2026 ICM -Aging and OA group- Question 14: "Do animal (especially mice) studies of aging-associated OA translate well to human diseases?"

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RESPONSE/RECOMMENDATION: Yes. Murine models of aging-related osteoarthritis (OA) show partial but meaningful translational relevance to human OA. Aging mouse models, primarily studied in C57BL/6 mice, recapitulate several key features of human disease, including substantial inter-individual variability, age-dependent molecular and proteomic changes, altered whole-joint tissue crosstalk, and a clinically relevant dissociation between structural damage and pain involving neuroimmune mechanisms. However, their translational value is limited by relatively mild structural pathology, occasional differences in compartmental involvement, compressed disease timelines, limited genetic diversity, species-specific endocrine aging, particularly in females, and limited characterization of the pain-related phenotype. Therefore, aging-related OA models should be used to complement rather than replace post-traumatic OA models, with careful consideration of age, sex, endocrine status, pain-related outcomes, and molecular context to maximize relevance to human disease.

LEVEL OF EVIDENCE: Moderate

RATIONALE: Osteoarthritis (OA) is the most prevalent form of arthritis, affecting over 500 million individuals, with aging being the strongest risk factor.[1] Although OA is observed across mammalian species and shares common structural hallmarks—including cartilage degeneration, subchondral bone remodeling, osteophyte formation, synovial inflammation, and pain-related functional decline—the translation of findings from animal models to effective human therapies has remained disappointing. In particular, no disease-modifying OA drug (DMOAD) has yet demonstrated clear structural efficacy in humans, despite repeated success in preclinical studies. Animal models, especially mice, dominate preclinical OA research due to their availability, genetic manipulability, and cost efficiency.[2,3] However, most mechanistic and therapeutic studies rely on surgically induced post-traumatic OA (PTOA) performed in young, genetically homogeneous animals, a scenario that poorly reflects the slow, multifactorial, aging-related OA that predominates in human populations.[4] This review evaluates whether murine models of natural aging recapitulate human aging-related OA at the phenotypic, molecular, and behavioral levels, and identifies key strengths and limitations affecting translational relevance. This review builds upon a prior systematic review by Iijima et al.,[5] which summarized 41 studies published up to June 2021,[6-46] by updating and extending the evidence base. An updated comprehensive literature search was conducted using PubMed, covering all relevant studies published up to December 2025. The search identified a total of 153 records. Among these, 35 studies were published after June 2021. After eligibility assessment, and in conjunction with manual reference searching, seven studies were ultimately identified as newly eligible,[47-53] and 48 studies were included in the narrative synthesis to update and extend the prior systematic review.[6-53]

Phenotypic and molecular features of age-related murine OA models

Histologic cartilage degeneration typically emerges around 12 months of age in mice, with more pronounced disease observed between 18 and 24 months, as summarized in a prior systematic review by Iijima et al,[5] noting that most of these findings are based on C57BL/6 mice. Similar patterns were also observed in studies identified in this updated review.[48,49,52,53] Similar to humans, age-related OA preferentially affects the medial compartment of the knee and exhibits marked inter-individual variability in severity.[9,28,48,49] However, some reports indicate more severe degeneration in the lateral compartment,[15,40,41,47] which may reflect species-specific differences in knee alignment, such as a valgus knee configuration in the C57BL/6 strain, compared with humans.[54] Proteomic profiling further revealed that middle-aged mice already exhibit shifts in protein expression,[49] including alterations in PI3K/Akt signaling, a pathway well-characterized in human OA pathology. Beyond articular cartilage, aging also alters whole-joint biology, as the infrapatellar fat pad from young mice promotes extracellular matrix production in chondrocytes, whereas age-related changes in the infrapatellar fat pad secretome attenuate this anabolic effect.[50] Similarly, meniscal changes worsen with age, with histologic analyses showing progressive degeneration paralleling that observed in articular cartilage.[23,24,29] These shared features suggest that murine aging

models capture important aspects of human OA, including biological heterogeneity and whole-joint tissue crosstalk. However, important limitations exist. Structural changes in aging mice, including cartilage and meniscus degeneration, are generally mild compared to advanced human OA. In addition, synovial inflammation is limited, osteophytes are relatively small, and full-thickness cartilage loss is uncommon even in very old animals.[48,49,52] Interestingly, subchondral bone changes have been less consistently reported, and studies using micro-computed tomography show quantitative and qualitative discrepancies between reports.[16,17,52]

Pain-related phenotypes and neuroimmune concordance

In contrast to structural outcomes, pain-related phenotypes in aged murine OA show greater concordance with human disease. In aged mice, pain-like behaviors increase with age and do not consistently correlate with the severity of histologic joint damage.[48] This dissociation between structure and pain mirrors a key clinical feature of human OA that is often underrepresented in structure-focused preclinical models. Mechanistically, aging-related pain behaviors in mice are linked to neuroimmune alterations, including increased macrophage and dendritic cell populations within the dorsal root ganglia (DRGs).[48] Importantly, these findings show partial cross-species conservation. Analyses of human DRGs from older adults with OA revealed age-dependent changes in chemokine expression, including CCL2 (MCP-1) and CCL3 (MIP-1α), supporting shared neuroimmune pathways contributing to OA pain.[48] Nevertheless, some studies report minimal changes in specific pain modalities, such as mechanical allodynia, with aging, highlighting phenotype- and assay-dependent variability.[30] However, pain phenotyping in aged mice with spontaneous OA remains underexplored relative to structural outcomes, limiting the generalizability of current conclusions.

Sex differences and the role of endocrine aging

Sex differences further modulate these pain and structural phenotypes and complicate translational interpretation. Histologically, spontaneous aging-related OA in mice is typically more severe in males than in females.[48,49] This pattern contrasts with human epidemiology, in which knee and hand OA are more prevalent and often more symptomatic in women, particularly after menopause.[1] One likely contributor is species-specific endocrine aging. Unlike women, aged female mice typically retain circulating estrogen levels comparable to those of young animals,[49] which may confer relative protection against joint degeneration and limit the translational relevance of naïve aging models. Despite milder structural disease, aged female mice often exhibit pain-like behaviors comparable to or exceeding those of males,[48] highlighting a sex-specific dissociation between joint pathology and symptomatology that parallels human OA. To better capture post-menopausal OA mechanisms, a chemically induced menopause model using 4-vinylcyclohexene diepoxide (VCD) was recently developed and validated in middle-aged female mice.[51] This model recapitulates hallmark features of the menopausal transition, including loss of circulating estradiol and progesterone, increased body temperature, and weight gain, and is accompanied by significantly worsened histologic cartilage degeneration over time, recapitulating post-menopausal OA pathology in human.[51] Incorporating VCD-induced menopause allows mechanistic investigation of female-specific, aging-related OA and improves the translational relevance of murine models.

Conclusion

Aging-related murine OA models, primarily studied in C57BL/6 mice, reproduce key aspects of human disease, including substantial inter-individual variability, age-dependent molecular and proteomic changes, and clinically relevant dissociation between structural damage and pain. Emerging evidence further indicates that aging alters whole-joint communication, as exemplified by age-dependent changes in the infrapatellar fat pad secretome that attenuate anabolic paracrine support to chondrocytes. However, important limitations remain, such as relatively mild pathology, occasional differences in compartmental involvement compared with humans, limited genetic diversity, species-specific endocrine differences, and compressed disease timescales. To improve translational relevance, preclinical studies should integrate both sexes, incorporate functional and pain outcomes, and model endocrine aging, including menopause. Aging models should complement, rather than replace, PTOA models, providing a framework to develop therapies that are effective across the heterogeneous, aging human population rather than only in young, injured animals.

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