What other aging-associated musculoskeletal diseases (e.g., osteoporosis, sarcopenia, neurodegenerative, etc.) contribute to age-associated OA in animals?

Authors: Mingde Cao, Michael Tim-yun Ong, Wing-hoi, Cheung, Alan Zhong Li, Patrick Shu-Hang Yung

Response/Recommendation: Sarcopenia and osteoporosis contribute to osteoarthritis (OA) development in animal models. These conditions share overlapping pathophysiological mechanisms including mitochondrial dysfunction, altered mechano-transduction, and dysregulated musculoskeletal crosstalk mediated by myokines and osteokines, creating a cascade that accelerates joint degeneration.

Level Of Evidence: Moderate

Delegate Vote: Agree (TBD), Disagree (TBD), Abstain (TBD)

Rationale: Multiple aging-associated diseases, such as osteoporosis, sarcopenia, and neurodegenerative disorders, are considered to have a partial causal relationship with OA. Several Mendelian randomization studies have supported the casual relationship apart from the association[1-3]. However, these findings should be interpreted with caution due to potential violations of MR assumptions. The aim of this review is to identify potential mechanisms by which osteoporosis, sarcopenia, and neurodegenerative diseases promote OA progression in animal models, thereby providing updated insights for the management of comorbidities collectively.

PubMed and Scopus were searched for potentially eligible studies from database inception to December 31, 2025. The search strategy included the following terms: “osteoporo*” OR “sarcopeni*” OR “neurodegenerative disease” AND “osteoarthriti*” restricted to ti/ab. The initial literature search retrieved 4,576 records. After removing 536 duplicates, 3,724 studies were screened based on titles and abstracts. Subsequently, 156 studies underwent full-text review. Ultimately, 22 studies were included in the review[4-25].

Sarcopenia emerges as a critical contributor to OA pathogenesis through multiple mechanisms.

Sarcopenia is not merely a consequence of OA pain and immobility but an active contributor to joint degeneration[4]. In senescence accelerated mouse prone 8 (SAMP8) mice, a model of sarcopenia[5], a more pronounced progression of OA can be observed compared with C57BL/6 mice without surgical induction[6]. However, the systemic accelerated aging inherent to the SAMP8 model may limit its suitability for elucidating the specific relationship between sarcopenia and OA. In rat MIA induced knee OA model, exercise-induced secretion of the myokine irisin was found to be chondroprotective[7]. Irisin is secreted primarily by muscle and could suppresses the NF-κB and MAPK signaling pathways in chondrocytes, downregulating MMP-13 and ADAMTS-5 while upregulating Type II collagen[7, 8]. Intra-articular Irisin injection attenuated OA progression in DMM mice by restoring Sirt3 and UCP-1 signaling, improving mitochondrial function and antioxidant capacity[9]. The loss of muscle mass in aging leads to reduced systemic irisin, removing this "brake" on catabolic enzymes and decreasing mitochondrial biogenesis. In a mouse ACL rupture model, although it is not a classic sarcopenia model, unresolved muscle weakness and post-traumatic osteoarthritis are present. Modulating GDF8/myostatin, an endogenous muscle inhibitory factors can promote recovery of muscle function and partially prevent PTOA[10]. Notably, GDF8 has also been identified as a key negative regulator of muscle mass in postmenopausal females[11].

Osteoporosis-OA represents a particularly detrimental combination.

Osteoporosis may directly contribute to OA by altering subchondral bone structure and remodeling in ways that exacerbate cartilage damage. In a female rabbit model, OVX-induced osteoporosis followed by ACLT resulted in greater cartilage damage compared with controls[12]. Likewise, in rats with medial meniscectomy induced knee OA, superimposed OVX-induced osteoporosis causes higher subchondral bone damage scores, more porous trabecular bone, and greater subchondral osteoclast density and aggravated OA pathology[13]. The weakened and highly remodeled subchondral bone, characterized by a low OPG/RANKL ratio and increased MMP9 expression, transmits abnormal mechanical stress and biochemical signals to the cartilage, accelerating cartilage degeneration and worsening OA[12, 14]. In addition, in female mice (26 weeks old) with osteopenic subchondral bone (SCB plate thickness, BMD, BV/TV↓) caused by osteoblast-specific estrogen receptor-α knockout (pOC-ERαKO), mechanical loading induces more severe cartilage damage and worse histologic OA scores than in littermate controls[15].

Bone-derived factors, or osteokines, which change in response to aging and mechanical loading, may represent another key class of mediators[16]. Osteoblasts, the primary bone-forming cells, are now recognized as mature endocrine cells. Several osteokines, including Tgfbi, osteonectin (Sparc), and osteopontin (SPP1), have been reported to be closely associated with the progression of OA[17-19].

Neurodegenerative disease and OA link is not clear

The relationship between OA and neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), remains incompletely understood[20]. Although chronic inflammation and oxidative stress—hallmarks of OA—are known contributors to neurodegeneration, current epidemiological and clinical evidence linking OA to AD or PD is largely correlational[21]. As a result, whether OA and neurodegenerative disease risk are mutually contributory remains unresolved.

Several studies suggest that OA pathology may exacerbate neurodegenerative processes. DMM-induced OA significantly increased pro-inflammatory cytokine expression in the brains of 5xFAD mice and accelerated Aβ plaque deposition and neuronal loss compared to sham control[22]. Similarly, in the APP/PS1; Col1-IL1β^{XAT} compound transgenic mice, induction of OA exacerbated and accelerated neuroinflammation, as evidenced by increased glial activation and worsened Aβ pathology[23]. However, a limitation of these studies is that it did not assess whether AD mice themselves develop a more severe OA phenotype than WT controls.

Recent study further highlights the coupling between brain health and musculoskeletal homeostasis. A study demonstrated that aged neurons in the hippocampus and cerebral corte produce elevated levels of WDFY1, which is transferred to bone via extracellular vesicles (EVs) and induce osteoporosis[24]. This finding suggest that the nervous system may influence cartilage health through paracrine signaling. In addition, neurodegeneration and aging—particularly of sensory neurons—are associated with chronic OA pain. 20-Mo male mouse DRGs showed increased expression of *Ccl2 and Ccl5*, and 20-Mo female mouse DRGs showed increased Cxcr4 and Ccl3 expression compared to 6-month-old mouse DRGs. with overall more severe pain-related behaviors than in young mice[25].

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