Consensus Response: Systemic Hormone Changes, Sex, Obesity, and Osteoarthritis
Consensus Question 15: Can/should we consider systemic hormone changes (e.g., menopause, andropause, pregnancy) and sex as biological variables in the interaction between obesity and osteoarthritis (OA)?

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Response / Recommendation
Yes. Hormonal regulation of obesity and osteoarthritis (OA) differs substantially by sex and life stage and should not be treated as a single unified variable. Women, in particular, experience large and repeated hormonal and weight fluctuations across their lifespan, including puberty, pregnancy, lactation, and menopause, which independently shape adipose distribution, metabolic state, pain sensitivity, and joint health. Despite strong epidemiologic and clinical evidence demonstrating sex-specific differences in OA progression and obesity phenotypes, relatively few studies explicitly examine the role of sex hormones or reproductive state as modifiers of OA risk and trajectory. This gap highlights a critical need to incorporate sex- and hormone-informed frameworks into obesity-associated OA research and therapeutic development.

Rationale

1. Menopause and Female-Specific Hormonal Transitions
The menopausal transition represents a major inflection point for both obesity and OA risk. Declining estrogen levels promote visceral and bone marrow adiposity, loss of muscle mass, and a shift toward a pro-inflammatory metabolic state, all of which accelerate joint degeneration. Importantly, women experience repeated and large hormonal and weight fluctuations across the lifespan, which should be considered independent biological variables rather than grouped into a single sex-based category[1,2].

Sex-specific fat distribution further modifies OA phenotypes. Visceral and subcutaneous adipose depots differ in inflammatory biology, and postmenopausal estrogen loss is associated with a shift toward greater visceral adiposity and metabolic inflammation; in OA, local joint adipose such as the infrapatellar fat pad can act as a source of pro-inflammatory mediators relevant to knee disease[3-6].Menopausal hormone therapy may be associated with preservation of joint structure or reduced OA risk in some studies, though findings are mixed; therefore, risks and benefits should be individualized, particularly in women with obesity, where baseline cardiometabolic and thromboembolic risks may differ[2,7].

2. Sex as a Biological Variable: Adiposity, Inflammation, and Pain
Sex hormones also directly influence nociception and pain processing. Estrogen modulates pain transmission at multiple levels of the nervous system, including peripheral nociceptors and dorsal root ganglia (DRG), through estrogen receptor–dependent mechanisms that alter mechanical and inflammatory pain sensitivity[8]. Detailed cellular and molecular evidence demonstrates that estrogen receptor signaling directly regulates ion channels, inflammatory mediators, and intracellular pathways in nociceptive neurons, contributing to sex-specific differences in pain processing[9]. Clinically, estrogen depletion states provide strong supporting evidence: women receiving aromatase inhibitor therapy to block estrogen production frequently develop joint pain and stiffness severe enough to limit treatment adherence, with reported arthralgia rates approaching 40–50%. Together, these findings

highlight the interaction between sex hormone signaling, adipose tissue-mediated hormone metabolism, and musculoskeletal pain outcomes in obesity-associated OA[1,7,10,11].

Females exhibit a higher prevalence and severity of OA than males, particularly after midlife. These differences extend beyond joint structure to include pain phenotypes, immune responses, and treatment tolerability. Adipose tissue functions as an endocrine and immune organ, and sex differences in adipose distribution, aromatase activity, and immune cell composition amplify inflammatory signaling in women with obesity[6,11].

3. Pregnancy and Lactation as Modifiers of Obesity-Associated OA

Pregnancy and lactation represent unique physiological states characterized by profound endocrine, metabolic, and biomechanical changes. These states act as metabolic stress tests, requiring coordinated energy allocation to support fetal growth, lactation, and maternal tissue maintenance. In the context of obesity, pregnancy-related changes may modify OA risk trajectories through combined effects on joint loading, connective tissue remodeling, and systemic inflammation[10,12,13].

Biomechanically, gestational weight gain increases joint loading, while pregnancy-associated hormones such as relaxin, estrogen, and progesterone alter collagen structure and ligament laxity. Human studies demonstrate that pregnancy can induce lasting changes in knee joint laxity and biomechanics that persist beyond the postpartum period, suggesting a plausible mechanical pathway linking reproductive history to later-life OA risk[12].

Metabolically, excessive gestational weight gain and postpartum weight retention strongly predict long-term obesity and prolonged exposure to meta-inflammation, insulin resistance, and adipokine dysregulation, which present as key drivers of OA. Gestational diabetes mellitus (GDM) further defines a clinically relevant metabolic endotype, as individuals with prior GDM face an elevated risk of future diabetes, metabolic syndrome, and potentially arthritis outcomes[14,15]. Postpartum lactation introduces additional complexity through transient bone loss, hormonal shifts, and changes in body composition. While lactation-associated bone loss is often reversible, it is not clear how lactation-induced bone loss interacts with obesity, parity, and metabolic health to influence long-term musculoskeletal outcomes and therefore warrants further study.

4. Andropause and Male Hormonal Aging

In men, age-related declines in testosterone (andropause) are associated with increased visceral adiposity, reduced muscle mass, and impaired joint support. Obesity further exacerbates this process by increasing aromatization of testosterone to estradiol in adipose tissue, leading to functional hypogonadism and heightened OA risk[16-18].

Implications for Research and Clinical Practice

Considering systemic hormone changes and sex as biological variables moves OA research beyond a one-size-fits-all framework. Incorporating reproductive history, hormonal status, fat distribution, and pain phenotypes may improve risk stratification, enable identification of metabolic OA endotypes, and support more personalized prevention and treatment strategies.

Key recommendations for study design

Future studies examining the interaction between obesity, osteoarthritis, and sex should explicitly account for differences between preclinical and human models and leverage the strengths of each. Rodent models remain highly informative for mechanistic studies of obesity, metabolic dysfunction, and pregnancy-related musculoskeletal changes, and are particularly well suited for controlled investigations probing acute and reproductive state specific effects that are difficult to isolate in humans. However, mouse models have limited capacity to capture the slow, decades-long progression of osteoarthritis and cumulative hormonal transitions that characterize human disease. Human studies should therefore prioritize longitudinal designs that track sex-specific hormonal milestones, such as puberty, contraceptive use, hormonal therapy, pregnancy, lactation, menopause, and andropause, alongside changes in body composition, metabolic status, pain phenotypes, and joint structure. Integrating mechanistic insights from animal models with lifespan and reproductive history informed human cohorts will be essential for accurately defining obesity-associated OA endotypes and for developing sex- and stage-specific prevention and intervention strategies.

Strength of Evidence

Strong (human epidemiology, clinical studies, and supportive mechanistic data).

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