2026 ORS ICM on OA Models and Consensus Articles -Obesity and OA group Question 14
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RECOMMENDATION:

Can/should we investigate the interaction between obesity, pain, and physical activity/exercise or function—and how this impacts osteoarthritis outcomes? Yes. These domains are interlinked via mechanical, metabolic, and inflammatory pathways and can influence clinical outcomes and interventions. Further investigation is warranted to better understand prescribed personalized interventions as current evidence suggests exercise-alone can reduce pain symptoms and improve function but may be insufficient to minimize or slow structural degradation in obesity-associated OA. Preclinical models provide a cost and time effective approach to systematically evaluate these various patient factors and interventions.

RATIONALE:

For decades, the primary clinical recommendation for patients with obesity-associated OA (ObOA) has been to lose weight and exercise. Obesity was originally viewed as a source of excessive mechanical stress on weight-bearing joints, with consequences exacerbated by abnormal gait. Our current understanding also highlights a chronic, low-grade systemic inflammatory state derived from adipokine-associated signaling that is independent of joint loading. Obesity, pain, and structural degradation represent interconnected biological pathways that must be deconstructed for effective therapeutic targeting. An integrative approach remains critical to better understand this unique phenotype. To this end, we completed a comprehensive literature search of preclinical and clinical studies within PubMed and Google Scholar using search words “(obesity OR high-fat diet OR diet-induced) AND osteoarthritis AND (exercise OR activity OR “treadmill running” OR “voluntary wheel running” OR pain OR function).” A small database generated from this initial search was used to prime Gemini AI before prompting it to provide a thorough list of scientific literature to answer the consensus question. Literature was screened to ensure studies covered pain, function, and/or exercise intervention in ObOA.

Mechanisms driving joint destruction in ObOA are often biologically separable from those driving chronic pain. Lipodystrophic mice lacking adipose tissue are protected from cartilage damage; reintroduction of fat or systemic leptin restores both structural damage and pain[1]. Deletion of complement factor D, which may be regulated by leptin, protects against structural degradation but increases hyperalgesia, highlighting the potential disconnect between structural and pain outcomes in ObOA[2]. This uncoupling of joint damage and symptoms is mirrored in clinical populations, where metabolic factors rather than mechanical joint loading appear to be the primary determinants of patient-reported pain severity. Analysis of 80,000+ patients in the Swedish Osteoarthritis Register revealed that overweight and obese patients experienced significantly worse OA pain at baseline and follow-ups compared to metabolically healthy individuals with OA, which is further exacerbated with hypertension and/or diabetes[3]. Further, obese class III patients with OA were significantly outperformed by non-overweight individuals with OA on nearly every measure of mobility, pain, and physical activity[4].

Weight loss can significantly reduce physical disability and pain symptoms[5] though this is unlikely to be due to a reduction in joint loading alone as pain either does not improve after bariatric surgery[6] or improvements were not proportional to weight loss[7]. Dietary interventions that reduce systemic inflammation improve pain outcomes in preclinical studies[8,9] yet treatment responsiveness is based on patient factors. For example, juvenile animals exhibit greater hypoalgesia and resolution of peripheral inflammation than adult mice with dietary interventions[10]. Male mice displayed prolonged hypersensitivity and increased spontaneous pain behavior with high-fat diet in models of postoperative pain or joint inflammation, whereas dietary effects in female mice were minor[11,12], though sex differences may be species, strain, and model dependent[13]. Dietary interventions to reduce systemic inflammation have also reported improvements in clinical OA pain outcomes[14–17]. These reductions in inflammation likely dampen nociceptor sensitization[18,19] and modulate macrophage infiltration into the central nervous system[20], thereby uncoupling pain from joint damage as observed in other OA models. However, neuro-adipokine crosstalk remains understudied in the context of OA.

While physical activity and exercise are universally accepted as cornerstones of OA management, their sufficiency as standalone interventions in the complex metabolic environment of ObOA remains debatable.

Preclinical studies demonstrate that aerobic exercise alone can exert potent analgesia in various models of OA[21–23]. Exercise may also positively modulate inflammation as it disrupts the co-expression and clustering of pro-inflammatory cytokines associated with adiposity[9]. Similar positive effects such as suppressing macrophage infiltration into adipose tissues and promoting phenotypic M1 to M2 switching have been reported in obese mice in non-musculoskeletal contexts[24,25]. The capacity of exercise to modify joint structure is context dependent. Voluntary wheel running protected against OA progression and improved glucose tolerance in mice fed a very high-fat diet without reducing body mass or body fat[26]. Other studies found no effect on tissue health[8,9].

The potency of exercise intervention has been extensively explored in clinical settings, particularly in the context of addressing the commonly observed altered lower extremity joint kinematics and kinetics during gait and other activities[27–30].These functional impairments, which generally worsen as OA disease severity progresses[27–30], often lead to muscle loss and high rates of prolonged sedentary behavior[31,32]. While exercises may help improve muscle strength and metabolic function[33], and reduce knee pain, exercise interventions often do not lead to meaningful changes in knee joint biomechanics[34] and have not yet replicated preclinical findings of resolving adipokine levels[35]. Critically, optimal exercise mode, intensity, and duration will likely need to be tailored based on obesity or metabolic state,[36] partially explaining the translational gap for exercise interventions. Extensive preclinical work has established distinctions between therapeutic and detrimental mechanical loading of resident cells in vitro and in naïve and post-injured knee joints.kaiser Elevated inflammation and adipokine levels can blunt cellular mechanotransduction or shift the balance between anabolic and catabolic responses[37], with complex interactions with sex hormones[38,39]. Work establishing the relationship between adipokines and mechanotransduction in chondrocytes and fibroblasts is ongoing[40,41]. Future work should address how to tailor exercise interventions based on patient and disease factors, including the inflammatory and metabolic status of the patient. Preclinical work is likely to be instrumental in providing guidelines to design these clinical studies.

Preclinical models combining dietary and exercise interventions for OA are sparse. Prebiotic fiber and exercise improved metabolism in obese rats but did not improve joint tissue health[8]. Metformin combined with exercise found reduced joint tissue damage in mice compared to either treatment alone[42]. Clinical studies similarly demonstrate that combined diet and exercise interventions provide the most comprehensive benefits. While exercise reliably reduces pain and improves physical function, it has minimal impact on systemic inflammation or radiographic disease progression[43,44]. Diet-induced weight loss robustly reduces systemic inflammation but produces smaller functional gains[5,45]. Combining diet and exercise yields the largest and most consistent improvements in pain and function, outperforming either modality alone[45–47]. Structural modification remains modest or absent over 12–18 months, reinforcing the dissociation between symptomatic relief and joint structure[45,46]. These findings underpin the guidelines from the American College of Rheumatology (ACR) and Osteoarthritis Research Society International (OARSI) that strongly recommend exercise for knee OA, while emphasizing that obesity amplifies pain-related barriers to physical activity, limiting the effectiveness of exercise-only strategies.[48,49] Collectively, the literature supports a paradigm in which exercise is necessary but often insufficient in ObOA, and optimal outcomes require integrated interventions that reduce metabolic inflammation, alleviate pain, and enable sustained physical activity. Yet, the underlying mechanisms and refined strategies for a spectrum of ObOA phenotypes remain unresolved. Substantial work needs to define windows of opportunity for intervention and establish the requirement of long-term maintenance of weight loss and/or exercise adherence to sustain metabolic and functional improvements.

In summary, preclinical and clinical studies routinely highlight the discordance between structure and pain in ObOA. Consequently, preclinical studies evaluating novel interventions should assess metabolic, functional, pain, and structural outcomes - even when targeting only one domain - to build a comprehensive therapeutic toolkit for addressing the multifactorial nature of ObOA. Tools for evaluating preclinical pain and function are abundant, as summarized elsewhere[50]. Strong evidence supports continued evaluation of exercise as an adjuvant, particularly in conjunction with metabolic-based interventions, though it is unlikely to be sufficient for ObOA. Preclinical work will remain instrumental in evaluating the potential of emerging therapies, including GLP-1 agonists and anti-inflammatory biologics, and will be particularly beneficial in parsing distinct ObOA endotypes to identify optimal treatment combinations that simultaneously address obesity, pain, and function.

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