Modified Q11: Should we determine pain mechanisms unique to obesity-associated OA, including central sensitization, peripheral nerve sprouting, or neuroinflammation? Should we consider pain and structure separately?

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Recommendation: YES. Obesity is a major risk factor for osteoarthritis (OA) and influences both joint pathology and pain through biomechanical loading and systemic metabolic/inflammatory mechanisms, yet most preclinical OA pain studies have not adequately accounted for whole-body adiposity or known mechanisms of obesity-associated pain like diabetic peripheral neuropathy (PDN). High-fat diet (HFD) models, widely used to study PDN, induce metabolic syndrome and cause sensory neuron dysfunction independent of, and often without reporting, joint pathology. In parallel, HFD exacerbates OA structural damage and accelerates or amplifies pain-like behaviors in models of OA and inflammatory arthritis, sometimes without proportional increases in joint swelling, suggesting dissociation between structural pathology and pain. Obese animals also exhibit altered body composition, bone remodeling, muscle mass, metabolic dysfunction, low-level systemic inflammation and potentially joint adipose tissue changes, all of which may confound behavioral pain assays and engage distinct mechanisms of peripheral and central sensitization, peripheral nerve sprouting, and neuroinflammation.

Level of Evidence: High.

Delegate Vote:

Rationale: Obesity is a major risk factor for OA in both weightbearing and non-weightbearing joints [1]. Local as well as systemic metabolic and biomechanical factors may link obesity to joint damage, inflammation, and pain in OA [2]. *In vivo* studies that aim to model pathogenesis of OA and OA pain in mice have largely omitted to factor in the effect of body weight/obesity/adiposity on the entire animal, and on OA disease progression in particular. For example, one key missing area of research is seeking to determine whether animals with obesity have more or less pain in relationship to the observed structural damage. A PubMed search was conducted using the search terms ((behavior) OR (pain) OR (hyperalgesia) OR (allodynia) OR (locomotion) OR (mechanical sensitization)) AND (mice) AND (pain) AND ((obesity) OR (adiposity) OR (fat pad) OR (fatpad)), which yielded 514 results. Adding “AND (osteoarthritis)” to the search reduced it to 36 papers. Search results were manually curated and categorized into relevant topics to be summarized.

Behavioral phenotypes associated with OA joint pathology in mice with altered body weight and/or adiposity- HFD is commonly used to induce obesity, with the caveat that significant variations exist in the phenotypic response to HFD in rats and C57BL/6 mice [3, 4]. The modifying effect of HFD/obesity on the severity of joint damage has been reported[5, 6], but only more recently are pain-dependent behaviors more systematically included in studies of arthritis in obese rodents. With age, female HFD-fed mice develop exacerbated joint pathology compared to control diet-fed mice, and this occurs in proportion to fat gain[7]. HFD also predisposes these mice to developing thermal hyperalgesia as well as anxiety-mediated behaviors, and this irrespective of fat gain – providing a glimpse into the complex differential effects of diet, weight, and adiposity on OA joint damage *vs.* pain [7]. Inflammatory arthritis induced by intra-articular Complete Freund’s Adjuvant (CFA) causes pain-like behaviors, including spontaneous nociceptive behaviors (flinching, guarding behavior) and weightbearing deficits, and this is markedly exacerbated in obese mice fed a HFD, even though the knee swelling is comparable to controls[8]. In wildtype mice fed a HFD, OA-associated weightbearing deficits have been reported to have a faster onset than in controls, as has been shown in the collagenase-induced arthritis model [9]. In mice, adipose tissue signaling is separable, necessary, and sufficient to drive OA damage and pain in the knee [10]. While leptin, complement factor D, and eicosanoids[11, 12] appear to be involved in the manifestation of pain, the factors that are driving the communication between fat, the knee joint, and the nervous system remain unclear[13].

Variables to be considered in mice with obesity or adiposity – When OA is experimentally induced in rodents on a HFD, for example by DMM surgery, it needs to be considered that these animals are fundamentally different from controls, which can affect pain studies in different ways:

1. *HFD alters the nervous system.* Rodents on a prolonged HFD develop metabolic syndrome, including obesity, impaired glucose tolerance, dyslipidemia, and peripheral neuropathy, and are widely used for the study of peripheral diabetic neuropathy (PDN)[14]. HFD-fed diabetic rats and mice initially develop thermal and mechanical hypersensitivity, followed by hypoalgesia at later disease stages[15]. These models of HFD-induced obesity are characterized by altered nerve conduction and loss of intra-epidermal nerve fiber density (IENFD) in the footpad, and DRG hyperexcitability. Short-term HFD (6 weeks) in young mice of both sexes results in mechanical allodynia without obesity or diabetes, accompanied by an increase in ATF3, a neuronal marker of injury, in DRG neurons[16]. Longer term HFD (10 weeks, 42% HFD) results in diabetes and obesity, where DRGs show hyperexcitability, as shown by *in vivo* calcium imaging in response to mechanical stimuli [17, 18]. This is a confounding factor in assessing joint-related pain. Studies reporting on HFD-induced PDN do not report knee pathology and it is not known how neuronal changes induced by HFD may have a direct effect on joint damage, further confounding pain readouts. This area constitutes an opportunity for future studies to fill the knowledge gap.

2. *HFD alters body composition*, with changes in muscle mass (fat/muscle ratio) and bone [2]. These can (a) affect pain assays independently of nociception[3, 7] (for example, weightbearing, gait, locomotion) and (b) recruit distinct mechanisms underlying pain.

3. *HFD may alter the local environment in the joint.* For example, there may be alterations in the fat pad of the knee [19-21]. There are no data on how obesity affects joint innervation, but it is known that adipose tissue is richly innervated.

4. *Obesity-induced OA affects all joints* (both knees but likely also other joints), while the absence of adipose selectively appears to affect the knee joint [10], and in roughly half of rats fed high fat/high sucrose diet, shoulder joints, but not hips [22]. Information about multi-joint OA is lacking in preclinical models of OA generally, and especially with obesity.

Interventional/Loss-of-Function Studies - Preclinical interventional studies in HFD and obesity-associated OA models suggest that metabolic and inflammatory modulation can attenuate joint pathology, and in some cases, pain-related behaviors. However, pain endpoints are inconsistently assessed and are often secondary to structural outcomes. Metformin [23, 24], omega-3 fatty acid supplementation (including fat-1 transgenic or gene therapy approaches) [25, 26], and resveratrol [27] have been shown to improve cartilage degeneration and synovial inflammation in obese OA models. However, pain endpoints are inconsistency assessed and are typically secondary to structural outcomes; only a subset of studies directly evaluated behavioral measures such as weightbearing deficits and mechanical hypersensitivity. Although several reports reference prior work demonstrating analgesic effects of these agents, such effects have not been systemically examined in the context of obesity-associated OA. Importantly, comparative evidence indicates that certain interventions may exert differential effects in HFD-fed mice relative to lean controls, supporting the concept that obesity establishes a distinct and potentially modifiable pain milieu [23]. Nevertheless, most studies prioritize cartilage and synovial pathology over detailed neurobiological pain mechanisms, highlighting a gap in directly interrogating peripheral and central sensitization, peripheral nerve alterations, and neuroimmune pathways in obesity-associated OA pain.

Conclusion: These findings support the need to determine whether obesity-associated OA involves unique pain mechanisms and to explicitly consider pain and structural outcomes as potentially separable domains in both experimental design and therapeutic targeting. Few studies directly compare interventions in lean vs. obese OA models, or the timing of dietary or transgenic intervention, or the potential confounding role of sex on pain phenotypes, highlighting a critical gap. The direct effect of adipose/obesity on the aging process is not known.

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