

Research in Orthopaedics Preclinical Model – a comprehensive Review

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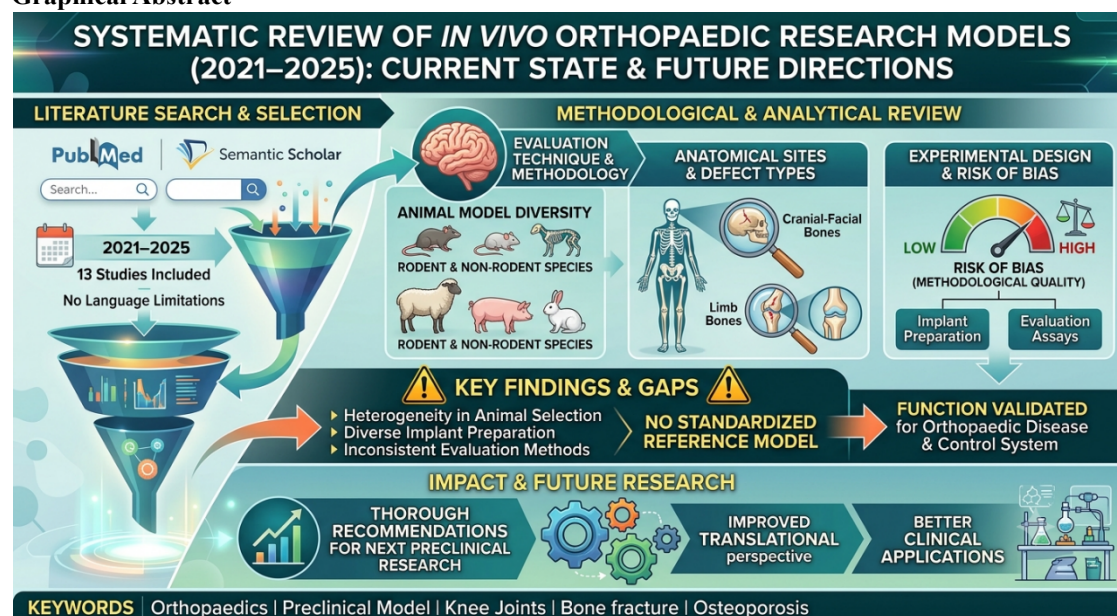
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Graphical Abstract



Abstract

In order to provide thorough recommendations for next preclinical research, this systematic review aims to examine the present state of *in vivo* research on orthopaedic treatment, with a particular focus on model selection, design, methodological, and analytical methodologies. To discover literature that investigated orthopaedics in animal models, web-based databases PubMed and Semantic Scholar were searched. There were also no language limitations on the selection of eligible studies. In order to perform qualitative analysis, data extraction was done. Because of numerous differences among the investigations, a meta-analysis was not performed. There were thirteen research articles that were published between 2021 and 2025. Techniques for evaluation, implant preparation, methodological quality, animal model, and publication details were retrieved. The methodological evaluation showed that the studies' risk of bias ranged from low to high. The cranial-facial and limb bones were among the anatomical sites for causing fractures, and both rodent and non-rodent species were chosen. The function of orthopaedic disease and the control system was validated by published *in vivo* studies. There is currently no standardised reference model, though, given the diversity in animal selection, implant preparation, and evaluation techniques. The systematic review may make it easier to design and carry out preclinical research from a translational perspective by analysing the data taken from included studies.

Keywords

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Introduction

Preclinical Orthopaedic Models, An Examination of Animal Models and Their Applicability to Patients with Orthopaedic Conditions (Wise et al., 2022). The objectives were to give orthopaedic surgeons interested in advancing translational studies guidance and a plan, as well as to present effective animal models from the past. These specialists specifically talked about orthopaedic disease models in animals (Lila et al., 2024).

Research and the invention of products and treatments Figure 1. Research that investigates mechanistic questions motivated by hypotheses is known as discovery research. They may result in the creation of intellectual property and the filing of patents. A value proposition that fills an unmet clinical need is usually at the heart of translational research that leads to commercialisation. Proof-of-concept studies are the first step in securing funding. In order to achieve regulatory permission, the derisking process keeps going as the degree of technological readiness rises. Product launch: Just as crucial to a product's development as regulatory approval is market acceptance and reimbursement.

The main issue that needs to be addressed is the necessity of using animal models to study orthopaedic issues and possible fixes. One could claim that animal testing is no longer required, given the advancements in robotic biomechanical testing, computer modelling, and cell and tissue cultures. Because of this, before these techniques and products are used in clinical settings, regulatory agencies like the Food and Drug Administration demand ethical, well-designed animal model studies that yield reliable preclinical data. Clinically useful information from animal models increases the possibility that clinical trials will be conducted safely and successfully.

The right animal model must be chosen in advance of the switch starts *in vitro* to *in vivo* animal models (Figure 2). While larger animal models like horses, lambs, pigs, or dogs give humans more realistic models, the most popular vertebrate models are rats, mice, or rabbits. They are easier to acquire and care for in huge quantities, and they are less costly (Barresinoussi and Montagutelli, 2015) When discussing results, it is clear that any linked preclinical models' constraints elaborate on the scientific context (Huang et al., 2020). There may be a "lull" in commercialisation during the early phases of translational research. Reducing risk is essential for securing funds and capital investment. This can be achieved by demonstrating that the product or therapy is safe, effective, able to be manufactured competitively, has the potential to provide

therapeutic value, and can be protected by intellectual property or trademark. In order to prove biological proof that this material functions and that the transition from *in vitro* to *in vivo* is feasible, methodical *in vitro* and *in vivo* testing is necessary.

Lastly, beginning with safety-confirming proof-of-concept research, provide data for calculating the appropriate sample size for pivotal studies meant to address scientific, regulatory, and market-based milestones toward market launch or clinical trials, support efficacy for targeted applications, and facilitate the transition to more clinically relevant models (size, geometry, mechanical loading, etc.) may be appropriate. Depending on the study's objectives, this could develop into a key investigation that uses a large, confirmed deficiency or lesion that is symptomatic and won't go away on its own. For pivotal studies to be conducted in accordance with good laboratory practice, they must contain strong and pertinent groups, last at least six months outcome measurements. Understanding how the animals will respond to the illness and/or treatment calls for further thought (Garg, 2016).

Preclinical animal models show variations in adaptive weight bearing following limb surgery, which is crucial for clinical application in the postoperative phase (Soufizadeh et al., 2024). For example, using a dog model to study hardware augmentation in relation to fragility fractures and early mobilisation in the elderly—specifically, per trochanteric femur fractures—would show less translational fidelity because dogs typically only learn to walk on three legs when one is painful (Migliorini et al., 2021). However, because pigs prefer to walk on four legs, they would have to bear weight on the operated leg right away while using the augmented gear, making it a more useful test device in clinical settings.

An experienced, enthusiastic, and well-organised team is needed for large animal translational research (Ameredes et al., 2015). Caretakers and test subjects will unavoidably develop an animal–human relationship. Because of the nature of terminal investigations in experimental models, this link is continuously broken (Chang and Grieder 2024). The most common cause for animal care workers to leave their jobs is compassion fatigue; it is crucial to recognise this and offer an open and honest support system where grieving is not only acceptable but also encouraged. Improvement of medical care can be honoured and valued with a straightforward memorial wall made of animals from previous studies (Srowen, 2020). In order to give useful advice for the next preclinical *in vivo* research, this work aims to perform a systematic literature analysis

on orthopaedic illness in animal models, with an emphasis on study design and evaluation technique selection.

Methodology

Search strategy

There were no prior relevant papers found when a literature search for systematic reviews of pre-clinical research about orthopaedics and disease was conducted. Then, using a combination of the following keywords, the PubMed and Semantic scholar collected literatures were searched to find papers for the relevant *in vivo* research of orthopaedics in animal models that were published between 2021 and 2025: A flow chart was utilized to record the screening and selection procedure, and the entire literature review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria Figure 1.

Search criteria

Both randomised *in vivo* studies that assessed orthopaedic disease in animal models utilising radiographic, biomechanical, histological, and other methods were found in the literature search. Original *in vivo* preclinical research and the use of animal models for orthopaedic tests in various disease models were the requirements for admission. Finally, providing postoperative data, such as radiographic and histological pictures of broken bones, or relevant proof derived from further assessment techniques.

The exclusion criteria were:

- (1) letters to the editor, abstract publications, review papers, and commentaries;
- (2) *in vitro* research devoid of *in vivo* assessment; and
- (3) animal studies that present orthopaedic model evaluation. The publications' language was not restricted in any way.

Selection of studies

Using the two online databases in duplicate, the authors conducted the selection procedure. then screened the abstracts and titles in the results that were listed, and then selected articles according to the inclusion and exclusion standards. The full texts of the pertinent papers were acquired, and the publications that were thought to possibly fit the aforementioned requirements were further examined for research design and methodology. In order to find more potentially relevant studies, the reference lists of these complete texts were also examined.

Data extraction

The author attentively read the whole text in the chosen results, and data extraction was done using standardised procedures. Eligible articles were searched for the following information: authors and country, year of publication, species, gender, number of animals, anatomical location of fracture, fracture induction techniques, control materials,

implant design, evaluation techniques, and key findings.

Reporting quality and analysis

The evaluation of methodological quality focused on the reporting of blindness, selection and dropouts. The following criteria were used by the author to identify, document, and evaluate each study's quality:

The study was categorised as having a low risk of bias when all three divisions were reported; a moderate potential risk of bias when one of the three components was missing; and a high potential risk of bias when two of these components were missing. The authors only carried out a thorough qualitative review because of the variations in animal models and assessment methods, and they refrained from performing a quantitative meta-analysis.

Results

Literature search results and study characteristics

After eliminating duplicates, 1673 records remained from the initial literature search, which found 623 and 2421 papers in PubMed and Semantic Scholar, respectively. After going over each abstract and title, the writers eliminated an extra 1475 records. After a thorough assessment of the study design and published results, 86 of the 99 potentially eligible papers were further eliminated for failing to meet the inclusion or exclusion criteria. Two of the remaining 13 papers included findings from several facets of a single animal investigation and were regarded as a single study. Ultimately, 20 publications that satisfied the inclusion criteria as preclinical *in vivo* studies of orthopaedic diseases utilising animal models of fracture healing were included in the systematic review Figure 1 and Table 1. From 2021 to 2025, the 13 included research were published Table 1.

Methodological quality assessment

Basic details on experimental design, animal housing, ethical approval, surgical techniques, and outcome evaluations were included in all studies; nevertheless, methodological details were typically insufficient. A moderate possible risk of bias was identified in half of the included studies,¹¹⁻²², while a high potential risk of bias was identified in the other half (Yang et al., 2025; Chang et al., 2021; Khademnematollahi et al., 2025; Zhou et al., 2023; Dong et al., 2025; Min et al., 2021; Arzi et al., 2011; menges et al., 2024; Lee et al., 2025; Jeong et al., 2024; Sen et al., 2022; Zhao et al 2021).

Selection of animal models

The two animal species that were most frequently employed were rats and rabbits. Out of all the included studies, only 25% employed mice and one study dog, while 55% chose rats, 40% chose rabbits, and 1% chose beagle dogs as model species (Figure 2 and Table 1). For rat investigations, a particular gender selection propensity was noted (5 out of 7 picked female rats). The included papers did not discuss statistical techniques for determining sample

size. The observation time settings are in the same predicament. For rat models of knee joints, the overall follow-up duration was 7–8 weeks; for mouse models of knee joint fractures, it was 5–6 weeks; and for mouse models of tibia and blood samples, it was 3.5–4 months. Studies involving dogs and pigs, respectively. A longer follow-up period often yielded more information on the degrading process of orthopaedic detection (Gerencser et al 2019).²³ The femur was chosen as the anatomical site for causing fractures in all experiments using rodents (mice and rats). Two studies focused on the knee joints of rabbits, whereas one study focused on the hindlimb. Seventy per cent of researchers used osteotomy to induce fractures, but there were alternative approaches as well, such as using three-point bending devices, bone cutters, or bone clamps. (Figure 3 and Table 1) provides a summary of the information.

Discussion

Although it is currently uncommon in animal research, the release of comprehensive evaluations has been widely acknowledged & prioritised in human investigations of innovative diagnostic and treatment approaches (Percie du Sert et al., 2020). A thorough review of earlier animal studies could be useful for organising translational research for the future on orthopaedic diseases, given the paucity of publications and the considerable difficulties in translating the findings of animal research into clinical use. In order to perform a concluded as opposed to a traditional, literature-based study, the authors hypothesised the quality methods, extracted data, and retrieved and selected eligible studies based on inclusion/exclusion criteria using a standard structured process.

Additionally, researchers can replicate the detrimental effects of common clinical comorbidities, such as osteoarthritis, osteoporosis, osteomyelitis, bone fracture, etc., on fracture healing by using suitable animal models. The authors discovered two studies employing rat models of ovariectomy-induced osteoporosis during the literature search procedure, without placing any constraints on the comorbidities in animal models (Yousefzaseh et al., 2020). In light of facility limitations and animal ethics, the authors advise researchers to think about using intricate fracture healing models with pathologies. The kind of study design will aid in investigating the possible clinical use of treatment in orthopaedics in individuals with comparable medical problems. In many situations, the translational utility and quality of animal research may still be challenging, and it may take a lot longer than *in vitro* experiments. Because of inadequate study design or inappropriate model selection, many animal studies have little value and are redundant from a translational standpoint, even though various radiological, histological,

mechanical, and other evaluation techniques are used.

Rats and rabbits were the most commonly used animal species in the included studies, making up 65% of all initiatives (Hickman et al., 2017). Compared to other larger animal species, mice are more affordable, require less room for husbandry, have a shorter recovery time, and can be genetically modified for a greater number of purposes (MilaniNejad and Janssen, 2014). Nevertheless, only one study employed mice as a research model. It's possible that the skeletal features and small size presented technical challenges for both surgery and fixation device preparation. Because only intramedullary fixation devices were chosen, the included research with rats likewise has similar technical challenges. For research involving large non-rodent species, there were more implant designs available. Additionally, the application areas were expanded to include more anatomical sites, including the cranial and facial bones, in addition to the extremities. Because of the anatomical similarities between their tibia and human bones, sheep and goats are considered good animal models for preclinical evaluation of orthopaedic implants, particularly when developing fixation devices for long-weight-bearing bones. Only one study, nevertheless, used goats.

In order to make up for the biological differences across animal species, it should also be standard procedure to evaluate a novel fracture-healing treatment before clinical application in rodents and non-rodents. However, the majority of recent *in vivo* research only includes one species, and there were significant differences in the post-operative follow-up time points for radiological and other assessments.

The osteotomy, which is used in the majority of research, should be the most effective technique for causing fractures since it produces repeatable outcomes Table 1. The authors suggest utilising relatively hard fixation techniques on unstable anatomical sites and reproducibly causing fractures with osteotomy tools in order to better replicate the clinical scenario and enhance the translation efficacy. Restoring bone quality and its metabolic function should be the primary goals of effective fracture treatment, in addition to reconstructing the continuity of bone tissues.

In addition to structural analysis, mechanical and metabolic studies should be taken into account while organising the preclinical examination. With high resolution that enables quantitative measurement of bone microstructure and implant degradation without the need for laborious tissue sample preparation, micro-CT has established itself as a non-destructive analysis method in bone research and offers a number of advantages over traditional histological techniques for structural evaluation of small animal bone specimens. According to the

findings of recent literature reviews, a number of factors should be taken into account when designing *in vivo* studies in order to achieve repeatable and transferable results as well as to guarantee the ethical use of lab animals.

All be carefully considered by researchers in order to get trustworthy data based the safety and efficacy of orthopaedic implants. These factors have a direct impact on implant design and fixation methods. Furthermore, suitable techniques must be selected for the evaluation of bone repair and implant degradation, and efficient animal models should replicate the desired clinical scenario. As the main techniques, the authors advise combining *in vivo* or *ex vivo* micro-CT with histology, biomechanical assessment, and serum biomarkers of bone metabolism. Furthermore, it should be acknowledged that, from an ethical and practical standpoint, it may be difficult to guarantee animal trials with high methodological standards, particularly in research involving intricate surgical techniques. Even yet, a careful examination of the above important factors during study design will help researchers create a comprehensive search strategy that has a high level of clinical significance.

Conclusions

According to recent data from preclinical studies, using orthopaedic disease detection and treatment can help to accelerate fracture repair. Nonetheless, there was a great deal of variation across trials in terms of animal type, implant preparation, surgery, and assessment methods.

The literature review also identified the methodological flaws and bias risk in *in vivo* surgical investigations, which should be fixed with careful planning and reporting of blindness, dropout, and randomisation. The results showed that a uniform reference model for creating orthopaedic treatment for fractures is still lacking. However, the technical information taken from published studies could serve as the foundation for a thorough study design and a standardised procedure. Planning and carrying out preclinical research from a translational viewpoint may benefit from the information this evidence-based systematic review offers on the design of implants, evaluation methods, and the selection of clinically relevant animal models.

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Conflict of interest

The author declares that there is no conflict of interest.

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Figures

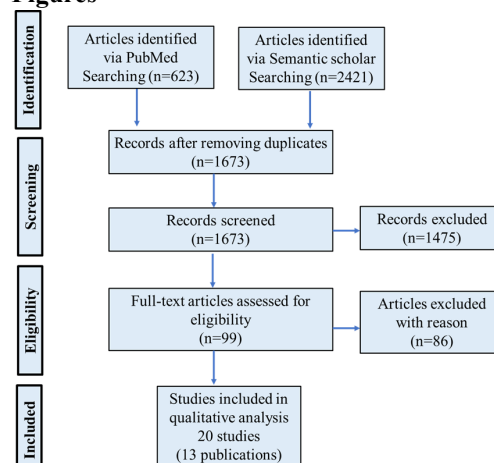


Figure 1. Systematic Flow diagram of literature retrieval and screening process.

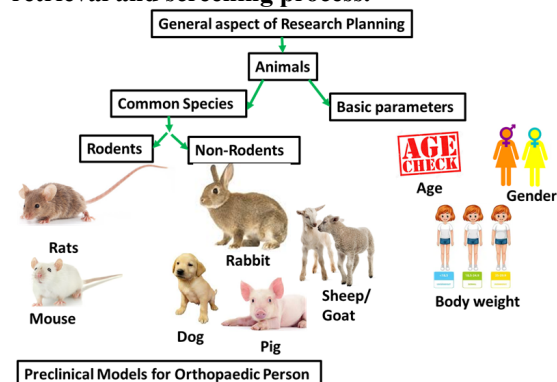


Figure 2. Orthopaedic devices and preclinical study models.

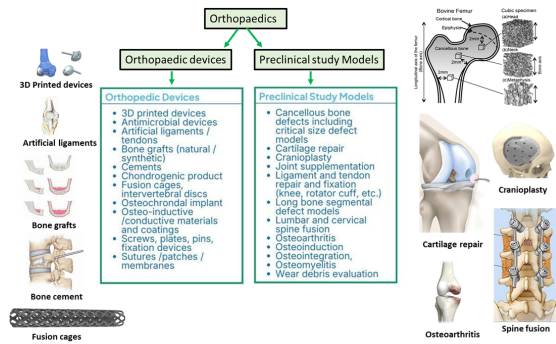


Figure 3. This Figure shows the General aspect of Research planning in Orthopaedics, using preclinical animal models.

SYSTEMATIC REVIEW OF IN VIVO ORTHOPAEDIC PRECLINICAL MODELS: SYNTHESIS & FUTURE DIRECTIONS (2021–2025)

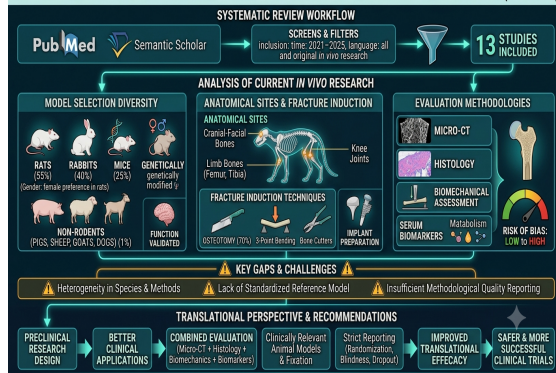


Figure 4. Over all Mechanism of Methodological workflow, current landscape, and translational roadmap for preclinical orthopaedic research. Workflow: Systematic selection of 13 eligible in vivo studies (2021–2025) from PubMed and Semantic Scholar. Current Practices: High reliance on small models (55% rats, 40% rabbits, 25% mice) versus large animals (1%), with osteotomy dominating fracture creation (70%). Outcome metrics focus on micro-CT, histology, biomechanics, and serum biomarkers. Identified Gaps: Variable risk of bias (low to high) caused by inconsistent reporting of blinding and randomization, combined with high methodological heterogeneity. Translational Strategy: Recommended standardization of animal selection, defect creation, and multi-modal outcome testing to improve clinical translation.