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The factors associated with pain severity in patients with knee osteoarthritis vary according to the radiographic disease severity: a cross-sectional study

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SUMMARY

Objectives: Knee osteoarthritis (OA) pain is suggested to be associated with inflammation and detrimental mechanical loading across the joint. In this cross-sectional study, we simultaneously examined the inflammation and alignment of the lower limb and examined how the pain components varied depending on the disease progression.

Design: One-hundred sixty female medial type of early- [$n = 74$ in Kellgren–Lawrence (K/L) 2] to advanced-stage ($n = 96$ in K/L >2) knee OA subjects (70.5 years on average) were enrolled. Knee pain was evaluated using a pain visual analog scale (VAS) and the pain-related subcategory of the Japanese Knee Osteoarthritis Measure (JKOM-pain). The serum interleukin (sIL)-6 level reflecting synovitis, and the high sensitivity C-reactive protein (hs-CRP) level were measured to evaluate the severity of inflammation. The anatomical axis angle (AAA) was measured as an alignment index. The β-coefficient was estimated after adjusting for age and the body mass index (BMI) using a multiple linear regression analysis.

Results: Multiple linear regression analyses showed that the sIL-6 levels, but not AAA, associated with the pain VAS [$\beta = 10.77$ (95% confidence interval (CI): 4.14–17.40), $P < 0.01$] and JKOM-pain scores [$\beta = 3.19$ (95% CI: 1.93–4.44), $P < 0.001$] in the early stage. Conversely, AAA, but not the sIL-6 levels, was found to be associated with the pain VAS [$\beta = -1.29$ (95% CI: −2.51 to −0.08), $P < 0.05$] and JKOM-pain scores [$\beta = -0.49$ (95% CI: −0.82 to −0.16), $P < 0.01$] in the advanced stage.

Conclusions: The presence of a higher level of sIL-6 and the varus alignment of the joint is associated with pain in early- and advanced-stage knee OA patients, respectively.

Introduction

Pain is the most prominent and disabling symptom of osteoarthritis (OA). Symptom-modifying therapy is the only available treatment for knee OA; therefore, it is important to understand the factors causing the pain in order to optimally treat this common disease. The pain in knee OA is a type of nociceptive pain[1]. It has been speculated that detrimental mechanical loading across the joint and inflammation, especially synovitis, may be the main factors associated with the severity of pain[1,2].

Detrimental mechanical loading across the knee joint is speculated to be one of the main factors in the pathophysiology of knee OA. The alignment of the lower limb has been reported to associate with pain in knee OA[3]. The malalignment of the lower limb and excess body mass have both been considered to be risk factors for the progression of knee OA, due to the association between these factors and the joint load[4–8].

Inflammation is also well known to be associated with the pathophysiology of knee OA. Synovitis in OA may be a secondary phenomenon related to the cartilage and bone alterations induced by the release of degenerative compounds from the extracellular

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matrix of articular cartilage into the synovial fluid[9]. This could further stimulate cartilage damage. Recently, the role of synovitis in OA has attracted particular attention, as synovitis has been revealed to be one of the potential indicators for knee pain and predictive factors for both structural and symptomatic progression of the disease[10–14].

Interleukin (IL)-6 is a proinflammatory cytokine that is produced in the synovium under conditions of synovitis. The serum levels of IL-6 in patients with rheumatoid arthritis (RA) were demonstrated to be related to both the symptoms and progression of the disease, and the inhibition of IL-6 improved the clinical outcomes in patients with RA[15]. IL-6 was also produced by the synovial membrane in patients with knee OA[16], and the serum levels of IL-6 were associated with the change in knee pain over 5 years[17] and with the future prevalence of radiological knee OA[18]. The serum levels of high sensitivity C-reactive protein (hs-CRP) were correlated with inflammatory cell infiltration in the synovial membrane and the levels of IL-6 in the synovial fluid[19]. The hs-CRP level was also reported to be a predictor of knee pain[17]. The serum levels of both IL-6 and hs-CRP were considered to be predictors of a decreased articular cartilage volume in patients with knee OA[19]. Therefore, IL-6, which is associated with synovitis, may also be involved in the pathogenesis of pain associated with knee OA.

While the detrimental mechanical loading across the joint and the synovitis are both speculated to be involved in the pain severity in knee OA, it still remained unclear how the pain components varied based on the progression of the disease. We hypothesized that the factors associated with pain in knee OA varied according to the disease progression. To verify this hypothesis, we divided the patients into two groups according to the radiographic severity of knee OA and investigated the pain severity, the serum IL-6 and hs-CRP levels and the alignment of the lower limb in patients with knee OA, and examined whether the factors associated with pain in knee OA varied according to the radiographic disease severity.

Methods

Subjects and methods

This study was approved by the ethics committee of our university. Patients who first visited the outpatient clinic of Juntendo Tokyo Koto Geriatric Medical Center to seek therapy for knee pain due to OA were asked to participate in the study. All patients who agreed to participate provided their written informed consent before enrollment in this study. All subjects were postmenopausal females with medial knee OA who underwent the initial medical examination at our outpatient clinic between October 2009 and December 2011. The sample size of this study was determined based on the number of patients who demonstrated all these conditions during the study period. The diagnosis of knee OA was established according to the American College of Rheumatology criteria[20]. The inclusion criteria for the present study were (1) subjects who were able to walk with or without walking aids and fulfilled the criteria for knee OA of the medial femoro-tibial joint, (2) subjects who were at least 50 years old, but less than 80 years old, and (3) all subjects had radiographic knee OA with Kellgren–Lawrence (K/L) grade 2 or more as evaluated by the weight-bearing antero-posterior X-rays of the tibio-femoral joint using the bilateral standing extended view[21,22]. The exclusion criteria included (1) patients who had received drugs for knee OA [oral (e.g., non-steroidal anti-inflammatory drugs (NSAIDs) and opioid) or intra-articular injection (e.g., hyaluronic acid and corticosteroids)] prescribed by physicians in the previous 3 months, (2) those who had RA or arthritis due to infection or injury, (3) patients who had undergone joint replacement surgery, (4) patients who had secondary knee OA, (5) patients with patello-femoral OA with a K/L grade of 3 or higher and (6) patients with severe OA (K/L grade 3 or higher) in their hip joint.

Radiographic evaluation of the stage of progression and alignment of the lower extremity

The staging of knee OA on radiograph was assessed using the K/L grade (scale 1–4)[21]. All radiographs were taken by experienced technicians and were quantified by two readers who were blinded to the clinical information of the patient (HK and YS). Both intra- and inter-observer reproducibility rates were good [interclass correlation coefficient (ICC): 0.97 (95% confidence interval (CI): 0.70–0.97) and 0.95 (95% CI: 0.93–0.98), respectively]. For the statistical analysis, the patients were divided into two groups according to the radiographic severity of knee OA, in line with the methodology of previous reports[17,23]: including an early-stage group (K/L grade of 2) and an advanced-stage group (K/L grade of 3 and 4) group.

The alignment angle was measured by the method reported previously[24–26]. The femoral anatomic axis was found by drawing a line from the center of the tibial spines to a point 10 cm above the tibial spines, midway between the medial and lateral femoral surfaces. For the tibial anatomic axis, a line was drawn from the center of the tibial spines to a point 10 cm below the tibial spines, midway between the medial and lateral tibial surfaces. The internal angles between the femoral and tibial axes were measured using a computer and the angle was designated as the alignment angle (anatomical alignment angle − AAA). In this method, AAA under 180 indicates varus knee alignment.

Knee OA pain

Pain was evaluated by a visual analog scale (VAS, 0–100) and the Japanese Knee Osteoarthritis Measure (JKOM) score[27]. The JKOM is a patient-based, self-answered evaluation score that includes four subcategories: pain and stiffness (JKOM-pain; total of eight questions, 0–32 points), activities of daily living (ADL) score (total of 10 questions, 0–40 points), participation in social activities score (total of five questions, 0–20 points), and general health conditions (total of two questions, 0–8 points) with 100 points as the maximum score. The JKOM score is higher in patients with more pain and physical disability, and this evaluation modality is considered to have sufficient reliability and validity for studies of the clinical outcomes of Japanese subjects with knee OA. The measure has also been shown to have reliability and validity by means of statistical evaluations and comparison with other health-related scales, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) in our previous study[27]. We assessed the pain severity using both the pain VAS score and JKOM-pain scores in this study.

Serum IL-6 and hs-CRP levels

Serum samples were obtained from all patients on the day that pain and function were assessed, and radiographs were taken. The non-fasting morning blood samples were collected from 9 to 11 in the morning at the outpatient clinic. The serum samples were stored at −80°C until they were analyzed. A chemiluminescent enzyme immunoassay was used for the measurement of the serum IL-6 concentration (minimum 0.2 pg/mL; reagent: human IL-6; cartridge and instrumentation: Lumipulse Forte; Fujirebio, Tokyo, Japan: intra-assay and interassay variations less than 5.2% and 6.5%, respectively). The serum hs-CRP concentration was measured by latex agglutination nephelometry (reagent: CardioPhase hs-CRP; instrumentation: BN