

IN BRIEF

RHEUMATOID ARTHRITIS

Tender joints might not indicate inflammation

Tender joint counts, part of the composite disease activity score (CDAS), correlated well with patient-reported outcomes in a longitudinal study of 209 patients with rheumatoid arthritis (RA), but did not correlate with the sum scores of either grey-scale or power Doppler ultrasonography. At 6 months, the baseline tender joint count positively predicted the CDAS ($P < 0.001$ – 0.019) but negatively predicted ultrasonography sum scores ($P < 0.001$) in patients with RA who were treated with biologic DMARDs, suggesting that the presence of tender joints might not be indicative of inflammation.

ORIGINAL ARTICLE Hammer, H. B. et al. Tender joint count may not reflect inflammatory activity in established rheumatoid arthritis patients – results from a longitudinal study. *Arthritis Care Res.* <https://doi.org/10.1002/acr.23815> (2018)

AUTOIMMUNITY

Low-dose IL-2 therapy for autoimmune diseases

Low-dose IL-2 therapy was well tolerated and showed indications of clinical efficacy in a phase I–IIa trial of 46 patients with any one of 11 autoimmune diseases (including rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus and several forms of vasculitis). Patients received low-dose IL-2 (1,000,000 IU/day) for 5 days, then once every 2 weeks for 6 months. Across all diseases, regulatory T cells, but not effector T cells, were expanded and activated following treatment, indicating a potential use for low-dose IL-2 therapy across the spectrum of autoimmune diseases.

ORIGINAL ARTICLE Rosenzweig, M. et al. Immunological and clinical effects of low-dose interleukin-2 across 11 autoimmune diseases in a single, open clinical trial. *Ann. Rheum. Dis.* <https://doi.org/10.1136/annrheumdis-2018-214229> (2018)

OSTEOARTHRITIS

Ultrasound thresholds for synovial abnormalities

The optimal cut-off points for ultrasonography-detected synovial thickness and effusion indicative of knee osteoarthritis have been determined in a community-dwelling cohort of men ($n = 152$) and women ($n = 147$) from the UK. 'Normal' effusion ranges were similar for men and women, but men had a wider 'normal' range for synovial hypertrophy than women. Optimal cut-off points for effusion were 7.4 mm and 5.3 mm for men and women, respectively, and 3.7 mm and 1.6 mm for synovial hypertrophy. A power Doppler signal was uncommon in healthy individuals in this cohort.

ORIGINAL ARTICLE Sarmanova, A. et al. Thresholds of ultrasound synovial abnormalities for knee osteoarthritis – a cross sectional study in the general population. *Osteoarthritis Cartilage* <https://doi.org/10.1016/j.joca.2018.09.018> (2018)

PAIN

Chronic opioid usage on the rise in RA

The percentage of patients with rheumatoid arthritis (RA) chronically using opioids in the USA has risen from 7.4% in 2002 to 16.9% in 2015, according to self-reported usage data from 33,739 patients in the CORRONA registry. Opioid usage was deemed chronic if reported in patient questionnaires at ≥ 2 consecutive rheumatology clinic visits. Factors associated with an increased risk of incident chronic opioid use in patients with RA included severe pain (HR 2.53, 95% CI 2.19–2.92), antidepressant use (HR 1.79, 95% CI 1.64–1.92), a high degree of disease activity (HR 1.55, 95% CI 1.30–1.84) and a high degree of disability (HR 1.45, 95% CI 1.27–1.65).

ORIGINAL ARTICLE Lee, Y. C. et al. Chronic opioid use in rheumatoid arthritis: prevalence and predictors. *Arthritis Rheumatol.* <https://doi.org/10.1002/art.40789> (2018)

EXPERIMENTAL ARTHRITIS

Joints can't take the strain

Why arthritis affects some joints and not others, or even specific sites within joints, has long remained an unsolved mystery. Ideas have ranged from site-specific differences in stromal cells to the affinity of autoantibodies for cells in the joints. New research published in *Nature Communications* is championing the response of stromal cells to biomechanical strain as a vital factor in the development of arthritis at specific locations.

“This work was initially inspired by our previous finding that in a mouse model of spondyloarthritis (SpA), the TNF^{ΔARE} model, enthesitis was lacking in mice that had undergone hind limb unloading,” explains corresponding author Dirk Elewaut. “We therefore thought this might be a general concept that could be applicable to other inflammatory arthritides such as rheumatoid arthritis (RA).”

To test this theory, Elewaut and colleagues investigated the effects of decreasing and increasing joint loading (via hind limb unloading and voluntary running, respectively) on the development of collagen-induced arthritis (CIA) in mice. Disease was almost completely abrogated in the unloaded hind limbs of mice with CIA, whereas arthritis onset was accelerated in voluntary-running mice. Disease was also exacerbated in voluntary-running TNF^{ΔARE} mice (in which TNF is overexpressed) compared with control mice (housed without access to a wheel). Similar results were also seen in mice with collagen antibody-induced arthritis (CAIA).

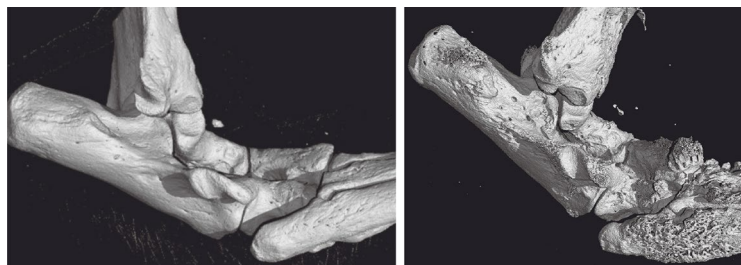
Linking biomechanical strain to inflammation, the researchers analysed gene expression arrays of Achilles tendon cells from healthy mice. Expression of chemokines and pro-inflammatory cytokines was increased in the tendons of voluntary-running mice but not of control mice. These findings were confirmed in vitro by stretching fibroblasts that had been grown on a flexible membrane, which prompted them to produce the chemokine CCL2 and thereby to recruit monocytes. Voluntary-running TNF^{ΔARE} mice also had increased numbers of monocytes in their synovium. Furthermore, in mice lacking CCL2, voluntary running did not exacerbate CAIA, suggesting a role for monocytes in initiating arthritis at mechanosensitive sites.

Using μ CT imaging, the researchers identified areas of the joint that were prone to developing bone erosions during arthritis. These areas contained a large number of tendon attachments, so were probably particularly sensitive to biomechanical strain.

Interestingly, similar patterns of bone erosion at sites of high biomechanical strain were seen in the feet of patients with RA or SpA. “This is a very significant finding in our opinion, as it explains to a large degree the patchy nature of joint inflammation in human arthritides and the clinical pattern of joint involvement,” says Elewaut.

Joanna Collison

ORIGINAL ARTICLE Cambre, I. et al. Mechanical strain determines the site-specific localization of inflammation and tissue damage in arthritis. *Nat. Commun.* **9**, 4613 (2018)



Lateral view of micro-CT scans of mice with collagen-induced arthritis under unloaded (left) and voluntary-running conditions (right). Adapted from Cambre, I. et al. Mechanical strain determines the site-specific localization of inflammation and tissue damage in arthritis. *Nat. Commun.* **9**, 4613 (2018). CC-BY-4.0.