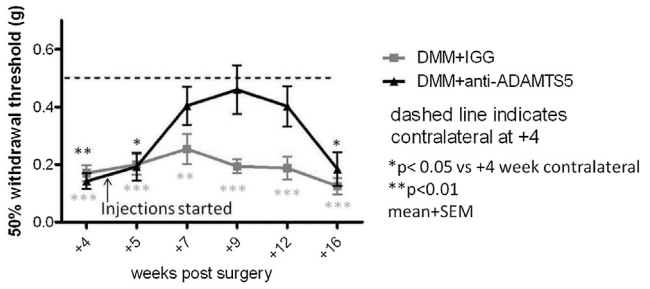

Fig 1. Mechanical Allodynia, Therapeutic Study

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CHARACTERISATION OF PAIN-RELATED BEHAVIOURS IN ASSOCIATION WITH JOINT PATHOLOGY IN AN 8-WEEK ANTIGEN-INDUCED ARTHRITIS MODEL

S. Zaki †, R.E. Miller ‡, A.-M. Malfait ‡, S. Smith †, P.B. Tran ‡, S. Ishihara ‡, C. Little †. †*Kolling Inst. of Med. Res., Univ. of Sydney, St Leonards, Australia;* ‡*Dept. of Internal Med. (Rheumatology), Rush Univ. Med. Ctr., Chicago, IL, USA*

Purpose: Inflammation and immune modulation play a role in processing of nociceptive input in the dorsal root ganglia (DRG), contributing to the development of chronic pain. Macrophage infiltration into DRG, first demonstrated in neuropathic pain models, has recently been implicated in pain and sensitization in animal models of inflammatory arthritis and osteoarthritis. The relationship between DRG macrophage infiltration, pain, and progression of joint pathology has not been studied. We investigated this relationship using a monoarticular antigen-induced arthritis (AIA) model in mice.

Methods: AIA was induced by intra-articular (IA) injection of mBSA into the right knee joint of 12-week old male C57BL/6 mice immunized intradermally 3 weeks and 1 week previously with mBSA in CFA. Immunized control (IC) mice received IA saline in place of mBSA. An operator blinded to treatment assessed mechanical allodynia (von Frey) and thermal hyperalgesia (hotplate) in the hindpaw, knee hyperalgesia (Pressure application measurement), hindlimb weight distribution (forceplate) and spontaneous behaviour (LABORAS) at 0, 1, 2, 4, 6 and 8 weeks after IA injection. At 1, 4 and 8 weeks mice (AIA and IC) were sacrificed and DRG and knee joints harvested. L3-L5 DRG neurons were cultured for 4 days and supernatant MCP-1 quantified by ELISA (n = 5); L2-5 DRG were immune-stained for F4/80 (n = 2); knees were histologically scored for synovitis, cartilage proteoglycan (PG) loss and erosion, subchondral bone (SCB) vascular invasion and sclerosis (n= 6).

Results: Joints in IC mice showed no histological change at any time. In AIA joints synovitis, SCB vascular invasion and cartilage PG loss peaked at W1. At W4, cartilage PG loss persisted and erosion started to develop, SCB vascular invasion decreased as SCB sclerosis started to develop, and synovitis persisted but was reduced. At W8, synovitis had significantly decreased while cartilage erosion and SCB sclerosis progressed. AIA mice developed ipsilateral secondary mechanical allodynia (W1 to W8), knee hyperalgesia (W2 to W6), and thermal hyperalgesia (by W6). AIA mice had a significant reduction in ipsilateral hindlimb weight bearing (W1), and a decrease in distance travelled and rearing frequency (W1) that resolved by W4. Interestingly, 40% of IC mice also developed ipsilateral mechanical allodynia at W1, and all IC mice had mechanical allodynia at W4, persisting until W8; these mice displayed no other pain-related behaviours. At W1 and W4, both AIA and IC mice had increased F4/80 expression in L2-L5 DRG, although greater in AIA compared to IC at W1. Four weeks post AIA, cultured DRG cells produced increased MCP-1 protein compared to age matched naïve mice.

Conclusions: In summary, AIA mice developed secondary mechanical and thermal sensitization. In addition, these mice developed pain-related behaviors such as changes in weight-bearing and locomotion changes in association with progressive joint pathology over 8 weeks. This was associated with macrophage infiltration in the ipsilateral DRG L2-5 and production of MCP-1 by DRG cells. IC mice also developed secondary mechanical allodynia, in the absence of joint pathology or any other pain-related behaviours. This was accompanied by F4/80 staining in the DRG at W1 and W4. These findings suggest that intradermal immunization alone is sufficient to trigger mechanical allodynia and concomitant cellular changes in the DRG, in the absence of joint pathology. However, joint pathology occurring as a result of intra-

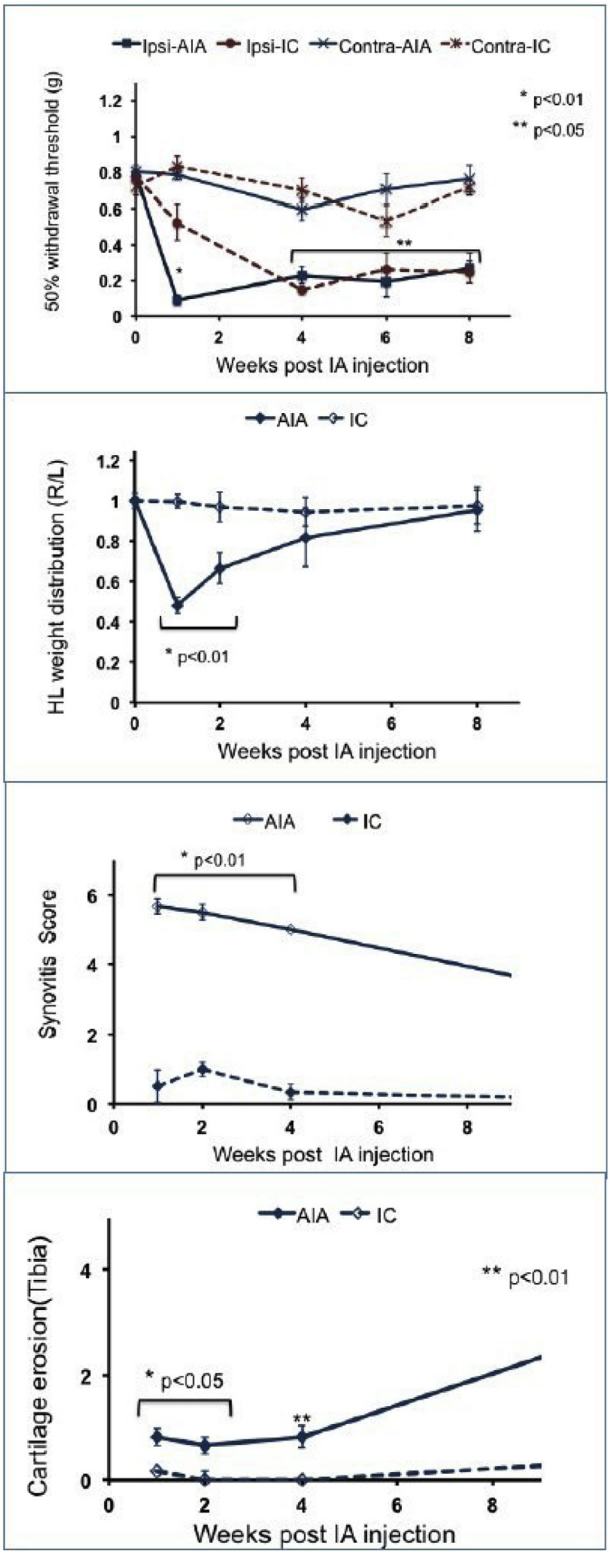

Figure 1. Temporal changes in (a) mechanical allodynia, (b) hindlimb weight distribution (R/L), (c) synovitis, and (d) articular cartilage erosion (tibia), in unilateral antigen-induced arthritis (AIA) or immunized control (IC) mice; as measured at W1, W2, W4 and W8. Values expressed are mean +/- S.E.

articular antigen leads to additional pain-related behaviours. This approach should enable us to dissect relationships between specific pain pathways and joint pathology.

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PAIN SIGNALLING IN RODENT JOINTS BY SERINE PROTEASES

J.J. McDougall, A. Reid, F.A. Russell. *Dalhousie Univ., Halifax, NS, Canada*

Purpose: Serine proteases modulate pain by either activating or disarming protease-activated receptors (PARs). The aim of the present study was to assess the effect of two serine proteases (cathepsin G and neutrophil elastase) on knee joint mechanosensitivity and pain in rodents.
Methods: Electrophysiological recordings from knee joint primary afferents were carried out in deeply anaesthetised male Wistar rats in response to normal and hyper-rotation of the knee. Animals were treated with either normal or denatured cathepsin G (1ng - 10μg; close intra-arterial injection) and nerve recordings repeated. In separate experiments, the effect of intra-articular injection of human neutrophil elastase (1-50μg rat; 1-5μg mouse) on pain behaviour in awake and unrestrained Wistar rats and c57bl/6 mice was determined by measurement of hindlimb incapacitance (weight bearing) and von Frey hair tactile allodynia.
Results: Peripheral administration of cathepsin G caused a dose-dependent reduction in joint mechanosensitivity compared to boiled enzyme, which had no discernible effect ($P<0.05$). The desensitizing effect of cathepsin G occurred with both normal and hyper-rotation of the knee, with the top dose of the enzyme reducing afferent activity by around 75%. Intra-articular injection of neutrophil elastase produced a significant ($P<0.05$) pain behavioural response in both rats and mice lasting several hours.
Conclusions: Cathepsin G reduced joint mechanosensitivity, probably by disarming PAR4 (which is pro-nociceptive), or activating PAR1, which is known to be anti-nociceptive in joints. Local injection of neutrophil elastase produced a robust pain response in rats and mice, possibly by activating PAR2. Future studies will determine the distinct PAR pathways involved in protease-induced pain regulation in arthritic joints.

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15 YEARS OF THE KOOS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF MEASUREMENT PROPERTIES

N.J. Collins †, R. Christensen ‡'§, C.A. Prinsen ‖, E.M. Bartels ‡, C.B. Terwee ¶, E.M. Roos §. † *Dept. of Mechanical Engineering, The Univ. of Melbourne, Melbourne, Australia;* ‡ *The Parker Inst., Copenhagen Univ. Hosp., Copenhagen, Denmark;* § *Inst. of Sports Sci. and Clinical Biomechanics, Univ. of Southern Denmark, Odense, Denmark;* ‖ *EMGO+ Inst. Inst. for Hlth.and Care Res., VU Univ. Med. Ctr., Amsterdam, Netherlands;* ¶ *Dept. of Epidemiology and Biostatistics and the EMGO+ Inst. for Hlth.and Care Res., VU Univ. Med. Ctr., VU Univ. Med. Ctr., Amsterdam, Netherlands*

Purpose: Patient reported outcomes (PROs) are used across medical disciplines to follow the course of a disease or evaluate the results of interventions, with regulatory agencies such as the US Food and Drug Administration requiring their use in medical product development. Since its publication in 1998, the 'Knee Injury and Osteoarthritis Outcome Score' (KOOS) has been widely utilised as a PRO in clinical and research evaluation of knee injuries and osteoarthritis (OA), with more than 77,000 unique patient datasets available in international registries. However, no studies to date have summarised the measurement properties of the KOOS across the available literature, or subjected individual studies to quality rating. The purpose of this study was to conduct a systematic review and meta-analysis of KOOS measurement properties.
Methods: In accordance with PRISMA guidelines, a search strategy incorporating terms for "KOOS" and "knee" was used to search six electronic databases with no language restrictions, with the final search conducted on 6th February 2013. Additional papers were identified from reference lists and the KOOS website. Two independent reviewers utilised defined criteria to screen for eligibility: i) primary aim was to evaluate at least one measurement property of the KOOS or KOOS-PS (physical function short-form) (e.g. reliability, validity, responsiveness, interpretability); ii) inclusion of participants of any age suffering from any knee condition, and/or asymptomatic controls; and iii) KOOS or KOOS-PS were patient-completed. Included studies underwent methodological quality assessment using the COSMIN Checklist by two independent reviewers. A third reviewer was consulted for discrepancies. Extracted data for test-retest reliability, internal consistency, and hypothesis testing was pooled where appropriate, using generic inverse variance (random effects) methodology. Reliability statistics (ICC values) were analyzed as Fisher-transformation of a correlation coefficient; having an approximate normal distribution with an estimable standard error. Inconsistency was assessed via I-squared (I2). This was performed for all studies (overall), and for subgroup analyses based on participant age, condition, intervention and language. Qualitative evidence synthesis was performed where data pooling was not possible.
Results: 954 unique records were identified by the search strategy, with 85 full-text articles assessed for eligibility. 30 studies evaluating 17 different language versions of KOOS, and including more than 5000 participants (mean age range 26 to 77 years), met all eligibility criteria and were included in subsequent analyses. Studies evaluated participants with knee injuries (ACL, meniscus, focal cartilage lesion) or OA, who underwent no intervention or exercise, weight loss, pharmacological, and surgical interventions. Pooled estimates for test-retest reliability from 23 very heterogeneous cohort findings ranged from 0.84 (sport/recreation subscale [95%CI: 0.78 to 0.88; I2=87%]) to 0.9 (activities of daily living [ADL] subscale [0.86 to 0.92; I2=84%]). Overall, KOOS subscales demonstrated adequate convergent and divergent construct validity in comparison with the SF-36. KOOS subscales showed stronger correlations with SF-36 bodily pain (mean r 0.45 to 0.69) and physical function (0.42 to 0.65) than with role-emotional (0.18 to 0.31) and mental health (0.04 to 0.33). Responsiveness data was available for 15 unique cohorts, although none followed COSMIN recommendations for hypothesis testing. KOOS subscales demonstrated largest effect sizes at 3 to 36 months for surgical interventions (ACL reconstruction, cartilage repair, total knee replacement) (mean effect size pain 1.63; symptoms 0.91; ADL 1.57; sport/recreation 1.19; quality of life 1.78). Only one study calculated the minimal important change (pain 11.2, symptoms 11.8, ADL 11.1, sport/recreation 12.1, quality of life 8.7).
Conclusions: Overall, data from meta-analysis revealed that KOOS demonstrates adequate test-retest reliability for groups (>0.8). As expected, KOOS is more strongly correlated with physical subscales of the SF-36 across different conditions, interventions and languages. While KOOS demonstrates large effect sizes post-surgery, future studies should prioritise evaluation of longitudinal validity to adhere with updated recommendations for evaluation of measurement properties.

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ALL-CAUSE MORTALITY AND SERIOUS CARDIOVASCULAR EVENTS IN PEOPLE WITH HIP AND KNEE OSTEOARTHRITIS: A POPULATION BASED COHORT STUDY

G.A. Hawker †'‡, R. Croxford §, A.S. Bierman †, P.J. Harvey †'‡, B. Ravi †, I. Stanaitis ‡, L.L. Lipscombe †'‡. † *Univ. of Toronto, Toronto, ON, Canada;* ‡ *Women's Coll. Hosp., Toronto, ON, Canada;* § *Inst. for Clinical Evaluative Sci. (ICES), Toronto, ON, Canada*

Purpose: Osteoarthritis (OA) is under-treated in part due to the high co-prevalence of other chronic conditions. Approximately 90% of people aged 65+ years with symptomatic OA have at least one additional chronic condition; OA and cardiovascular disease, CVD, are among the most common dyads seen in clinical practice. CVD, in particular, may be perceived as precluding the use of OA therapies (e.g. NSAIDs). Inadequately treated, people with OA may manage their OA by avoiding activities, like walking, that exacerbate symptoms. Reduced physical activity may further increase these individuals' CVD risk. We therefore examined the contribution of OA disability to other CVD risk factors, including prior history of a CVD event, on risk for CVD events.
Methods: This retrospective cohort study used data from a population cohort with symptomatic hip and knee OA that was recruited from 1996-98 through a screening survey of 100% of the population aged 55+ years in two Ontario regions (n=2225 had OA confirmed on examination and x-ray). The baseline survey assessed: socio-demographics; smoking; self-reported height, weight and NSAID use; comorbidity (including physician diagnosis and treatment in the past year for high blood pressure, diabetes, and heart problems); and mental health status. OA disability was assessed using the WOMAC function subscale, use of a walking aid (yes/no) and the Health Assessment Questionnaire walking disability subscale (0–3; higher scores indicate greater disability). The current study used baseline surveys linked to provincial health administrative databases.