

Comparison of Predisposing Factors Between Pain on Walking and Pain at Rest in Patients with Knee Osteoarthritis

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Purpose: Patients with knee osteoarthritis (OA) complain of various types of pain, divided into two main categories: pain on movement and pain at rest. A thorough understanding of pain is essential for managing knee OA; however, few studies have investigated the mechanisms underlying the two different types of pain. This study aimed to clarify the predisposing factors for pain in patients with knee OA with a focus on differences between pain on walking and pain at rest.

Patients and Methods: This study involved 93 patients, aged 44–90 years, with knee OA, including 74 women. We assessed demographic variables (sex, age, body mass index [BMI], side), visual analogue scale (VAS) score on walking, VAS score at rest, Kellgren and Lawrence (KL) grade on radiograph, synovitis score and bone marrow lesion (BML) score on magnetic resonance imaging, and pressure pain threshold (PPT), and used univariate and multiple regression analyses to investigate factors predisposing patients to pain at rest or pain on walking.

Results: In the univariate analyses, we found significant correlations between VAS score on walking and BMI ($r=0.31$, $p<0.01$), KL grade ($r=0.40$, $p<0.01$), synovitis score ($r=0.26$, $p=0.01$), and BML score ($r=0.36$, $p<0.01$), whereas VAS score at rest correlated with PPT ($r=-0.23$, $p=0.02$) and BMI ($r=0.26$, $p=0.01$). Multiple regression analysis showed that significant explanatory factors for VAS score on walking were BMI ($\beta=0.22$, $p=0.03$) and KL grade ($\beta=0.27$, $p=0.03$). By contrast, PPT was the only significant explanatory factor for VAS score at rest ($\beta=-0.27$, $p=0.01$).

Conclusion: Predisposing factors were significantly different between pain on walking and pain at rest, indicating that different pain mechanisms exist in the two types of pain. Pain on walking was more strongly associated with mechanical and structural factors, while pain at rest was associated with mechanical hyperalgesia of the knee.

Clinical Registration: University Hospital Medical Information Network Clinical Trials Registration number; 000041190.

Keywords: knee osteoarthritis, pain at rest, hyperalgesia

Introduction

Knee osteoarthritis (OA) is one of the most common causes of physical disability and has become a major public health problem worldwide.^{1,2} Symptomatic knee OA occurs in 20%–30% of the elderly population aged 65 years and older.^{3,4} Its prevalence is increasing, partly because of the aging population.⁵ Pain is the most common reason that patients seek medical care. No cases of halting the progression of OA joint damage exist; therefore, its treatment focuses on relieving pain and maintaining function.⁶

Knee OA pain had been thought to be the result of wear and tear on joints for many years, radiography has been assessed for the severity of knee OA. However, a discordance between the radiographic grading of knee OA and pain severity was demonstrated.⁷

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Although recent studies⁸ using magnetic resonance imaging (MRI) for knee OA have shown a correlation between pain severity and MRI findings, such as effusion synovitis and bone marrow lesion (BML), the pain experienced in OA cannot be fully explained even by advanced imaging techniques. Much attention has been given to neurobiological mechanisms to fill the gap between structural changes and pain in OA. Accumulating evidence suggests that sensitization has an important role in structure–symptom discordance.⁹ Among various approaches available for quantitative sensory testing, the pressure pain threshold (PPT) has been widely utilized to assess pain sensitization.¹⁰ Recently, the etiology of pain in OA is recognized to be multifactorial including biological and psychosocial factors,¹¹ numerous researches for pain are done from different angles.

Patients with knee OA suffer from various types of pain in the affected area, divided into two main categories: pain on movement and pain at rest.¹² The understanding of pain mechanisms is essential for managing knee OA, and there may be different approaches between pain on movement and pain at rest. However, few studies have investigated the mechanisms underlying the two different types of pain. This study aimed to clarify the predisposing factors for pain in patients with knee OA with a focus on differences between pain on walking and pain at rest.

Patients and Methods

Patients

This is a retrospective study involving 93 patients with a diagnosis of knee OA (Kellgren and Lawrence [KL] grade ≥ 2),¹³ who visited our hospital between January 2017 and June 2020 and were recruited by using convenience sampling. The exclusion criteria were mental handicaps or psychiatric conditions precluding adequate communication, a history of surgery on the target knee, and systemic inflammatory diseases such as rheumatoid arthritis. Ethical approval was obtained from the institutional committee of our university (no. 2020–61). This study was planned in a form of opt-out on the website of the university, which did not require to obtain informed consent from each patient, but we handled personal information in a form that could not identify an individual. This study was conducted in compliance with the Declaration of Helsinki.

Assessment

Demographic data (eg, sex, age, and body mass index [BMI]) and clinical characteristics of the affected knee were assessed

in all patients. Pain on walking and pain at rest were separately evaluated using a visual analogue scale (VAS).¹⁴ Patients were asked to estimate their knee pain for the last week (prior to visit) and to place a mark on a 100-mm line with its endpoints indicating “no pain” and “worst pain imaginable.” The distance (mm) measured from the “no pain” endpoint to the point marked by the patient, was reported as the VAS score.

All patients underwent MRI (Signa HDxt 1.5T [GE Healthcare, Chicago, IL, USA], 68 knees; MAGNETOM Aera 1.5T [Siemens, Munich, Germany], 1 knee; SIGNA Architect 3.0T [GE Healthcare], 23 knees; Ingenia 3.0T [Philips, Amsterdam, Netherlands], 1 knee) and knee X-ray examinations that included standing anteroposterior and lateral radiographs. All images were evaluated by one author (YS). Radiographic severity was assessed using the KL grade (0 = “none,” 1 = “doubtful,” 2 = “minimal,” 3 = “moderate,” and 4 = “severe”). Synovitis and BML were assessed using the whole-organ MRI score.¹⁵ The synovitis score was graded from 0 to 3, based on the estimated maximal distention of the synovial cavity (0 = normal, 1 = <33% of the maximum potential distention, 2 = 33–66% of the maximum potential distention, 3 = >66% of the maximum potential distention). The BML was graded from 0 to 3 at all 15 areas around the knee joint (0 = none, 1 = <25%, 2 = 25–50%, 3 = >50%). The sum of BML grade at 15 areas was calculated as the BML score.

PPT was measured at the center of patellar tendon using a digital hand algometer (SBMEDIC Electronics, Solna, Sweden) with a 1 cm² probe by two raters (YS and YI). For evaluating mechanical hyperalgesia of the knee, the patellar tendon was representatively selected because of easy palpation, high reproducibility, and less effect of pain due to patellofemoral osteoarthritis.¹⁶ Pressure was applied at a rate of 30 kPa/s until patients experienced pain. PPT was measured five times at 20-second intervals. The middle three values among the five values were averaged. Timing of the measurement was inconsistent during the day.

Statistical Analysis

Univariate analyses between VAS score on walking or at rest and demographic factors (ie, sex, age, BMI, side [right/left]), KL grade, synovitis score, BML score, and PPT were performed by using Spearman’s rank correlation coefficient. Additionally, multiple regression analysis was conducted using VAS scores on walking and at rest as the objective variables, and the other variables as the explanatory variables. The explanatory variables age and BMI were categorized into two groups (age, ≥ 65 ; BMI, ≥ 25) to focus on clinically careful

Table 1 Baseline Characteristics of Patients in This Study (n = 93)

| | |
|---------------------------------------------------|---------------|
| Female patients (%) | 74 (79.6) |
| Age (y), mean (SD) | 72.6 (8.8) |
| BMI ^a (kg/m ²), mean (SD) | 26.2 (4.4) |
| Right Side (%) | 45 (48.4) |
| VAS ^b score on walking (mm), mean (SD) | 42.4 (25.5) |
| VAS ^b score at rest (mm), mean (SD) | 16.4 (21.1) |
| KL ^c grade | |
| 2 (%) | 23 (24.7) |
| 3 (%) | 25 (26.9) |
| 4 (%) | 45 (48.4) |
| Synovitis score (0–3), mean (SD) | 1.2 (0.7) |
| BML ^d score (0–45), mean (SD) | 6.7 (5.5) |
| PPT ^e (kPa), mean (SD) | 472.8 (195.2) |

Notes: ^aBody mass index; ^bvisual analogue scale; ^cKellgren and Lawrence; ^dbone marrow lesion; ^epressure pain threshold.

patients with high age and obesity. Bell Curve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan) was used for statistical analysis. A p-value <0.05 was considered statistically significant.

Results

Patients' Characteristics

Table 1 shows the demographic characteristics of all patients. Seventy-four patients were women, and the

mean age of the patients was 72.6 years (range, 44–90 years). The mean VAS score was higher for walking than for rest (42.4 mm [0–94] versus 16.4 [0–83]). Table 2 shows the characteristics of each KL grade patients. KL grade 4 patients had higher VAS score on walking than other grades. By contrast, VAS score at rest was not significantly different between KL grades.

Univariate Analysis

Significant correlations were found between VAS score on walking and BMI ($r=0.31$, $p<0.01$), KL grade ($r=0.40$, $p<0.01$), synovitis score ($r=0.26$, $p=0.01$), and BML score ($r=0.36$, $p<0.01$). Significant correlations were also found between VAS score at rest and PPT ($r=-0.23$, $p=0.02$) and BMI ($r=0.26$, $p=0.01$) (Table 3).

Multiple Regression Analysis

In the multiple regression analysis (best-subset), the significant explanatory factors for VAS score on walking were BMI ($\beta=0.22$, $p=0.03$) and KL grade ($\beta=0.27$, $p=0.03$). By contrast, PPT ($\beta=-0.27$, $p=0.01$) was the only significant explanatory variable for VAS score at rest, suggesting that patients with lower PPT had higher VAS scores at rest even after controlling confounding factors (Table 4).

Table 2 Characteristics of Each KL^a Grade Patients (n = 93)

| | KL ^a Grade | | | p |
|---------------------------------------------------|-----------------------|---------------|----------------|-------|
| | 2 | 3 | 4 | |
| Number of patients | 23 | 25 | 45 | |
| Female (%) | 17 (73.9) | 18 (72.0) | 39 (86.7) | 0.26 |
| Age (y), mean (SD) | 69.1 (11.2) | 71.4 (8.6) | 75.0 (6.9) | 0.12 |
| BMI ^b (kg/m ²), mean (SD) | 24.0 (2.4) | 26.3 (4.3) | 27.3 (5.0) * | <0.01 |
| Right side (%) | 13 (56.5) | 12 (48.0) | 20 (44.4) | 0.64 |
| VAS ^c score on walking (mm), mean (SD) | 29.3 (23.0) | 36.9 (23.5) | 52.2 (24.3) *† | <0.01 |
| VAS ^c score at rest (mm), mean (SD) | 11.6 (16.9) | 16.9 (20.5) | 18.5 (23.3) | 0.43 |
| Synovitis score (0–3), mean (SD) | 0.5 (0.7) | 1.2 (0.5) * | 1.5 (0.6) * | <0.01 |
| BML ^d score (0–45), mean (SD) | 2.5 (2.8) | 5.9 (4.6) * | 9.3 (5.6) *† | <0.01 |
| PPT ^e (kPa), mean (SD) | 486.3 (143.4) | 474.7 (199.0) | 464.8 (218.3) | 0.57 |

Notes: Chi-Square, Kruskal Wallis, Steel-Dwass test. *Statistically significant ($p<0.05$) compared with KL grade 2. †Statistically significant ($p<0.05$) compared with KL grade 3. ^aKellgren and Lawrence; ^bbody mass index; ^cvisual analogue scale; ^dbone marrow lesion; ^epressure pain threshold.

Table 3 Univariate Analysis for VAS Scores on Walking/at Rest (n = 93)

| | VAS ^a Score on Walking | | VAS ^a Score at Rest | |
|---------------------------------------------------|-----------------------------------|-------|--------------------------------|------|
| | r | p | r | p |
| Sex | -0.11 | 0.29 | -0.08 | 0.42 |
| Age (≥65 y or <65 y) | 0.07 | 0.49 | -0.11 | 0.29 |
| BMI ^b , kg/m ² (≥25 or <25) | 0.31 | <0.01 | 0.26 | 0.01 |
| Affected side | -0.04 | 0.73 | 0.11 | 0.30 |
| KL ^c grade | 0.40 | <0.01 | 0.09 | 0.41 |
| Synovitis score | 0.26 | 0.01 | 0.12 | 0.25 |
| BML ^d score | 0.36 | <0.01 | 0.09 | 0.37 |
| PPT ^e | -0.02 | 0.87 | -0.23 | 0.02 |

Notes: ^aVisual analogue scale; ^bbody mass index; ^cKellgren and Lawrence; ^dbone marrow lesion; ^epressure pain threshold.

Table 4 Multiple Regression Analysis for VAS Scores on Walking/at Rest (n = 93)

| | VAS ^a Score on Walking | | VAS ^a Score at Rest | |
|---------------------------------------------------|-----------------------------------|------|--------------------------------|------|
| | β | p | β | p |
| Sex | -0.05 | 0.62 | -0.04 | 0.70 |
| Age (≥65 y or <65 y) | -0.06 | 0.56 | -0.16 | 0.14 |
| BMI ^b , kg/m ² (≥25 or <25) | 0.22 | 0.03 | 0.19 | 0.07 |
| Affected side | -0.11 | 0.25 | 0.03 | 0.78 |
| KL ^c grade | 0.27 | 0.03 | -0.006 | 0.97 |
| Synovitis score | -0.03 | 0.83 | -0.009 | 0.95 |
| BML ^d score | 0.16 | 0.20 | 0.23 | 0.08 |
| PPT ^e | -0.003 | 0.98 | -0.27 | 0.01 |

Notes: ^aVisual analogue scale; ^bbody mass index; ^cKellgren and Lawrence; ^dbone marrow lesion; ^epressure pain threshold.

Abbreviation: β, standardized partial regression coefficient.

Discussion

This study aimed to clarify the predisposing factors for pain in patients with knee OA, especially regarding differences between pain on walking and pain at rest. We found that significant differences existed in the predisposing factors between the two types of pain. To our knowledge,

this is the first study to comprehensively evaluate the factors affecting pain in OA with a focus on differences between the two types of pain.

Pain in knee OA is a complex subjective phenomenon.¹¹ Our results suggested that pain on walking was significantly associated with BMI and KL grade, which indicated that mechanical and structural factors were involved in the mechanism. By contrast, pain at rest was significantly associated with PPT, showing that mechanical hyperalgesia of the knee possibly contributes the mechanism of pain at rest. In fact, four patients in this study had higher VAS scores at rest than on walking, suggesting that pain on walking is not simply the addition of a loading effect to pain at rest.

A growing body of evidence indicates that peripheral and central sensitization plays an important role in pain mechanism in knee OA patients.⁹ Mechanical hyperalgesia at the patella tendon partly explains peripheral sensitization in patients with symptomatic knee OA, which has been reported as an evident trigger of central sensitization.^{6,17,18} Although this study could not directly demonstrate the relationship between the central sensitization and rest pain because of the single PPT measurement, the degree of hyperalgesia at representative knee structure was surely associated with intensity of pain at rest.

Although OA pain is traditionally considered to be nociceptive, there has been reported that approximately 5.4–28% of knee OA patients have components of neuropathic pain evaluated by questionnaires such as painDETECT.^{19,20} While neuropathic pain and central sensitization sometimes exhibit similar clinical features,²¹ they are not always identical conditions¹⁷ and the usefulness of neuropathic pain questionnaires for assessing pain sensitization in OA still remains controversial.^{22,23} Therefore, we did not include such questionnaires in this study. However, Power et al²⁴ recently reported that neuropathic pain is more strongly associated with pain at rest than on activity in patients with end-stage hip and knee OA. They mentioned that clinical presentation of pain at rest may warrant more thorough evaluation for potential neuropathic pain, which may open an interesting aspect of pain at rest and probably support our findings.

This study showed that VAS score on walking was significantly correlated with BMI, KL grade, synovitis score, and BML score in the univariate analysis. However, the significant explanatory variables were BMI

and KL grade in the multiple regression analysis. In another univariate analysis (data not shown), the synovitis score and BML score significantly correlated with KL grade. Therefore, a possible explanation for the change in the explanatory variables was that synovitis score and BML score were confounding factors for the KL grade.

This study has several limitations. First, selection bias possibly exists because this study was a retrospective cross-sectional study. Second, nearly one-half of the patients had KL grade 4 OA; therefore, these results may not be applicable to patients with early OA. Third, we did not measure PPT at multiple locations, so we could not directly demonstrate the relationship between pain at rest and central sensitization. Finally, factors affecting pain severity, such as other painful disorders, psychosocial problems and treatment including medicines, were not evaluated in this study.

Conclusions

Predisposing factors were significantly different between pain on walking and pain at rest, indicating that different pain mechanisms exist in the two types of pain. Pain on walking was more strongly associated with mechanical and structural factors, while pain at rest was associated with mechanical hyperalgesia of the knee.

Abbreviations

BMI, body mass index; BML, bone marrow lesion; KL, Kellgren and Lawrence; MRI, magnetic resonance imaging; OA, osteoarthritis; PPT, pressure pain threshold; VAS, visual analogue scale.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author.

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Author Contributions

Study design: YS, MI, KA, NS, M Ikeuchi. Data collection: YS, YI. Data analysis: YS, MI, KA, M Ikeuchi. Drafting

manuscript: YS and M Ikeuchi. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Dr Yoshinori Satake and Dr Masahiko Ikeuchi report grants from Eli Lilly Japan K. K., during the conduct of the study. Nao Sasaki is an employee of Eli Lilly Japan K. K. The authors report no other competing interests in this work.

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