**Question 9 DELPHI Response – ORS JOR Preclinical Models of OA Consensus Process**
*Can/should we stratify and align preclinical models with specific human endotypes/phenotypes of obesity-related OA (e.g., metabolic, mechanical, inflammatory)?*

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Yes. Preclinical OA models should be stratified and explicitly **aligned with specific human endotypes** — particularly metabolic, mechanical, and inflammatory phenotypes — to enhance translational relevance, improve mechanistic clarity, and accelerate targeted therapeutic development. Obesity-related OA is not a homogeneous condition but reflects a spectrum of biological processes that include systemic metabolic dysregulation, innate immune activation, and biomechanical stress. A systemic OA framework underscores how metabolic dysfunction, adipose tissue signaling, and maladaptive immune responses contribute to joint pathology beyond classical load-driven mechanisms, thus supporting the need for endotype-aligned modeling.[1]

Clinical epidemiologic data further illustrate heterogeneity within obesity-related OA phenotypes. In community cohorts, metabolic syndrome and its components (central adiposity, dyslipidemia, hypertension, insulin resistance) are differentially associated with incident OA across joints; whereas metabolic syndrome may predict hip OA in women, mechanical factors (e.g., obesity without metabolic syndrome) may predominate in men.[2] This divergent pattern suggests metabolic versus mechanical drivers that are not fully captured by body mass index alone and argues for phenotype-specific preclinical alignment. Moreover, longitudinal human studies of hand OA demonstrate that metabolic syndrome per se was not consistently associated with radiographic progression, highlighting that structural phenotypes may diverge from systemic metabolic measures.[3]

Importantly, mechanistic clinical work emphasizes that systemic inflammatory mediators (e.g., leptin and high-sensitivity C-reactive protein) partially mediate associations between higher BMI and pain severity in hand OA, pointing to **inflammatory pathways** that may be particularly relevant for pain phenotypes associated with metabolic dysregulation.[4] Phenotype analyses in OA also reveal heterogeneous pain patterns that cannot be explained solely by structural damage, indicating that distinct pain endotypes exist and are shaped by inflammatory and sensory mechanisms.[5]

Experimental preclinical evidence supports these concepts. Diet-induced obesity (DIO) in rodents recapitulates many features of human metabolic OA, including systemic inflammation, adipokine alterations, and joint structural degeneration independent of sheer mechanical load, whereas exercise can ameliorate joint pathology through metabolic, not purely mechanical, improvements.[6],[7] Models that combine DIO with joint injury (e.g., DMM) further exemplify mixed phenotypes wherein metabolic and mechanical drivers together modulate OA outcomes. Additionally, recent molecular endotyping studies in human synovium identify distinct fibroblast and inflammatory profiles associated with obesity that vary across joints, reinforcing the idea that endotype stratification reflects true underlying biology.[8]

Aligning preclinical models with human endotypes offers several advantages. First, it promotes **mechanism-specific insights**; for example, metabolic models can be used to test interventions targeting adipokine signaling or insulin resistance. Second, it facilitates **biomarker discovery** by enabling correlation of systemic metabolic or inflammatory signatures with structural and pain outcomes within defined phenotype contexts. Third, it enhances reproducibility by encouraging standardized reporting of metabolic status (e.g., glucose tolerance, adipokines), inflammatory markers, and biomechanical metrics alongside structural measures.

We therefore recommend that preclinical OA studies clearly **define the intended human phenotype(s) being modeled** — metabolic, mechanical, inflammatory, or mixed — and justify model selection accordingly. Stratification should encompass comprehensive metabolic phenotyping (body composition, glucose/insulin dynamics, adipokines), inflammatory profiling (cytokines, immune cell phenotypes), and biomechanical assessments (load distribution, cartilage stress). Moreover, sex as a biological variable should be included, given documented sex differences in metabolic vs. mechanical OA drivers.[2]

In summary, stratifying and aligning preclinical models with specific human endotypes of obesity-related OA is both feasible and necessary. Doing so will improve the predictive value of animal models, clarify distinct pathogenic mechanisms, and ultimately accelerate the development of targeted OA therapies that address the true biological diversity of obesity-related OA phenotypes.

**Selected PubMed-Indexed Studies Supporting This Summary**


1. Collins KH, Haugen IK, Neogi T, Guilak F. Osteoarthritis as a systemic disease. *Nat Rev Rheumatol.* 2026;22(2):105-117. PMID:41339496 — systemic OA framework emphasizing metabolic and inflammatory contributions.
2. Cheng KY, Strotmeyer ES, Kado DM, et al. Association of metabolic syndrome and obesity with clinical hip OA in women and men. *ACR Open Rheumatol.* 2023;5(3):115-123. PMID:36694301 — metabolic vs. mechanical associations by sex.
3. Strand MP, Neogi T, Niu J, Felson DT, Haugen IK. Association between metabolic syndrome and radiographic hand OA: community longitudinal study. *Arthritis Care Res (Hoboken).* 2018;70(3):469-474. PMID:28544753 — metabolic syndrome not uniformly associated with structural hand OA.
4. Gløersen M, Pettersen PS, Neogi T, et al. Associations of BMI with OA pain and the mediating role of inflammatory biomarkers. *Arthritis Rheumatol.* 2022;74(5):810-817. PMID:35137553 — inflammation mediates obesity–pain links.
5. Mulrooney E, Neogi T, Dagfinrud H, et al. Hand OA phenotypes and biopsychosocial associations with pain. *Osteoarthritis Cartilage.* 2024;32(8):963-971. PMID:38697510 — OA pain heterogeneity and phenotype patterns.
6. Griffin TM, Huebner JL, Kraus VB, Yan Z, Guilak F. DIO induces metabolic inflammation and OA in mice; short-term exercise modifies joint outcomes. *Arthritis Rheum.* 2012;64(2):443-453. PMID:21953366 — metabolic OA model.
7. Griffin TM, Fermor B, Huebner JL, et al. Diet-induced obesity differentially regulates OA risk factors in mice. *Arthritis Res Ther.* 2010;12(4):R130. PMID:20604941 — metabolic and mechanical influences.
8. Obesity defined molecular endotypes in synovium of OA patients suggests distinct inflammatory signatures with obesity. *Clin Transl Med.* 2023;13:e15250. PMID:37006170 — molecular endotypes linked to obesity.