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Consistency of Knee Pain: Correlates and Association with Function

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Abstract

Objective—The extent and factors associated with knee pain fluctuation are not well-known. We evaluated the prevalence, correlates, and association with function of consistency of knee pain.

Design—Participants of The Multicenter Osteoarthritis (MOST) Study, a cohort of individuals with or at high risk of knee osteoarthritis (OA) had baseline knee x-rays, questionnaires, and a question about frequent knee pain (FKnP) (pain on most of the past 30 days) at two time points: a telephone screen and a later clinic visit. We computed the prevalence of inconsistent knee pain (positive answer to FKnP question at only one time point) and consistent knee pain (positive answer to FKnP question

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Author contributions

All authors made substantial contributions to all three of:

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The authors have no conflicts of interest to declare.

at both time points). We evaluated the association of consistency of FKnP with a number of sociodemographic factors, pain severity, and function.

Results—There were 2940 participants with complete data (5867 knees) (mean age 62, mean BMI 30.7, 60% female). Of those, 2977 knees had pain, with 43% having inconsistent and 57% having consistent knee pain. Those with radiographic OA (OR 0.46), depressive symptoms (OR 0.73), and widespread pain (OR 0.68) (all $p<0.05$) were less likely to have inconsistent compared with consistent knee pain. Pain, function, and strength were significantly better in persons with 2 knees that had inconsistent compared with consistent pain.

Conclusions—A substantial proportion of persons with knee pain have inconsistent knee pain, associated with better physical function and strength (adjusting for pain severity). Such pain may be suggestive of an earlier stage of disease.

Keywords

Osteoarthritis; Knee pain; Temporal pattern; function

Introduction

While pain related to knee osteoarthritis (OA) may generally be considered to be chronic, it is known that such pain can fluctuate. For example, a key distinguishing feature of OA-related pain from that of inflammatory arthritis-related pain is that the pain of OA is typically worsened with activity and relieved with rest. Pain in persons with OA is a key determinant for seeking medical care.[1] Further, presence of pain related to knee OA and its severity are associated with disability and radiographic severity and progression.[2–4] Yet, despite the importance of pain in OA, relatively little research has been conducted to better understand the determinants and potential consequences of different patterns of knee pain. More recently, qualitative data support the concept of different “stages” of knee OA as defined by pain patterns, with those in the earlier stages of OA experiencing predictable episodes of pain triggered by an activity, those in middle stages of OA experiencing some constant pain along with predictable and unpredictable episodes of pain accompanied by some functional limitations, while those in the advanced stages of OA have more constant pain with episodes of unpredictable pain accompanied by substantial functional limitations.[5]

While these knee OA stages related to pain have now been described, repeated assessments of subjects over short time intervals has been lacking in most prior studies, making it difficult to characterize pain patterns in individuals over time and in turn, study risk factors and consequences epidemiologically. Many studies that have attempted to understand factors associated with pain in OA have often been limited to assessment of pain symptoms at a single time point.[6–10] Studies that are able to elicit pain status over multiple study visits are also limited by quantifying pain at each visit as being present or absent, or by its severity at that particular time. Indeed, some of the so-called radiographic-symptom discordance in knee OA may be in part related to the fluctuating nature of knee pain, with studies in which knee pain is only assessed at a single time point possibly misclassifying individuals with respect to their pain status. A more comprehensive evaluation of temporal knee pain patterns related to knee OA are required to better understand potential pathophysiology and the impact of the disease. Further, such pain fluctuation also has implications for trial enrolment[11] as treatment effects may be difficult to discern, and for treatment itself in terms requirement of daily versus episodic therapy.

We took advantage of a study of a large cohort of individuals with or at high risk for knee OA in which a question about the presence of frequent knee pain was asked twice approximately one month apart to determine the prevalence of and factors associated with consistency of knee pain.

Methods

Study Population

The Multicenter Osteoarthritis (MOST) Study is a prospective cohort study of 3026 individuals aged 50 to 79 years whose goal is to identify risk factors for incident symptomatic knee OA and progressive OA in a sample either with or at high risk of OA. All MOST subjects were recruited from 2 communities in the US, Birmingham, Alabama and Iowa City, Iowa. Details of the study population have been published elsewhere.[12] The study protocol 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.

Pain Assessment

We were able to undertake this study because the parent study by design asked participants about presence of frequent knee pain at two time points within close proximity of one another. At baseline, participants were asked a knee-specific question regarding frequent knee pain, as follows: "During the past 30 days, have you had pain, aching, or stiffness in your knee on most days?" This question was administered at two time points: a telephone screen followed by a clinic visit which occurred on average 35.7 days (SD 27.3; median 33 days, interquartile range 24–41 days) after the telephone screen. The telephone screen and clinic visit assessments were independent of one another with no information about the response to the telephone screen available at the time of the clinic visit.

Positive responses to the frequent knee pain question were considered to indicate presence of frequent knee pain; negative responses were considered to indicate the absence of frequent knee pain. Because some of the factors we assessed, such as radiographic OA status, were knee-based, and other factors, such as function measures, were measured on a person-level, we defined consistent and inconsistent pain at a knee level and on a person level. For a knee-based definition, a knee was considered to have ***consistent knee pain*** if the participant answered "yes" to the frequent knee pain question at both the telephone screen and clinic visit for a given knee, or to have ***inconsistent knee pain*** if they answered "yes" to that question at only one of the telephone screen or clinic visit for a given knee. ***No frequent knee pain*** was present when the participant answered "no" at both times. For a person-based definition, because numerous combinations of knee pain patterns can exist for two knees within a person, we limited our investigation to those who had the same pain pattern in each knee. Specifically, a person was considered to have either two knees with no frequent pain, two knees with consistent pain, or two knees with inconsistent pain. For this latter group (those with two knees with inconsistent pain), the presence of pain was contemporaneous with the clinic visit to coincide with the person-level clinic visit measures (such as function) occurring at the same time as frequent pain being present (Table 1). This latter group was also chosen to help determine whether knowing a study participant's prior/recent frequent knee pain status when they are reporting presence of frequent knee pain at a clinic visit offers a further means to help more accurately phenotype one's pain status.

For pain severity assessments, a knee-specific WOMAC pain questionnaire[13] and a knee-specific pain VAS were administered.

Factors potentially associated with pain pattern

Factors potentially associated with pain were chosen based upon those previously noted in the literature. All factors were assessed at the baseline clinic visit, including age and sex. Weight

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was measured without shoes or heavy jewelry in lightweight clothing using a standard balance beam scale. Height was measured at baseline without shoes at the peak of inhalation using a Harpenden stadiometer. Body mass index (BMI) was calculated as weight in kg divided by height in m^2.

All participants underwent bilateral weight-bearing fixed-flexion posteroanterior (PA) and lateral radiographic evaluation of the knee.[14] Radiographs were scored by a musculoskeletal radiologist and a rheumatologist, both experienced in reading study films, with a standardized adjudication process and blinded to clinical information. Each knee joint was scored for Kellgren and Lawrence (KL) grade (0–4).[14–16] Radiographic OA was defined as KL grade ≥ 2.

Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression scale (CES-D) instrument.[17] Depressive symptoms were considered to be present if the CES-D score was ≥ 16. Presence of widespread pain was determined from pain reported on a homunculus using a previously validated definition.[18] Medication use was ascertained by interviewer-administered questionnaire. Participants brought their prescription and non-prescription medications to the clinic visit and were asked if each medication was used on a regular or intermittent basis. Medications that were considered to be “pain” medications included NSAIDs (including cox-II inhibitors), non-opioid analgesics such as acetaminophen and opioid analgesics. Additional sensitivity analyses were conducted including muscle relaxants, neuroleptics, antidepressants and anxiolytics.

For function assessments, WOMAC function questionnaire,[13] SF-12 physical component summary score,[19] and Physical Activity Scale for the Elderly (PASE)[20] were administered. Muscle extensor strength was ascertained isokinetically (Cybex 350, HUMAC software version 4.3.2/Cybex 300 for Windows98, Avocent, Huntsville, AL).

Statistical Analyses

We evaluated the association between a number of potential factors and consistency of knee pain. Specifically, among those with frequent knee pain at one or both of the telephone screen and clinic visit, we evaluated the relation of various factors to inconsistent compared with consistent knee pain. Generalized estimating equations (GEE) were used to account for correlations between knees within individuals.[21] Potential correlates included age, sex, BMI, radiographic OA, depressive symptoms, widespread pain, and pain medication use. We evaluated the differences in severity of knee pain as well as quadriceps strength among knees with consistent and inconsistent knee pain using multivariable linear regression. For person-level measures of function scores, we evaluated differences in function scores using the person-based definitions of knee pain patterns described above (*i.e.*, consistent pain in both knees, inconsistent pain in both knees, and no frequent pain in both knees) using multivariable linear regression. Finally, we evaluated the association of pattern of pain medication use with inconsistent versus consistent knee pain using logistic regression with GEE. All analyses were adjusted for each of the potential correlates assessed, the number of days between the telephone screen and clinic visit, and pain severity in those analyses in which pain severity was not the primary focus (*e.g.,* function, strength, pain medication use analyses).

All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

Results

At baseline there were 2940 participants for whom all measures were available, contributing 5867 knees. Their mean age was 62.3 (SD 8.1) with mean BMI 30.7 (SD 6.0). Sixty percent were female, and 36.6% of knees had radiographic OA. Overall, 50.5% of knees had pain at one or both of the telephone screen and clinic visit. Of the 2977 knees with pain, 1280 (43%) had inconsistent knee pain and 1697 (57%) had consistent knee pain. Of those with inconsistent knee pain, 39% had radiographic OA, compared with 56% of those knees with consistent pain.

Higher radiographic K/L grades, depressive symptoms and widespread pain were significantly associated with lower odds of having inconsistent knee pain rather than consistent knee pain (Table 2). Specifically, there appeared to be a dose-response relation for K/L grade, such that each successive higher K/L grade was associated with lower odds of inconsistent knee pain compared with consistent knee pain. Further, in separate analyses, radiographic OA itself was associated with lower odds of inconsistent than consistent knee pain (adjusted OR 0.46, 95% CI 0.39–0.55). Age was also significantly associated with inconsistent pain; for each 10 year increase in age, there was a 1.21 (95% CI 1.08–1.34) times higher odds of having inconsistent pain compared to consistent pain. In contrast, sex and BMI were not associated with inconsistent knee pain. In additional adjusted analyses, presence of pain in the lower back or other lower extremity sites other than the knee (i.e., hip, ankle, or foot) was not significantly associated with presence of inconsistent knee pain (adjusted OR 0.85, 95% CI 0.68–1.07).

Knee pain was, on average, significantly milder in knees with inconsistent knee pain than in knees with consistent pain (Table 3), and pain reporting was higher in those with inconsistent knee pain than in those knees without frequent pain. For example, the WOMAC pain score was 6.5, 3.8, and 1.5, for consistent, inconsistent, and no frequent knee pain, respectively, and the VAS global knee pain score was 37.2, 20.3, and 7.7, respectively. Muscle strength was also significantly different across the different knee pain temporal patterns, even after accounting for knee pain severity. Knees with consistent pain had the lowest quadriceps strength (82.2 Nm), while those with inconsistent pain had intermediate quadriceps strength (90.6 Nm), and those with no frequent knee pain had the greatest quadriceps strength (99.1 Nm).

Similar patterns were noted when evaluating person-level knee pain patterns in relation to function scores (Table 4). For both the WOMAC physical function and the SF-12 physical component summary score, persons with two knees with consistent pain had significantly worse scores than those with two knees that had inconsistent pain. While the WOMAC physical function score was significantly worse in those with inconsistent knee pain than individuals with two knees that had no frequent pain, there was no such difference on the SF-12 physical component summary score. There were no differences among the groups with respect to the PASE scores.

Finally, there was no significant difference in regular or intermittent use of pain medications between those with inconsistent pain and consistent pain (Table 5). However, those with inconsistent pain were more likely to not use any pain medications than those with consistent pain (OR 1.75 (95% CI 1.22–2.50)). In additional analyses in which we also considered use of muscle relaxants, neuroleptics, antidepressants, and anxiolytics, those with inconsistent pain were 1.89 times more likely to not use any such medications compared with those with consistent pain (p=0.04).

Discussion

In this large cohort in which presence of frequent knee pain was ascertained at two time points approximately one month apart, a substantial proportion had inconsistent knee pain. A number of factors distinguished inconsistent knee pain from consistent knee pain. The presence of inconsistent knee pain was associated with a lower prevalence of radiographic OA, older age, less depressive symptoms, milder knee pain severity scores, more quadriceps strength, less functional limitation, and less pain medication use compared with those with consistent knee pain. In contrast, sex and BMI were not associated with having inconsistent versus consistent

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knee pain, although these factors are often thought to be associated with pain. One caveat about interpreting the BMI findings in this cohort is that BMI was generally high. Therefore there may not have been a sufficient number of thinner subjects to adequately assess the relation of BMI to temporal knee pain pattern. It's not clear as to why older age appears to be associated with greater chance of having inconsistent compared with consistent knee pain. Other factors, such as physical activity immediately prior to the pain assessment, or history of OA "flares", may also contribute, but such data was not available to us in this study. Nonetheless, these findings have implications for the approach to management of knee pain, and for studying pain-related treatments as well as function. The general approach of defining pain as present versus absent, even when using a question that inquires about the prior 30 days, appears to capture a more heterogeneous population than previously recognized. This group is, in fact, comprised of persons with inconsistently frequent knee pain as well as those who have more consistently frequent knee pain. The differences in function and other characteristics between these groups of people, both of whom report having frequent knee pain at a clinic visit, may affect our ability to understand risk factors for and consequences of pain in knee OA. Further, it is apparent from these results that radiographic severity of OA alone does not account for differences in consistency of knee pain between persons.

Why may there be variability in subjects' reports of pain over time? Persons can adapt over time to their pain, making accommodations to avoid painful activities, or even potentially rate pain as being less severe since they have managed to cope with it.[22] It should be noted that these temporal knee pain patterns are in keeping with the concept of different stages of knee OA-related pain;[5] thus it is possible that persons with consistent knee pain have longer duration of disease than those with inconsistent knee pain. We could not evaluate this possibility in this cohort. Certain factors can contribute to fluctuation of knee pain by influencing pain perception. While pain itself can lead to more depressive symptoms, the impact of existing depressive symptoms on the experience of pain also needs to be explored. Indeed, some studies have examined the potential contribution of psychosocial factors to the experience of pain or functional limitations in knee OA.[6–10, 23, 24] Importantly, fluctuations in psychological factors reflecting mental well-being are associated with fluctuations in pain severity.[25] Additionally, some of the OA-related pathology itself can change or fluctuate over time, which in turn alters the nociceptive input and therefore the pain experience.[26] Finally, developing more persistent pain over time may be a reflection of the development of central sensitization.[27]

The inconsistent temporal knee pain pattern may also be reflective of milder knee pain not being consistently characterized as having pain on "most days" of the prior 30 days. This may in part be a reflection of cognitive heuristics in that more recent and more severe symptoms are likely to be more easily recalled. Nonetheless, milder pain as seen with inconsistent knee pain may also have less impact on physical functioning than does more severe pain which may also be more consistently present. Thus, such episodic knee pain may not require chronic therapy upon initial presentation. However, our results suggest that although inconsistent knee pain is associated with milder knee pain severity than is consistent knee pain, consistency of knee pain may not simply be a proxy for knee pain severity. In this study, the differences in physical function and strength were significant between those with consistent versus those with inconsistent knee pain. These differences were noted even though pain severity was adjusted for and both groups reported having frequent knee pain at the time of the clinic visit's assessment of function and strength. This highlights the difficulties in examining pain relationships when pain is ascertained at a single time point, despite inquiring about pain over a certain period of time (*e.g.*, prior 30 days) that may be expected to capture such patterns. In support of the temporal pattern of knee pain being important, we have recently demonstrated that consistency of knee pain predicts risk for total knee replacement independently of demographic, clinical, radiographic factors as well as, importantly, pain severity.[28] For example, even with individuals who have what would be considered to be severe knee pain, knowing whether or not that pain was present consistently or inconsistently added to the ability to predict joint replacement over 30 months. We have also demonstrated that inconsistent knee pain is associated with less radiographic severity than consistent knee pain when eliminating between-person confounding.[3] Thus, it does appear that this temporal knee pain pattern is an important domain of pain independent of pain severity alone.

Limitations of the study are worth noting. First, this is a cross-sectional study, and therefore comments about causality cannot be made. Second, the parent study was not specifically designed to address this question. We used the data available in the parent study, and as such, other relevant time intervals, or the number of time intervals required to best define pain fluctuation is not known. Third, because the pain data was obtained through two different methods (telephone screen and in-person at clinic visit), there is potential for misclassification due to method of ascertainment rather than actual change in frequency of knee pain. Such misclassification would tend to dilute any differences noted between the groups. Further, we found that the frequencies with which a knee was painful at the telephone screen but not at the clinic visit and *vice versa* were the same.

In conclusion, we were able to explore an additional dimension of pain by evaluating the presence of frequent knee pain at more than a single time point within a short interval. This study highlights the importance a more comprehensive approach to pain assessment in OA research. A better understanding of the pain experience in knee OA will improve our ability to study pain mechanisms in OA and move toward more rational treatment strategies for pain in OA.

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Table 1

Person-level knee pain pattern definitions

Person-level knee pain pattern	Knee pain question responses at the:			
	Telephone Screen		Clinic Visit	
	Left knee	Right knee	Left knee	Right knee
2 knees with no frequent pain: (n=1034)	N	N	N	N
2 knees with consistent pain: (n=442)	Y	Y	Y	Y
2 knees with inconsistent pain: (n=254)	N	N	Y	Y

Table 2

Factors Associated with Presence of Inconsistent Compared with Consistent Knee Pain

	OR* (95% CI)
	Inconsistent vs Consistent pain
Age (per 10 year increase)	1.21 (1.08–1.34)
Sex (female referent)	1.07 (0.90–1.28)
BMI (per 5 unit increase)	0.96 (0.90–1.03)
K/L grade: 0 (referent)	1.0 (referent)
1	1.01 (0.80–1.27)
2	0.78 (0.61–0.99)
3	0.51 (0.41–0.63)
4	0.27 (0.18–0.36)
Depression present (defined as CES-D score ≥ 16)	0.73 (0.58–0.91)
Widespread pain present	0.68 (0.57–0.81)

*each OR is adjusted for the other variables as well as # days between telephone screen and clinic visit

Table 3

Association of Consistency of Knee Pain with Pain Severity and Quadriceps Strength

	Mean difference in score (95% CI)[*] [#]		
	Knees with Consistent Pain (N=1697)	**Knees with Inconsistent Pain (N=1280)**	**Knees with No Frequent Pain (N=2982)**
Pain Severity			
Knee-specific WOMAC pain (range 0–20) (higher worse)	6.5 (6.3–6.7)	3.8 (3.6–3.9)	1.5 (1.4–1.6)
Knee-specific VAS pain (range 0–100) (higher worse)	37.2 (36.1–38.3)	20.3 (19.3–21.3)	7.7 (7.2–8.2)
Quadriceps Strength (Nm)[¶]			
(higher better)	82.2 (80.5–83.8)	90.6 (88.8–92.4)	99.1 (97.9–100.2)

[*] adjusted for age, sex, BMI, CES-D, OA status, widespread pain, # days between telephone screen and clinic visit

[#] p<0.0001 for all between-group comparisons

[¶] additionally adjusted for pain severity

Table 4

Association of Consistency of Knee Pain with Physical Function

	Mean scores per type of person#		
	2 consistently painful knees	**2 inconsistently painful knees**	**2 knees with no pain**
WOMAC physical function	14.9*	12.6*	10.2*
(range 0–40) (higher worse)	*p-value <0.0001 between all 3 groups		
SF-12 physical scale	44.7*	48.2*¶	47.6*¶
(range 0–100) (lower worse)	*p-value <0.0001 between 1st group and other groups; ¶No significant differences between 2nd and 3rd groups		
PASE	173.6	182.2	181.8
(range 0–400) (lower worse)	No significant differences between the 3 groups		

#adjusted for age, sex, BMI, CES-D, OA status, widespread pain, # of days between telephone screen and clinic visit, and pain severity

Table 5

Association of Consistency of Knee Pain with Pain Medication Use

Type of Pain Medication Use	OR* (95% CI) for having inconsistent knee pain
Regular Use of Pain Medications	0.71(0.47–1.08)
Intermittent Use of Pain Medications	1.24 (0.91–1.70)
No Use of Pain Medications	1.75 (1.22–2.50)

*adjusted for age, sex, BMI, CES-D, OA status, widespread pain, # of days between telephone screen and clinic visit, and pain severity