**Methods:** A convenience sample of 28 individuals was studied. All participants had to be ≥40 yr of age and meet the ACR definition for knee OA. There was no requirement for minimum pain intensity and management was to be continued as required. All participants were asked to respond to pings prompted from their smart phones and subsequently rate their knee pain (0: no pain, 10: worst possible) three times per day over 3 months. Each of three daily pings was programmed to occur at random in each of three 4-hour blocks (8am-noon, noon-4pm, and 4pm-8pm). To characterize the statistical properties of the time series of pain ratings, the means of the pain ratings in three blocks were calculated and compared by one way analysis of covariance. As well, fractal dimension, D, was calculated using rescaled range analysis to characterize the OA participants’ pain fluctuations.

**Results:** Thirty-two individuals participated in the study (18 females, age (mean, standard deviation) 59.7 ± 6.9 yr; 10 males, 55.3 ± 6.7 yr). As shown in Figure A, there is no significant difference among the three blocks of time for the mean rating of pain. Figure B displays the distribution of fractal dimension, D, calculated for each individual’s mean daily pain intensity. The mean fractal dimension, D, for the population is 1.65 ± 0.04, which signifies an anti-persistent pain time series.

**Conclusions:** This is the first analysis to characterize the fractal dimension of OA pain. The finding of anti-persistent time series means that on average more intense pain is followed by lesser pain, a finding very similar to that reported for chronic low back pain and in contrast to both purely neuropathic pain and acute pain. Whereas these previous studies were over short time periods, this study suggests that power law scaling can be preserved for much longer periods of time (weeks or months), which is significant for clinical application. The anti-persistent pattern of pain is consistent with the concept of central pain processes activated to modulate peripheral pain input in OA.

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THE SOURCES OF PAIN IN KNEE OSTEOARTHRITIS ARE CHANGING DEPENDENT UPON THE PROGRESSION OF THE DISEASE

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**Purpose:** Pain is the most prominent and disabling symptom of osteoarthritis (OA). Thus, it is important to understand the cause of pain to optimally treat this common disease. Pain in knee OA is involved in nociceptive pain, of which inflammation and the detrimental mechanical stress to the joint are main cause. Recent studies have shown that OA is associated with the signs and symptoms of inflammation, and synovitis is common in OA. Serum levels of interleukin-6 (IL-6) and C-reactive protein (CRP) are reported to be associated with synovitis and pain severity in knee OA. Walking analysis showed that pain induced by detrimental mechanical stress due to the knee deformity was positively correlated with pain severity only in advanced stage of knee OA. However, it’s still remained unclear which of these two factors dominantly contribute to knee OA pain, or do their contributions to knee OA pain may change according to the OA severity? This study was conducted to answer these questions by obtaining data from knee OA patients.

**Methods:** In this prospective cohort study, one-hundred sixty post-menopausal women with knee OA, who had complained of knee pain and provided written informed consent, were enrolled between Oct. 2009 and Dec. 2011. The severity of knee OA was classified by Kellgren-Lawrence (K/L) grading scale based on standing extended-knee X-ray images. Pain was evaluated by a visual analogue scale (VAS, 0-100) and pain and stiffness sub-category of Japanese Knee Osteoarthritis Measure (JKOM-pain), which is a patient-oriented outcome measure for knee OA with sufficient reliability and validity, similar to WOMAC and SF-36. Serum levels of IL-6 and CRP were measured to monitor the inflammation of knee OA. Anatomical axis angle (AAA) on standing radiograph was measured as the objective indicator for mechanical stress for lower limb. Univariate and multivariate analyses were conducted to examine the relationships between the pain severities and several clinical manifestations of knee OA patients.

**Results:** When a univariate analysis was conducted in all patients, there was no significant correlation between pain scores (pain VAS and JKOM-pain) and the baseline characteristics, serum levels of IL-6 and CRP, and radiographic OA severity, including in AAA. When the patients were divided into two groups according to the radiographic severity of knee OA, the early- (K/L2-67) and advanced-stage (K/L3 and 4; 93), there was significant positive correlation between serum IL-6 level and both pain VAS score (r=-0.411, p=0.001) and JKOM-pain score (r=-0.526, p=0.001) in the early stage, while in advanced stage no significant correlations were found between these parameters. On the other hand, there was significant positive correlation between AAA and both pain VAS score (r=0.224, p=0.033) and JKOM-pain score (r=0.298, p=0.030) in the advanced stage, while in early stage no significant correlations were found between these parameters. Next, a multivariate analysis was conducted to find out the factors those can explain the pain severity by loading of age, BMI, serum IL-6 level, serum hs-CRP level and AAA. No factors were found to explain the pain severity when all patients were included in the analysis. However, when the analysis was conducted to the patients in early stage, only serum IL-6 level was significantly correlated with both the JKOM-pain score (β=0.566, p=0.001) and pain VAS score (β=0.411, p=0.002). When the analysis was conducted to the patients in advanced stage, only AAA was significantly correlated with both the JKOM-pain score (β=0.330, p=0.004) and pain VAS score (β=0.240, p=0.037).

**Conclusions:** The present study suggests that the components of knee OA pain are changing dependent upon the progression of the disease; the pain severity in knee OA patients is mainly affected by inflammation, probably synovitis, in early stage, while that of those by detrimental mechanical stress in advanced stage.

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EXPLORATORY EVALUATION OF A TREADMILL WALKING MODEL TO ASSESS TREATMENT-RELATED ANALGESIA IN SUBJECTS WITH OSTEOARTHRITIS KNEE PAIN

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**Purpose:** Sensitive, relevant and reliable measurements of pain levels and their relationship to physical function are important for the development of novel therapeutics for knee osteoarthritis (KOA). We modified a previously-reported treadmill walking test protocol and explored its capacity to measure analgesic efficacy at baseline and during paced walking. We hypothesized this would facilitate subject enrollment and provide direct static and dynamic assessments of KOA pain intensity and a response to acute treatment with conventional doses of naproxen.

**Methods:** This was a randomized, double-blind, 3-period crossover study performed at one site. Subjects with documented KOA were screened to confirm that their pain intensity (PI) scores were > 1 point higher on an 11 point NRS scale after two weeks withdrawal of their regularly prescribed NSAID. They then were randomized (1:1) to receive different sequences of three 4-day courses of blinded capsules of BID doses of 500mg naproxen (N) or placebo (P): N-P-P or P-N-N with 4 day insubstantial washouts. At each visit, the treadmill walking protocol required four 20-min walks with 40 min rest periods. Subjects had one predetermined self-paced (SP) walk prior to dosing on Day 4, then took