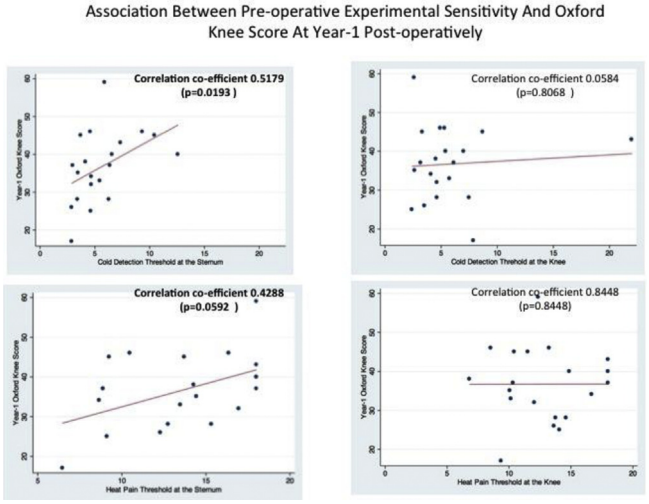

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RELATIONSHIP BETWEEN MUSCLE STRENGTH AND KNEE PAIN IN KNEE OSTEOARTHRITIS PATIENTS

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Purpose: Knee osteoarthritis is a motor disorder that leads to decreased QOL and physical function in old age, and is one cause of the need for nursing care. The prevention of knee osteoarthritis and amelioration of its symptoms are an urgent issue today with rapidly increasing elderly populations. The importance of knee muscle strength training in conservative treatment is well known, and it effects have been verified. To elucidate the relationship between muscle strength and pain symptoms, we investigated the relationship between muscle strength, measured with a knee extension and flexion strength measurement instrument we are currently developing, and knee pain in activities of daily living.
Methods: The subjects were 92 women (mean age 73.8 ± 8.6 years) with knee osteoarthritis who were being treated in the orthopedics department of our center, comprising 160 knees (right 75, left 85) that had not been treated surgically. Standing frontal X-ray images of the knee were evaluated and knee pain during activities of daily living (level ground walking, stair climbing, lying down, standing up, and sitting on floor with legs folded underneath the body) was surveyed with a questionnaire. Knee extension and flexion strength was measured using a prototype measuring instrument developed jointly with the Department of Gerontechnology at our center. The knee extension and flexion measuring instrument can be transported on a cart, and uses an Imada Co., Ltd. force gauge for measuring the precision of industrial products. With subjects in a sitting position with legs flexed 90° and a strap on the ankle joint, knee extension and flexion strength were measured isometrically for 3 seconds. Knee flexion strength and extension strength were measured two times each in the left and right legs and the better value for each side was utilized. Knee extension and flexion strength were expressed as the proportion to body weight, and the difference of the two, (extension strength/weight) minus (flexion strength/weight), was also calculated. The correlation between those indices and the knee pain score during activities of daily living was investigated.
Results: In the right knee, significant correlations were seen between knee extension strength/weight and the scores for knee pain during level ground walking, stair climbing, and sitting on the floor with legs underneath the body (walking, stair climbing $p < 0.01$, sitting on the floor with legs underneath $p < 0.05$). In the left knee, significant correlations were seen between knee extension strength/weight and knee pain scores during level ground walking, stair climbing, standing up, and sitting on the floor with legs underneath the body (walking, standing up, sitting on the floor with legs underneath $p < 0.01$, stair climbing $p < 0.05$). Knee flexion strength/weight was found to be significantly correlated with knee pain during level ground walking in the right knee ($p < 0.05$). The correlation with the knee pain score and the difference between extension strength/weight and flexion strength/weight were significant in all activities in the right knee (walking, stair climbing $p < 0.01$, others $p < 0.05$), while in the left knee these values were significant during walking, standing up, and sitting on the floor with legs underneath (standing up $p < 0.01$, walking, sitting on the floor with legs underneath $p<0.05$).
Conclusions: In knee osteoarthritis patients, knee pain during activities of daily living increases with decreases in knee extension strength in both left and right legs. Differences were seen between right and left in the activities in which a relation between muscle strength and knee pain appeared. Investigations that consider leg strength in proportion to weight or include flexion strength are considered to be useful.

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EFFICACY OF PERIARTICULAR MULTIMODAL DRUG INJECTION IN TOTAL KNEE ARTHROPLASTY FOR PAIN MANAGEMENT AND REHABILITATION

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Purpose: Recently many authors have reported on the benefits of using multimodal drug injections in total knee arthroplasty (TKA) which assist pain relief in the early post-operative stages. This study aims to clarify the effects of periarticular multimodal drug injection on postoperative pain, nausea, rehabilitation, and period of hospitalization.
Methods: From August 2012, we performed 66 consecutive TKA operations over a one year period. From this sample group, we excluded those patients with rheumatoid arthritis and revision surgery to leave a total of 48 knees for detailed analysis of which 5 were male and 43 were female. All patients had been diagnosed with osteoarthritis and both general anesthesia and epidural anesthesia were administered to each patient prior to the surgery. Patients were then divided into three groups which administered multimodal injections in a mixture including ropivacaine: one including 10 mg of morphine, another 5 mg of morphine, and the third including PSS. There were 18 knees in the group including 10 mg of morphine (M10), 13 in the group with 5 mg of morphine (M5) and 17 in the PSS control group (P). Data was collected on how many times a patient took a painkiller, how many times they took an anti-nausea drug, the degrees of flexion angle of the knee after 7 days, how many days it took to walk with a T-cane, how many days it took to climb stairs, and the total period of hospital stay. For comparison of the clinical results between the groups, the Mann–Whitney *U* test was used. Statistical significance was set at $p < 0.05$.
Results: The findings show a significant difference between M10 and M5 groups and the P group in terms of how many painkillers were taken. However, there was little difference between the M10 and M5 groups. There was no significant difference between the three groups in terms of how many anti-nausea drugs were taken. The M10 group had a deeper flexion than the P group, though the differences between the M10 and M5, and M5 and P group were not significant. There was no significant difference between the 3 groups regarding either the time taken to walk with a walking stick, or the time taken to walk up and down stairs. In terms of hospital stay, M10 showed a significantly

shorter period of hospitalization than M5; however, there was no significant difference between M10 and P.
Conclusions: In conclusion, the research shows that there is a noticeable effect of multimodal drug cocktail on ROM rehabilitation and pain control. However, it is difficult to see any clear effects of the drugs on ability to walk. I believe that this could be due to preexisting conditions (preoperative) that restrict the patients' potential to walk.

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PAIN MECHANISMS IN OA: QUANTITATIVE SENSORY TESTING AND PATIENT REPORTED OUTCOMES

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Purpose: Arthritis pain symptoms do not correlate with radiographic damage in knee osteoarthritis, and central pain sensitization (neurobiological alterations in pain signaling) may play a role in some patients. Some patients with chronic OA have suboptimal pain relief and the comorbid prevalence of pain sensitivity phenotypes in OA patients is unknown. Prospective studies may help identify predictors of suboptimal pain management, and a composite index may be useful as part of an initial assessment.
Methods: The SOAR (Pain sensitivity in osteoarthritis research) cohort is a prospective, longitudinal study of patients with chronic knee pain and radiographic osteoarthritis. At baseline, patients completed self-report questionnaires, including the PainDETECT survey, Brief Pain Inventory, and a body map. Quantitative sensory testing and conditioned pain modulation was evaluated using the MAST device. Descriptive statistics and correlational analyses examined the results.
Results: 60 patients were enrolled at the time of the evaluation; enrollment is ongoing for this cohort. Patient scores on pain assessments were normally distributed. Pain scores did not correlate with radiographic severity. A composite index score for centrally mediated pain was directly correlated with baseline pain intensity and neuropathic pain complaints, Differences were noted in pressure pain thresholds between men and women, but no gender differences were seen in conditioned pain modulation. The impact of caffeine intake on QST results was assessed.
Conclusions: In a medically managed cohort of patients with knee osteoarthritis, radiographic indices did not correlate with pain scores. A higher composite index score of centrally mediated pain complaints and symptoms was correlated with self-report of higher pain and more neuropathic pain descriptors. Future studies on predictors of pressure pain thresholds and limited conditioned pain modulation may help identify patients who preferentially respond to targeted therapies.

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DAMPS PROVIDE A LINK BETWEEN JOINT TISSUE DAMAGE AND PAIN THROUGH DIRECT ACTIVATION OF TLR4 EXPRESSED BY SENSORY NEURONS

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Purpose: Damage-associated molecular patterns (DAMPs) are generated in the joint during the course of osteoarthritis (OA). These DAMPs have been shown to activate pattern recognition receptors (PRR, such as TLRs and RAGE) on chondrocytes and synovial macrophages, thus promoting cartilage degradation and synovitis in OA. Here, we hypothesized that DAMPs may directly activate nociceptors through TLR4. We thus investigated the effects of S100A8 and α2-macroglobulin on cultured sensory neurons and tested the effects of blocking toll-like receptor (TLR)4, using the destabilization of the medial meniscus (DMM) surgical model.
Methods: Knee innervating dorsal root ganglia (DRG) neurons (L3–L5) were isolated from naïve C57BL/6 mice (at least 10 weeks of age), plated on coverslips, and cultured in neurogenic medium for either (1) calcium mobilization, or (2) stimulation assays. For calcium mobilization assays, cultures were loaded with a fluorescent calcium indicator dye on day 4, and responses to S100A8 (1 μg/mL) or α2-macroglobulin (50 μg/mL) were recorded. For stimulation assays, cultures were treated overnight with S100A8 (1 μg/mL) or α2-macroglobulin (50 μg/mL), with or without the selective TLR4 inhibitor, TAK242 (Tocris, 1 μM). Supernatants were collected for ELISA analysis of the pro-algesic chemokine, MCP-1. We chose release of MCP-1 as a marker of activation because we have previously shown that this is an important mediator of pain in this model.
DMM or sham surgery was performed in the right knees of 10-week old male C57BL/6 mice. A set of $n = 4$ mice/group were taken down at 8 or 16 weeks post surgery and knee-innervating DRG L3-L5 were harvested for culture of sensory neurons as above with or without the TLR4 inhibitor. After 4 days, culture supernatants were analyzed for MCP-1 protein levels via ELISA. Additional mice were perfused at 8 weeks post surgery for immunohistochemistry of the DRG (L2-L5) using anti-TLR4 (Abcam).
Results: Naïve DRG neurons rapidly responded to S100A8 as indicated by increased calcium mobilization, suggesting that DRG neurons expressed excitatory receptors for this protein. In addition, overnight stimulation with S100A8 resulted in 6-fold upregulation in MCP-1 protein production compared to unstimulated neurons ($p < 0.0001$), which is on par with the effects of TNF-α or IL-1. A small molecule TLR4 inhibitor was able to significantly decrease the ability of S100A8 to stimulate MCP-1 production ($p < 0.01$) (Fig 1).
α2-macroglobulin was also able to induce calcium mobilization responses in naove DRG neurons. In addition, overnight stimulation resulted in a 1.3-fold upregulation of MCP-1 protein production ($p = 0.12$ compared to unstimulated neurons). Again, blocking TLR4 decreased this MCP-1 upregulation ($p < 0.05$).
At 8 and 16 weeks post DMM, unstimulated DRG neurons produced increased amounts of MCP-1 compared to age-matched naïve and sham DRG neurons. Including a small-molecule selective TLR4 inhibitor in the culture medium significantly reduced the amount of MCP-1 produced by the DMM DRG cells at both time points (Fig 2).
Finally, immunohistochemistry of the innervating DRG showed that TLR4 expression increased at 8 weeks post DMM, compared to age-matched naïve DRG.
Conclusions: These studies suggest that sensory neurons have the ability to respond to tissue damage products produced during the course of progressive osteoarthritis, and that this pathway may play a role in the initiation and maintenance of osteoarthritis-associated pain.