Q2: Can/should we determine the specific effects of dietary composition (e.g. sugar, fat, ultra-processed foods) on OA development, independent of obesity or weight gain?

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RESPONSE/RECOMMENDATION:
YES. Osteoarthritis (OA) is increasingly recognized as both a systemic, metabolically influenced disease and a consequence of mechanical joint loading. While excess body weight due to obesity remains a significant risk factor for OA, clinical observations suggest that dietary patterns associate with OA risk, pain, and progression in ways not fully explained by body mass alone. However, because dietary exposures in humans are deeply intertwined with adiposity, lifestyle, and comorbidities, preclinical models are essential for determining the direct biological effect of diet composition from those of weight gain. Emerging preclinical evidence demonstrates that dietary composition independently shapes OA development and progression. Diets high in saturated fats, refined sugars, or specific lipid profiles alter systemic metabolism, inflammatory tone, lipid-mediated signaling, and gut-joint interactions, directly affecting cartilage, synovium, and subchondral bone even in the absence of body weight changes. These findings indicate that diet-driven metabolic and inflammatory dysregulation can contribute to joint pathology. Therefore, disentangling dietary effects in preclinical systems is both feasible and necessary to advance mechanistic models of OA and to guide preventative and therapeutic strategies that can ultimately be tested and refined in patient populations.

LEVEL OF EVIDENCE: Strong.

RATIONALE/ELIGIBILITY CRITERIA: A PubMed search was performed to identify preclinical studies examining the effects of dietary composition on osteoarthritis-related outcomes independent of obesity or weight gain.

MECHANISTIC OUTCOMES AND RECOMMENDATIONS FOR STUDY DESIGN:
Preclinical models consistently demonstrate that dietary composition, particularly diets high in saturated fats, ω-6 polyunsaturated fatty acids (PUFAs), and refined carbohydrates, induces a systemic metabolic-inflammatory state that directly contributes to OA development independently of body mass. Across mouse and rat models, western-style (high ω-6/ω-3 PUFA ratios) and high fat diets (HFD) increase synovitis, cartilage degeneration, osteophyte formation, and subchondral bone remodeling, including studies that minimized loading(*1-8*). These studies also show that diet induces obesity and alters systemic cytokine and adipokine profiles, expands and inflames the infrapatellar fat pad, and promotes immune cell infiltration(*3, 4, 6, 9, 10*). Dietary composition alone - independent of total caloric intake or adiposity - can regulate OA severity, pain behaviors, and repair responses, with specific lipid and carbohydrate profiles driving distinct outcomes(*11-16*). Notably, iso-caloric purified control diets differing only in sucrose or starch content produced diet-specific metabolic signatures and distinct histopathological joint changes despite no differences in body mass or fat, demonstrating that even subtle macronutrient differences can materially influence OA pathology(*12*). Similarly, ketogenic diets, despite being high in fat, produce divergent OA phenotypes from conventional HFD models, demonstrating that nutrient quality, rather than fat content alone, shapes outcomes(*17, 18*). Caloric restriction delays OA onset and reduces disease severity, but these protective effects are blunted or lost in the context of high-fat feeding, indicating that dietary composition can override caloric intake in shaping joint vulnerability. Consistent with this concept, emerging work from the aging and metabolic disease fields show that restriction of specific amino acids can remodel mitochondrial function, lipid metabolism, and inflammatory tone independent of adiposity(*19-22*). Although not yet tested in OA models, these paradigms highlight a largely unexplored dimension of dietary composition with high relevance to joint aging and metabolic OA(*23-26*).

At the molecular level, diet-induced OA is accompanied by profound metabolic reprogramming within joint tissues. High-fat and high-sugar diets alter circulating and local metabolite profiles - including phospholipids,

lysophospholipids, ceramides, and eicosanoids - that drive inflammation, oxidative stress, and matrix turnover(*11, 27, 28*). Moreover, HFD mice often have a distinct and sustained metabolic plasma profile even after resumption of a normal chow diet, and specific lipid species predict the type of diet and OA risk with high accuracy(*11*). Within cartilage, dietary stress promotes lipid accumulation, shifts in substrate utilization, and mitochondrial dysfunction, directly impairing matrix homeostasis. Studies manipulating mitochondrial enzymes - like Sirt3 and 5 - and lipid metabolic pathways attenuate diet-induced dysregulation, directly linking altered metabolism to structural outcomes(*29-32*).

Beyond the direct effects of absorbed nutrients on host metabolism, dietary patterns exert powerful influences on OA progression through modulation of the gut microbiome and its downstream signaling to the host. HFD can disrupt microbial composition, increase intestinal permeability, and elevate endotoxin burden, triggering systemic inflammation, synovial macrophage accumulation, and worsening of cartilage pathology(*33-35*). Microbiome-targeted interventions (e.g., prebiotics, probiotics, exercise) partially normalize metabolic and inflammatory profiles and protect against diet-induced joint damage(*34, 35*). Emerging work further indicates that specific microbial taxa are associated with cartilage degeneration independently of adiposity, supporting a causal gut–joint axis rather than a secondary consequence of obesity(*33*).

Recommendations for Study Design

1. *Disentangle dietary composition from body mass:* Include early time-point assessments prior to weight divergence, longitudinal metabolic phenotyping, and quantitative measures of adiposity rather than relying on body weight alone. Pair-feeding, isocaloric paradigms, and controlled macronutrient substitution designs are encouraged to isolate the biological effects of dietary components from caloric excess. Where feasible, incorporate experimental strategies that bypass mechanical loading to strengthen causal inference regarding diet-driven joint degeneration.
2. *Precisely define diet composition:* Dietary interventions should be explicitly reported including fat and carbohydrate composition, protein content, fiber, and relevant micronutrients. Feeding schedules, age of initiation diet duration, and timing relative to joint injury should be standardized and transparently reported.
3. *Integrate systemic and joint-level outcomes:* Both systemic and joint-specific measures should be included, encompassing cartilage, bone, and synovium structure, pain phenotypes, gait, stress, and circulating biomarkers. Incorporation of metabolomic, lipidomic, and mitochondrial functional assays is particularly encouraged. Embedding these approaches alongside histopathology and overall behavior assessments will enable identification of mechanistic intermediates linking diet to joint degeneration.
4. *Enhance translational relevance:* Inclusion of both sexes, use of aging models, and consideration of metabolic comorbidities will better reflect OA vulnerability across the lifespan.

Conclusion: Diverse dietary patterns - including high-fat, high-sugar, Western-style, and ketogenic diets - produce distinct OA phenotypes and systemic metabolic signatures in preclinical models, underscoring that the quality, timing, and context of nutrient exposure critically shape joint vulnerability. While diet composition alone is generally insufficient to induce overt OA, a large body of preclinical evidence demonstrates that dietary patterns robustly exacerbate disease. These findings establish dietary composition not simply as a correlate of obesity, but as an independent and biologically meaningful experimental variable that modifies the severity, trajectory, and mechanistic phenotype of OA beyond mechanical loading alone. By defining how specific dietary features influence joint tissue biology and systemic metabolism under controlled conditions, preclinical models provide a critical foundation for interpreting human associations and for designing rational, mechanism-based dietary interventions in OA.

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