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Development of Osteoarthritis Animal Models and Severity Assessment Based on Histopathological Scoring

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Abstract

Background: Osteoarthritis (OA) is a prevalent degenerative joint disease worldwide, and its pathophysiology remains incompletely understood. Clinical studies in humans face limitations due to variability in disease progression, slow onset, and numerous confounding factors. Therefore, animal models are essential for exploring OA mechanisms and potential interventions. **Objective:** This study aims to identify various methods for developing OA animal models and the histopathological scoring systems used to assess disease severity. **Method:** A systematic literature review was conducted using databases including PubMed, ScienceDirect, and Google Scholar, targeting articles published between 2015 and 2025. Keywords included "osteoarthritis," "animal models," and "histopathological assessment." Totally 18 articles were analyzed. **Result:** The review found that OA models can be induced through natural aging, genetic modification, surgical destabilization, mechanical loading, or chemical induction (e.g., monoiodoacetate injection). Histopathological evaluation, commonly using Hematoxylin-Eosin and Safranin-O staining, is crucial to determine cartilage degradation and disease progression. Among scoring systems, the Mankin and OARSI methods are most widely used. OARSI scoring is simpler and faster but requires expertise for consistent interpretation. **Conclusion:** In conclusion, selecting appropriate animal models and histological scoring systems is critical for OA research, depending on study goals and available resources.

Keywords: Osteoarthritis; animal model; histopathologic score.

Introduction

Osteoarthritis (OA) is a chronic joint disease affecting 15% of the global population over the age of 30.[1] The most commonly affected joints are the knees, followed by the hips and hands. The knee joint consists of two compartments: the tibiofemoral (TF) joint and the patellofemoral (PF) joint. Knee osteoarthritis may occur in the TF, PF, or both compartments[2–5].

The pathophysiology of OA is not yet fully understood; however, several risk factors contribute to its progression, including age, joint injury history, musculoskeletal abnormalities, and obesity[6–8]. Many studies have attempted to elucidate OA pathophysiology and identify potential interventions to prevent or slow its progression. Nevertheless, clinical studies in humans face numerous limitations and challenges, such as variability in disease progression, slow onset, difficulty in controlling confounding variables, and the presence of multiple contributing risk factors[1,9–13].

Various OA animal models have been developed to study the disease, with rodents—particularly rats—being the most frequently used for knee OA research. Advantages of

using rodents include accessibility, low cost, and ease of breeding. Rats are preferred over mice due to their thicker cartilage layer[10,14–16]. Several induction methods have been applied to develop knee OA models, categorized into primary (naturally occurring) and secondary (induced by various risk factors such as surgery, trauma exposure, and intra-articular injection of chondrotoxic or proinflammatory substances)[9,16–19].

Following OA induction, histopathological evaluation is essential to assess disease onset and progression. Common staining techniques include hematoxylin-eosin (HE), safranin-O, and toluidine blue. The stained sections are analyzed microscopically to determine OA severity in the joint. Several scoring systems have been developed, with the most widely used being the Mankin score, Osteoarthritis Research Society International (OARSI) score, and Osteoarthritis Bone Score (OABS)[20–22].

Despite the extensive availability of OA animal models and histopathological scoring systems, the is currently no standardized guideline or consensus regarding the selection of the most appropriate OA model or scoring sustem for knee OA research. This lack of standarization has resulted in substantial heterogeneity across preclinical studies, limiting comparability, reproducibility, and translational relevance of findings.

Therefore, this literature review aims to systematically identify and compare commonly used knee OA animal models and histopathological scoring systems. By critically synthesizing existing evidence, this study seeks to hihlight the strengths and limitations of each approach and to address the existing gap in standardized methodological guidance. The findings are expected to support researchers in selecting appropriate preclinical OA models and scoring systems, thereby improving study quality and facilitating more consistent and translatable OA researcg outcomes.

Materials and Methods

Study Design

This study employed a systematic literature review, providing an in-depth and structured analysis of relevant previous studies to identify, evaluate, and synthesize evidence regarding the development of OA animal models and histopathological scoring systems.

Sample

The sample in this study consisted of scientific articles relevant to the development of osteoarthritis (OA) animal models and histopathological scoring systems for assessing OA severity. Articles were obtained from ScienceDirect, PubMed, and Google Scholar using the keywords “osteoarthritis,” “development of osteoarthritis animal models,” and “histopathological assessment systems of osteoarthritis animal models.” The included articles were written in Indonesian or English, available in full text, published between 2015 and 2025, and directly related to OA animal models or histopathological evaluation methods. Articles that were irrelevant to the study topic or published as commentaries were excluded. After the screening and eligibility process, 18 articles were selected and reviewed as the final sample.

Data Collection Technique

Literature searches were conducted using specific keywords: “osteoarthritis,” “development of osteoarthritis animal models,” and “histopathological assessment systems of osteoarthritis animal models” across ScienceDirect, PubMed, and Google Scholar databases. Inclusion criteria were articles written in Indonesian or English, available in full text, and published between 2015 and 2025. Exclusion criteria included articles with irrelevant topics and those published as commentary.

Data Analysis Technique

The article selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Records identified through database searching were screened based on titles and abstract, followed by full-text aseessment for eligibility. A PRISMA flow diagram was used to document the identification, screening, eligibility, and inclusion stages of the reviewed studies. The findings were then synthesized to provide a comprehensive overview of OA model development and histopathological scoring methods.

Data synthesis was conducted using a thematic qualitative analysis. Findings were grouped according to (1) OA induction methods (spontaneous, surgical, mechanical loading, and chemical induction) and (2) histopatological scoring systems (Mankin, OARSI, and OABS). This approach enabled systematic comparison of methodological characteristics, advantages, limitations, and applicability of each model and scoring system.

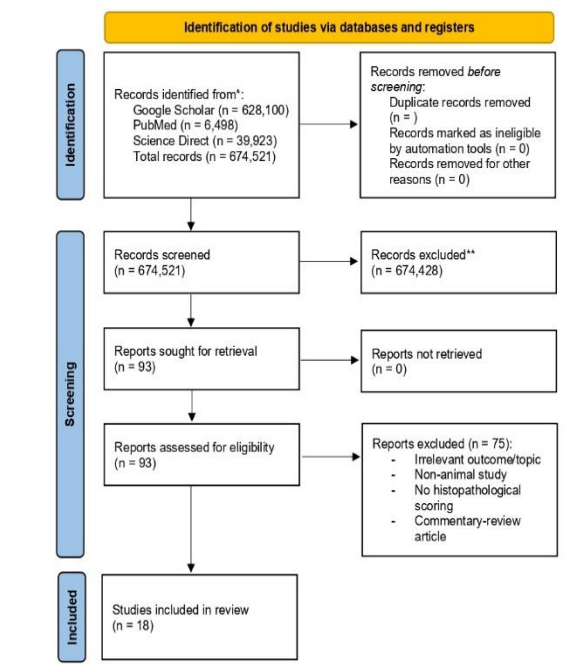

Figure 1. PRISMA 2020 flow diagram of study slection

Ethical Consideration

This study did not involve direct human subjects and therefore di not require ethical approval. Research ethics principles were still applied to ensure the literature sources used were from legitimate publications to maintain transparency in data compilation and respecting the copyrights of the original authors.

Results

Using the predetermined keywords, a total of 628,100 articles were found on Google Scholar, 6,498 articles on PubMed, and 39,923 articles on ScienceDirect. Subsequently, a screening process was conducted based on the defined inclusion and exclusion criteria, resulting in a total of 18 articles that were reviewed in this study.

The methodological quality of the included animal studies was assesed using SYRCLE's risk of bias tool. Overall, most studies demonstrated a low risk of bias in baseline characteristics, incomplete outcome data, and selective outcome reporting. However, insufficient reporting regarding randomization procedures, allocation concealment, and blinding resulted in several domains being rated as unclear or high risk. These limittaions reflect common reporting challenges in preclinical OA research and should be considered when interpreting study findings.

Discussion

Development of Osteoarthritis Animal Models

OA animal models are categorized based on induction methods, which also reflect the clinical classification of OA according to its etiology, as defined by the American College of Rheumatology.

Spontaneous OA Models

Spontaneous OA models are developed from genetically modified animals or those that naturally develop OA with aging. These models

mimic non-traumatic OA progression and are considered more representative of human OA[23].

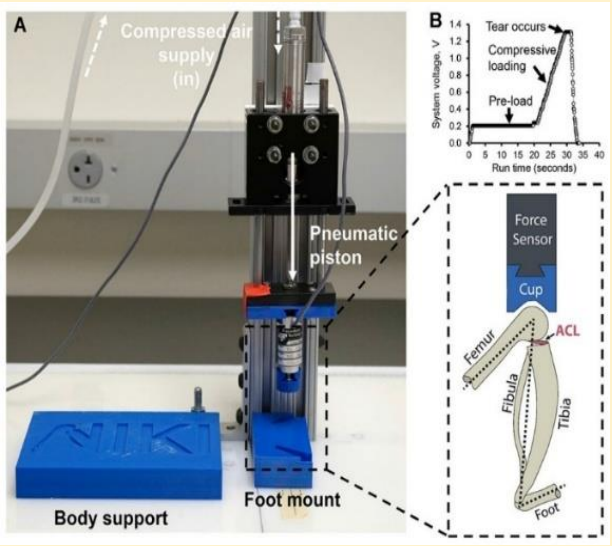

Figure 2. NIKI device used to induce ACL rupture through excessive compressive loading

Mice, rabbits, dogs, horses, and some types of guinea pigs are commonly used. Certain mouse strains such as STR/ort and C57BL/6 are genetically prone to spontaneously develop OA. Studies show that 80% of 18-month-old C57BL/6J mice and 93% of 17-month-old male STR/ort mice exhibit knee OA, attributed to medial patellar dislocation and tibial internal torsion due to aging[23].

Genetic Mutation and Knockout Models

Genetically modified OA models include transgenic mice lacking collagen alpha-1 type IX (Col9a1). Articular cartilage in mammals contains types II and IX collagen, surrounding the chondrocytes. Mutations in these collagens are associated with cartilage degradation resembling OA. Col9a1 mice do not express type IX collagen, which binds with type II fibrils, resulting in OA-like joint degeneration starting at 3 months of age[23].

Joint Loading (Dynamic) Models

Dynamic OA models involve non-invasive external joint injury to create OA-like defects. Common dynamic models in mice include intra-articular tibial plateau fractures, tibial compression, and anterior cruciate ligament (ACL) rupture induced by excessive compression[3,24].

Tibial plateau fractures simulate high-energy trauma injuries such as those caused by vehicle accidents in humans. In this model, the mouse knee is bent, and a wedge-shaped load applicator applies compressive force to the tibia, causing articular fracture. The force and displacement can be controlled to achieve desired outcomes. This model is ideal for investigating regenerative therapies and simulates post-traumatic OA[24].

Axial loading of the tibia in the rat knee joint causes anterior displacement of the tibia relative to the femur. Repetitive loading induces lesions and subchondral changes resembling osteoarthritis (OA). This model allows the study of long-term effects of joint injury[24].

The anterior cruciate ligament (ACL) rupture model, induced by excessive compressive loading on the knee, causes joint instability and increased anterior tibial translation relative to the femur. One method used to induce this condition involves a device known as the Non-Invasive Knee Injury (NIKI) system. For injury induction, a static load of approximately 5.4 N is applied for 15–25 seconds, followed by an increasing compressive load at a rate of 3.26 ± 0.28 N/sec until rupture occurs. The rupture is identified by a “popping” sound and/or cranial displacement of the distal femur from the patella. As a result, knee biomechanics are altered, leading to chondrocyte apoptosis and articular cartilage erosion. This method is particularly useful for studying sports injuries and therapeutic approaches following acute trauma[24].

Joint loading models can also be developed through obesity induction in animal models. Obesity is a known risk factor for the onset and

progression of OA. Therefore, the relationship between obesity and knee OA can be further studied by establishing an obesity model using a high-fat diet. Excessive and abnormal fat accumulation increases mechanical stress on weight-bearing joints and is a major risk factor for the development of knee OA. However, the consistency between OA lesions induced by this model and the severity of human knee OA remains to be further explored[25].

Surgical Induction Model

Surgical OA models aim to destabilize the joint by transecting ligaments or removing fibrocartilaginous tissues to induce progressive joint degeneration. The progression rate of OA and the resulting OA score depend on the level of joint instability caused by each surgical method. These models closely resemble post-traumatic OA in humans, as they induce joint instability and alter the load distribution in the knee.[3,9,23] Structures that can be transected to develop knee OA models include: Anterior cruciate ligament (ACL); patella ligament; posterior cruciate ligament (PCL); medial meniscus; lateral meniscus; medial collateral ligament (MCL); medial meniscotibial ligament (MML) and lateral collateral ligament (LCL) [26,27].

The most common surgical method to induce knee OA is ACL transection (ACLT). ACL injury causes knee joint destabilization due to the loss of anterior translation control, which alters the load distribution and accelerates cartilage degeneration, resulting in lesions similar to human OA[24].

Various meniscal surgical manipulations can also induce OA by altering meniscal morphology and joint function. Gowler et al. compared traditional medial meniscus destabilization (DMM) with a modified technique where the MMTL is preserved, and the coronary ligament is transected instead. MMTL secures the medial meniscus to the tibial plateau, so ligament disruption destabilizes the meniscus, leading to its medial displacement and reducing the load-bearing area. This increases mechanical pressure and accelerates OA development.[24] Both traditional and modified DMM surgeries resulted in comparable joint pathology, with mild joint damage visible at 4 weeks post-surgery, worsening over time. Significant chondropathy and synovitis were observed by the 16th week, along with osteophyte formation[9]. These morphological changes closely resemble human osteoarthritis resulting from medial meniscus tears, which can be visualized radiographically up to 20 years after the initial meniscal injury[24].

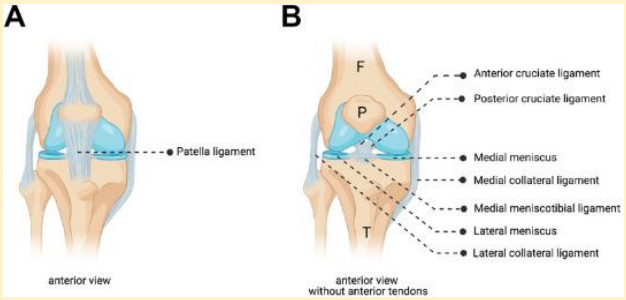

Figure 3. Anatomical structure of the knee joint related to the development of OA animal models using surgical methods[23].

Development of Chemically Induced Models: Intra-Articular Monoiodoacetate (MIA) Injection

Chemically induced OA models are less invasive than surgical models, making them easier to apply and allowing studies of OA lesions at various stages. Among the chemical induction methods, MIA is the most widely used due to its ability to replicate human-like OA lesions.

MIA is a metabolic inhibitor that disrupts the aerobic glycolytic pathway in cells, inducing cell death by inhibiting the activity of glyceraldehyde-3-phosphate dehydrogenase an essential enzyme in chondrocyte glycolysis [17,28]. The doses of MIA used to induce OA in rats range from 0.5 to 4.8 mg, with 1 mg and 3 mg being the most commonly used[1]. OA

induced by MIA injection is characterized by rapid onset, joint function decline, and pain.

Histopathological progression in the MIA model shows that cartilage lesions in the knee joint appear as early as day one, while subchondral bone lesions emerge by day seven post-injection. As cartilage degradation progresses, mechanical load increases on the subchondral bone, leading to further bone lesions and subsequent remodeling. In addition to changes in the articular cartilage, intra-articular MIA injection also induces alterations in the synovial membrane and the surface of the infrapatellar fat pad (IFP)[17,18,23,28].

The amount of MIA injected plays a critical role in determining the progression rate of OA in animal models. A study by Takahashi compared the histopathological progression in the patellofemoral and tibiofemoral joints of MIA models using 0.2 mg and 1 mg doses. In both groups, HE staining showed nuclear enlargement, nuclear disintegration, and variation in nuclear size in the patella and femur from day three to two weeks post-injection. In the 0.2 mg group, cartilage surface irregularities were not detected until week 8, while in the 1 mg group, early OA changes such as fibrillation and fissures appeared by week 4. Advanced OA changes, including erosion, denudation, and replacement of articular cartilage with fibrous tissue, were observed after 8 weeks. The study concluded that 1 mg of MIA induces faster histopathological changes compared to 0.2 mg[17].

Development of Chemically Induced Models: Collagenase and Papain

Another commonly used chemical method involves enzymatic induction with collagenase. This procedure uses high-purity type II collagenase injected intra-articularly, affecting joint ligaments and resulting in joint instability. Yu et al. injected 25 µL of 500 U type II collagenase dissolved in saline into the right knee joint of rats using a microsyringe. Micro-computed tomography (micro-CT) examination revealed cartilage damage by week three, with synovial hyperplasia and osteophyte formation observed by week six[16].

Papain is a proteolytic enzyme historically used for OA induction. It breaks down proteoglycans, key components of cartilage that provide compressive resistance through water absorption. In this model, 0.15 mL of a mixture solution (2% papain: 0.03 mol/L L-cysteine = 2:1) is injected into the right knee joint using a 1 mL syringe, with repeated injections on days 4 and 7. The papain induction model is suitable for short-term studies aimed at observing pathological changes during the late stages of OA[16].

Table 1. Comparison of Common Knee OA Animal Models

Model	Induction Method	Advantages	Limitations	Translational Relevance
Spontaneous aging	Natural/genetic	Mimics human OA progression	Long duration, high cost	High
Surgical (ACLT/DMM)	Joint destabilization	Reproducible, rapid OA	Invasive, trauma-related	Moderate-High
Mechanical loading	External compression	Non-invasice, controlled injury	Specialized equipment	Moderate
MIA Injection	Chemical	Rapid, cost-effective	Non-physiological, acute damage	Moderate
Collagenase/Papain	Enzymatic	Joint instability model	Less commonly standardized	Low-Moderate

Histopathological Evaluation of Knee Osteoarthritis in Rats

Studies using rat models for OA development typically apply hematoxylin and eosin (HE) and Safranin O staining to evaluate joint tissue histopathology. HE staining visualizes tissue structure and inflammation, while Safranin O stains cartilage proteoglycans and helps detect cartilage degradation and OA progression[22,29].

HE staining is a general histological technique that uses two dyes: hematoxylin (which stains cell nuclei blue/purple) and eosin (which stains cytoplasm and extracellular matrix pink/red). In rat OA models, HE staining can reveal: inflammation around cartilage and chondrocytes, disorganization of cartilage and chondrocytes, synovitis, osteophyte formation, and changes in subchondral bone[30]. Safranin O is a cationic dye that binds specifically to proteoglycans in cartilage, which are crucial components of the cartilage matrix. In rat OA models, Safranin O staining is useful for: assessing cartilage degradation and OA progression, identofying regions with proteoglycan loss, visualizing cartilage irregularities and reduced staining intensity, and detecting areas of cartilage breakdown[22,30,31].

Histopathological Scoring of Knee Osteoarthritis in Rats

Several scoring systems have been applied to assess knee OA in rat models. Some focus solely on cartilage damage, while others include additional features such as bone alterations, osteophytes, and synovial changes.

Mankin Scoring System

The Mankin scoring system, introduced by Collins and McElligot in the 1960s and published in 1971 for human hip OA evaluation, was later adapted for histological evaluation in various animal OA models, including rats. The Mankin score focuses on cartilage changes, including structure (0–6), chondrocyte cellularity (0–3), Safranin O staining (0–4), and tidemark integrity (0–1).[20,30,32] Scores from each parameter are summed to determine OA severity, ranging from 0 (normal) to 14 (most severe OA). Despite its frequent use, the Mankin system has limited reproducibility in distinguishing between mild and moderate OA and does not assess the extent of cartilage surface involvement[1]. Various modifications have been made to enhance the system's sensitivity and ease of use. Modified Mankin scoring involves evaluating surface integrity, cellularity (changes in cell count), cell cloning, and Safranin O staining intensity. These parameters are assessed throughout all cartilage layers: superficial, middle, and deep zones.[30] The assessment characteristics and severity grading based on the modified Mankin scoring system are described in Table 2.

Osteoarthritis Research Society International (OARSI) Scoring System

OARSI formed a working group to publish a new OA scoring system in 2006. The OARSI scoring system for rodent models was published in 2010[20,22,31]. The OARSI scoring system is based on evaluation of the following components: cartilage damage, osteophyte formation and synovitis.

Scoring for cartilage damage is based on lesion depth, ranging from superficial fibrillation to lesions penetrating the subchondral bone. Criteria for osteophyte formation is based on the size and extent of osteophytes. Furthermore, scoring for synovitis is based on the number of synovial lining cells[31]. These criteria are applied to four quadrants of the joint: medial femoral condyle (MFC), medial tibial plateau (MTP), lateral femoral condyle (LFC), and lateral tibial plateau (LTP). OA severity is determined by summing scores across all quadrants[29].

Table 2. Modified Mankin Scoring System [32]

Category	Subcategory	Score
Surface Integrity	Normal	0
	Mild surface irregularity	1
	Moderate surface irregularity	2
	Severe surface irregularity	3
	Cleft extending into the transitional zone	4
	Cleft extending into the radial zone	5
	Cleft extending into the calcified zone	6
	Fibrillation and/or loss of the transitional zone	7
	Fibrillation and/or loss of the radial zone	8
	Fibrillation and/or loss of the calcified zone	9
	Fibrillation and/or loss of the subchondral zone	10
Selularitas	Normal	0
	Mild increase or decrease	1
	Moderate decrease	2
	Severe decrease	3
	No cells	4
Cell cloning	Normal	0
	Few doublets	1
	Numerous doublets	2
	Doublets dan triplet	3
	Several cell nests	4
Safranin-O staining	Normal	0
	Slight reduction	1
	Loss in the radial layer	2
	Loss in the interterritorial layer	3
	Only present in the pericellular matrix	4
	No staining	5
Total		0-23

Table 3. Tissue Criteria in the OARSI Scoring System[22]

Grade	Cartilage Damage
0	Normal
0,5	Loss of Safranin-O staining without structural changes
1	Minor fibrillation without cartilage loss
2	Vertical clefts into the layer just below the surface and some surface lamina loss
3	Vertical clefts/erosion into calcified cartilage involving <25% of the articular surface
4	Vertical clefts/erosion into calcified cartilage involving 25–50% of the surface
5	Vertical clefts/erosion into calcified cartilage involving 50–75% of the surface
6	Vertical clefts/erosion into calcified cartilage involving >75% of the surface

Grade	Criteria
0	Intact surface, normal cartilage morphology; Matrix: normal appearance; Cells: intact, properly oriented
1	Intact surface; Matrix: intact superficial zone, edema and/or superficial fibrillation (abrasion), focal matrix condensation; Cells: death, proliferation, hypertrophy
2	Surface discontinuity; Matrix: discontinuity in the superficial zone (deep fibrillation); Cells: death, proliferation, hypertrophy; Matrix staining: reduction in upper 1/3, focal perichondral staining; Chondrocyte column disorientation
3	Vertical fissures into the middle zone, branching fissures; Matrix staining reduced to lower 2/3 of cartilage; New collagen formation; Cell changes adjacent to fissures
4	Erosion; Loss of cartilage matrix; Delamination of superficial zone; Mid-zone cyst formation; Loss of superficial and mid-zone matrix
5	Denudation; Surface: sclerotic bone or reparative tissue including fibrocartilage within the exposed area
6	Deformation; Bone remodeling (beyond osteophyte formation); Includes microfractures and extensive fibrocartilaginous repair

Osteoarthritis Bone Score (OABS) Scoring System

The previously developed histological scoring systems, such as OARSI and the Mankin chondropathy score, were primarily aimed at evaluating changes in articular cartilage[20]. However, bone marrow lesions (BML), detectable via Magnetic Resonance Imaging (MRI), have been shown to be associated with OA-related pain. BMLs are metabolically active structures, characterized by angiogenesis, increased fibrous connective tissue, and gene expression linked to cartilage formation and bone resorption[21,33].

Seven pathological domains related to BMLs have been identified: cysts, subchondral fibrosis, hypervascularity, new cartilage formation, trabecular thickening, and cellular infiltrates indicative of inflammation. Each feature is scored as 0 (absent) or 1 (present) in this semi-quantitative system, which is applicable in routine laboratory settings[21].

Although both Mankin and OARSI scoring systems are widely used, important discrepancies exist in their sensitivity and applicability. The Mankin score, originally described by Collins and McElligot (1971), provides detailed assessment of cartilage structure and cellularity, making it more sensitive for detecting early OA changes. However, its complexity and limited reproducibility reduce inter-observer reliability. In contrast, the OARSI system offer a simpler and faster evaluation framework, particulary suitable for large-scale studies, but may be less sensitive in identifying subtle early-stage cartilage degeneration. These methodological differences partly explain inconsistencies across preclinical OA studies.

The lack of standardized guidelines for selecting OA animal models and histopathological scoring systems has boarder implications beyond experimental research. Standardization of preclinical methodologies may enhance data comparability, improve reproducibility, and accelerate translational pathways, particulary in preclinical drug development and regenerative therapy testing. Harmonized scoring sustems could facilitate regulatory evaluation of disease-modifying OA

drugs (DMOADs) and support evidence-based decision-making in musculoskeletal research policy.

Table 4. OABS Scoring Criteria

Grade	Chara
Cysts	
0	Absent
1	Present (at least one)
Fibrosis	
0	Absent
1	Present (at least one)
Blood vessels	
0	Normal (0-15)
1	Increased (>16)
New cartilage in Bone	
0	Absent
1	Present
Trabecular Thickening (≥ 2 trabeculae > 200 µm)	
0	Normal
1	Increased thickness
Tidemark Thickening	
0	Intact
1	Penetrated by at least one blood vessel
Inflammation (celular infiltration)	
0	Absent
1	Present
Total	**7**

Conclusion

The development of OA animal models using rats can be selected based on specific research goals and references to prior studies to determine the appropriate duration and procedure. Histopathological evaluation is used to assess OA severity in these models, typically involving Hematoxylin-Eosin, Safranin-O, and Toluidine Blue staining. Several scoring systems exist for evaluating OA severity, with the Mankin and OARSI systems being the most commonly used. The OARSI system is reported to be quicker and easier to apply due to fewer parameters, but may be more difficult for inexperienced readers to interpret accurately.

This review has several limitations. Fist, only articles published in English and Indonesian were included, potentially excluding relevant studies in other languages. Second, the review focused primarily on rodent models, which may limit generalizability to large-animal or clinically relevant joint biomechanics. Third, quantitative meta-analysis was not feasible due to methodological heterogenity across studies.

Future studies should focus on validating widely used histopathological scoring systems, such as OARSI, in large-animal OA models and integrating multidisciplinary approaches combining histology, imaging, biomechanics,

and molecular biomarkers to improve translational relevance.

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Conflict of Interest Statement

The author(s) declare no commercial, financial, or personal conflicts of interest related to this research. All authors approved the final manuscript and consented to its publication in *Healthy Tadulako Journal*.

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