**PTOA Question 2: Is there a clear understanding of how current major "PTOA" models induce disease? A) Joint destabilization, B) Mechanical loading, C) Osteochondral fragments**

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**RESPONSE/RECOMMENDATION: Yes**

Current preclinical PTOA models induce disease through varying combinations and temporal sequences of three interconnected pathophysiologic processes: (1) tissue injury (mechanical disruption of cartilage, bone, ligament, or meniscus), (2) inflammatory cascade (synovitis, cytokine and protease release, immune cell infiltration), and (3) chronic alterations in joint mechanics (instability and/or abnormal loading patterns). Destabilization models induce PTOA via sustained mechanical instability, resulting in chronic abnormal joint loading and concurrent inflammation. Mechanical loading models initiate disease by inducing tissue injury, triggering an early inflammatory response, followed by secondary mechanical and structural dysfunction. Osteochondral fragment models combine acute tissue injury with persistent intra-articular debris, resulting in chronic synovitis.

**LEVEL OF EVIDENCE:** Moderate

**DELEGATE VOTE:** [To be determined]

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**RATIONALE:** A systematic literature search was conducted using PubMed and Web of Science databases (1995-2026) with search terms: "post traumatic osteoarthritis OR post-traumatic osteoarthritis OR posttraumatic osteoarthritis OR PTOA OR trauma-induced osteoarthritis OR injury-induced osteoarthritis" AND "animal model* OR preclinical model* OR experimental model*" AND "meniscus OR meniscal OR meniscectomy OR DMM OR cruciate OR ACL OR ACLT OR osteochondral fragment* OR impact OR impactor OR mechanical injury OR cyclic loading." Systematic searches identified 1,354 studies; after de-duplication and screening, 437 advanced to full-text review. Studies were evaluated by the authors with preference for studies examining model mechanisms of disease. However, treatment-based studies with a mechanistic focus were also included. Studies focused solely on therapeutic interventions or using in silico/in vitro models were excluded.

**A. Joint destabilization models**

**I. Meniscal pathology models**

**Destabilization of the medial meniscus (DMM):** DMM is performed by surgically transecting the meniscotibial ligament, creating joint instability without removing meniscal tissue.[1,2] This model has been used extensively as a reproducible model of PTOA with moderate disease progression due to abnormal loading patterns resulting from the loss of meniscal stabilization. The pathophysiology involves progressive cartilage matrix depletion, subchondral bone sclerosis, and osteophyte formation developing over 8-16 weeks post-surgery. The model produces a detectable

pain response of tactile allodynia and mechanical hyperalgesia at all stages (acute inflammatory, early-OA, late-OA).[3] The same study also demonstrated phenotype-specific changes in dorsal root ganglia (DRG) gene expression in murine DMM, including late-stage upregulation of Calca (CGRP), Trpa1, Trpv1, and Trpv4, which correlated with subchondral bone sclerosis. These molecular changes were distinct from those observed in inflammatory arthritis models despite comparable joint pathology.[4] This model has been extensively used in rodents, predominantly mice, but is also used to an extent in rats,[5] pigs,[6–8] and sheep.[9]

**Meniscectomy:** Medial meniscectomy (partial or total) removes meniscal tissue, causing immediate alterations in load distribution and joint contact mechanics.[10–12] Following meniscal resection, abnormal joint contact mechanics promotes cartilage matrix degradation characterized by proteoglycan depletion and increased cartilage hydraulic permeability,[12] with cartilage and meniscal degradation over time.[13] Complete meniscectomy produces more severe and rapid OA development compared to partial meniscectomy or meniscal tear models.[11,14] making it suitable for studying advanced disease stages. In rabbits, longitudinal meniscal tear models demonstrate progression to advanced cartilage erosion by 9 weeks post-surgery.[14] In large animal models such as sheep, total meniscectomy leads to early-to-moderate degenerative changes by 12 weeks.[11] Meniscectomy models are also used in rats,[15] rabbits and less commonly in pigs.[6]

### II. Anterior Cruciate Ligament Models

**Surgical ACL transection (ACLT):** ACLT is performed via parapatellar incision, patellar dislocation, and sharp ACL transection. This model combines two disease mechanisms: (1) immediate joint destabilization creating abnormal kinematics and chronic cartilage overload, and (2) acute surgical inflammation from tissue trauma.[16] In rodents, ACLT consistently produces OA within 8-12 weeks. Disease is accompanied by synovial inflammation with elevated leukocyte counts and cytokine concentrations (TNF-α, IL-1β, IL-10, IL-17).[17] In addition, subchondral bone marrow perfusion abnormalities develop in the patellofemoral joint visible on MR.[18] along with osteoclast-derived apoptotic bodies are increased.[19] Periarticular bone microstructural changes occur as early as 3 weeks post-transection, with sustained subchondral and epiphyseal bone remodeling throughout disease progression.[16,20] This model has been performed in rodents, rabbits, and large animals. In a sheep model, partial ACLT produces gross macroscopic damage including cartilage erosions, osteophytosis, and meniscal pathology by 40 weeks with accompanying kinematic gait changes.[21,22] Canine and porcine models of ACLT demonstrate similar findings with substantial structural altercations in cancellous bone[23] and gait abnormalities, synovial inflammation and elevated inflammatory mediators including IL-1β, IL-6, and TNF-α.[24,25] ACLT is most commonly performed in rats,[17] rabbits[14] and mice[26] but has also been described in sheep,[21] pigs,[27] and dogs.[25]

**Non-invasive ACL rupture:** Non-surgical ACL rupture is induced by mechanically applying a dynamic compression cycle, either targeting a force or end-point displacement, resulting in tensile

failure of the ACL.[16,26,28–30] This approach eliminates confounding surgical inflammation, potentially providing a more clinically relevant model of disease progression.[1,16] Given the absence of confounders from surgical injury that requires 2-4 weeks of healing, this model is also particularly well-suited for the study of early injury-induced events (i.e. hours or days after injury)[26,31,32]. The model has established effects on mechanical allodynia, intra-articular matrix metalloproteinase activity, trabecular and subchondral bone remodeling, osteophyte formation, synovial inflammation and fibrosis, and nociceptor sprouting.[33] Comparative studies show non-invasive rupture produces different temporal patterns of cartilage degeneration and bone changes compared to surgical transection.[16] Because failure mode and severity depend on loading parameters, non-invasive rupture can produce partial versus complete mid-substance tears and variable early disease onset.[34] However, the injury mechanism more closely reflects non-contact human ACL rupture biomechanics caused by high-rate tibiofemoral compression and anterior tibial translation rather than surgical transection.[16,26,28,34] Bone loss after PTOA induction cannot be fully explained by disuse alone,[35] suggesting active pathological bone remodeling independent of mechanical unloading occurs with this model.[16] This model is performed in mice,[1,33] rats[34] and less frequently in rabbits.[36]

**B. Mechanical Loading models**

**I. Single impact injury:** These models induce post-traumatic osteoarthritis (PTOA) by delivering a controlled, high-rate mechanical load to articular cartilage using drop towers or instrumented impactors, producing focal chondral or osteochondral trauma without ligament disruption.[37] A single high-energy impact causes immediate, spatially localized chondrocyte death and extracellular matrix damage, including proteoglycan loss and deterioration of cartilage mechanical properties.[37–39] Impact magnitude and loading rate critically influence injury severity, and focal subchondral bone microdamage may occur without gross fracture, contributing to early osteochondral remodeling.[40] Over subsequent weeks to months, impacted regions develop progressive focal cartilage degeneration characterized by surface fibrillation and increased histologic osteoarthritis scores.[37,41,42] In large animals, including sheep and horses, controlled focal impact reliably produces defined cartilage lesions however, disease progression depends on impact magnitude and contact area.[43–46] In the equine talar impact model, the parameters used resulted in focal cartilage degeneration with only mild synovial changes by 3 months, stable synovial fluid cellularity, no sustained elevation of pro-inflammatory cytokines (including TNF-α), and minimal histologic synovitis.[47,48] This model has been used in rabbits,[37] horses[47] and an injury model combining an impact with partial meniscectomy has been used in sheep.[10]

**II. Cyclic compression loading:** Cyclic axial loading of the murine limb without ligament disruption is an established non-invasive method for inducing osteoarthritis after approximately six weeks.[49] Cyclic compressive loading produces progressive cartilage degeneration characterized by proteoglycan loss, surface fibrillation, cartilage thinning, osteophyte formation and associated subchondral bone adaptation.[49,50] Subchondral bone responses are load- and strain-dependent, with cyclic compression altering bone plate morphology without inducing

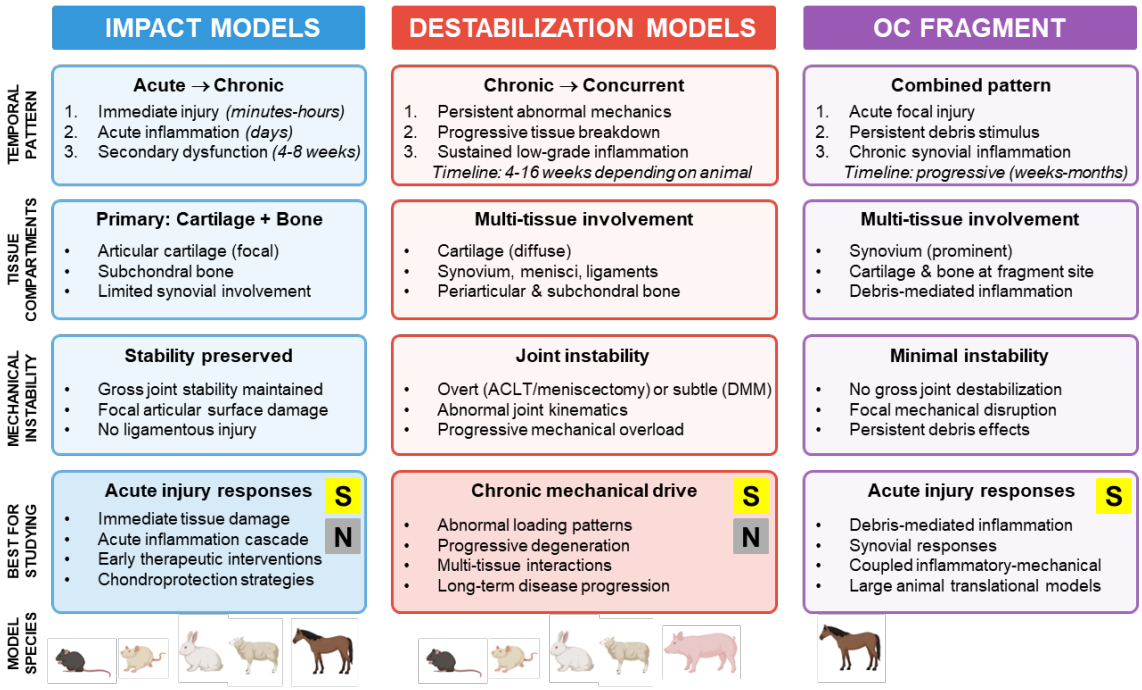
ligamentous injury, distinguishing this approach from joint destabilization models.[49,50] Cyclic mechanical loading also induces catabolic cartilage responses, including increased expression of matrix-degrading enzymes such as MMP13.[51,52] The joint response, though, is magnitude-dependent; while injurious cyclic loading induces PTOA-changes, low-level cyclic tibial compression within a physiologic strain range has been shown to attenuate cartilage degeneration and osteophyte formation following joint injury in mice.[53] As such, cyclic compression models are well suited for studying load-driven cartilage degeneration relevant to repetitive occupational or athletic overuse injuries.[52] This model is used in mice with very limited use in rats.[49]

### C. Osteochondral fragment models

The equine osteochondral fragment model is most commonly established in the carpal joint, typically the middle carpal joint, by arthroscopically creating a focal osteochondral fragment followed by controlled exercise.[54–56] A smaller number of studies have adapted osteochondral fragment techniques to the metacarpophalangeal (MCP) joint, using a combined fragment–groove procedure to induce earlier clinical lameness and joint pathology. In the MCP model, objective lameness can be detected within 1-2 weeks post-operatively, with histologic and biochemical evidence of cartilage degeneration and synovitis confirmed by 11-16 weeks.[57,58] In contrast, the classic middle carpal osteochondral fragment model typically produces moderate lameness and degenerative changes over approximately 16-22 weeks, with mild radiographic changes often detectable around 90 days post-surgery.[56,59,60]

Disease progression in this model arises from both mechanical and inflammatory mechanisms, including direct cartilage and subchondral bone injury at fragment creation, persistent intra-articular debris, and exercise-driven loading of the injured surface, resulting in chronic synovitis and progressive cartilage degeneration.[54,55,57] Horses develop mild to moderate lameness, synovial hyperplasia and hyperemia, cartilage wear lines, and biochemical alterations in synovial fluid lubricants such as hyaluronic acid and lubricin, consistent with PTOA development.(Feeney et al., 2019; Peal et al., 2020) This model is particularly useful for studying chronic synovial inflammation and cartilage degeneration in the absence of gross joint instability, as the retained osteochondral fragment provides a sustained intra-articular stimulus while overall joint alignment and ligament integrity are preserved.[61,62]

## Comparative pathophysiology across PTOA models




**Surgical (S) versus non-surgical (N) model selection** involves critical methodological trade-offs. Surgical PTOA models introduce confounding inflammatory responses related to capsular incision, tissue trauma, and wound healing, which may obscure or amplify disease-specific inflammatory pathways.[1,16,17] However, they do offer precise anatomical targeting, and standardized disease progression timelines, making them well suited for mechanistic studies.[2,11,16] Non-surgical models eliminate surgical confounding and more closely recapitulate spontaneous traumatic injuries, such as non-contact ACL rupture, but their dependence on loading parameters and resulting injury pattern can introduce heterogeneity in injury severity and temporal disease progression if rupture is not consistently confirmed and experimental conditions are not carefully controlled, potentially impacting reproducibility.[34] Species-specific considerations also influence model selection: rodents provide cost-effectiveness and genetic tractability but limited translational anatomy;[16,26,28,29] large animals (sheep, pigs, horses) offer human-scale joints and clinically relevant biomechanics but require specialized facilities and veterinary expertise.[11,21,55] The optimal model depends on whether the research question prioritizes mechanistic control, reproducibility, clinical relevance and/or elimination of surgical artifacts.

## Less common PTOA models

Several additional PTOA models have been described but were not emphasized in this consensus due to limited adoption, increased technical complexity, or restricted applicability. These include **intra-articular fracture models** (e.g., tibial plateau, acetabular), which closely replicate post-fracture osteoarthritis but exhibit high variability in injury severity and disease trajectory.[63–65] **Combined injury models** (e.g., ACL injury with meniscal or cartilage damage) accelerate disease progression but introduce compounded surgical confounding, limiting mechanistic specificity.[66] **Exercise-based or overload models**, including treadmill running or forced

mobilization, primarily modulate disease severity after injury rather than independently inducing PTOA.[67–69] **Inflammatory or chemical models**, such as intra-articular monoiodoacetate or collagenase injection, reliably induce synovitis, cartilage degeneration, and pain response, but lack an initiating mechanical insult and therefore model inflammatory osteoarthritis rather than PTOA induction.[4,70] **Genetic or conditional murine knockout models** paired with injury or overload injury models provide mechanistic insight but are not standalone PTOA induction models.[71]

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