International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

The Role of Animal Models in Tendon Research

Mahmoud Elsayed Gouda, Mohamed Metwally Ahmed Ebrahim, Ahmed Ali Khashaba

Plastic and Reconstructive Surgery Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Mohamed Metwally Ahmed Ebrahim

Abstract:

Background: Animal models play a fundamental role in tendon research by enabling controlled investigation of tendon injury mechanisms, healing processes, biomechanical properties, and treatment outcomes. These models provide opportunities for biochemical, histological, and molecular analyses that cannot be fully achieved in human studies. Among the various experimental models, Achilles tendon injury models are the most extensively studied because of their anatomical accessibility and clinical relevance. Different animal species, including rats, rabbits, sheep, goats, cattle, and pigs, have been utilized to simulate tendon pathology and repair under controlled conditions. Each model offers distinct advantages and limitations regarding tendon size, biomechanics, surgical feasibility, and translational applicability. Understanding the characteristics and suitability of these animal models is essential for selecting appropriate experimental approaches and improving the translation of preclinical findings into clinical tendon therapies.

Keywords: Animal models; Tendon research; Achilles tendon; Tendinopathy; Tendon healing; Experimental studies; Biomechanics; Tendon repair

Introduction:

Experimental animal models are frequently used and have great value in the scientific scenario because they allow biochemical, histological, cellular, and temporal analyses **(1)**. Further, the success of the physical and/or pharmacological treatments may be assessed directly and indirectly using these animal models. An ideal animal model should include as criteria: (1) appropriate tissue type modelled, (2) accurate simulation of the injury conditions, (3) reproduction in animal tissues of lesions similar to human diseased tissues, and finally (4) ease of application **(2)**.

Animal models offer an attractive framework to investigate the etiology of tendinopathy. Unlike human tissue, which only can be examined during end-stage chronic pathology, animal models provide the opportunity to obtain tissue during all stages of tendinopathy. Additionally, animal models provide the ability to reproduce consistent and repeatable injuries that can be treated in a controlled and quantifiable manner and also allow the evaluation of invasive treatments and assessments that would be unethical with human subjects. Another unique advantage of animal models is the capability of modifying the genome, particularly in the murine model. This technology allows for the comparison of tendon properties in mice with and without the ability to express a particular gene globally, in a particular tissue, or at a particular time **(3)**.

However, animal models of tendinopathy cannot truly replicate the human condition. Many lab animals are quadrupeds and subject their tendons to different magnitudes of load than their human counterparts, making it difficult to replicate the pathology seen clinically. Additionally, molecular differences between animals and humans further confound the ability to make direct comparisons between species. Despite these limitations, the rat model is still widely used, as it is considered a good choice given the practical considerations **(4)**.

Overall, it is important to understand that while translational research is the goal, animal models allow researchers to understand cellular and tissue-level principles in the context of a living organism **(4)**.

Achilles tendon injury model

As the largest and longest tendon of the human body, the Achilles tendon can typically bear more than 12.5 times the weight of the individual. This, along with other factors, likely contributes to substantial Achilles tendon pathology and highlights the need for both surgical and conservative Achilles tendon research **(5)**.

The Achilles tendon is also one of the most thoroughly researched elements of animal models of tendon pathologies. It is advantageous to study because of its superficial parts, convenience of operation, and ease of sampling, which are conducive to the study of the mechanisms of tendinopathy **(6)**.

The Achilles tendon has been widely used in a variety of animal models **(3)**. Rats models have many advantages for preclinical work in general, rats are amenable to an increasing array of functional outcome measures (e.g., gait analysis, range of motion, imaging), many of which have clinical equivalents. Thus, as with every model, while there are limitations, the rat's Achilles tendon provides many valuable opportunities to study developmental tendon biology and regeneration, injury, rehabilitation, repair, and homeostatic responses **(6)**.

Rats have been used frequently to model Achilles tendon rupture and tendinopathy, using primarily one of two methods of inducing injury; mechanical or chemical. Silva et al. evaluated Achilles tendinosis pathogenesis, using a rat overuse induction model with active muscle contraction through repetitive running **(2)**.

In addition, a rat model has been used to elucidate the deleterious effect of diabetes on tendons and tendinopathy. This work points to the importance of moderate exercise in diabetic patients, while also suggesting that the healing response of tendons in such patients is indeed impaired **(7)**.

There is a variety of protocols for Achilles tendon repair, and animal models have been valuable in defining areas for human study. Oztermeli and Okyay investigated the efficacy of fat grafting in primary tendon healing through immunohistochemical and biomechanical examinations of 10 rats **(8)**.

In general, rats are often used to explore the factors affecting tendon-bone healing **(9)**, the molecular mechanisms underlying ectopic ossification in tendinopathy and inflammation and scar formation in the injury tendon healing **(10)**.

Despite their low cost and ease of rearing, the small size of rats has an impact on surgical approaches, non-invasive imaging techniques, and biomechanical testing. Moreover, the relevant results still need to be applied to large animals and clinical trials to ensure safety and effectiveness **(11)**.

Large animals such as sheep or cattle are popular due to the appropriate size of their Achilles tendon, the weight bearing similar to humans, and their suitability for clinical evaluation. Achilles tendon rupture is common in sheep Achilles tendon injury models. Bruns et al. studied the spontaneous healing process of sheep Achilles tendons after transection and partial resection by means of histological and biomechanical analyses **(12)**.

Dündar et al. used the sheep Achilles tendon tear model to compare the biomechanical properties of modified Kessler, Bunnell, and Tsuge technology in repairing sheep Achilles tendon tears **(13)**.

Leung et al. simulated bone–bone, bone–tendon and tendon–tendon repairs with osteotomy of the calcaneus, reattachment of Achilles tendon to the calcaneus after removal of the insertion, and tenotomy of the Achilles tendon resection in 47 goats **(14)**.

Cattle Achilles tendons are larger and are often used for improvements in surgical suture techniques. Tian et al. designed the Locking Block Modified Krackow (LBMK) peri-tendon fixation technique for minimally invasive surgery and then compared the biomechanics of LBMK with Kessler and percutaneous Achilles repair system techniques with a simulated early rehabilitation program **(15)**

Rabbits are also suitable for Achilles tendon injury models because their Achilles tendon size allows for surgical approaches and accurate specimen examination **(16)**.

Skalec et al. conducted an anatomical and histological analysis on eight female New Zealand rabbits and comprehensively described the macroscopic and microscopic morphology of their Achilles tendon and its related structures **(17).**

The Achilles tendon transection model is a common model of injury that is used to study the biomechanical properties of healed tendons and the degree of adhesion formation **(18)**, as well as the time-dependent changes of strain ratios (SRs) and the correlation between SRs and mechanical and histological properties of healed tissue **(19)**. It was also used to compare the effects of early activity and fixation on postoperative healing of rabbit Achilles tendon rupture **(20)**.

Furthermore, a rabbit model of ischemic injury caused by Achilles tendon ligation was used to compare a series of changes in Achilles tendon morphology and strain in the early stage of Achilles tendinopathy **(21)**.

There are few studies on pigs as animal models for Achilles tendon injury. Previous studies used pigs to study the biological characteristics of Achilles tendons or collected the Achilles tendons of pigs as materials for tendon injury repair. Zhang et al. characterized the structural components, vascularity, and resident tendon cells of the porcine Achilles tendon **(22)**.

References:

1. Lake SP, Ansorge HL, Soslowsky LJ. Animal models of tendinopathy. Disabil Rehabil. 2008;30(20–22):1530–1541.
2. Silva RD, Glazebrook MA, Campos VC, Vasconcelos AC. Achilles tendinosis model. Int J Clin Exp Pathol. 2011;4(7):683–691.
3. Hast MW, Zuskov A, Soslowsky LJ. The role of animal models in tendon research. Bone Joint Res. 2014;3(6):193–202.
4. McGonigle P, Ruggeri B. Animal models of human disease. Biochem Pharmacol. 2014;87(1):162–171.
5. O'Brien M. Anatomy of Achilles tendon. Foot Ankle Clin. 2005;10(2):225–238.
6. Thomopoulos S, Parks WC, Rifkin DB, Derwin KA. Tendon injury mechanisms. J Orthop Res. 2015;33(6):832–839.
7. De Oliveira RR, Bezerra MA, de Lira KD, Novaes KA, Teixeira MF, Chaves CC, et al. Aerobic physical training restores biomechanical properties of Achilles tendon in rats chemically induced to diabetes mellitus. J Diabetes Complications. 2012;26(3):163–168.
8. Oztermeli A, Okyay MF. Fat graft in tendon healing. J Orthop Surg (Hong Kong). 2023;31:10225536231220839.
9. Nakagawa H, Morihara T, Fujiwara H, et al. Footprint preparation and tendon-to-bone healing. Arthroscopy. 2017;33(8):1482–1492.
10. Geng X, Li Y, Zhang L, Chen H. Molecular mechanisms of ectopic ossification and scar formation in tendon injury and tendinopathy. J Orthop Res. 2020;38(7):1502–1514.
11. Zhang G, Zhou X, Hu S, et al. Large animal tendon models. Front Cell Dev Biol. 2022;10:1031638.
12. Bruns J, Kampen J, Kahrs J, Plitz W. Achilles tendon rupture: experimental results on spontaneous repair in a sheep-model. Knee Surg Sports Traumatol Arthrosc. 2000;8(6):364–369.
13. Dündar N, Güneri B, Uzel M, Doğaner A. Biomechanical comparison of Bunnell, modified Kessler, and Tsuge tendon repair techniques using two suture types. Acta Orthop Traumatol Turc. 2020;54(1):104–113.
14. Leung KS, Chong WS, Chow DH, Zhang P, Cheung WH, Wong MW, et al. A comparative study on tendon-to-bone healing. Am J Sports Med. 2015;43(6):1413–1421.
15. Tian J, Rui Y, Xu Y, et al. Achilles tendon repair techniques. Arch Orthop Trauma Surg. 2020;140(11):1775–1782.
16. Doherty GP, Koike Y, Uhthoff HK, Lecompte M, Trudel G. Comparative anatomy of rabbit and human Achilles tendons with magnetic resonance and ultrasound imaging. Comp Med. 2006;56(1):68–74.
17. Alrashid, I. M. H. (2011). A Comparative Study: The effect of pulsed and static magnetic field on the healing of rupture of achilles tendon in rabbits. Journal of Basrah Research ((Sciences)), 37(4A), 56-65.

18. Meier Bürgisser G, Calcagni M, Bachmann E, et al. Rabbit Achilles tendon transection model. Biol Open. 2016;5(9):1324–1333.
19. Yamamoto Y, Yamaguchi S, Sasho T, et al. US elastography in tendon healing. Radiology. 2017;283(2):408–417.
20. Jielile J, Asilehan B, Wupuer A, Qianman B, Jialihasi A, Tangkejie W, et al. Early ankle mobilization promotes healing in a rabbit model of Achilles tendon rupture. Orthopedics. 2016;39(1):e117–126.
21. Ahn KS, Lee NJ, Kang CH, Lee YH, Jeon HJ. Serial changes of tendon histomorphology and strain elastography after induced Achilles tendinopathy in rabbits: an in vivo study. J Ultrasound Med. 2017;36(4):767–774.
22. Zhang S, et al. Porcine Achilles tendon structure. J Anat. 2021;239(5):1120–1132.