2026 ICM -Obesity and OA group- Question 4: "Can/should we investigate the role of systemic and local immune responses, including adipose tissue inflammation and macrophage polarization, in obesity-induced OA?"

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RESPONSE/RECOMMENDATION: Yes, with caution and limited to preclinical investigation. Investigation of the role of systemic and local immune responses, including adipose tissue inflammation and macrophage polarization, can be considered within preclinical research settings. Evidence from controlled preclinical models, in which systemic and/or local inflammatory or immune pathways are experimentally manipulated, suggests that immune–metabolic mechanisms may influence osteoarthritis-related structural and pain outcomes in the context of obesity. However, the available evidence is confined to preclinical studies, and conclusions should be interpreted as mechanistic and hypothesis-generating, rather than definitive.

LEVEL OF EVIDENCE: Low–Moderate (preclinical evidence only)

DELEGATE VOTE: Agree: [XX/100% vote], Disagree: [XX/100%], Abstain: [XX/100%]

RATIONALE: Obesity is a well-established risk factor for osteoarthritis (OA),[1,2] yet its biological contribution to joint degeneration has not been fully explained by mechanical factors alone.[3] To examine potential non-mechanical mechanisms, this systematic review was intentionally limited to preclinical studies that employed controlled experimental designs in which systemic and/or local inflammatory or immune pathways were directly manipulated in the context of obesity-related OA. The purpose of this approach was not to model the full complexity of OA, but to isolate mechanistic contributions of immune–metabolic signaling under defined experimental conditions.

A systematic literature search was conducted using PubMed, covering studies published up to December 2025, in conjunction with manual reference searching. The electronic database search identified 224 records, which were screened based on titles and abstracts. Eligible studies included animal models of obesity-related OA in which inflammatory mediators, immune cell populations, or immune-related metabolic pathways were experimentally manipulated. Based on predefined inclusion criteria, seven studies met eligibility and were synthesized narratively.[4-10] Given heterogeneity in model systems, interventions, and outcome measures, quantitative analysis was not performed.

Across these controlled preclinical studies, manipulation of systemic immune–metabolic signaling such as adipokines or lipid-mediated inflammatory responses consistently altered OA-related joint pathology.[4-7,9,10] Notably, adipose tissue itself has been shown to play a causal role, as mice lacking adipose tissue were protected from obesity-related OA despite similar body weight and systemic inflammation.[10] These findings suggest that inflammatory signals associated with obesity can modify cartilage degeneration and synovial changes independent of gross mechanical load, at least within experimental settings. Importantly, these effects were observed only when immune or inflammatory pathways were directly perturbed, indicating the mechanistic nature of the evidence.

In parallel, studies examining local immune modulation within joint tissues have revealed a complex, context-dependent role for macrophages in obesity-related OA.[8,9] Conditional systemic depletion of macrophages in obese mice failed to attenuate OA severity and instead exacerbated joint inflammation

through immune dysregulation, including increased neutrophil infiltration and elevated proinflammatory cytokine levels.[8] In contrast, local intra-articular depletion of synovial macrophages in obese post-traumatic OA models attenuated synovial inflammation and cartilage degeneration, resulting in reduced OA severity without altering systemic metabolic parameters.[9] Together, these findings indicate that obesity-related OA is characterized by persistent non-resolving joint inflammation and that the impact of macrophage depletion depends on the spatial and immunological context, with local modulation of synovial macrophages conferring protective effects on joint tissues.

However, important limitations should be acknowledged. Most included studies combined diet-induced obesity with surgically induced post-traumatic OA in relatively young animals and the majority used male animals rather than modeling spontaneous or age-related OA in both sexes. In addition, most studies relied on high-fat diet–induced obesity models, which capture specific aspects of metabolic inflammation but may not fully reflect the heterogeneity of obesity-related phenotypes. These design features constrain interpretation and limit generalizability across sexes, ages, and OA contexts

Despite these limitations, the reviewed preclinical studies converge on a consistent mechanistic theme. When immune or inflammatory pathways associated with obesity were directly manipulated under controlled experimental conditions, OA-related joint pathology was modified in a manner that could not be readily explained by changes in mechanical loading alone. These observations support the concept that immune–metabolic signaling contributes to joint degeneration in obesity-related OA at least within defined experimental contexts

Taken together, the current evidence provides biological plausibility that obesity-related OA is influenced by immune and inflammatory mechanisms that operate independently of gross mechanical load. However, given the small number of heterogeneous preclinical studies and their reliance on specific experimental models, these conclusions should be viewed as hypothesis-generating rather than definitive. Future studies that incorporate age-related and spontaneous OA models include both sexes and systematically distinguish local from systemic immune effects will be essential to clarify the relevance of these pathways to the broader spectrum of obesity-related OA

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