PTOA Question 3: Do age and post-injury time-point influence the biological response to joint injury and progression to PTOA?

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RESPONSE/RECOMMENDATION: Yes

Based on this systematic review of trauma-induced osteoarthritis animal models, the following evidence-informed recommendations are proposed.

1. Age at injury should be explicitly reported and biologically justified in all studies.
2. Given the predominance of young animals, inclusion of skeletally mature and aged cohorts should be considered where feasible to better model typical human PTOA demographics.
3. Post-injury assessment time-points should be selected in relation to the intended stage of disease being modeled.
4. Most studies evaluated early to mid-term post-injury intervals, highlighting limited assessment of later disease stages.
5. Accordingly, studies aiming to model chronic or progressive osteoarthritis should consider later follow-up time-points (>12 weeks) when appropriate.
6. Use of multiple post-injury time-points may strengthen characterization of the temporal evolution of disease.

LEVEL OF EVIDENCE: Moderate

This ICM statement is based exclusively on preclinical *in vivo* animal studies evaluating trauma-induced osteoarthritis. No human participants, clinical cohorts, or patient-derived data were included. Accordingly, the evidence synthesized reflects experimental and translational preclinical research, rather than clinical effectiveness or patient outcomes.

The overall certainty of evidence is moderate (preclinical). Confidence is strengthened by consistent patterns across multiple independent animal studies and model systems, but is limited by heterogeneity in species, age at injury, and post-injury selection of time-points for analysis, as well as the absence of direct clinical correlation.

DELEGATE VOTE: Agree: ___%, Disagree: ___%, Abstain: ___%

RATIONALE:

Systematic Review of Age on PTOA. A meticulous systematic review was conducted. A comprehensive literature was performed in PubMed, Embase, and Web of Science from database inception to December 15, 2025. The search strategy combined controlled vocabulary and free-text keywords related to post-traumatic osteoarthritis ('ptoa' OR 'post-traumatic osteoarthritis' OR 'traumatic osteoarthritis') AND ('small animal' OR 'animal model') AND ('age' OR 'aging' OR

'ageing'). Searches were limited to English language papers. Reference lists of included studies and relevant reviews were manually screened to identify additional eligible studies. All retrieved citations were imported into a reference manager, and duplicates were removed. Two reviewers independently screened titles and abstracts against predefined eligibility criteria. Full texts were then assessed independently for inclusion. Discrepancies were resolved by consensus or adjudication by a third reviewer. The selection process was documented using a PRISMA flow diagram (Figure S1).

Studies were included if they met all the following criteria:

- Original research involving an *in vivo* model of osteoarthritis induced by joint injury (PTOA) or clearly defined injury-related OA paradigm.
- Reported age at injury and at least one post-injury time point.
- Reported at least one OA-relevant outcome (e.g., histopathology, imaging, biomarkers, biomechanics/functional measures).
- Provided sufficient methodological detail to extract key model characteristics (e.g., species/strain, induction method, age/time-point, sample size).

A standardized extraction form was used to collect study-level data, including: author/year, species and strain, in vivo OA induction method, sample size, age at injury/surgery, time-points assessed, treatment or intervention, and key findings. Given heterogeneity in species, injury paradigms, interventions, and outcome measures, results were synthesized qualitatively. Studies were summarized by species/strain, injury model type, age and timing, and intervention class, and key outcomes were reported descriptively. Where applicable, frequencies and proportions of model characteristics were tabulated.

Results. A systematic literature search was conducted in PubMed, Embase, and Web of Science to identify studies describing trauma-induced osteoarthritis (OA) animal models (Figure S1). The search yielded 665 records in total (PubMed, n = 142; Embase, n = 152; Web of Science, n = 371). After removal of 359 duplicate records, 306 records were screened by title and abstract. Of these, 88 records were excluded, leaving 218 reports sought for full-text retrieval. Full texts were obtained and assessed for 117 reports, while 101 reports were excluded at this stage because they did not involve trauma-induced OA models. Following full-text review, 35 reports were excluded for not meeting inclusion criteria. Ultimately, 82 studies met all eligibility criteria and were included in the qualitative synthesis [1-83]. Most studies used rodents, particularly mice. Mouse models accounted for 61/82 (74.4%) studies, followed by rat 11/82 (13.4%) and rabbit 5/82 (6.1%). Large-animal models were infrequent: horse 2/82 (2.4%), pig 1/82 (1.2%), cat 1/82 (1.2%), and pony 1/82 (1.2%).

OA induction / injury model distribution. The most common OA induction paradigm was destabilization of the medial meniscus (DMM) (43/82, 52.4%), followed by anterior cruciate ligament transection (ACLT) (19/82, 23.2%). We included a small number of

spontaneous/age-associated OA models when they informed the interaction between age and joint degeneration following injury (4/82, 4.9%), meniscectomy or medial collateral ligament injury (MCL) + meniscus variants (3/82, 3.7%), osteochondral/chondral defect models (2/82, 2.4%), and non-invasive ACL rupture via compression (2/82, 2.4%). ACLR/ACL rupture was explicitly listed in 1/82 (1.2%), while other/mixed induction descriptions comprised 7/82 (8.5%).

Age profile in rodent studies. Rodent studies (mouse + rat) comprised 72/82 (87.8%) studies. Using the minimum stated age per study (converted to weeks when possible), most rodent experiments were performed in young animals: 6–15 weeks ("young adult") in 41/72 (56.9%) and <6 weeks ("juvenile/adolescent") in 20/72 (27.8%). Only 4/72 (5.6%) used 16–51 weeks ("adult"), and 1/72 (1.4%) used ≥52 weeks ("aged"). Age was not stated/parsable for 6/72 (8.3%) rodent studies (Table 1).

Commented [ZL1]: I suggest adding a section on the post-injury time-points. It's clear in the table, but a summary of key findings here would be helpful. We may move some of the texts from Conclusions? or your consideration please.

Commented [AM2R1]: Clear enough in the table, and we have another question looking at timing.

Commented [ZL3]: Should we also mention the ages of larger animals in the other 10 studies?

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Table 1: Age at injury and post-injury time-point distribution of trauma-induced osteoarthritis animal models. Summary of included studies stratified by age at the time of injury and duration of post-injury follow-up. Most studies employed young animals and focused on early to mid post-injury time-points, whereas middle-aged and aged cohorts, as well as late-stage (>12 weeks) disease assessments, were infrequently represented. Percentages are calculated relative to studies reporting age (72 of 82 included studies).

	Post-injury follow-up			
Age at Injury	**Early** (≤4 weeks)	**Mid** (5–12 weeks)	**Late** (>12 weeks)	**Total Studies (%)**
Young (≤12 weeks)	Predominant	Common	Rare	41 (56.9%)
Skeletally Mature Adult	Common	Predominant	Limited	20 (27.8%)
Middle-aged	Rare	Limited	Occasional	4 (5.6%)
Aged	Rare	Rare	Occasional	1 (1.4%)
Age not specified	—	—	—	6 (8.3%)
Total (Age reported)	—	—	—	72 / 82 (87.8%)

Treatments/interventions evaluated. Interventions were heterogeneous. Genetic manipulation studies represented 24/82 (29.3%), and pharmacologic/biologic interventions represented 15/82 (18.3%). Mechanical/rehabilitation-type interventions were rare (2/82, 2.4%), as were cell/biomaterial therapies (1/82, 1.2%). Interventions that did not clearly fit these categories or were insufficiently described were grouped as "other/unclear" 40/82 (48.8%).

Conclusion. Current PTOA animal studies are heavily weighted toward young rodents and demonstrate substantial variability in post-injury assessment timepoints, limiting comparability and clinical translation. Because aging alters the degree of inflammation and its resolution,

capacity for repair and OA progression, future work should standardize both animal age strata and windows for assessment post-injury. We recommend routinely including an aged cohort as well as young adults, with prespecified early, mid, and late temporal endpoints aligned to biological phases (inflammation, remodeling, degeneration). Harmonized reporting of age, maturity, and time after injury will strengthen reproducibility and optimal timing for therapeutic interventions.

Both age and post-injury time-point substantially shape the biological response to joint injury and the pace and phenotype of PTOA[76; 84]. Older age is associated with a heightened or prolonged inflammatory response[85; 86], reduced capacity for repair[7; 87], increased cellular senescence[66; 88; 89], and faster structural degeneration[7; 76]. Early post-injury windows capture acute inflammation and stress of the chondrocytes and soft tissues, whereas later time-points reflect soft tissue and bone remodeling, osteophyte development, and established structural OA[84; 90-92]. As most human PTOA arises in middle-aged or older adults with comorbidities, whereas the preclinical literature is in young, healthy rodents. Pre-clinical studies should therefore explicitly define age strata and align outcome measures to biologically meaningful post-injury stages to improve the predictive validity of preclinical studies for human clinical trials.

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Supplementary Materials

Figure S1 PRISMA 2020 flow diagram of study selection. Flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies evaluating trauma-induced osteoarthritis animal models. A total of 665 records were identified across PubMed, Embase, and Web of Science. After duplicate removal, 306 records were screened, and 82 studies met inclusion criteria and were included in the qualitative synthesis.