2026 ORS ICM on OA Models and Consensus Articles -Obesity and OA group Question 5
Antoine Dufour, David Hart, Roman Krawetz, Walter Herzog, Nidhi Bhutani

RECOMMENDATION:

Can/should we explore genetic, epigenetic and multi-omic mechanisms underlying the onset and progression of obesity-associated OA, including the influence of environmental and genetic factors*?*

Yes. We should explore genetic, epigenetic, and broader multi-omic mechanisms underlying the onset and progression of obesity-associated osteoarthritis (ObOA), alongside environmental and genetic risk factors, because emerging data show that obesity drives OA through far more than excess joint loading. Multi-omic studies in cartilage, synovium, subchondral bone, infrapatellar fat pad, and circulating compartments have begun to identify obesity-linked molecular signatures (including inflammatory, metabolic, and microbiome-related changes) that associate with OA incidence, severity, and progression. Parallel work in OA genetics and epigenetics, including genome-wide association studies and epigenome-wide profiling of DNA methylation, histone marks, and non-coding RNAs, supports a substantial heritable component and demonstrates that environmental exposures and metabolic stressors can reprogram joint tissues in ways that promote catabolism and inflammation[1–7]. Interrogating these pathways in an integrated, multi-omic framework (genomics, epigenomics, transcriptomics, proteomics, metabolomics and microbiome data) offers a route to: 1) distinguish obesity-driven OA endotypes from other OA subtypes; 2) identify causal mechanisms linking adiposity, systemic inflammation, microbiome dysbiosis and joint degeneration; and 3) discover biomarkers and therapeutic targets for risk stratification, early detection and personalized interventions.

Why obesity-associated OA needs this?

Obesity and metabolic syndrome increase OA risk and progression through mechanical overload and systemic metabolic/inflammatory disturbances, not just body weight alone. Metabolic perturbations (insulin resistance, dyslipidemia, chronic low-grade inflammation) affect circulating plasma, cartilage, bone, and synovium, producing a recognizable “metabolic” or “obesity-associated” OA phenotype. The “obesogenic joint” concept explicitly links joint overload, systemic inflammation, microbiome dysbiosis and epigenetic reprogramming as a positive feedback loop that drives early-onset OA, suggesting that traditional load-only models are insufficient[1–4]. This heterogeneity creates a compelling need to dissect genetic, epigenetic, transcriptomics, proteomics and metabolomic mechanisms to allow to distinguish ObOA from other OA endotypes. This is aimed to generate process-specific drug targets, biomarkers and prognostic markers for early-ObOA and ObOA.

Genetics and gene–environment interplay

Family and population studies show a substantial heritable component to OA, and genome-wide association studies have identified multiple OA-risk loci (e.g., in cartilage ECM, inflammation and bone signaling pathways)[1,8–10]. However, genetic risk does not act in isolation; obesity, metabolic syndrome, occupational loading, diet and other environmental exposures modify the penetrance and expression of these loci[8–10]. Studying genetics together with detailed environmental data (e.g., physical activity, diet quality, pollutants, sleep) will help us better clarufy gene-environment interactions that specifically predispose to ObOA rather than OA in general. It will also help identify individuals in whom obesity or metabolic syndrome unmasks an underlying genetic vulnerability in joint tissues such as mutations in specific genes that may be linked, directly or indirectly, to OA risks. Therefore, these analyses will provide a mechanistic basis for precision prevention (e.g., more aggressive weight/metabolic management in genetically high-risk individuals).

Epigenetic and transcriptional reprogramming

Epigenetic mechanisms (DNA methylation, histone modifications, non-coding RNAs) regulate expression of key transcription factors, cytokines, matrix proteins and proteases involved in OA pathogenesis. In obesity-associated OA, systemic inflammation, adipokines (e.g., leptin) and altered microbiome metabolites appear to reprogram chondrocytes and synovial cells epigenetically, locking in catabolic and inflammatory gene

expression patterns[8–10]. Obesity and metabolic stress are linked to persistent epigenetic changes in joint tissues and immune cells that may precede overt structural damage[3,8]. Specific microRNAs and other non-coding RNAs contribute to loss of anabolic checkpoints (e.g., miR-140) and maintenance of pro-inflammatory signaling (e.g., NF-κB activation) in the obesogenic joint[3,8–11]. These features make epigenetic marks attractive as both early biomarkers and therapeutic targets (e.g., epigenetic drugs, miRNA-based interventions) in obesity-associated OA. One important comparison urgently needed is if the epigenetic, genetic and transcriptomic changes also result in changes in protein levels and post-translational modifications of proteins[7,11–13].

Proteomic analsysis and multi-omic integration

Genes and transcripts tell you what might happen; proteins (enzymes, structural proteins, cytokines, hormones) are what actually execute cartilage breakdown, synovitis and pain. In ObOA, key mediators include adipokines (e.g., leptin, adiponectin), inflammatory cytokines, matrix metalloproteinases (MMPs), aggrecanases, complement proteins and oxidative stress–related enzymes—all protein species that proteomics can quantify and characterize. Proteomic profiling of synovial fluid, serum/plasma and infrapatellar fat pad can show how obesity-related systemic changes (adipokines, lipoproteins, inflammatory mediators) map onto local joint-tissue injury[7]. Comparing the proteome of ObOA versus non-obese OA can identify signatures that are truly obesity-driven rather than generic OA changes, helping define a distinct molecular endotype. Additioally, many OA genome wide association study (GWAS) hits and epigenetic changes converge on pathways like extracellular matrix (ECM) remodeling, TGF-β/Wnt signaling, immune activation and lipid metabolism, but we do not know which nodes are functionally most important. Proteomics shows which pathway components are actually activated or dysregulated at the protein level. Recent work argues that OA and particularly metabolic/ObOA require integrative, systems-level approaches that combine genomics, epigenomics, transcriptomics, proteomics, metabolomics and microbiome profiling[1,7]. Our multi-omic integration will provide a new perspective of what preObOA and ObOA looks like. We will map how obesity-related exposures (diet, microbiome, adipokines, systemic inflammation) propagate from genome and epigenome through transcriptome and proteome to actual metabolic changes in joint tissues[6,7,12,14–19]. We will examine distinct molecular endotypes within ObOA (e.g., predominantly inflammatory vs predominantly metabolic vs microbiome-driven), which may respond differently to weight loss, exercise, or pharmacologic therapies[18,20]. We will profile circulating or synovial fluid biomarkers that reflect specific pathways (e.g., adipokine signaling, oxidative stress, microbial metabolites) and can be used for early detection, patient stratification, and monitoring response to interventions[1,18,20,21]. Because obesity, metabolic syndrome and the gut–joint axis interact tightly, multi-omic profiling that includes the overall proteome, microbiome and metabolome is particularly well-suited to uncover novel mechanisms, drug targets, biomarker and prognostic markers.

Clinical and translational impact

A focus on risk stratification and prevention is urgently needed. Genetic risk scores plus epigenetic and metabolic signatures could identify high-risk obese individuals who might benefit most from intensive weight management, metabolic control or early joint-protective therapies[10,22]. Mechanistic insights can guide repurposing or development of treatments targeting inflammatory, metabolic, epigenetic or microbiome pathways instead of relying solely on analgesia and joint replacement[8,10]. Molecular markers, biomarkers and prognostic markers derived from multi-omic studies can enrich trials for patients with the target drug therapies, increasing the likelihood of demonstrating disease-modifying effects in ObOA[7,8,10]. Given the rising global burden of obesity and OA and the current lack of disease-modifying OA drugs, a focused exploration of genetic, epigenetic, proteomics via multi-omic mechanisms, explicitly incorporating environmental and genetic factors, is both scientifically warranted and clinically urgent.

References:

1. Liu, Y., Molchanov, V., Brass, D. & Yang, T. Recent advances in omics and the integration of multi-omics in osteoarthritis research. *Arthritis Res. Ther.* **27**, 100 (2025).

2. Kiełbowski, K. *et al.* The Role of Genetics and Epigenetic Regulation in the Pathogenesis of Osteoarthritis. *Int. J. Mol. Sci.* **24**, (2023).

3. Chinyere Nkemjika, A. *et al.* The Obesogenic Joint Revisited: Mechanobiological, Microbial, and Epigenetic Interfaces in the Pathogenesis of Early-Onset Osteoarthritis. *F1000Res.* **14**, 1306 (2025).

4. Mocanu, V., Timofte, D. V., Zară-Dănceanu, C.-M. & Labusca, L. Obesity, Metabolic Syndrome, and Osteoarthritis Require Integrative Understanding and Management. *Biomedicines* **12**, (2024).

5. Ailixiding, M. *et al.* Pivotal role of Sirt6 in the crosstalk among ageing, metabolic syndrome and osteoarthritis. *Biochem. Biophys. Res. Commun.* **466**, 319–326 (2015).

6. Das, N. *et al.* Tryptase β regulation of joint lubrication and inflammation via proteoglycan-4 in osteoarthritis. *Nat. Commun.* **14**, 1910 (2023).

7. Bhardwaj, S. *et al.* Integrating the analysis of human biopsies using post-translational modifications proteomics. *Protein Science* **33**, (2024).

8. Ghezai, Y. T., Farhat, N. M., Ibrahim, S. M. S. & Rai, M. F. Epigenetics in osteoarthritis: emerging mechanistic and translational landscape. *Connect. Tissue Res.* **66**, 313–322 (2025).

9. Zhang, M. & Wang, J. Epigenetics and Osteoarthritis. *Genes Dis.* **2**, 69–75 (2015).

10. Huang, S. *et al.* Inflammatory mechanisms underlying metabolic syndrome-associated and potential treatments. *Osteoarthr. Cartil. Open* **7**, 100614 (2025).

11. Luiz GN de Almeida, Hayley Thode, Yekta Eslambolchi, Sameeksha Chopra, Daniel Young, Sean Gill, Laurent Devel, A. D. Matrix Metalloproteinases: From Molecular Mechanisms to Physiology, Pathophysiology, and Pharmacology. *Pharmacol. Rev.* **74**, 712–768 (2022).

12. Wang, L., Main, K., Wang, H., Julien, O. & Dufour, A. Biochemical Tools for Tracking Proteolysis. *J. Proteome Res.* **20**, 5264–5279 (2021).

13. Klein, T., Eckhard, U., Dufour, A., Solis, N. & Overall, C. M. Proteolytic Cleavage—Mechanisms, Function, and “Omic” Approaches for a Near-Ubiquitous Posttranslational Modification. *Chem. Rev.* **118**, 1137–1168 (2018).

14. Pettersen, V. K., Dufour, A. & Arrieta, M.-C. Metaproteomic profiling of fungal gut colonization in gnotobiotic mice. *Anim. Microbiome* **4**, 14 (2022).

15. Pettersen, V. K., Antunes, L. C. M., Dufour, A. & Arrieta, M.-C. Inferring early-life host and microbiome functions by mass spectrometry-based metaproteomics and metabolomics. *Comput. Struct. Biotechnol. J.* **20**, 274–286 (2022).

16. Rosin, N. L. *et al.* Targeted proteomic approach for quantification of collagen type I and type III in formalin-fixed paraffin-embedded tissue. *Sci. Rep.* **14**, 17769 (2024).

17. Krawetz, R. J. *et al.* Mesenchymal progenitor cells from non-inflamed versus inflamed synovium post-ACL injury present with distinct phenotypes and cartilage regeneration capacity. *Stem Cell Res. Ther.* **14**, 168 (2023).

18. Lozinski, B. M. *et al.* Exercise rapidly alters proteomes in mice following spinal cord demyelination. *Sci. Rep.* **11**, 7239 (2021).

19. Luiz Gustavo N de Almeida, Daniel Young, Lorraine Chow, Joshua Nicholas, Adrienne Lee, Man-Chiu Poon, Antoine Dufour, E. O. A. Proteomics and Metabolomics Profiling of Platelets and Plasma Mediators of Thrombo-Inflammation in Gestational Hypertension and Preeclampsia. *Cells* **11**, 1256 (2022).

20. Donald, A. M. H. *et al.* Longitudinal Proteomic Profiling of Cognition across an Aerobic Exercise Intervention. *Ann. Neurol.* **97**, 1007–1018 (2025).

21. Guss, J. D. *et al.* The effects of metabolic syndrome, obesity, and the gut microbiome on load-induced osteoarthritis. *Osteoarthritis Cartilage* **27**, 129–139 (2019).