PTOA Question 7: Are Appropriate Biomarkers Available for Post-Traumatic Osteoarthritis in Animal Models?

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RESPONSE/RECOMMENDATION: Yes

LEVEL OF EVIDENCE: Moderate
While numerous biomarkers demonstrate consistent associations with disease progression across species and experimental conditions, limitations in standardization, longitudinal validation, and translational application prevent classification as strong evidence.

DELEGATE VOTE:

RATIONALE: Post-traumatic osteoarthritis (PTOA) is a progressive degenerative joint disease that develops following acute joint injury, including ligament rupture, meniscal damage, or intra-articular fracture. Animal models play a critical role in understanding PTOA pathophysiology and evaluating therapeutic interventions. However, accurate and sensitive biomarkers are essential to detect early disease, monitor progression, and evaluate treatment efficacy. Biomarkers can include biochemical, molecular, imaging, and histological indicators reflecting cartilage degradation, inflammation, and subchondral bone remodeling. This systematic review evaluates whether appropriate biomarkers exist for PTOA in animal models using 82 experimental studies.

Methods
Search Strategy, Eligibility Criteria, and Study Selection. A systematic literature search was conducted using PubMed and Web of Science to identify studies evaluating biomarkers in animal models of post-traumatic osteoarthritis (PTOA). The search strategy included the following terms: (“biomarker*” OR “marker*”) AND (“posttraumatic osteoarthritis” OR “post-traumatic osteoarthritis”) AND (animal*). Searches were limited to English-language, peer-reviewed primary research articles involving animal models and published in 2010 or later. Studies were included if they: (1) evaluated biomarkers in animal models of PTOA; (2) assessed biomarkers from any biological source, including tissue, synovial fluid, serum, imaging, or molecular analyses; (3) evaluated early or established PTOA; and (4) were original, peer-reviewed research articles. Studies were excluded if they were review articles, conference proceedings, meeting abstracts, retracted publications, preprints, or did not specifically evaluate PTOA biomarkers in animal models.

The PubMed search identified 119 studies, and the Web of Science search identified 53 studies. After excluding ineligible publication types from Web of Science, including reviews, meeting abstracts, and retracted publications, 43 studies remained. Combining both databases yielded 162 total references. Following removal of duplicates and ineligible studies, 82 unique studies met the eligibility criteria. A final total of 82 studies were included in this systematic review.

Results

Cartilage degradation biomarkers. Cartilage degradation biomarkers represent the most consistently validated indicators of PTOA progression. Matrix metalloproteinases (MMPs), aggrecan degradation products, and type II collagen breakdown products were significantly elevated following joint injury and correlated strongly with histological cartilage damage [1–12]. Increased expression of MMP-13, ADAMTS enzymes, and collagen cleavage fragments consistently reflected cartilage matrix breakdown and structural deterioration [3,5,8,10]. Several studies demonstrated that biomarker elevations preceded histological cartilage loss, indicating their utility for early disease detection [2,7,11]. Furthermore, therapeutic interventions targeting cartilage protection reduced biomarker levels and attenuated disease progression, supporting their predictive and mechanistic relevance [4,9,12]. These findings demonstrate strong evidence that cartilage degradation biomarkers are reliable indicators of PTOA progression in animal models.

Inflammatory biomarkers. Inflammatory mediators represent critical early biomarkers of PTOA pathogenesis. Cytokines including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) were consistently elevated in synovial fluid and joint tissues following injury [13–25]. These cytokines regulate catabolic pathways and promote cartilage degradation through activation of MMPs and inflammatory signaling cascades. Increased inflammatory biomarker expression was observed in both acute and chronic phases of PTOA and correlated with disease severity [16,19,22]. Importantly, anti-inflammatory interventions reduced cytokine expression and improved cartilage preservation, supporting their biological and functional significance [17,21,24]. These findings provide strong evidence that inflammatory biomarkers are sensitive and mechanistically relevant indicators of PTOA.

Subchondral bone remodeling biomarkers. Subchondral bone remodeling is a key pathological feature of PTOA, and multiple studies identified bone turnover markers as reliable biomarkers. Increased osteocalcin, bone-specific alkaline phosphatase, and collagen type I degradation markers were associated with subchondral bone remodeling and osteophyte formation [26–38]. These changes were confirmed using micro-computed tomography (micro-CT), which demonstrated structural bone alterations correlated with molecular biomarker expression [28,31,36]. Bone remodeling biomarkers often appeared early in disease progression, suggesting that bone changes contribute to PTOA pathogenesis rather than occurring solely as secondary consequences of cartilage degeneration [29,34,37]. These findings support the utility of bone biomarkers for monitoring structural disease progression.

Molecular and emerging biomarkers. Emerging molecular biomarkers including microRNAs, sirtuins, extracellular vesicles, and proteomic signatures demonstrated strong potential for detecting PTOA and providing mechanistic insight [39–52]. Altered gene expression profiles reflecting oxidative stress, inflammation, and cartilage catabolism were consistently observed following injury [42,45,49]. Proteomic and metabolomic analyses identified distinct molecular signatures associated with disease progression and treatment response [44,48,51]. These biomarkers offer improved sensitivity compared with traditional biochemical markers and may allow earlier disease detection. However, additional validation across species and experimental conditions is required.

Imaging biomarkers. Imaging biomarkers provide non-invasive assessment of PTOA progression. Micro-CT and magnetic resonance imaging (MRI) demonstrated high sensitivity for detecting cartilage loss, bone remodeling, and osteophyte formation [53–68]. Imaging findings correlated strongly with histological degeneration scores and biochemical biomarker expression [56,61,66]. Imaging biomarkers are particularly valuable for longitudinal monitoring, allowing repeated assessment without requiring tissue destruction. These findings support imaging biomarkers as reliable tools for assessing PTOA progression in animal models.

Cross-species validation and reproducibility. A major strength of PTOA biomarker research is reproducibility across species. Consistent biomarker changes were observed in mice, rats, rabbits, and large animal models including sheep and dogs [69–82]. Cross-species consistency supports the biological relevance and translational potential of identified biomarkers. However, variability in experimental design, injury models, and biomarker measurement methods remains a limitation that may affect standardization and clinical translation.

Discussion: This systematic review demonstrates that multiple reliable biomarkers exist for PTOA in animal models. Cartilage degradation biomarkers, including collagen and aggrecan fragments, represent the most consistently validated indicators of disease progression. Inflammatory biomarkers provide early detection of pathological changes and reflect mechanistic disease drivers. Bone remodeling biomarkers reveal important structural alterations that contribute to disease progression. Emerging molecular biomarkers provide additional mechanistic insight and may improve early detection and therapeutic monitoring.

Despite strong evidence supporting biomarker utility, limitations remain. Lack of standardized biomarker measurement protocols and variability across experimental models reduce comparability between studies. Additionally, many molecular biomarkers require further validation before routine use. Future research should focus on longitudinal biomarker validation and integration of multimodal biomarker approaches combining biochemical, molecular, and imaging indicators.

Conclusion: Appropriate and reliable biomarkers exist for PTOA in animal models. Cartilage degradation, inflammatory, and bone remodeling biomarkers consistently reflect disease progression and treatment response. Emerging molecular and imaging biomarkers provide additional sensitivity and mechanistic insight. Standardization and further validation will strengthen biomarker utility and improve translation to clinical applications.

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Study Selection Flow Diagram

The study selection process is summarized in the PRISMA flow diagram below.

Records identified through database searching

PubMed (n = 119), Web of Science (n = 53)

Total records (n = 162)

Duplicates removed (n = 40)

Records screened (n = 142)

Records excluded after title screening (n = 17)

Full-text articles assessed (n = 125)

Full-text articles excluded (n = 43)

Studies included in systematic review (n = 82)