



Preclinical models of elbow injury and pathology

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Abstract: The human elbow is a complex joint that is essential for activities of daily living requiring the upper extremities; however, this complexity generates significant challenges when considering its response to injury and management of treatment. The current understanding of elbow injury and pathologies lags behind that of other joints and musculoskeletal tissues. Most research on the elbow joint is mainly focused on the late-disease stages when irreversible damage has occurred. Consequentially, the specific contribution and relative time course of different elbow tissues in disease progression, as well as optimized approaches for treating such conditions, remains largely unknown. Given the challenge of studying elbow pathologies in humans, preclinical models can serve as ideal alternatives. However, a limited number of preclinical models exist to investigate elbow injury and pathology. This review highlights significant clinical elbow diseases and the preclinical models currently available to recapitulate these diseases, while also providing recommendations for the development of future preclinical models. Overall, this review will serve as a guide for preclinical models studying injuries and pathologies of the elbow, with the long-term goal of developing novel intervention strategies to improve the treatment of elbow diseases in human patients.

Keywords: Elbow; injury; pathology; preclinical models

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Introduction

Musculoskeletal tissues and joints are critical for daily living. While decades of research have focused on the physiology and pathophysiology of major musculoskeletal joints (e.g., knee and shoulder), the elbow remains relatively understudied. The elbow is a complex joint in terms of both anatomy and functionality. Due to its complex nature, the elbow is challenging to study and prone to injury and secondary pathologies. Thus, an urgent need exists to understand the etiology and pathogenesis of elbow pathologies and to develop novel therapeutic strategies to treat such conditions.

Clinically, the elbow is subjected to various pathologic conditions: injury/dislocation, joint stiffness and contracture,

immobilization, overuse, post-burn contracture, arthritis, and osteophytes/heterotopic ossification. Each elbow condition can occur as a distinct entity or concomitantly with other symptoms. Significant advancements have been achieved in how many of these elbow conditions are treated; however, difficult challenges persist and will require continued work to elucidate novel therapeutic strategies. A comprehensive presentation of the various therapies currently in clinical use is beyond the scope of this review but is discussed in many references used herein.

Although elbow pathologies have been clinical problems for decades, researchers have only recently started to identify and unravel the etiology and pathogenesis for some of these conditions. Unfortunately, most elbow conditions are studied at the late-disease stages when irreversible

damage has already occurred in the elbow (i.e., contracted elbow); warranting future work to understand early disease stages. It is challenging and often not feasible to study joint conditions in humans, in part, because humans' disease progresses relatively slowly and obtaining normal and diseased tissue is difficult. To overcome these limitations, preclinical models (*in vivo*, *in situ*, *ex vivo*, *in vitro*) can serve as valuable alternatives because of greater experimental control, faster disease progression, and increased access to tissue. Unfortunately, no preclinical model can recapitulate every aspect of human elbow anatomy and pathology; nonetheless, each model can provide valuable information towards at least some understanding of elbow pathologies.

Currently, only a handful of preclinical models have been used to investigate elbow injury and pathology, and as such there are many opportunities for advances in this area. This review will discuss relevant considerations for using animal models to simulate human conditions, current preclinical models of elbow diseases, then conclude by offering some ideas for potential future directions.

Elbow anatomy in humans and other mammalian species

The human elbow is one of the most complex and highly congruent joints, where three distinct bones (humerus, radius, and ulna) join to form three articulating surfaces (1-8). These surfaces are surrounded by a joint capsule and numerous ligaments (1-8), as well as several muscles (1,2,4,5,8,9). Intertwined among these tissues of the elbow is an extensive network of nerves (4,8,10-13) and vasculature (14). Collectively, these periarticular soft tissues allow for elbow stability and the motions of flexion-extension (normal range: $\sim 0^\circ$ to 150° ; functional range: $\sim 30^\circ$ to 140°) and pronation-supination (normal range: $\sim 155^\circ$ – 175° total motion between $\sim 75^\circ$ – 85° pronation and $\sim 80^\circ$ – 90° supination; functional range: $\sim 100^\circ$ total motion between 50° pronation and 50° supination) (1,2,5-8,15,16). The elbow is vital to countless daily activities, such as opening a door, typing, eating, personal hygiene, or using a telephone (5-7,15,16). The ability of the elbow to enable these activities is unlike other musculoskeletal joints (e.g., knee and hip) and is largely unique to humans, particularly in how pronation and supination is utilized. During normal daily activities, the elbow experiences a wide range of forces that largely originate from the periarticular tissues stabilizing the elbow (1,2,4-8,17). During heaving lifting and dynamic loading, the elbow experiences stress as high as

3–6× bodyweight (5,6,15,17,18). Overall, the elbow presents itself as a complex and challenging joint to study in humans, as well as in other mammalian species.

Given the complexity of the elbow joint, it is important to highlight some of the similarities and differences of the elbow between humans and other commonly used mammalian species for biomedical research (e.g., horses, primates, dogs, rats, rabbits, and mice). Many mammals other than humans, whether bipedal or quadrupedal, have elbows that are similar in anatomy to humans and can perform the flexion-extension motion. However, elbows of most mammals cannot pronate and supinate to the same extent as human elbows do. A few exceptions include some non-human primates and a specific breed of rats (i.e., Long-Evans) that can pronate and supinate over ranges that are similar to humans (19,20). As a result, these species perhaps are more clinically relevant to study the human elbow, although other species may still be valuable for research questions that are not as dependent on this type of motion. Regardless, the selection of species and the joint is critical to consider when designing preclinical models to study the elbow's normal physiology and pathophysiology.

Current preclinical models of elbow injury and pathology

In the following sections, common elbow injuries and pathologies and corresponding preclinical models that have been used to recapitulate each disease are reviewed. Preclinical models considered and discussed herein were included based upon the model's relevance to pathologic conditions of the elbow specifically; and, any therapeutic strategy using these preclinical models is not discussed.

Trauma, immobilization, and post-traumatic contracture of the elbow

Elbow trauma (e.g., dislocation and soft-tissue injury) and subsequent complications (e.g., pain, joint immobilization, contracture, stiffness, and arthritis) are some of the most common elbow pathologies observed clinically (5,21-29). Unfortunately, injuries are poorly tolerated in the elbow, leading to debilitating consequences for the patient (5,21-29). The elbow can experience various types of injuries including intra-articular fractures, soft tissue and ligament damage, as well as simple and complex dislocations (without or with concurrent bony fracture, respectively) (5,21-29). Typically, the elbow is immobilized post-injury to stabilize the joint;

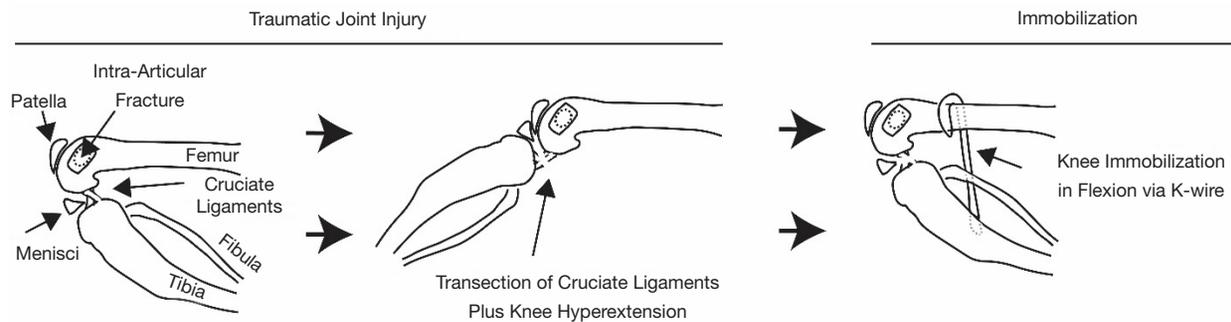


Figure 1 Preclinical knee models of post-traumatic joint contracture. Schematic of knee models initially used in the mid-2000's to study post-traumatic joint contracture with respect to the elbow. In these rabbit and rat knee models, an invasive surgical procedure is undertaken to cause an intra-articular fracture only, or in combination with transection of the cruciate ligaments and knee hyperextension, followed by Kirschner wire (K-wire) placement for joint immobilization; this leads to permanent knee contracture and pathologic conditions seen in contracted elbows clinically.

however, extended joint immobilization post-injury could induce unwanted elbow contracture (23,26,28,30,31). Generally, the most common elbow complaints following injury are increased elbow pain, stiffness, or limited range of motion.

A full picture of the post-injury response of elbow tissues leading to elbow contracture/stiffness remains unclear. Some clinical evidence of pathological changes in the elbow synovial capsule suggests that the capsule becomes fibrotic and restricts the elbow range of motion (3,21,32,33). Furthermore, in fibrosis of the elbow (21,33-35) and other joints (31,34,36), fibroblasts within the joint capsule have been observed to take on a pro-fibrotic phenotype by transitioning to myofibroblasts. Myofibroblasts are the effector cells that release pro-fibrotic factors and over-produce extracellular matrix, leading to capsule stiffness and joint contracture. Indeed, studies have demonstrated the presence of myofibroblasts and high levels of matrix metabolism in the contracted human elbow capsule (3,33-35,37-39). In contrast, at least one study did not observe increased number of myofibroblasts at chronic-disease stages (40). This contradiction suggests that disease stage and patient variability may complicate human findings; preclinical models could allow for greater experimental control to study myofibroblasts temporally. Generally, the primary goal of preclinical models recapitulating post-traumatic elbow contracture is to cause similar cellular (i.e., myofibroblasts) and tissue-level (i.e., capsular) changes and permanent loss of elbow joint motion post-trauma.

Since the early 2000s, Hildebrand and colleagues have pioneered preclinical work in the context of post-

traumatic joint contracture with respect to the elbow (41). In their preclinical model of joint contracture, a surgical procedure was performed on the rabbit knee to induce an intra-articular fracture combined with immobilization via Kirschner wire (K-wires) (Figure 1). After 8 weeks of immobilization, K-wires are removed, followed by a period of remobilization (0,8,16, and 32 weeks), mimicking the clinical treatment paradigm of elbow injuries of injury, immobilization, and then remobilization. Using this preclinical model, Hildebrand and colleagues identified a reduced range of motion following immobilization (~30°) and remobilization (~25° at 8 weeks; ~10° at 16 and 32 weeks), as well as increased myofibroblasts, mast cells, neuropeptides, and pro-fibrotic factors in the capsule (41-45). Results from their work demonstrated that this rabbit knee model could induce changes similarly seen in contracted elbows of humans.

Building upon the rabbit animal model developed by Hildebrand and colleagues (41), Nesterenko and Abdel *et al.* developed a similar yet more severe and permanent joint contracture in the rabbit knee (46-48). In their model, the cruciate ligaments are transected and the knee is hyperextended in addition to an intra-articular fracture and K-wire immobilization (Figure 1). Indeed, their model produced more severe knee contracture and reduced range of motion at both the end of the 8 weeks immobilization (~76°) and 16 weeks of remobilization (~45°). Interestingly, Abdel *et al.* (47) observed a different pattern of myofibroblasts compared to Hildebrand *et al.* (41), which may be related to differences in model severity. Other groups have found similar findings using the more

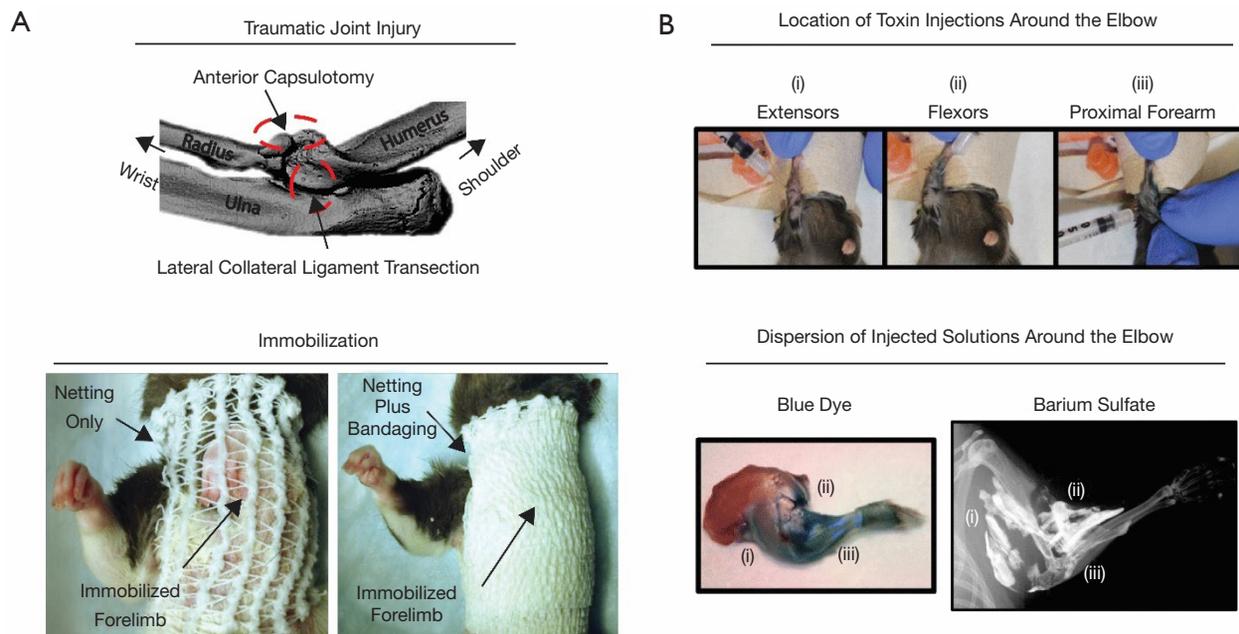


Figure 2 Preclinical elbow models of post-traumatic joint contracture. (A) Micro-computed tomography reconstruction and animal images highlight the soft-tissue injury and netting/bandages, respectively, to induce traumatic injury and immobilization in the rat elbow leading to permanent elbow contracture. (B) Animal and radiographic images show the multiple injection locations of cardiotoxins around the mouse elbow. These cardiotoxin injections, combined with researcher-induced plasminogen deficiency (not shown), leads to elbow contracture/stiffness. Image is adapted from Moore-Lotridge *et al.*, *Journal of Experimental Orthopaedics*, 2018, with permission (<http://creativecommons.org/licenses/by/4.0/>).

severe model by Nesterenko and Abdel *et al.* in the rat knee (49-51). While knowledge obtained by these models has been critical towards the understanding of post-traumatic joint contracture, each of these studies utilized the knee joint. Knee models are useful towards understanding general concepts related to joint contracture; however, due to anatomical and functional differences between the knee and elbow, results may be limited in understanding aspects of elbow-specific injury and contracture.

Nearly a decade after the initial work by Hildebrand *et al.* (41), our research group developed a preclinical model of post-traumatic elbow contracture specific to the elbow (52,53). In our model, we utilized the Long-Evans rat, which has similar anatomy and functionality (flexion-extension and pronation-supination movement) as the human elbow (19,20,52). To induce permanent post-traumatic elbow contracture, we performed an anterior capsulotomy and lateral collateral ligament transection, followed by 6 weeks of immobilization (IM) using wrapping/bandage, and then an additional 6 weeks of free mobilization (FM) (Figure 2A). Our model caused a time-dependent reduction in the range of motion of the elbow with a peak loss following 6-weeks

of IM and with a less severe loss after 6-weeks of FM in both flexion-extension ($\sim 43^\circ$ and $\sim 26^\circ$, respectively) and pronation-supination ($\sim 40^\circ$ and $\sim 37^\circ$, respectively) motion (52-57). Ultimately, loss of motion caused permanent deficits in functional measures of grip strength and gait (58). We also confirmed the thickening of the capsule with increased cellularity and presence of myofibroblasts, as well as altered matrix integrity and composition of both the capsule and cartilage surfaces (52,53,55). Additionally, we determined that the major periarticular tissue contributors to contracture in our model were largely the anterior capsule and lateral ligament complexes, not periarticular muscles (56,57). Overall, our work has advanced the field forward by creating the first animal model of joint contracture using the elbow.

Soon after the development of our elbow-specific model, Moore-Lotridge *et al.* created a mouse model of post-traumatic joint contracture (stiffness) of the elbow (59). In this model, injury to the periarticular soft-tissues (i.e., capsule ligaments, and surrounding musculature) of the elbow was induced by local injections of cardiotoxin combined with researcher-

imposed plasminogen deficiency (*Figure 2B*). After 28 days post-injury, this study showed a significant loss of elbow motion accompanied by an altered gait, muscle fibrosis and inflammation, thickening of the joint capsule, and heterotopic ossification in the muscle (59). Given these findings, this mouse model of post-traumatic elbow contracture replicates many of the same changes seen in human contracted elbows.

In addition to using an animal model of post-traumatic joint contracture, Hildebrand and colleagues have explored other preclinical models of elbow contracture (60). Namely, they used an *in vitro* collagen gel contraction assay to mimic capsule contracture in the elbow (60). In this *in vitro* model, Hildebrand *et al.* isolated primary capsule cells from contracted human elbow capsule and resuspended them in a collagen matrix with mast cells, another cell type thought to be involved in joint contracture (23,33,60,61). In these studies, elbow capsule cells contracted the collagen gels, which was enhanced with the addition of mast cells. In a set of gel contraction studies by another group, Mattyasovszky and colleagues found that inflammatory cytokines could modulate gel contraction of human capsule cells obtained from elbows undergoing arthroplasty (62,63). Results of these collagen gel contraction models have shown that capsule cells from contracted human elbows are contractile and can be modulated by mast cells and inflammatory cytokines to influence the contraction of *in vitro* tissue analogs.

Overall, this section highlighted the progression of various preclinical models for post-traumatic elbow contracture. While each model uses different species, joints, injuries, and outcomes, they all each provided insights into the etiology and pathology of post-traumatic elbow contracture. Future work is necessary to fully elucidate the contributions of each elbow tissue, create new models to address other types of traumatic injuries, and determine the translatability of each preclinical model attempting to recapitulate the human condition.

Elbow overuse

Another common elbow pathology is elbow overuse, where repetitive use of the elbow can cause overstrain and microtrauma of ligaments around the elbow (64-66). Signs of elbow overuse are increased pain, point tenderness, and difficulty in grasping items. Elbow overuse is common in individuals whose jobs and household tasks are repetitive and require the elbow and other motions involving extensive wrist use (65-70). While many individuals are at risk for overusing

the elbow, athletes such as pitchers, golfers, and tennis players are at exceptionally high risk (64-69). Elbow overuse is often referred to as tennis or golfer elbow, but clinically described as lateral and medial epicondylitis, respectively (64-69). While the terminology describing elbow overuse is still debated in the field, lateral epicondylitis is thought to occur in the absence of inflammation and resemble tendinosis (64-69). Significant progress has been made clinically to characterize the pathogenesis of elbow overuse, which has identified important structural and cellular changes in these tendons along with various neuropeptides thought to cause pain (64-69).

To date, only two preclinical models in the context of elbow overuse exist. One study by Nakama and colleagues used a rabbit model to induce medial epicondylitis (71). In this model, the flexor digitorum profundus muscle, which transmits forces through a tendon that inserts into the medial epicondyle, was stimulated repeatedly for 80 hours a week for 14 weeks (71). Results from this study demonstrated that the tendon at the insertion site of the medial epicondyle underwent significant increases in size, as well as an increase in the number and size of tears within the tendon (71).

Another group developed a rat model to explore repetitive, upper-extremity tasks required for reaching and grabbing with the wrist, elbow, and shoulder (72). In this model, rats repeatedly elevated their shoulder, fully extended their elbow, and gripped with their wrist to obtain food on cue, which caused repetitive muscular activation (72). While this group's primary focus was on changes to the wrist, they did evaluate the elbow in this model and found that the elbow was unaffected (72).

Each of the aforementioned preclinical models of elbow overuse has provided preliminary insights into the etiology and pathogenesis of elbow overuse/epicondylitis/tendinopathy. Future investigations utilizing these established, as well as novel, preclinical models are warranted to elucidate the mechanisms involved fully with elbow overuse. Perhaps other preclinical models previously used to examine degenerative changes in other tendons, such as the Achilles or the rotator cuff in the shoulder, could provide insights to assist the study of elbow related tendon issues (73-75).

Elbow arthritis

Arthritis occurs in the elbow and can take the form of either idiopathic osteoarthritis (OA), post-traumatic osteoarthritis

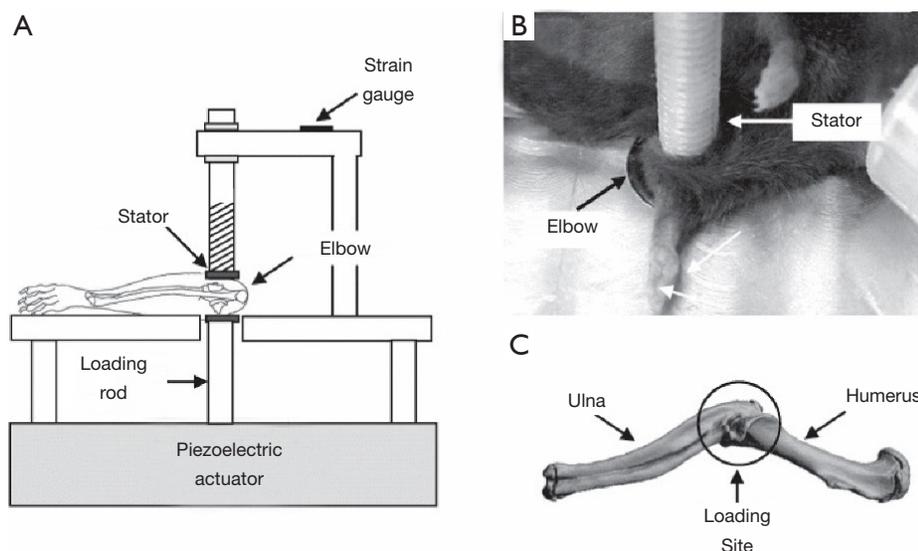


Figure 3 Preclinical elbow model to study cartilage metabolism and osteoarthritis. Schematic of the experimental setup (A), animal image (B), and micro-computed tomography reconstruction (C) highlight the loading location in a mouse elbow used to study cartilage metabolism and osteoarthritis. Image is reprinted from Sun *et al.*, *Connective Tissue Research*, 2012, with permission from the publisher (Taylor & Francis Ltd, <http://www.tandfonline.com>).

(PTOA), and rheumatoid arthritis (RA). All three types of arthritis ultimately lead to cartilage degeneration, pain, loss of joint function, and a need for arthroplasty. While OA in the elbow is rare (~2% of all joints with OA and of patients with elbow arthritis), the etiology and pathogenesis remain unclear (17,18,76-83). There are some risk factors for OA such as aging and overuse. A more common risk factor for developing elbow OA is a traumatic joint injury, which accelerates the development of OA; referred to as PTOA, this condition is also relatively uncommon in the elbow (17,18,76,77,79,84-86). Despite the rarity, OA and PTOA in the elbow are debilitating for patients once the disease initiates and progresses. Although reporting on prognosis is mixed, treated intra-articular elbow fractures can lead to at least a 50% chance of developing PTOA as early as 10 years post-injury (17,84), which are similar odds in other joints such as the knee and ankle (86,87). This high occurrence is concerning since elbow trauma frequently occurs in younger (28,29,79,85,88) and active individuals including athletes (29,79) and military service members (89,90). Besides OA and PTOA, the next most common form of arthritis affecting the elbow is RA, inflammatory-driven arthritis (17,76,91). RA isolated to the elbow alone occurs in ~5% of patients with RA (92); however, ~20–50% of patients with RA in other joints or organs also have signs RA in the elbow (76,92).

A few preclinical models exist addressing elbow arthritis. In the context of idiopathic OA, preclinical studies have evaluated cartilage damage, joint space narrowing, gait, and lameness in pig (93), cats (94-97), and dogs (98-106) with signs of elbow OA. Although informative, these studies recruited animals with naturally occurring OA and were unable to control the onset of degenerative changes. An alternative model with more experimental control is the mouse elbow/ulna loading models, which have historically been used to study the bone response of the elbow/ulna under controlled loading rate and magnitude (107,108). Recently, an elbow loading model was used to evaluate cartilage metabolism in the proximal ulna and distal humerus following mechanical stimuli (*Figure 3*) (109). Additional studies, however, are needed to validate the OA-like phenotype of the elbow in this model. In the context of PTOA, Dunham *et al.* minimally evaluated changes in the cellularity and matrix integrity of the cartilage (55). No preclinical models currently exist to study RA in the elbow. Although limited effort has been made to study elbow arthritis using preclinical models, the etiology and pathogenesis of elbow arthritis remain unclear.

Some knowledge about elbow arthritis and guidance on preclinical models could be inferred from arthritis in other joints. For instance, countless preclinical models have

been created to study arthritis in the knee, including OA (110-112), PTOA (110,112-114), and RA (115-118). Most commonly, *in vivo* models of OA and PTOA include the use of chemicals, genetic manipulation, aging, or surgically and non-surgically induced traumatic injuries, while models of RA include injections of compounds inducing an immune response. To study interactions between various tissues of the joint that are otherwise challenging *in vivo*, researchers have turned to *ex vivo* and *in vitro* preclinical models of arthritis (112,119). While these established models of arthritis in other joints can provide insights for models of elbow arthritis, researchers should be aware that the cartilage structure and cellularity is different between joints, potentially causing differences in cartilage response to arthritic stressors (120).

Post-burn elbow contracture

Post-burn contracture is defined as a contracture of the skin or joint following a significant burn. Contracture can develop following a burn in many parts of the body, including the knee (121) and non-musculoskeletal tissues (122); however, the elbow is one of the most commonly affected joints (123-125). While the skin and other soft tissues may play a role in post-burn contracture, the pathogenesis and scope of tissues involved in this condition in the elbow remain unclear. One of the most common symptoms that occur following burns is the formation of heterotopic ossifications (see next section), which is thought to reduce the range of motion in the elbow (123-125).

Current preclinical models of post-burn injury include the use of various species such as mice and rats; however, no model has been used to address post-burn elbow contracture (126). Caution must be taken when choosing a species to study post-burn elbow contracture, partly because the structure of the skin and the post-burn severity and response in other species may not translate to humans (122,126). In the future, the development of preclinical models will be necessary to shed insights into the etiology and pathogenesis of post-burn elbow contracture.

Osteophyte formation and heterotopic ossification in elbow pathologies

Among many of the elbow pathologies clinically, there is the concurrent formation of osteophytes and heterotopic ossification (HO). Osteophytes are defined as bony outgrowths or spurs that form; in the elbow, these tend

to form along the joint margins of the ulna, radius, and humerus (79,85,127-129). The formation of osteophytes ultimately causes significant pain and reduces the joint space, limiting the elbow range of motion (79,85,127-129). In addition to osteophyte formations, HO in the elbow has recently gained attention in the literature (27,130-133). HO is an aberrant bone formation that can contribute to elbow pain and reduction in elbow range of motion. Although osteophytes and HO are prevalent in diseased elbows, how osteophytes and HO form and what their full role in various elbow pathologies remains unknown.

Unfortunately, the preclinical evaluation of HO and osteophytes in the elbow has been limited. To date, only one preclinical study has addressed the presence of HO in elbow contracture/stiffness (*Figure 4A*) (59), and only a few have evaluated osteophytes in elbow osteoarthritis (*Figure 4B*) (96,97,100-103,105). To study osteophytes and HO in the elbow, researchers can study the current preclinical models of elbow pathologies mentioned above or other preclinical models that may be appropriate. For example, researchers have performed intra-articular injection of pro-fibrotic factors into mouse knees, causing the formation of osteophytes (134). Although these pro-fibrotic factors can induce osteophytes in the knee, it is not known whether the same effects would be seen in the elbow. Overall, a need exists for preclinical models to investigate HO and osteophytes in all elbow pathologies.

Osteochondritis dissecans

Another common clinical elbow pathology is osteochondritis dissecans (OCD) (17,135-137). OCD is the process by which the articular cartilage separates from the underlying subchondral bone, leading to fragmentations of cartilage in the joint space, pain, and a reduced range of motion in the elbow (17,29,135-137). In the elbow, OCD is typically observed in young, over-head throwing athletes at the humeral capitellum (17,29,135-137). The etiology of OCD formation and its role in elbow pathologies remains to be elucidated (17,29,135,136). It has been suggested that genetics, repetitive injury, subchondral bone abnormalities (e.g., loss of vasculature and becoming necrotic), and excessive force applied to the cartilage potentially contribute to OCD symptoms (17,29,135,136). Regardless of the etiology, OCD may make the surrounding cartilage prone to further degeneration, leading to arthritis (17).

Unfortunately, no preclinical study has investigated the etiology or pathogenesis of OCD in the elbow. OCD has



Figure 4 Preclinical models evaluating heterotopic ossification and osteophytes in elbow. (A) Micro-computed tomography reconstruction demonstrates severe heterotopic ossification (white arrows) following a soft-tissue injury to induce elbow contracture/stiffness in mice. Image is adapted from Moore-Lotridge *et al.*, *Journal of Experimental Orthopaedics*, 2018, with permission (<http://creativecommons.org/licenses/by/4.0/>). (B) Radiographic images highlight an arthritic elbow with osteophytes (white arrows) accompanying naturally occurring osteoarthritis in dogs. Image is adapted from Hurlbeck *et al.*, *Research in Veterinary Science*, 2014, with permission from Elsevier.

been researched in preclinical models of other joints, such as the knee (138-140). However, it should be cautioned that the etiology and pathogenesis of OCD in other joints could be different than in the elbow, partly because of differences in biomechanical forces experienced (e.g., weight *vs.* non-weight bearing), structure, and cellularity of different joint's cartilage (120,141). To investigate OCD in the elbow, preclinical models could be non-invasive, repeated motion overuse models; however, these models don't exist for the elbow. Given that the etiology and pathogenesis of OCD in the elbow is unknown, current and novel preclinical models of the elbow, especially trauma and overuse models, may note that OCD lesions develop.

Elbow pain and innervation

Most elbow pathologies are associated with some degree of pain; however, the pathomechanisms causing pain are still up for debate in the elbow and have received little attention. One potential source of pain could arise from the extensive network of nerves and nerve endings throughout the elbow

(4,8,10-13). While the nerve supply for each elbow tissue is different, neuroinflammatory pathways, which involve neuropeptides (substance-P) and mast cells (23,33,42,61), may play a role in elbow pain. It remains to be determined if other inflammatory and nerve cells are also involved with neuroinflammatory pathways. In addition to sensing pain, nerves of the elbow are prone to complications such as nerve entrapment and neuropathy, particularly after an injury, capsulectomy, or arthroplasty (22,142-145).

To date, no preclinical models of elbow pathologies exist that have directly evaluated pain and innervation. The most relevant preclinical studies addressing any degree of pain and innervation are those preclinical studies that have indirectly assessed the role of innervation through studying neuropeptides (substance-P) and mast cells in post-traumatic elbow contracture (23,33,42,61). However, a few studies have begun to directly address elbow innervation under non-pathological conditions in monkey (146) and rat elbows (147,148). Thus, future work is warranted to understand the etiology and pathogenesis of pain and innervation in every elbow pathology.

Future considerations for preclinical models of elbow diseases

This review has demonstrated and summarized in *Table 1* that only a limited number of preclinical models exist to study elbow diseases. Future studies are warranted to refine and create new preclinical models to elucidate the etiology and pathogenesis of common elbow pathologies. Research groups interested in pursuing future work in elbow pathologies might consider looking to other joints with more mature research results to gain valuable guidance for developing new preclinical models of elbow pathologies. To help facilitate the implementation of novel preclinical elbow models, the following section will highlight some critical points to consider and will provide some suggestions for appropriate next steps.

Considerations for refining and developing preclinical models of elbow pathologies

An important consideration when refining or developing a preclinical model for the elbow is to specify which elbow pathology will be studied. As highlighted previously, each elbow pathology involves different tissues and cells, as well as having a different time scales of etiology and pathogenesis; thus, a “gold-standard” for preclinical models would be to closely mimic the clinical observations of the specific elbow condition under investigation.

After deciding an elbow pathology to study, the next likely consideration is which type of preclinical model to use: *in vivo*, *in situ*, *ex vivo*, or *in vitro* model systems. Each type of model has important trade-offs worth considering. For example, *in vivo* and *in situ* models allow for the study and interaction of all tissues in the body, including the full biological response, enabling for the closest translation of findings to the human disease. A critical consideration when choosing an *in vivo* and *in situ* model is how closely the anatomy and functionality of the animal of choice mimic the human elbow. Additionally, another consideration is whether to use an invasive or non-invasive approach to induce a traumatic elbow injury. An invasive model requires a surgical incision that may induce an unwanted and confounding biological response that would otherwise not be present in the human; thus, non-invasive animal models would be more clinically relevant. While *in vivo* models are more representative of the human situation, they require the use of animals, which are accompanied by ethical concerns and other requirements (149). Thus, it is critical

to follow the recommended guidelines of animal research: reduction, refinement, and replacement (149).

Ex vivo and *in vitro* models can serve as alternatives to *in vivo* and *in situ* models of elbow pathologies and be used to achieve many samples while minimizing the need for many animals. Furthermore, *ex vivo* and *in vitro* allow the following: (I) more control of the experimental design and variables involved; (II) the ability to isolate and study the interaction of certain experimental variables between tissues/cells; and (III) the introduction of endogenous factors (e.g., growth factors and inflammatory cytokines) in a controlled manner. However, a downside to both *ex vivo* and *in vitro* models is that the tissues/cells are removed from the body, and thus, results may not necessarily translate to the *in vivo* condition. Nonetheless, all models have positive and negative aspects and can each help provide insight into the etiology and pathogenesis of elbow conditions.

Considerations for experimental outcomes and model variables

An essential aspect of any elbow preclinical model is the experimental outcomes used to assess a model's ability to mimic aspects of elbow pathologies. Importantly, it is critical for these outcome measures to be well defined and in-depth enough to understand the disease process, but also universal enough and not too specialized, such that outcome measures can be compared across research laboratories. Outcome measures can range from the molecular and cellular level to the tissue and functional level; such a multi-level approach will allow for easier translation to the clinic. Preclinical studies should continue to assess these outcome measures but implement additional approaches that have not been applied to the elbow. For instance, non-invasive imaging, such as micro-computed tomography, magnetic resonance, and ultrasound techniques, could be used to assess structural and compositional changes in the elbow. Additionally, local and systemic biochemical outcome measures could be defined, such as the establishment of synovial fluid and serum biomarkers of elbow pathology.

A limitation of this overview relates to the obvious challenge to discuss every type of elbow pathology and potential confounding variables in detail. The effects of species sex, age, and other conditions, such as diabetes, joint dysplasia, changes to the microbiome, and sedentary versus active lifestyle, could impact the progression of elbow pathologies and are worth considering. Furthermore, it's

Table 1 Summary of major clinical pathologies in the elbow joint and current preclinical models

Clinical elbow pathology	Preclinical model type	Model description	Species and joint studied	Outcome measurements	Key references
Trauma, immobilization, and post-traumatic contracture	<i>In vivo</i>	Surgically induced fracture plus immobilization via K-Wires for 8 weeks; removal of K-Wires followed by 0, 8, 16 or 32 weeks of remobilization	New Zealand White female rabbit knee	Range of motion, histology, immunohistochemistry, gene expression, protein expression	Hildebrand <i>et al.</i> 2004 (41), 2004 (45), 2006 (43), 2008 (42,44)
	<i>In vivo</i>	Surgically induced fracture and knee hyperextension plus immobilization via K-Wires for 8 weeks; removal of K-Wires followed by 0 or 16 weeks of remobilization	New Zealand White female rabbit knee	Range of motion, histology, immunohistochemistry, gene expression	Nesterenko <i>et al.</i> 2009 (46); Abdel <i>et al.</i> 2012 (47,48)
	<i>In vivo</i>	Surgically induced fracture and knee hyperextension plus immobilization via sutures for 8 weeks	Lewis female rat knee	Range of motion, histology, immunohistochemistry, protein expression	Li <i>et al.</i> 2013 (49); Sun <i>et al.</i> 2016 (50)
	<i>In vivo</i>	Surgically induced fracture and knee hyperextension plus immobilization via K-Wires for 4 weeks; removal of K-Wires followed by 8 weeks of remobilization	Sprague Dawley male rat knee	Range of motion	Baranowski <i>et al.</i> 2018 (51)
	<i>In vivo</i>	Surgically induced anterior capsulotomy and lateral collateral ligament transection plus immobilization via wrapping/bandage for 6 weeks; removal of wrapping/bandage followed by addition 6 weeks of remobilization	Long-Evans male rat elbow	Range of motion, grip strength, gait, histology, immunohistochemistry, gene expression	Lake <i>et al.</i> 2016 (52); Dunham <i>et al.</i> 2017 (53,54), 2018 (55,56), 2019 (57); Reiter <i>et al.</i> 2019 (58)
	<i>In vivo</i>	Local injections of cardiotoxin around the elbow combined with researcher-imposed plasminogen deficiency	C57BL/6 male mouse elbow	Range of motion, grip strength, gait, histology, immunohistochemistry, micro-computed tomography	Moore-Lotridge <i>et al.</i> 2018 (59)
	<i>In vitro</i>	Encapsulation of isolated capsule cells with and without mast cells into collagen matrix to allow for collagen gel contraction	Contracted human elbow capsule cells with and without human mast cell line	Gel contraction	Hildebrand <i>et al.</i> 2014 (60)
	<i>In vitro</i>	Encapsulation of isolated capsule cells with and without inflammatory cytokines into collagen matrix to allow for collagen gel contraction	Human elbow capsule cells from elbow arthroplasty	Immunohistochemistry, cell viability, collagen gel contraction, gene expression	Mattyasovszky <i>et al.</i> 2017 (62,63)
Overuse	<i>In vivo</i>	Forearm muscle stimulation to induce tendinopathy/epicondylitis at elbow medial epicondyle	New Zealand White female rabbit forearm	Histology	Nakama <i>et al.</i> 2005 (71)
	<i>In vivo</i>	Repetitive movement of shoulder, elbow, and wrists to reach food	Sprague Dawley female rat forearm	Cytokine array	Driban <i>et al.</i> 2011 (72)

Table 1 (continued)

Table 1 (continued)

Clinical elbow pathology	Preclinical model type	Model description	Species and joint studied	Outcome measurements	Key references
Idiopathic osteoarthritis	<i>In vivo</i>	Naturally occurring osteoarthritis	Pig, cat, and dog elbow	Gait, histology, immunohistochemistry, gene expression, radiography, pain, cytokine array	Pig: Kirk <i>et al.</i> 2008 (93) Cat: Freire <i>et al.</i> 2014 (94) and 2011 (96), Ryan <i>et al.</i> 2013 (95), Lascelles <i>et al.</i> 2010 (97) Dog: Kapatkin <i>et al.</i> 2006 (98), Spahni <i>et al.</i> 2009 (99), Clements <i>et al.</i> 2009 (100), Alves <i>et al.</i> 2017 (101), Hurlbeck <i>et al.</i> 2014 (102), Goldhammer <i>et al.</i> 2010 (103), Kunst <i>et al.</i> 2014 (105), Bockstahler <i>et al.</i> 2009 (106)
	<i>In vivo</i>	Elbow loading via indentation on proximal ulna and distal humerus	C57BL/6 female mouse elbow	Gene expression, enzyme activity	Sun <i>et al.</i> 2012 (109)
Post-traumatic osteoarthritis	<i>In vivo</i>	Surgically induced anterior capsulotomy and lateral collateral ligament transection plus immobilization via wrapping/ bandage for 6 weeks; removal of wrapping/bandage followed by addition 6 weeks of remobilization	Long-Evans male rat elbow	Histology	Dunham <i>et al.</i> 2018 (55)
Osteophytes	<i>In vivo</i>	Naturally occurring osteoarthritis	Cat and dog elbow	Micro-computed tomography	Cat: Freire <i>et al.</i> 2011 (96), Lascelles <i>et al.</i> 2010 (97) Dog: Clements <i>et al.</i> 2009 (100), Alves <i>et al.</i> 2017 (101), Hurlbeck <i>et al.</i> 2014 (102), Goldhammer <i>et al.</i> 2010 (103), Kunst <i>et al.</i> 2014 (105)
Heterotopic ossification	<i>In vivo</i>	Local injections of cardiotoxin around the elbow combined with researcher-imposed plasminogen deficiency	C57BL/6 male mouse elbow	Micro-computed tomography and histology	Moore-Lotridge <i>et al.</i> 2018 (59)
Rheumatoid arthritis	N/A	N/A	N/A	N/A	N/A
Post-burn contracture	N/A	N/A	N/A	N/A	N/A
Osteochondritis dissecans	N/A	N/A	N/A	N/A	N/A
Pain and innervation	<i>In vivo</i>	Surgically induced fracture plus immobilization via K-Wires for 8 weeks; removal of K-Wires followed by 0, 8, 16 or 32 weeks of remobilization	New Zealand White female rabbit knee	Immunohistochemistry	Hildebrand <i>et al.</i> 2008 (42)

worthwhile to consider clinical complications with post-surgical treatments, implants, devices, and infection.

Conclusion

The human elbow is one of the most complicated musculoskeletal joints and critical for many daily activities that require the upper extremity; yet, to date, the elbow is a relatively understudied musculoskeletal joint. Due to its complex nature, the elbow has high susceptibility to injury and pathologies, such as joint contracture, stiffness, and arthritis. Unfortunately, limited therapies exist to treat elbow pathologic conditions, which only offer limited clinical success. To develop alternative therapeutic strategies for elbow conditions, it is essential to understand the etiology and pathogenesis of common elbow pathologies better; preclinical models serve as ideal alternatives to pursue such topics. This review has highlighted major clinical elbow diseases and the preclinical models currently available to recapitulate these diseases, while also providing recommendations for future preclinical models. Overall, this review could serve as the foundation for preclinical models to study the etiology and pathogenesis of elbow pathologies with the goal of better understanding elbow function and joint health, and for developing therapeutic intervention strategies to improve treatment of elbow conditions.

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