Q2. Can/should we define a minimum set of OA structural measures/outcomes (and their severity) to be used to define OA and thus OA-associated pain for each preclinical model?

Christopher B. Little, Carina L. Blaker, Patrick Haubruck, Cindy C. Shu, Sanaa Zaki, Anne-Marie Malfait

Response/Recommendation: YES
A key goal of pre-clinical OA research is to define the sources and mechanisms of OA pain and their relationship to different tissue pathologies, in order to develop therapies that are ideally both symptom- and disease-modifying. The development of effective therapies will be enhanced if preclinical models can be aligned with different human OA phenotypes. To accomplish this, it is critical that, along with pain, the structural features of OA are described in as much detail as possible, irrespective of the species, model, or joint studied.

Level of evidence for the response/recommendation:
Low that a minimum structural change can and/or should be used to define the dichotomous "*presence" or "absence"* of OA;
Strong that we can and should define a minimum/core set of measures/outcomes that includes all joint tissues to ensure the joint-wide structural OA features in all pre-clinical models and joints are optimally described, defined, and quantified.

Delegate Vote: Agree: Disagree: Abstain:

Rationale:
Human OA & clinical evidence: The clinical definition of OA, according to multiple international bodies and guidelines, includes both symptomatic and structural features[1-5]. While originally thought of as a disease of articular cartilage, these agencies and the worldwide OA clinical and research community now considers the structural features of OA to include variable levels of pathology in any/all tissues of the affected joint and associated peri-articular and distant tissues: cartilage (proteoglycan loss, fibrillation erosion), bone (subchondral remodeling, marginal osteophyte formation), synovium and joint capsule (inflammation and fibrosis), intra- and extra-articular ligaments (tears, degeneration, fibrosis), menisci (tears, degeneration), intra-articular fat-pads (inflammation, fibrosis), synovial fluid (loss of viscosity, inflammation), muscle (atrophy, fat deposition, fibrosis), tendon (tears, degeneration, fibrosis)[1-26].

In people there is only modest correlation between OA symptoms and structural changes particularly those detected by X-ray, although some stronger associations are found for specific MRI and US pathologic features[23; 27-54]. In-vivo and ex-vivo studies have demonstrated correlation between different imaging features and *bone fide* pathologic and histopathologic measures of OA structural disease in different joint tissues[55-68]. While soluble biomarkers are being developed and tested for use to monitor aspects of structural disease activity and progression, they are not yet sufficiently validated to use as surrogates for *bone fide* imaging or pathology/histopathology evaluation[69; 70]. Disparity between individuals in pain processing and psychosocial factors that impact the pain experience, plus variability in neuroplastic and neuropathic components of chronic pain, may in part account for the OA structure:symptom discordance[7; 71-82]. Nevertheless, it is evident that a substantial proportion of individuals with imaging-based structural diagnostic criteria consistent with OA or specific OA features, have no pain[83-90]. Human clinical studies and trials therefore evaluate symptomatic (SOA) and structural OA (particularly ROA) in parallel when evaluating extant and progressive disease. Differences in structural and symptomatic features are being used to stratify OA patients into phenotypic clusters that provide prognostic insights on disease progression and potential therapeutic variation[13; 46; 48; 91-100].

Pre-clinical OA models: Animal models mirror the joint wide pathology of OA seen in people[6; 8-12; 14-19; 21; 101-116]. Additionally, different models show differences in the degree of pathology in different joint tissues and different trajectories in their progression[12; 117-123]. Where it has been studied, animal models of OA also show a generally poor correlation between pain and various joint pathologies e.g. cartilage erosion in both the native state and in response to treatment[124-130]. Recently, it is becoming apparent that neuronal plasticity occurs in murine knees with experimental OA, with sprouting of nociceptors in the synovium and subchondral bone, and this may help in defining the relationship with pain[131; 132]. Neuronal sprouting has also been shown at the osteochondral junction in human OA knees[131]. While not uniformly identified across different OA models, there is some evidence that the pathology:pain relationship may be age, strain and sex dependent, with for example equivalent pain in male and female mice despite disparate stage-specific joint pathology in wild-type and genetically-modified animals[128-130; 133; 134]. Taken together this suggests that pre-clinical models reflect the diversity of OA phenotypic clusters identified in people with regard not only to inciting cause (induction method) but also structural variation and its association with different pain outcome measures.

Histology and histopathological scoring have been and remains the most common method for evaluating OA structural pathology in pre-clinical models, with methods available to evaluate and all possible OA-affected tissues[6; 8-12; 14-19; 21; 101-116]. Clinically relevant (X-ray, CT, MRI, US) and more exploratory experimental imaging methods have also been widely reported in pre-clinical OA models to describe different aspects of structural disease[135-181]. Some of these imaging methods allow longitudinal evaluation and help address ethical and 3Rs issues of cross-sectional histology-based studies. As in people, correlation between many different imaging outcomes and “gold-standard” pathology/histopathology has been reported. In addition to available structural outcome measures, preclinical models offer the opportunity to use experimental therapeutics and therapeutic strategies to target specific mechanisms/pathways involved in either OA structural pathology or pain e.g. genetically modified mice, viral over-expression or inhibition, mRNA inhibition etc[7; 117-121; 182]. When used in combination with validated structural pathology outcome measures this provides the opportunity to dissect in exquisite detail the OA pathology:pain relationship and define the underlying molecular mechanisms[126; 128; 129; 133]. Such analysis, not possible in human patients/cohorts, is critical for the discovery and development of new and effective therapeutics.

Summary: Defining the OA structure:pain association, how it differs/changes between different OA phenotypes and patient clusters/cohorts, and defining the molecular mechanisms that underpin this is a clinically important and unmet research need. Pre-clinical OA models offer an opportunity to address this effectively. While the necessary histopathology and/or imaging methods are available to fully characterize the joint-wide and more distant OA structural pathology features, there is a lack of uniformity in their application, such that many studies continue to report on only one (typically cartilage) or at best a few features. While it is unlikely that the specific methods used can or will be standardized across studies, defining a minimum/core set of OA pathologies to report (e.g. cartilage, subchondral bone, osteophytes, synovitis, fibrosis) would enhance pre-clinical research outcomes and translation. There are many available and validated methods for describing and scoring/grading pathology in all potential OA-affected tissues across the spectrum of pre-clinical species and models. While histopathology is most commonly used, clinically relevant imaging modalities (X-ray, CT, MRI, US) are also available. Used with therapeutic interventions or genetically modified mice, where specific pain and/or OA pathology mechanisms and outcomes can be targeted and modified, allows for detailed dissection of the OA pain:pathology relationship and mechanisms.

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