

# DENEY HAYVANLARINDA OSTEOARTRİT MODELLERİ

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BÖLÜM

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Osteoartrit (OA) dünyanın en yaygın kronik hastalıklarından biri olup, milyonlarca kişi bu hastalıktan etkilenmektedir. OA, yalnızca eklem kıkıldığını etkileyen kronik bir hastalık değil, aynı zamanda subkondral kemik, sinovyal membranlar ve periartiküler dokularında etkilendiği bir hastalık. İnflamatuar olmayan bir hastalık olarak tanımlanmış olmasına rağmen, mevcut kanıtlar inflamasyonun patogenezinde temel bir rol oynadığını göstermektedir. Bu hastalıkla ilgili birçok çalışma yapılmış olup hastalık çok iyi bilinmesine rağmen erken evre OA'ın patogenezini tam olarak bilinmemektedir (1). Bu durum erken teşhis ve tedavi yaklaşımını sınırlamaktadır. Hayvan deneyleri hem OA'ın doğal seyrini hem de tedavisini belirlemek için anlamlı bilgiler elde etmemizi sağlar. Uzun zamanдан beri hastalığın erken teşhis ve tedavisiini aydınlatmak için birçok kendiliğinden ve uyarılmış deneysel OA hayvan modeli çalışmaları yapılmaktadır. Bu çalışmalarla fareden insana benzeyen primatlara kadar birçok hayvan deneysel çalışmalarla kullanılmıştır. Her modelin kendisine göre avantaj ve dezavantajları mevcuttur (1-5). Araştırmacılar için en önemli zorluk, birçok hayvan modelinden hangisinin yapacakları araştırmaya uygun yöntem olduğunu belirlemektir. Bu çalışmada deneysel OA çalışmala-

rında kullanılan hayvanlar, geliştirilen modeller ve bu modellerin sonuçları hakkında bilgiler vermeye çalıştık.

## DENEYSEL OSTEOARTRİT MODELLERİNDE KULLANILAN HAYVAN TÜRLERİ

Çalışmalarda seçilecek hayvanın yaşı, cinsiyeti, boyutu, üreme özellikleri, saklanma koşulları ve maliyeti önemlidir. Yenilenme kapasitesinin en aza indirilmesi için olgun çaga gelmiş hayvanların kullanılması insanda uygulanabilir bilgiler elde edilmesi için gereklidir. Küçük hayvanların (fare, sıçan, tavşan, kobay) seçilmesi barınma, maliyet, genetik müdahale, daha hızlı OA oluşturulabilmesi ve toplumsal yaklaşım açısından daha avantajlıdır. Büyük hayvanlar (köpek, koyun, keçi, at, pramat) ise insanlara olan anatomik ve biyomekanik benzerliklerinden dolayı rutin tanısal testlerin uygulanabilmesi, arthroşkopik girişimlere uygun olmaları biyomekanik çalışmalarla elverişli olmaları, biyokimyasal çalışmalar için yeterince doku elde edilebilmesi gibi avantajlara sahiptirler. Bu sebeple küçük hayvan modelleri özgün hastalık mekanizmalarını araştırırken ve tedavi edici ajanların ilk deneysel uygulamalarında seçilmelidir (2,3). Bu modellerde uygulanan tedavilerin etkisi insanla-

**Anahtar Kelimeler:** Hayvan Modelleri, Osteoartrit, Eklem kıkırdağı, Deneysel Çalışma

## KAYNAKLAR

1. Bapat S, Hubbard D, Munjal, A. et al. Pros and cons of mouse models for studying osteoarthritis. *Clin Trans Med* 7, 36 (2018). <https://doi.org/10.1186/s40169-018-0215-4>
2. McCoy AM. Animal Models of Osteoarthritis: Comparisons and Key Considerations. *Vet Pathol.* 2015 Sep;52(5):803-18. doi: 10.1177/0300985815588611. Epub 2015 Jun 10.
3. Gregory MH, Capito N, Kuroki K, Stoker AM, Cook JL, Sherman SL. A review of translational animal models for knee osteoarthritis. *Arthritis.* 2012;2012:764621. doi: 10.1155/2012/764621. Epub 2012 Dec 27.
4. Teeple E, Jay GD, Elsaid KA, et al. Animal models of osteoarthritis: challenges of model selection and analysis. *AAPS J.* 2013 Apr;15(2):438-46. doi: 10.1208/s12248-013-9454-x. Epub 2013 Jan 18.
5. Longo UG, Loppini M, Fumo C, et al. Osteoarthritis: new insights in animal models. *Open Orthop J.* 2012;6:558-63. doi: 10.2174/1874325001206010558. Epub 2012 Nov 30.
6. Fang H, Beier F. Mouse models of osteoarthritis: modelling risk factors and assessing outcomes. *Nat Rev Rheumatol.* 2014 Jul;10(7):413-21. doi: 10.1038/nrrheum.2014.46. Epub 2014 Mar 25.
7. Thysen S, Luyten FP, Lories RJ. Targets, models and challenges in osteoarthritis research. *Dis Model Mech.* 2015 Jan;8(1):17-30. doi: 10.1242/dmm.016881.
8. Legrand CB, Lambert CJ, Comblain FV, et al. Review of Soluble Biomarkers of Osteoarthritis: Lessons From Animal Models. *Cartilage.* 2017 Jul;8(3):211-233. doi: 10.1177/1947603516656739. Epub 2016 Jul 7.
9. Gerwin, N, Bendele AM, Glasson S. et al. The OARSI histopathology initiative – recommendations for histological assessments of osteoarthritis in the rat. *Osteoarthritis Cartilage* 18 Suppl. 3, S24-S34.
10. Laverty S, Girard CA, Williams JM, et al. The OARSI histopathology initiative – recommendations for histological assessments of osteoarthritis in the rabbit. *Osteoarthritis Cartilage* 18 Suppl. 3, S53- S65.
11. Serra CI, Soler C. Animal Models of Osteoarthritis in Small Mammals. *Vet Clin North Am Exot Anim Pract.* 2019 May;22(2):211-221. doi: 10.1016/j.cvev.2019.01.004.
12. Molinet M, Alves N, Vasconcelos A, et al. Comparative study of osteoarthritis (OA) induced by monoiodoacetate (MIA) and papain in rabbit temporomandibular joints: macroscopic and microscopic analysis. *Folia Morphol (Warsz).* 2019 Sep 30. doi: 10.5603/FM.a2019.0104.
13. Li W, Lin J, Wang Z, et al. Bevacizumab tested for treatment of knee osteoarthritis via inhibition of synovial vascular hyperplasia in rabbits. *J Orthop Translat.* 2019 Apr 28;19:38-46. doi: 10.1016/j.jot.2019.04.002. eCollection 2019 Oct.
14. Kraus VB, Huebner JL, DeGroot J, et al. The OARSI histopathology initiative – recommendations for histological assessments of osteoarthritis in the guinea pig. *Osteoarthritis Cartilage* 18 Suppl. 3, S35-S52.
15. Wallace IJ, Bendele AM, Riew G, et al. Physical inactivity and knee osteoarthritis in guinea pigs. *Osteoarthritis Cartilage.* 2019 Nov;27(11):1721-1728. doi: 10.1016/j.joca.2019.07.005. Epub 2019 Jul 11.
16. Chouhan DK, Dhillon MS, Patel S, et al. Multiple Platelet-Rich Plasma Injections Versus Single Platelet-Rich Plasma Injection in Early Osteoarthritis of the Knee: An Experimental Study in a Guinea Pig Model of Early Knee Osteoarthritis. *Am J Sports Med.* 2019 Aug;47(10):2300-2307. doi: 10.1177/0363546519856605. Epub 2019 Jul 3.
17. Ringe J, Hemmati-Sadeghi S, Fröhlich K, et al. CCL25-Supplemented Hyaluronic Acid Attenuates Cartilage Degeneration in a Guinea Pig Model of Knee Osteoarthritis. *J Orthop Res.* 2019 Aug;37(8):1723-1729. doi: 10.1002/jor.24312. Epub 2019 Apr 29.
18. Kim JE, Song DH, Kim SH, et al. Development and characterization of various osteoarthritis models for tissue engineering. *PLoS One.* 2018 Mar 13;13(3):e0194288. doi: 10.1371/journal.pone.0194288. eCollection 2018.
19. Cook JL, Kuroki K, Visco D, et al. The OARSI histopathology initiative – recommendations for histological assessments of osteoarthritis in the dog. *Osteoarthritis Cartilage* 18 Suppl. 3, S66- S79.
20. Cuervo B, Rubio M, Chicharro D, et al. Objective Comparison between Platelet Rich Plasma Alone and in Combination with Physical Therapy in Dogs with Osteoarthritis Caused by Hip Dysplasia. *Animals (Basel).* 2020 Jan 21;10(2). pii: E175. doi: 10.3390/ani10020175.
21. Robertson-Plouch C, Stille JR, Liu P, et al. A randomized clinical efficacy study targeting mPGES1 or EP4 in dogs with spontaneous osteoarthritis. *Sci Transl Med.* 2019 Oct 30;11(516). pii: eaaw9993. doi: 10.1126/scitranslmed.aaw9993.
22. Little CB, Smith MM, Cake MA, et al. The OARSI histopathology initiative - recommendations for histological assessments of osteoarthritis in sheep and goats. *Osteoarthritis Cartilage.* 2010 Oct;18 Suppl 3:S80-92. doi: 10.1016/j.joca.2010.04.016.
23. Beveridge JE, Shrive NG, Frank CB. Meniscectomy causes significant in vivo kinematic changes and mechanically induced focal chondral lesions in a sheep model. *J Orthop Res.* 2011 Sep;29(9):1397-405. doi: 10.1002/jor.21395. Epub 2011 Mar 22.
24. Rothrauff BB, Sasaki H, Kihara S, et al. Point-of-Care Procedure for Enhancement of Meniscal Healing in a Goat Model Utilizing Infrapatellar Fat Pad-Derived Stromal Vascular Fraction Cells Seeded in Photocrosslinkable Hydrogel. *Am J Sports Med.* 2019 Dec;47(14):3396-3405. doi: 10.1177/0363546519880468. Epub 2019 Oct 23.
25. Wang Z, Zhai C, Fei H, et al. Intraarticular injection autologous platelet-rich plasma and bone marrow concentrate in a goat osteoarthritis model. *J Orthop Res.* 2018 Feb 21. doi: 10.1002/jor.23877. [Epub ahead of print]
26. McIlwraith CW, Frisbie DD, Kawcak CE, et al. The OARSI histopathology initiative – recommendations

- for histological assessments of osteoarthritis in the horse. *Osteoarthritis Cartilage.* 2010 Oct;18 Suppl 3:S93-105. doi: 10.1016/j.joca.2010.05.031.
27. Broeckx SY, Martens AM, Bertone AL, et al. The use of equine chondrogenic-induced mesenchymal stem cells as a treatment for osteoarthritis: A randomised, double-blinded, placebo-controlled proof-of-concept study. *Equine Vet J.* 2019 Nov;51(6):787-794. doi: 10.1111/evj.13089. Epub 2019 Apr 13.
  28. McIlwraith CW, Lattermann C. Intra-articular Corticosteroids for Knee Pain-What Have We Learned from the Equine Athlete and Current Best Practice. *J Knee Surg.* 2019 Jan;32(1):9-25. doi: 10.1055/s-0038-1676449. Epub 2018 Dec 18.
  29. Liu G, Zhang L, Zhou X, et al. Selection and Investigation of a Primate Model of Spontaneous Degenerative Knee Osteoarthritis, the Cynomolgus Monkey (*Macaca Fascicularis*). *Med Sci Monit.* 2018 Jul 1;24:4516-4527. doi: 10.12659/MSM.908913.
  30. Jiang L, Ma A, Song L, et al. Cartilage regeneration by selected chondrogenic clonal mesenchymal stem cells in the collagenase-induced monkey osteoarthritis model. *J Tissue Eng Regen Med.* 2014 Nov;8(11):896-905. doi: 10.1002/term.1676. Epub 2013 Jan 21.
  31. Ogawa S, Natsume T, Takamatsu H. Pharmacological profile of a novel nonhuman primate model of knee osteoarthritis. *Nihon Yakurigaku Zasshi.* 2018;152(3):132-138. doi: 10.1254/fpj.152.132.
  32. Ogawa S, Awaga Y, Takashima M, et al. Antinociceptive effect of clinical analgesics in a nonhuman primate model of knee osteoarthritis. *Eur J Pharmacol.* 2016 Sep 5;786:179-185. doi: 10.1016/j.ejphar.2016.06.008. Epub 2016 Jun 4.
  33. Kuyinu EL, Narayanan G, Nair LS, et al. Animal models of osteoarthritis: classification, update, and measurement of outcomes. *J Orthop Surg Res.* 2016 Feb 2;11:19. doi: 10.1186/s13018-016-0346-5.
  34. Teeple E, Jay GD, Elsaied KA, et al. Animal models of osteoarthritis: challenges of model selection and analysis. *AAPS J.* 2013 Apr;15(2):438-46. doi: 10.1208/s12248-013-9454-x. Epub 2013 Jan 18.
  35. Pelletier JP, Boileau C, Altman R, et al. Experimental models of osteoarthritis: Usefulness in the development of disease-modifying osteoarthritis drugs/agents. *Therapy.* 7. 621-634. doi.org/10.2217/thy.10.75
  36. Vincent TL, Williams RO, Maciewicz R, et al. Mapping pathogenesis of arthritis through small animal models. *Rheumatology (Oxford).* 2012 Nov;51(11):1931-41. doi: 10.1093/rheumatology/kes035. Epub 2012 Mar 16.
  37. Staines KA, Poulet B, Wentworth DN, et al. The STR/ort mouse model of spontaneous osteoarthritis - an update. *Osteoarthritis Cartilage.* 2017 Jun;25(6):802-808. doi: 10.1016/j.joca.2016.12.014. Epub 2016 Dec 11.
  38. Kyostio-Moore S, Nambiar B, Hutto E, et al. STR/ort mice, a model for spontaneous osteoarthritis, exhibit elevated levels of both local and systemic inflammatory markers. *Comp Med.* 2011 Aug;61(4):346-55.
  39. Griffin TM, Fermor B, Huebner JL, et al. Diet-induced obesity differentially regulates behavioral, biomechanical, and molecular risk factors for osteoarthritis in mice. *Arthritis Res Ther.* 2010;12(4):R130. doi: 10.1186/ar3068. Epub 2010 Jul 6.
  40. Lankau EW, Turner PV, Mullan RJ, et al. Use of non-human primates in research in North America. *J Am Assoc Lab Anim Sci.* 2014;53(3):278-82.
  41. Higuchi Y, Nishida Y, Kozawa E, Zhuo L, Arai E, Hamada S, Morita D, Ikuta K, Kimata K, Ushida T, Ishiguro N. Conditional knockdown of hyaluronidase 2 in articular cartilage stimulates osteoarthritic progression in a mice model. *Sci Rep.* 2017 Aug 1;7(1):7028. doi: 10.1038/s41598-017-07376-5.
  42. Lorenz J, Grässel S. Experimental osteoarthritis models in mice. *Methods Mol Biol.* 2014;1194:401-19. doi: 10.1007/978-1-4939-1215-5\_23.
  43. Bayyurt S, Küçükpalp A, Bilgen MS, et al. The chondroprotective effects of intraarticular application of statin in osteoarthritis: An experimental study. *Indian J Orthop.* 2015 Nov-Dec;49(6):665-71. doi: 10.4103/0019-5413.168751.
  44. Lampropoulou-Adamidou K, Lelovas P, Karadimas EV, et al. Useful animal models for the research of osteoarthritis. *Eur J Orthop Surg Traumatol.* 2014 Apr;24(3):263-71. doi: 10.1007/s00590-013-1205-2. Epub 2013 Mar 13.
  45. Fang H, Beier F. Mouse models of osteoarthritis: modelling risk factors and assessing outcomes. *Nat Rev Rheumatol.* 2014 Jul;10(7):413-21. doi: 10.1038/nrrheum.2014.46. Epub 2014 Mar 25.
  46. (\*)Sudirman S, Ong AD, Chang HW, et al. Effect of Fucoidan on Anterior Cruciate Ligament Transection and Medial Meniscectomy Induced Osteoarthritis in High-Fat Diet-Induced Obese Rats. *Nutrients.* 2018 May 28;10(6). pii: E686. doi: 10.3390/nu10060686.
  47. Ahern BJ, Parviz J, Boston R, Schaer TP. Preclinical animal models in single site cartilage defect testing: a systematic review. *Osteoarthritis Cartilage.* 2009 Jun;17(6):705-13. doi: 10.1016/j.joca.2008.11.008. Epub 2008 Nov 21.
  48. Bei MJ, Tian FM, Xiao YP, et al. Raloxifene retards cartilage degradation and improves subchondral bone micro-architecture in ovariectomized rats with patella baja-induced - patellofemoral joint osteoarthritis. *Osteoarthritis Cartilage.* 2019 Jul 18. pii: S1063-4584(19)31140-9. doi: 10.1016/j.joca.2019.06.014.
  49. Xu X, Li X, Liang Y, et al. Estrogen Modulates Cartilage and Subchondral Bone Remodeling in an Ovariectomized Rat Model of Postmenopausal Osteoarthritis. *Med Sci Monit.* 2019 Apr 29;25:3146-3153. doi: 10.12659/MSM.916254.
  50. Castañeda S, Largo R, Calvo E, et al. Effects of estrogen deficiency and low bone mineral density on healthy knee cartilage in rabbits. *J Orthop Res.* *J Orthop Res.* 2010 Jun;28(6):812-8. doi: 10.1002/jor.21054.
  51. Qin Y, He J, Xia L, et al. Effects of electro-acupuncture on oestrogen levels, body weight, articular cartilage histology and MMP-13 expression in ovariectomised rabbits. *Acupunct Med.* 2013 Jun;31(2):214-21. doi: 10.1136/acupmed-2012-010289. Epub 2013 Mar 21.
  52. Yamada H, Ochi Y, Mori H, et al. Cortical bone mineral density is increased by the cathepsin K inhibitor ONO-5334, which leads to a robust increase in bone

- strength: results from a 16-month study in ovariectomised cynomolgus monkeys. *J Bone Miner Metab.* 2019 Jul;37(4):636-647. doi: 10.1007/s00774-018-0968-2. Epub 2018 Oct 24.
53. Molinet M, Alves N, Vasconcelos A, et al. Comparative study of osteoarthritis (OA) induced by moniodoacetate (MIA) and papain in rabbit temporomandibular joints: macroscopic and microscopic analysis. *Folia Morphol (Warsz).* 2019 Sep 30. doi: 10.5603/FM.a2019.0104.
  54. Kalbhen DA. Chondroprotective and antiarthrotic properties of glycosaminoglycan polysulfate (GAGPS) in gonarthrosis in animal experiments. *Z Rheumatol.* 1982 Sep-Oct;41(5):219-29.
  55. Pomonis JD, Boulet JM, Gottshall SL, et al. Development and pharmacological characterization of a rat model of osteoarthritis pain. *Pain.* 2005 Apr;114(3):339-46. Epub 2004 Dec 19. DOI: 10.1016/j.pain.2004.11.008
  56. O'Brien M, Philpott HT, McDougall JJ. Understanding osteoarthritis pain through animal models. *Clin Exp Rheumatol.* 2017 Sep-Oct;35 Suppl 107(5):47-52. Epub 2017 Sep 28.
  57. Christiansen BA, Guilak F, Lockwood KA, et al. Non-invasive mouse models of post-traumatic osteoarthritis. *Osteoarthritis Cartilage.* 2015 Oct;23(10):1627-38. doi: 10.1016/j.joca.2015.05.009. Epub 2015 May 21.
  58. Poulet B, Hamilton RW, Shefelbine S, et al. Characterizing a novel and adjustable noninvasive murine joint loading model. *Arthritis Rheum.* 2011 Jan;63(1):137-47. doi: 10.1002/art.27765.
  59. Lockwood KA, Chu BT, Anderson MJ, et al. Comparison of loading rate-dependent injury modes in a murine model of post-traumatic osteoarthritis. *J J Orthop Res.* 2014 Jan;32(1):79-88. doi: 10.1002/jor.22480. Epub 2013 Sep 9.
  60. Maerz T, Kurdziel MD, Davidson AA, et al. Biomechanical characterization of a model of noninvasive, traumatic anterior cruciate ligament injury in the rat. *Ann Biomed Eng.* 2015 Oct;43(10):2467-76. doi: 10.1007/s10439-015-1292-9. Epub 2015 Mar 17.
  61. Mrosek EH, Lahm A, Erggelet C, et al. Subchondral bone trauma causes cartilage matrix degeneration: an immunohistochemical analysis in a canine model. *Osteoarthritis Cartilage.* 2006 Feb;14(2):171-8. Epub 2005 Oct 19. DOI: 10.1016/j.joca.2005.08.004
  62. Rundell SA, Baars DC, Phillips DM, et al. The limitation of acute necrosis in retro-patellar cartilage after a severe blunt impact to the in vivo rabbit patello-femoral joint. *J Orthop Res.* 2005 Nov;23(6):1363-9. Epub 2005 Aug 15. DOI: 10.1016/j.orthres.2005.06.001.1100230618
  63. Ewers BJ, Jayaraman VM, Banglmaier RF, et al. Rate of blunt impact loading affects changes in retropatellar cartilage and underlying bone in the rabbit patella. *J Biomech.* 2002;35(6):747-55. DOI: 10.1016/s0021-9290(02)00019-2