

**Comment on Surgical restabilization reduces the progression of post-traumatic osteoarthritis initiated by ACL rupture in mice” by Lin et al. (2024), and recommendations for non-invasive knee joint injury models**

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With great interest, we read the article “Surgical restabilization reduces the progression of post-traumatic osteoarthritis initiated by ACL rupture in mice” by Lin et al. (2024), recently published in *Osteoarthritis and Cartilage*.<sup>1</sup>

The authors’ work was motivated by the interesting hypothesis that anterior cruciate ligament (ACL) injury repair may prevent or decelerate post-traumatic osteoarthritis (PTOA) development. Previous studies have shown the benefits of knee joint stabilizing surgery in a PTOA model of ACL transection.<sup>2, 3</sup> In their paper, Lin et al. rightfully stated that the use of a non-invasive injury model would mimic ACL injuries better than the surgical ACL transection model.

The authors analyzed PTOA incidence (and progression) following surgical knee joint stabilization<sup>3</sup> compared to conservative treatment in a murine non-invasive knee injury PTOA model. The model is described as an ACL injury model, based on a single tibial compressive overload of ~10–12 N. Details of the method developed by the authors have been described previously and include the description of a transient anterior subluxation of the tibia relative to the femur.<sup>4</sup>

In Figures 5 and 6 of their article, the authors display the injury using “representative” sagittal toluidine blue sections.<sup>1</sup> However, the images do not show results of simple ACL injuries, but of complete and severe knee joint dislocations. The day 14 image in Figure 6 shows the femoral condyle without articulating contact with the tibial plateau, and the day 49 image in Figure 6 depicts a significantly displaced and depressed posterior tibial plateau fracture. This is presumably the result of a severe knee joint dislocation injury. Figure 4d again displays a dislocated knee joint as a 3D reconstructed  $\mu$ -computed tomography ( $\mu$ CT) image.

The injury in question represents a limb-threatening emergency in humans and is considerably more severe than an ACL injury. Such multi-ligament injuries are rare and often affect the joint capsule, menisci, cartilage, bone, and neurovascular structures.<sup>5</sup> The displaced tibial plateau fracture in Figure 6 suggests excessive trauma to which the knee joint was exposed. In humans, such injuries typically result from motor vehicle accidents or falls from great heights.<sup>5</sup> While conservative treatment may be a reasonable consideration for ACL injuries, knee joint dislocations require surgical ligament repair and/or joint reconstruction within three weeks of the injury.<sup>6</sup>

Therefore, we find several statements in this work problematic and misleading, and we disagree with the conclusions of this paper, while urging the authors to critically re-evaluate their PTOA model. The authors should preferably not draw any conclusions on the potentially beneficial treatment of stabilizing ACL injuries when presenting data on knee joint dislocations. Of note, other authors have succeeded in employing non-invasive knee joint injury models in animals, to mimic ACL injury, indicated by histology sections that depict articulating and intact knee joint surfaces.<sup>7</sup>

While the work shows that surgical stabilization of knee joint dislocations may decelerate the development of PTOA, it has been clearly established that these injuries cannot be treated conservatively. Most cases require a series of surgeries due to the severity and complexity of the injury.<sup>5</sup>

To ensure that no excessive knee joint injuries result from this and other experimental model(s), and to standardize injury patterns across experimental PTOA studies, we propose radiological quality control to be performed following the intervention. This can be achieved using in vivo measurements such as fluoroscopy to exclude knee joint dislocations and fractures,  $\mu$ CT<sup>8</sup> to exclude fractures, and/or magnetic resonance imaging<sup>9</sup> to confirm ligamentous injury and exclude injuries beyond the desired severity. Only if animals pass this quality control step should the experiment be continued.

To date, there is no disease modifying treatment available for osteoarthritis (OA). One major reason why replicating preclinical results in human OA patients fails is a mismatch between preclinical models and human disease.<sup>10</sup> This disparity most commonly concerns preclinical testing in PTOA models, and clinical testing in primary OA. Yet, the work by Lin et al. illustrates how relevant the injury type and severity are when investigating ACL injury and PTOA models within the context of clinical relevance.

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### **Author contributions**

TM and TW drafted the commentary and JB, AM, FNF, FE, and NMB critically revised it. All authors discussed and reviewed the paper in question, and agreed to the submission and publication of this commentary.

### **Conflict of interest**

None in relation to the publication.

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