Q14: Can/should we study the interorgan crosstalk between joint tissues and distant organs (e.g., brain, adipose tissue, gut, cardiovascular system, reproductive system) in obesity and OA?

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RESPONSE/RECOMMENDATION:

YES. Obesity, along with advanced age, female sex and joint injury, is a major risk factor for OA[1, 2]. Beyond increased mechanical loading, obesity affects joint tissues and distant organs, such as the brain, adipose tissue, gut, cardiovascular system, and reproductive system through systemic inflammation, altered metabolism, and adipokine signaling. Characterizing the interorgan crosstalk between joint tissues and these distant organs is critical to understanding the mechanisms and pathophysiology of OA in the context of obesity, particularly given the strong modifying effects of sex and aging on metabolic and inflammatory biology. Such research could elucidate how systemic inflammation, co-morbid conditions, gut microbiota dysbiosis, adipose tissue dysfunction, menopause, and neuroimmune interactions exacerbate joint degeneration OA symptoms, the OA experience, and OA phenotypes, paving the way for targeted interventions that address both localized joint damage, systemic contributors to disease, and systemic effectors of disease. With the majority of individuals with OA having at least one and usually 2 or more co-morbid diseases[3], investigating these interconnections is not only warranted but essential for developing holistic and effective therapeutic strategies for OA in individuals with obesity.

LEVEL OF EVIDENCE: Strong

RATIONALE/ELIGIBILITY CRITERIA: A scoping review of literature search was conducted on "crosstalk between joint tissues" and "osteoarthritis" focused on pre-clinical and translational studies indexed on pubmed. Preprints listed on pubmed at the time of the search were included.

The literature supports the need for focused investigation on how obesity-related systemic factors interact with joint tissues and distant organs, including the brain, adipose tissue, gut, cardiovascular system, and reproductive system, to exacerbate OA pathophysiology and clinical outcomes. Mechanistic insights support the notion that obesity contributes to OA through both biomechanical and systemic pathways. Adipokines and cytokines, metabolic dysregulation, gut microbiota dysbiosis, and neuroimmune signaling are critical systemic factors driving mechanisms of joint degeneration, damage, pathology, pain and dysfunction. There is also a need to define the analytical or mechanistic strategy to link obesity, OA, and distant organ involvement beyond the tissue or molecular assessment.

1. *Multi-modal structural assessments of tissues*: Extracellular matrix properties, spatial and dissociative profiling that captures **all known tissue and cell types in the joint organ system**, including neurons innervating the joint to capture pain-related changes in an obesity context. This should include, but not be limited to, cartilage (chondrocytes), bone (osteocytes, osteoblasts, osteoclasts, vascular cells, adipocytes, immune cells), synovium/joint-capsule (synovial fibroblasts, immune cells, vascular cells), meniscus, intra-articular fat pad (adipocytes, immune cells), adipocytes, intra- and peri-articular ligaments/tendons/fascia (fibroblasts), muscle, (myocytes, stromal cells), sensory neurons (dorsal root ganglia cells), and autonomic neurons.
2. *Immunometabolic profiles*: Obesity promotes low-grade systemic inflammation through the secretion of adipokines such as leptin, adiponectin, and resistin, as well as pro-inflammatory cytokines like TNF and IL-6[4]. These mediators not only accelerate cartilage destruction and synovial inflammation and pain pathology locally but also influence distant organs, including adipose tissue and the cardiovascular system, exacerbating systemic metabolic disturbances. Comprehensive profiling using flow cytometry, sequencing, proteomics, cytokine panels, and other available tools are required to understand the complex immunometabolic landscape across the joint and how that influences the organism's systemic physiology (blood, serum, distant organ systems). It is also unclear how co-morbidities affect the immunometabolic profiles like diabetes[5] and cardiovascular disease[6].
3. *Gut Microbiota Dysbiosis*: Obesity-induced alterations in gut microbiota composition have been linked to increased intestinal permeability and systemic subclinical endotoxemia, which may drive inflammatory responses in joint tissues[7]. Short-chain fatty acids (SCFAs), bile acids[8] and gut-derived metabolites may further modulate immune responses and cartilage homeostasis. Data from mice suggest surgically induced post-traumatic OA but not sham surgery induces microbiome changes reciprocally, suggesting a bidirectional relationship between gut health and joint integrity[9].(R
4. *Neuroimmune Interactions*: Obesity-related inflammation extends to neuroimmune signaling pathways, with implications for pain sensitization and central nervous system involvement in OA progression[10-13]. Obesity induced by a high fat diet drives hyperalgesia in mice. Recent studies[14] have reported expression of neurodegenerative molecules, like ApoE, and B-amyloid plaques, in knee joint tissues suggesting shared inflammatory or metabolic pathways. How neuroinflammation[15] and altered autonomic nervous system activity may exacerbate OA-related pain[16] and dysfunction is a promising area of future work. The recent findings that incretin drugs may mitigate pain in OA also may have underlying neuro-immune mechanisms[17].
5. *Cardiovascular and Metabolic Drivers and Consequences:* Cardiometabolic comorbidities frequently observed in obese patients may indirectly worsen CV comorbidity and mortality[18, 19], and may directly impact OA through endothelial dysfunction, oxidative stress, and systemic inflammation. Insulin resistance and metabolic syndrome further contribute to the dysregulated cartilage metabolism and impaired repair mechanisms observed in OA. Recent studies suggest that cardiovascular and metabolic changes may occur as a result of joint damage, not only as a result of pain and reduced activity but also affect biological signalling from injured joint tissues either directly or through pain and reduced function. This possibility warrants further investigation to understand the impact of OA on healthy aging trajectories.
6. *Sex as a Biological Variable in OA*: Obesity-related changes in reproductive hormones, such as estrogen and androgens, may influence joint homeostasis, particularly in postmenopausal women, who are more likely to report joint complaints, even when adjusted for age. Hormonal imbalances may directly contribute to cartilage degeneration and bone remodeling. These interactions can be reshaped by chronological age as individuals enter menopause and andropause. These mechanistic influences should be studied in relevant models of menopause, andropause, etc with and without co-morbid obesity to understand the context-

relevant impact on the biology of sex differences with OA. Recent studies also demonstrate the potential impact of cell-intrinsic sex differences via chromosomal sex. This is likely an important area of consideration with obesity and OA, and when possible to consider using transgenic mice or in microphysiological systems approaches.

CONCLUSION

The necessity of studying interorgan crosstalk in the context of obesity-related OA, as systemic factors play a crucial role in disease progression and severity. This is of particular importance in the setting of obesity, as mechanistic insights into adipokine signaling, gut microbiota dysbiosis, neuroimmune interactions, and hormonal imbalances highlight the influence of obesity on the complexity of OA pathophysiology and provide a foundation for future research. Although challenging to study, by adopting integrative, multidisciplinary collaborative study designs that account for systemic contributors, researchers can uncover novel therapeutic targets and develop holistic strategies to mitigate the impact of obesity on OA.

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