Preclinical Models of OA and Obesity

Mechanism Question 3: "Should we determine whether metabolically healthy obesity (i.e. obesity without metabolic syndrome), body fat distribution or body composition contributes to OA risk, and how this compares to metabolically unhealthy obesity and fat dysfunction"

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RESPONSE/RECOMMENDATION: The separate and compounding influences of mechanical loading (i.e., MHO) and metabolic/fat dysfunction (i.e., MUO) should be discerned in preclinical models examining obesity and OA. Impaired body composition and distribution of body fat may have additional distinct influences on OA risk, and should also be investigated.

COMPONENT	DEFINITION/CONSIDERATIONS	INFLUENCE ON OA RISK
Metabolically healthy obesity (MHO)	A higher body weight//body mass index (e.g. BMI ≥30 kg/m^2) but no identified metabolic syndrome or fat tissue dysfunction. MHO imparts increased mechanical joint loading.	• Strong evidence that a higher BMI increases risk for knee OA. Moderate influence of higher BMI on risk for hand and hip OA. • Evidence is based on BMI, not MHO vs MUO distinctions.
Fat tissue dysfunction, and Metabolically Unhealthy Obesity (MUO)	Impaired fat tissue health, influencing inflammation and/or metabolic dysfunction in addition to mechanical joint loading. MUO is defined by a higher body weight/BMI (e.g. BMI ≥30 kg/m^2) with metabolic dysfunction.	• Conflicting evidence from systematic reviews on the BMI-independent relevance of metabolic dysfunction for OA risk. • MUO may have an additive influence on knee and hip OA risk compared to MHO.
Body fat distribution	Location of fat tissue, including in subcutaneous (e.g. abdominal, gluteal, thigh), visceral (e.g. intra-abdominal), and ectopic (e.g. liver, muscle tissue) depots.	• The location of excess body fat may affect both joint mechanics and loading (e.g. shear stress, range of motion), and inflammation and metabolic dysfunction.
Body composition	Amount of fat, muscle, and bone in the body. BMI ≠ body composition; there is substantial variability in body composition among individuals with equivalent BMIs.	• A low muscle to fat mass ratio independently impacts knee OA risk. • Potential BMI-independent impacts of higher fat mass and bone mineral density on knee and hip OA risk.

LEVEL OF EVIDENCE: Mixed

DELEGATE VOTE:

RATIONALE: We systematically examined the literature for evidence on mechanistic contributions of metabolically healthy/unhealthy obesity, fat tissue dysfunction, body fat distribution, and body composition on osteoarthritis (OA) risk. Different terms and definitions for these components were found in the literature, so we have grouped these according to similarities. Our review prioritized systematic reviews and meta analyses, and included primary studies only when higher level evidence was unavailable. Notably, evidence supporting the relevance of obesity for incidence and progression of OA in humans is largely based on studies where body mass index (BMI) was used to define obesity[1–11]. BMI is an anthropometric biomarker, calculated as weight (kg) divided by height (meters squared), and while BMI is correlated with fat mass at the population level, this relationship is weak on an individual level, inaccurate in older adults, and prone to sex and racial biases[12–15]. BMI is no longer

accepted as a diagnostic measure of adiposity-related disease (i.e., clinical obesity)[16,17] in individuals. Further, metabolic dysfunction and BMI are highly correlated in population studies, so it is difficult to disentangle their independent influence on OA risk. Preclinical models are instrumental[18] in this regard to distill obesity-related pathogenic factors and causal pathways of metabolically induced joint degeneration that can be targeted for OA prevention efforts in individuals with a higher body weight.

Metabolically healthy vs unhealthy obesity (i.e., with fat tissue/metabolic dysfunction): We found three systematic reviews examining metabolic syndrome[19–21] and eight examining specific metabolic-dysfunction factors and their relationship with OA risk[22–28]. Li and Felson[19] found no relationship between metabolic syndrome and knee OA after adjustment for BMI, no relationship with hip OA, and insufficient data in hand OA. Nie et al.[20] reported similar non-significant findings after BMI-adjustment in a meta-analysis of knee OA studies, but noted a potential sex-difference with relevance in females. This contrasted with Xie et al.[21] who found an association between metabolic syndrome and hypertension with knee OA. Conflicting findings are also noted in longitudinal cohort studies of obesity with metabolic dysfunction, some reporting a BMI-independent influence[29,30], whereas others finding no relationship after BMI-adjustment[31,32]. The relevance of metabolic dysfunction differs with structural or symptomatic definitions of OA[21,33–35], and by definitions used to define metabolic syndrome [i.e., commonly by the presence of at least three indicators of visceral fat-tissue dysfunction, including increased waist circumference, dyslipidemia (e.g. high triglycerides and/or low high-density lipoprotein), hypertension, and hyperglycemia]. Several systematic reviews have examined these individual components, identifying a relationship between dyslipidemia and both hand[23] and knee OA[36], and a BMI-independent relationship between hypertension and radiographic knee OA[22]. Vascular impairment with dyslipidemia may also influence bone lesion pathogenesis in knee OA[24]. Conflicting results have been found in examinations of the BMI-independent relationship between hyperglycemia or type II diabetes with OA risk[25–28]. A weakness in several studies is the use of BMI as a criterion indicator for metabolic dysfunction, and/or not adjusting for BMI in analyses, confounding distinction between loading and metabolic impacts. We did not find any systematic reviews specifically comparing metabolically healthy (MHO) vs metabolically unhealthy (MUO) obesity. However, several cohort and cross-sectional studies have examined associations between these phenotypes and OA, identifying increased symptomatic knee, hip, and potentially hand OA in MUO compared to MHO[29,30,37–39]. In summary, based on the existing evidence, metabolic dysfunction may amplify the association between BMI-related loading and OA risk, but its absence does not eliminate risk. There may be a gradient relationship with a higher risk in MUO vs MHO[39], particularly for symptomatic OA criteria[37].

Body composition and body fat distribution: We found five systematic reviews examining body composition and OA risk[40–44]. Mezhov et al.[40] identified a BMI-independent detrimental impact of higher fat mass on cartilage defects in knee OA, and potential protective effects of higher fat free mass. This contrasted with other studies suggesting that higher fat free mass or lean soft tissue (i.e., weak surrogates of muscle mass)[45,46] confers increased joint loading, confounding the potential protective relationship[42,44]. Data from Wu et al.[43] and Long et al.[44] suggest that a ratio of low muscle with high fat mass may be most relevant for knee OA risk. A relationship between increased bone mineral density and knee OA has also been identified[41,47]. Notably, body composition is an understudied but likely relevant factor influencing OA risk in individuals with obesity[12,48]. We did not identify any systematic reviews specific to body fat distribution in obesity and OA risk. However, data from cohort and cross-sectional studies debate whether higher visceral fat[49–51], subcutaneous fat[52–54], and fat deposition in skeletal muscle[55,56] may have BMI-independent impacts on OA risk. This uncertainty suggests a need for more robust investigation in these areas.

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