterns (outcomes) using proportional odds logistic regression with GEE. Similarly, we hypothesized that those with greater ROA severity and duration would likely have a more advanced ICOAP pain pattern. To evaluate this, we examined the relation of ROA severity and duration (exposures) with ICOAP pain patterns (outcomes) using proportional odds logistic regression with GEE. All analyses were adjusted for age, sex, BMI, WSP, depressive symptoms, pain catastrophizing, and clinic site. KL grade and race were additionally adjusted for in the knee pain severity analyses. All analyses were performed using SAS 9.3 (SAS Institute, Gary, North Carolina, USA).

Results

At the 60-month visit, there were 2322 participants (4632 knees) with ICOAP data (mean age 68.8 sd 8, BMI 31.0 sd 6, 60% female). The majority of knees (62%) had neither intermittent nor constant pain, 30% had intermittent pain only, 4% had constant pain only, and 4% had both. 60% of knees had no ROA while 5.5% had incident ROA at the 60-mo visit (shortest duration of OA), 5.5% had incident ROA at the 30-mo visit, and 29.5% had ROA at the baseline visit (longest duration of OA) (Table 1).

Knee pain severity

By both the WOMAC and VAS scores, approximately 55% of knees had mild to moderate pain and approximately 11% had severe/extreme pain. Mean WOMAC pain (1.2, 4.9, 8.2 and 9.0) and mean VAS pain (6.0, 27.5, 43.5, 53.2) increased with each successive ICOAP pain pattern category, i.e., No Intermittent or Constant pain, Intermittent pain only, Constant pain only and Constant plus intermittent pain. ICOAP pain patterns (as per our definitions), were associated with greater likelihood of being in a higher pain severity category by WOMAC and VAS. Specifically, those with a mix of constant and intermittent pain had 43 and 71 times higher odds of having greater pain severity than those without either type of pain (OR [95%CI] 43.2 [26.4–61.3] for the WOMAC; OR 71.2 [45.7– 110.9] for VAS (Figure 1). Additionally, greater WOMAC and VAS pain severity categories had higher odds of being associated with constant rather than intermittent pain only. For example, those with

severe/extreme pain and those with mild/moderate pain by WOMAC had 3.8 times (95% CI 1.5–9.4) and 1.4 times (95% CI 0.6, 3.3) higher odds of having constant versus intermittent pain only compared with those with WOMAC pain score of 0, respectively. For VAS, those with scores greater than 4 (OR 4.7 (1.7–12.6)) and those with pain scores between 1–4 (OR 1.2 (0.5–3.3)) similarly had higher odds of having constant versus intermittent pain only compared with those whose VAS score was 0 (Table 2).

ROA severity and duration

As shown in Table 3, those with greater ROA severity and a longer duration of knee ROA had higher odds of having pain patterns hypothesized to be associated with such a disease status (i.e., both intermittent and constant pain at the 'highest' end of the ICOAP pain pattern). For ROA severity, there was a significant trend of having increasing odds (1.3, 2.0, and 3.7 respectively) of higher KL grade with combined constant and intermittent pain compared with neither pain being present. Similarly, a significant trend was observed for ROA duration. When we limited our analysis to those with some pain (i.e., excluded those that reported no pain on ICOAP; final column of Table 3), those with the shortest duration of OA had a similar likelihood of having constant versus intermittent pain as those with no ROA (OR 0.7, 95%CI (0.4– 1.3). Those with longer durations of OA, i.e., present for at least 60 months, had 1.4 times higher odds of having constant versus intermittent pain OR 1.4 (1.0 – 2.0).

Discussion

Previously published qualitative data have suggested that with progression of knee OA over time, the pain associated with knee OA transitions from intermittent to constant pain, punctuated by intermittent unpredictable pain(2). This served as the foundation for the development of the ICOAP measure. In light of this information, we sought to evaluate whether these identified conceptual clinical pain patterns, regardless of pain severity and as assessed by the ICOAP, were associated with expected increments in radiographic disease severity and longer duration of radiographic disease, as well as greater pain severity. We found that knee pain patterns defined by the ICOAP instrument were associated with greater ROA severity and duration. We note that the ICOAP-defined pain patterns indicative of later stage disease, regardless of symptom severity on the ICOAP instrument, were associated with greater pain severity by both WOMAC and VAS.

These ICOAP-defined pain patterns to our knowledge have not been analyzed in this manner in prior published work. Therefore similar comparisons are not possible as typically only the summed subscale scores, and/or their correlations with, for example, the WOMAC pain subscale, have been published (5, 14). It would not be surprising that the summed scores would be associated with pain severity by WOMAC since the ICOAP summed score includes an element of pain severity in some of the questions. Our evaluation of the knee pain patterns were defined without regard to pain severity (i.e., intermittent or constant pain was defined by their reported presence). Additionally, the ICOAP assesses symptoms during the past week while WOMAC and VAS pain scales assessed pain in the past 30 days, allowing us to examine the implications of the knee pain patterns outside of the one-week

time frame. It should be noted that while the odds ratios were large, the confidence intervals were wide demonstrating imprecision of the estimates, reflecting the lower prevalence of constant pain and of constant plus intermittent pain in this community-based sample. Perhaps the closest approximation of our results come from a previous study of MOST data that focused on consistency of knee pain symptoms over 1 month. Although the ICOAP was not used, it was reported that knee pain severity was higher in those with consistent pain (present on most days over a two-month period) compared to inconsistent pain (only present on most days over one month) and those with ROA were less likely to have inconsistent pain(15).

We found that greater severity and longer duration of ROA were associated with greater likelihood of constant plus intermittent pain compared with neither pain type being present. In addition, longer ROA duration was also associated with constant pain only versus intermittent pain only and there was a dose-response relationship. These results suggest the possibility that differing pain mechanisms underlie intermittent and constant pain. For example, constant pain found in later stages of disease severity may be representative of central pain sensitization, whereas earlier intermittent pain may be largely peripherally-driven nociceptive input(16). This speaks more broadly to the need to understand other pain dimensions, such as these pain patterns, beyond pain severity alone to truly understand symptomatic disease progression.

The relation of ICOAP-defined pain patterns to ROA duration and severity is novel and lends new support to previous longitudinal studies that have demonstrated the presence of different pain patterns and their variability(17). This provides, for the first time, proof-of-concept evidence that these pain patterns do indeed track with OA structural disease. This work supports a relationship between the pain experience and its association with ROA severity and duration, which have had conflicting correlations with pain severity(17). These results point to the likelihood that pain severity itself is not an adequate metric to understand the stage of symptomatic OA disease. Our data suggest that clinicians may be able to use the ICOAP as a tool to effectively track knee OA progression, and this approach may potentially help mitigate the so-called ‘structure-symptom’ discordance. Studies are needed to understand what may trigger the transition to more advanced pain patterns. However, discerning at what stage of OA pain patterns change from being intermittent in nature to constant and then to constant with unpredictable intermittent pain will require longitudinal data in which greater variety in duration (and severity of OA) is captured along with the unpredictability of the intermittent pain.

Our main study limitation is that we were unable to ascertain the influence of the onset or frequency of unpredictable intermittent pain that occurs after a specific trigger. This information may provide further discrimination of the stage of disease. Strengths of our study include the examination and validation of ICOAP-defined pain patterns with important indicators of stage of disease with adjustment for known confounders and relevant covariates, in addition to our use of standardized and validated questionnaires. Further, this is the largest study to date to validate ICOAP with high quality standardized radiographs.

In conclusion, ICOAP-derived knee pain patterns (intermittent, constant, constant + intermittent) are associated with overall pain severity symptoms, disease duration and severity of ROA. This supports previous qualitative work that described a progression from intermittent to constant pain, culminating in a combination of the two as the OA disease process progresses. These findings highlight the need for a broader approach to understanding pain and its mechanisms that likely differ by stage of disease. Importantly, while pain severity alone is insufficient to understand disease stage and progression, these knee pain patterns appear to likely be more useful for understanding symptomatic disease progression.

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Significance and Innovations

- In a cross-sectional analysis of a prospective cohort of people with or at risk of knee osteoarthritis, knee pain patterns (intermittent pain, constant pain or constant + intermittent pain) were associated with radiographic disease stage and duration, as well as pain severity.
- These findings highlight the importance of pain patterns for understanding symptomatic disease progression.

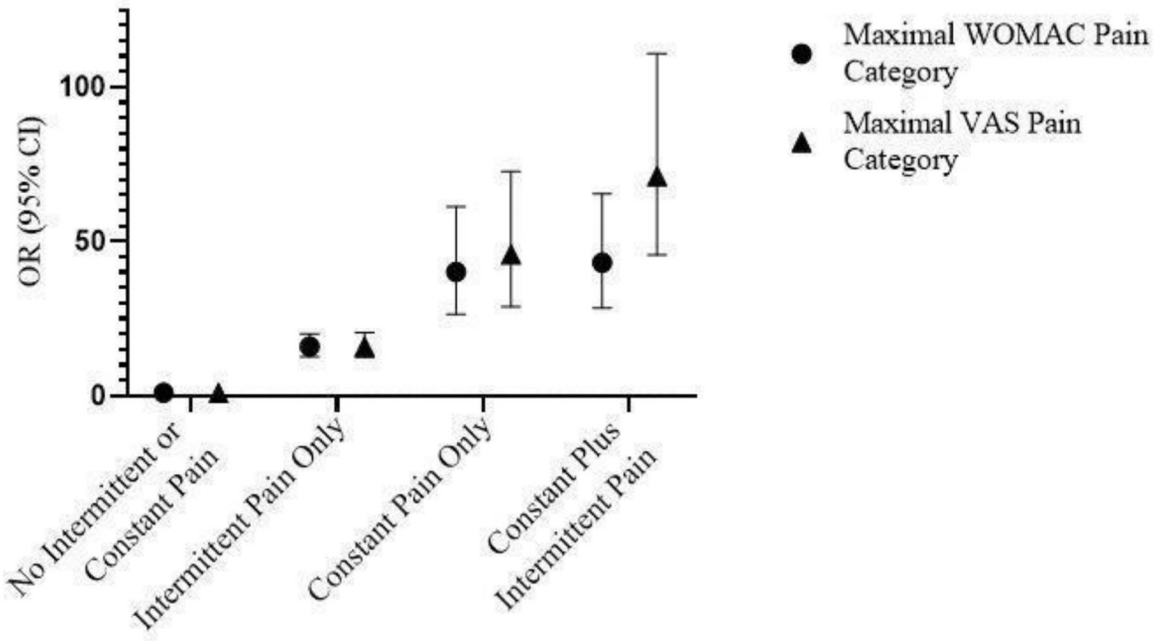

Figure 1.

Maximal Womac and VAS pain category by pain patterns

Adjusted for age, sex, BMI, catastrophizing, depressive symptoms, WSP, race, KL grade and clinic site

P for linear trend <0.0001 for both WOMAC and VAS

Table 1.

Participant characteristics

Characteristic	N= 2322 (4632 knees)
Age, years, (mean (SD))	68.8 (8.0)
Female (%)	60
BMI, kg/m^2 (mean (SD))	31.0 (6.0)
ICOAP pain patterns N (%) (knees)	
No intermittent or constant pain	2873 (62)
Intermittent pain only	1389 (30)
Constant pain only	185 (4)
Both constant and intermittent pain	185 (4)
KL grade N (%) (knees)	
0	2130 (46)
1	649 (14)
2	834 (18)
3 or 4	1019 (22)
Radiographic knee OA status N (%) (knees)	
No OA	2779 (60)
Incident at 60-mo (shortest duration)	255 (5.5)
Incident at 30-mo	255 (5.5)
Prevalent at baseline (longest duration)	1343 (29)

Table 2

Association of WOMAC and VAS categories with ICOAP Constant vs Intermittent pain

	ICOAP constant vs intermittent pain adj OR* (95% CI)
Maximal WOMAC knee pain:	
1. None (n=1638)	(ref)
2. Mild/moderate pain (n-2471)	1.4 (0.6 – 3.3)
3. Severe/extreme pain (n=514)	3.8 (1.5 – 9.4)
	P for linear trend <0.0001
Maximal VAS knee pain	
1. 0 (n=1560)	(ref)
2. 1–4 (n=2529)	(0.5 – 3.3)
3. >4 (n=534)	4.7 (1.7 – 12.6)
	P for linear trend <0.0001

*Adjusted for age, sex, BMI, catastrophizing, depressive symptoms, WSP, race, KL grade and clinic site

Table 3.

Association of radiographic severity and duration of OA with ICOAP

†Knee OA Severity	†ICOAP 4-level outcome *Adjusted OR (95% CI)	Knee OA Duration	†ICOAP 4-level outcome *Adjusted OR (95% CI)	++ICOAP constant vs intermittent pain only *Adjusted OR (95% CI)
KL=0 (N=2130, 46%)	1.0 (ref)	No OA (N=2779)	1.0 (ref)	1.0 (ref)
KL=1 (N=649, 14%)	1.3 (1.1–1.7)	Incident OA at 60-mo (shortest duration) (N=255)	1.8 (1.3–2.4)	0.7 (0.4 – 1.3)
KL=2 (N=834, 18%)	2.0 (1.6–2.5)	Incident OA at 30-mo (N=255)	2.3 (1.7–3.1)	1.5 (0.9 – 2.5)
KL=3 or 4 (N=1019, 22%)	3.7 (3.1–4.6)	Prevalent at 1st study visit (longest duration) (N=1343)	2.9 (2.5–3.5)	1.4 (1.0 – 2.0)
P for linear trend:	<0.0001	P for linear trend:	<0.0001	0.03

*Adjusted for age, sex, BMI, catastrophizing, depressive symptoms, WSP and clinic site

†ICOAP pain patterns modeled as 4-level ordered outcome as defined in methods

++ICOAP pain modeled as any constant pain vs intermittent pain only