Osteoarthritis and Cartilage 19 (2011) 1076–1077

Osteoarthritis and Cartilage

Letter to the Editor

The recent paper "Multimodal imaging demonstrates concomitant changes in bone and cartilage after destabilization of the medial meniscus and increased joint laxity"

The recent paper "Multimodal imaging demonstrates concomitant changes in bone and cartilage after destabilization of the medial meniscus and increased joint laxity"[1], explores an important issue i.e., the relationship between cartilage and bone pathology, and the role of joint laxity in post-traumatic osteoarthritis (OA). However, there are several concerns as to whether the model used was indeed the medial meniscal destabilization (DMM) model, and therefore whether the conclusions drawn are valid. In light of the widespread use of different surgical models of OA in a variety of species including mice, recent steps towards standardization of histological outcome measures have been made to enable better comparison between different studies[2,3]. Our concerns with the current paper (as outlined below) are a timely reminder that standardization and validation of the procedures/methods used to induce OA is also necessary and critical to facilitate comparative evaluation between publications involving different research groups.

In the current paper, analysis of joints immediately following (what is described as DMM) surgery, revealed an increase (albeit with marked variance) in anterior and posterior tibial displacement. The authors conclude that: "DMM surgery caused a significant increase of tibial anterior-posterior (AP) range of motion, particularly with the tibia moving in an anterior direction with respect to the femur". In separate groups of mice at 4 and 8 weeks after DMM surgery, the bone and cartilage pathology was examined using μCT and inverted confocal laser microscopy. In 13/23 specimens (6/11 at 4 weeks and 8/12 at 8 weeks after surgery), marked posterior medial tibial plateau erosion (at times down to or through the growth plate) was observed, while this was not apparent in the remaining animals.

The inconsistent joint laxity and pathology (particularly the posterior tibial bone erosion) may be explained by a highly variable induction of instability, and are consistent with inadvertent anterior cruciate ligament (ACL) transection in a proportion of mice. The authors did discuss the possibility that their data "… may be a result of surgery affecting the ACL to different extents". As published with both surgical (129/SvEv[4] and C57BL/6[5]) and enzymatic[6] methods, loss of ACL integrity in mice causes significant AP laxity, and marked posterior tibial bone erosion. In contrast, it is our combined experience that no manually discernable anterior drawer is observed after validated DMM surgery where no ACL injury occurs. Most importantly, in no cases have we seen the marked posterior tibial bone erosion as described in the current study following DMM, even when mice are maintained for 4–6 months post-surgery[7–14]. Indeed, the DMM model, far from showing tibial bone erosion, is typified by increased subchondral bone formation[7].

The authors considered it "… conceivable that during meniscal transection, damage is done to the ACL". Unfortunately, no gross or histological examination was undertaken either immediately, or at the 4 or 8 weeks post-surgery time points in the current study, to confirm the presence or absence of ACL injury. Such damage can be readily identified in serial coronal (and sagittal) sections[4]. No biomechanical or histological evaluation of the joints was conducted, and therefore a correlation between AP laxity, the severity of joint pathology and ACL integrity could not be made.

Mouse strain is proposed as a possible reason for the discrepancy between the observed pathology and that reported in the literature. However, previous studies, not cited in the current paper[11,12], have used C57BL/6 mice in the DMM model and did not observe the extensive posterior bone erosion reported here. The location of the pathology in the DMM model is consistently in the mid-anterior region of the tibial plateau in over 12 different strains investigated including C57BL/6[4,7–14], and not in the posterior aspect of the joint reported in the Moodie paper. While a difference in absolute severity of histologic OA can be seen with different strains[14], the location of the pathology does not appear to change appreciably.

Moodie *et al.* also suggest that assessment technique may also contribute to the discrepancy stating that "coronal histologic section in mid-plateau may overlook the loss occurring in the posterior region". It should be clarified that the published coronal histologic sections we have performed[4,7–10] and that are recommended in the OARSI guidelines[3], utilize serial sections through the depth of the entire joint encompassing the posterior tibial plateau, so that overlooking of posterior erosions is not possible. Furthermore, in several studies[11–13] sagittal rather than coronal sections have been used, with no reports of the severe posterior tibial erosion described in the present paper.

Animal models, and particularly recent studies using genetically-modified mice, have added significantly to our understanding of the pathophysiology and potential treatment of OA. In this regard the question addressed in the current study by Moodie *et al.* regarding global joint pathology and the interaction between different tissues is important, and can only be appropriately addressed with *in vivo* studies. However, as recently highlighted[15], many of the published studies utilizing animal models have reporting deficiencies that make subsequent systematic reviews of the literature difficult, if not impossible. One such issue, that is critical to such systematic review, is appropriate validation of the animal model used. The purpose of our letter therefore is not to contest the data presented in the current paper, but rather to suggest that it may represent a mixture of two models that have quite

1063-4584/$ – see front matter
doi:10.1016/j.joca.2011.04.018

different pathology timelines and endpoints in the mouse, namely DMM ± ACL deficiency. Appropriate validation such as gross and ideally histological examination of the ACL would have not only resolved this issue but also potentially allowed subsequent stratification of the outcomes into the two models. It would also strengthen the power of conclusions despite the reduced "n" in each group, by reducing the variance which may well be OA-model related. Greater investments in validating a model for each research group, and indeed each surgeon within a group, and/or collaborating where the time investment cannot be made, will ensure the correct application of animal models, limit the need to replicate animal studies, and enhance our ability to conduct systematic reviews of the literature.

Conflict of interest

S. Glasson and C. Little provide consulting services on preclinical models to both Universities and pharmaceutical companies. No funding was received for this letter. Dr Little is an Associate Editor of Osteoarthritis and Cartilage but was not involved in the review or editorial process of the paper by Moodie *et al.*

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