Can/should we prioritize testing of obesity-related OA therapeutics in preclinical models, including targeting systemic inflammation, mechanical overload, or neuroimmune pathways?

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Response/Recommendation: Yes. Obesity-related OA therapeutics span multiple aspects of OA pathoetiology, including systemic inflammation, mechanical overloading, and neuroimmune sensitization. Notably, the relationship between obesity and OA is complicated, and obesity-associated OA constitutes a distinct OA phenotype that requires different therapeutic strategies than other OA subtypes. Rigorous testing of obesity-related therapeutics in preclinical models offers a powerful opportunity to advance mechanistic understanding and therapeutic development across both OA and obesity fields.

Strength of evidence: Strong

Rationale: Obesity is one of the most predominant disease risk factors for OA, driven by both increased mechanical stress from excess body weight and systemic inflammation from adipose tissue[1-4]. Obese individuals have a substantially higher risk of developing OA and often experience more severe pain[5-8]. Emerging evidence also highlights the contributions of obesity-related metabolic dysfunction and insulin resistance to OA development[9-11]. Although obesity-associated OA may represent a unique OA phenotype, obesity-related OA therapeutics remain broadly relevant and may benefit the wider OA population.

1. Targeting Systemic Inflammation

OA is often associated with low-grade systemic inflammation. In obesity, excess adipose tissues release inflammatory mediators that create a pro-inflammatory environment, impacting both weight-bearing and non-weight-bearing joints[12, 13]. Obesity also alters local fat depots within the joint, such as the infrapatellar fat pad (IPFP), promoting immune cell infiltration and synovitis[14, 15]. Therefore, targeting systemic inflammation, especially in obese OA patients, warrants further investigation from genetic and epigenetic perspectives[16, 17].

a. **Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and Disease-Modifying Antirheumatic Drugs (DMARDs).** Guidelines recommend oral NSAIDs for hand, knee, and hip OA, topical NSAIDs for knee OA, and short-term intra-articular corticosteroid injections for hip and knee OA[18], mainly for pain and symptomatic relief. DMARDs have not shown clinically meaningful pain relief in OA based on meta-analysis[19], but some mixed results suggest that methotrexate may relieve pain and joint symptoms in hand or knee OA patients, particularly those with synovitis[20, 21].

b. **Cytokine Inhibitors.** Clinical trials of TNF-α inhibitors (e.g., etanercept, infliximab, and adalimumab) have not demonstrated consistent efficacy[22-26], though mixed results suggest that etanercept may offer modest long-term benefit in subsets of hand OA patients with high levels of joint inflammatory[21, 22]. Therapies that target IL-1 (e.g., AMG108, anakinra, canakinumab, and lutikizumab) have largely failed knee OA clinical trials[27-30], but post hoc analysis suggests that canakinumab may reduce total knee and hip replacement risks[28], and lutikizumab may improve pain in patients with more severe knee OA[30], underscoring the need for improved patient stratification in future trials[18, 31]. Recently, encouraging outcomes have been reported from clinical trials of IL-1 receptor antagonist (PCRX201 and GNSC-001) and IL-6 vaccine (PPV-06) in knee OA patients, highlighting the potential of gene and immune therapies in future OA interventions[32-34].

c. **Other/Emerging Targets.** Mounting preclinical evidence supports targeting systemic inflammation through specific signaling pathways, including inhibition of adipokine signaling (e.g., leptin)[35, 36], suppression of inflammasomes (e.g., NLRP3)[37, 38]; modulation of macrophage polarization[39, 40]; and regulation of key inflammation-related pathways (e.g., NF-κB, JAK, and IL-6/gp130)[41-46], several of which have progressed toward clinical evaluation[47, 48]. Additionally, growing attention has focused on the modulation of the gut-joint axis to attenuate obesity-associated OA inflammation and correct gut microbiota dysbiosis[49-52].

   Recently published studies highlight metabolic abnormalities in OA and obesity, specifically by altering the metabolic profiles of lipids, amino acids, and carbohydrates[53-55]. Restoration of normal metabolic activity has been shown to alleviate pain and slow OA progression in preclinical models[51, 56], consistent with the favorable outcomes from human trials of glucagon-like peptide-1 (GLP-1) receptor agonists and metformin in individuals with knee OA[57-62]. These observations suggest targeting metabolism as a promising strategy for OA treatment, in conjunction with or independent of targeting inflammation and weight loss.

2. Targeting Mechanical Overload

Mechanical overload, described as supraphysiological joint loading resulting from traumatic injury, abnormal joint alignment, obesity, or repetitive stress, plays a crucial role in OA pathogenesis and progression[63-65]. Meta-analyses have demonstrated a strong association between body mass index (BMI) and OA risk[66]. Targeting mechanical overload for OA encompasses both physical interventions aimed at reducing joint stress and molecular/biochemical approaches that modulate biological pathways dysregulated by mechanical stress.

a. Physical interventions

Guideline-recommended physical interventions include weight loss, exercise/physical therapy, and patient education/self-management[4]. In individuals with mild-to-moderate knee OA, achieving a 5–10% reduction in body weight is associated with significant improvements in pain and joint function[67]. Meta-analyses revealed that supervised exercise is effective in reducing pain and improving physical function across OA populations, including individuals with overweight or obesity, although 87% of people with knee OA do not meet recommended physical activity guidelines due to substantially reduced activity levels[68-71].

b. Targeting Mechanotransduction Signaling Pathways

Mechanotransduction underlies how joint cells convert mechanical cues, such as compression, tension, shear, and hydrostatic pressure, into intracellular biochemical responses. Cartilage, bone, and synovial cells sense mechanical stimuli through mechanoreceptors, including integrins and ion channels (e.g., TRPV4, Piezo1, and Piezo2), which activate downstream signaling cascades such as MAPK, NF-κB, YAP/TAZ, and Wnt pathways[64, 72-75]. Importantly, distinct mechanosensitive channels can engage unique components of the cellular “mechanome” and operate in cell-type-specific contexts, resulting in diverse biological outcomes ranging from matrix remodeling to cartilage repair[75-77]. Targeting mechanotransduction in OA holds therapeutic promise for several key disease-modifying objectives:

- **Dampening inflammation.** Mechanical stress induces inflammatory mediators (e.g., NF-κB, TNF-α, IL-6, and IL-1), which can further sensitize Piezo1-dependent mechanotransduction, creating a pathogenic feed-forward loop in OA[78].
- **Preventing cell death and senescence.** Mechanical overload can trigger chondrocyte ferroptosis via Piezo-mediated GPX4 reduction[79, 80], and promote cell senescence through downregulating FBXW7[81].
- **Restoring mitochondrial function and alleviating oxidative stress.** Mechanical overload can cause mitochondrial dysfunction and lead to increased Reactive Oxygen Species (ROS)[82-84].

3. Targeting Neuroimmune Pathways

OA pain is partially driven by nociceptor sensitization and maladaptive neuroplasticity in joint and peripheral nervous tissues[4]. Obesity is associated with a higher risk of OA accompanied by more severe pain, supporting the concept of neuroimmune sensitization that links meta-inflammation and the pain processing in OA[8].

a. Targeting nerve signal

Many mediators present in OA joints contribute to nociceptor sensitization, including pro-inflammatory cytokines and chemokines, disease-associated molecular patterns, and nerve growth factor (NGF)[85-88]. Inhibition of NGF demonstrated early promise in pain relief, but the clinical trial was halted due to the rapid progression of OA in a subset of patients[87, 88]. Elucidating the mechanisms underlying the side effects will be critical for understanding the relationship between pain and joint integrity. In parallel, TRPV1 and Piezo2 channels in the nerve have emerged as potential targets for pain control in OA[89-91].

b. Targeting immune cells

OA progression and pain are usually associated with the sprouting of nociceptors in the subchondral bone, osteochondral channels, and synovium[92-95]. Immune cells, especially macrophages, can release mediators that sensitize nociceptors and mediate neuronal growth[96-98]. Macrophages also infiltrate the dorsal root ganglia, and depletion of macrophages in the nervous system alleviates pain in experimental models[99, 100].

Conclusion and Outlook:

Obesity-related OA therapeutics represent promising avenues for advancing OA research and treatment. A major challenge remains the translation of preclinical discoveries into effective clinical therapies, likely due to the biological and clinical heterogeneity of OA, including sex as an important biological variable. In parallel with ongoing clinical efforts to identify reliable biomarkers that enable patient stratification into distinct endotypes, preclinical studies should place greater emphasis on defining mechanisms that are either specific to unique OA subtypes (e.g., obesity-associated OA) or broadly applicable across multiple OA etiologies.

References

1. Park D, Park YM, Ko SH, Hyun KS, Choi YH, Min DU, Han K, Koh HS. Association of general and central obesity, and their changes with risk of knee osteoarthritis: a nationwide population-based cohort study. Sci Rep. 2023;13(1):3796. Epub 20230307. doi: 10.1038/s41598-023-30727-4. PubMed PMID: 36882508; PMCID: PMC9992488.
2. Balogun S, Scott D, Aitken D. Association between sarcopenic obesity and knee osteoarthritis: A narrative review. Osteoarthr Cartil Open. 2024;6(3):100489. Epub 20240514. doi: 10.1016/j.ocarto.2024.100489. PubMed PMID: 38832052; PMCID: PMC11145545.
3. Misra D, Fielding RA, Felson DT, Niu J, Brown C, Nevitt M, Lewis CE, Torner J, Neogi T, study M. Risk of Knee Osteoarthritis With Obesity, Sarcopenic Obesity, and Sarcopenia. Arthritis Rheumatol. 2019;71(2):232–7. Epub 20190104. doi: 10.1002/art.40692. PubMed PMID: 30106249; PMCID: PMC6374038.
4. Tang S, Zhang C, Oo WM, Fu K, Risberg MA, Bierma-Zeinstra SM, Neogi T, Atukorala I, Malfait AM, Ding C, Hunter DJ. Osteoarthritis. Nat Rev Dis Primers. 2025;11(1):10. Epub 20250213. doi: 10.1038/s41572-025-00594-6. PubMed PMID: 39948092.
5. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2015;23(4):507–15. Epub 20141129. doi: 10.1016/j.joca.2014.11.019. PubMed PMID: 25447976.
6. Schepman P, Thakkar S, Robinson R, Malhotra D, Emir B, Beck C. Moderate to Severe Osteoarthritis Pain and Its Impact on Patients in the United States: A National Survey. J Pain Res. 2021;14:2313–26. Epub 20210728. doi: 10.2147/JPR.S310368. PubMed PMID: 34349555; PMCID: PMC8326774.
7. Ribeiro Rosa K, Fruschein Annichino R, de Azevedo ESMM, Gomes Machado E, Marchi E, Castano-Betancourt MC. Role of central obesity on pain onset and its association with cardiovascular disease: a retrospective study of a hospital cohort of patients with osteoarthritis. BMJ Open. 2022;12(12):e066453. Epub 20221223. doi: 10.1136/bmjopen-2022-066453. PubMed PMID: 36564108; PMCID: PMC9791386.
8. Binvignat M, Sellam J, Berenbaum F, Felson DT. The role of obesity and adipose tissue dysfunction in osteoarthritis pain. Nat Rev Rheumatol. 2024;20(9):565–84. Epub 20240807. doi: 10.1038/s41584-024-01143-3. PubMed PMID: 39112603.
9. Batushansky A, Zhu S, Komaravolu RK, South S, Mehta-D'souza P, Griffin TM. Fundamentals of OA. An initiative of Osteoarthritis and Cartilage. Obesity and metabolic factors in OA. Osteoarthritis Cartilage. 2022;30(4):501–15. Epub 20210917. doi: 10.1016/j.joca.2021.06.013. PubMed PMID: 34537381; PMCID: PMC8926936.
10. Courties A, Sellam J, Berenbaum F. Metabolic syndrome-associated osteoarthritis. Curr Opin Rheumatol. 2017;29(2):214–22. doi: 10.1097/BOR.0000000000000373. PubMed PMID: 28072592.
11. Tchetina EV, Markova GA, Sharapova EP. Insulin Resistance in Osteoarthritis: Similar Mechanisms to Type 2 Diabetes Mellitus. J Nutr Metab. 2020;2020:4143802. Epub 20200521. doi: 10.1155/2020/4143802. PubMed PMID: 32566279; PMCID: PMC7261331.
12. Felson DT. Risk factors for osteoarthritis: understanding joint vulnerability. Clin Orthop Relat Res. 2004(427 Suppl):S16–21. doi: 10.1097/01.blo.0000144971.12731.a2. PubMed PMID: 15480060.
13. Nedunchezhiyan U, Varughese I, Sun AR, Wu X, Crawford R, Prasadam I. Obesity, Inflammation, and Immune System in Osteoarthritis. Front Immunol. 2022;13:907750. Epub 20220704. doi: 10.3389/fimmu.2022.907750. PubMed PMID: 35860250; PMCID: PMC9289681.
14. Zapata-Linares N, Eymard F, Berenbaum F, Houard X. Role of adipose tissues in osteoarthritis. Curr Opin Rheumatol. 2021;33(1):84–93. doi: 10.1097/BOR.0000000000000763. PubMed PMID: 33186248.
15. Belluzzi E, El Hadi H, Granzotto M, Rossato M, Ramonda R, Macchi V, De Caro R, Vettor R, Favero M. Systemic and Local Adipose Tissue in Knee Osteoarthritis. J Cell Physiol. 2017;232(8):1971–8. Epub 20170303. doi: 10.1002/jcp.25716. PubMed PMID: 27925193.
16. Shen J, Abu-Amer Y, O'Keefe RJ, McAlinden A. Inflammation and epigenetic regulation in osteoarthritis. Connect Tissue Res. 2017;58(1):49–63. Epub 20160707. doi: 10.1080/03008207.2016.1208655. PubMed PMID: 27389927; PMCID: PMC5266560.
17. Raman S, FitzGerald U, Murphy JM. Interplay of Inflammatory Mediators with Epigenetics and Cartilage Modifications in Osteoarthritis. Front Bioeng Biotechnol. 2018;6:22. Epub 20180314. doi: 10.3389/fbioe.2018.00022. PubMed PMID: 29594113; PMCID: PMC5861204.
18. Kennedy S, Tambiah JRS, Lane NE. Osteoarthritis today: Lost in translation? Best Pract Res Clin Rheumatol. 2022;36(4):101810. Epub 20230113. doi: 10.1016/j.berh.2022.101810. PubMed PMID: 36642619.
19. Persson MSM, Sarmanova A, Doherty M, Zhang W. Conventional and biologic disease-modifying anti-rheumatic drugs for osteoarthritis: a meta-analysis of randomized controlled trials. Rheumatology (Oxford). 2018;57(10):1830–7. doi: 10.1093/rheumatology/key131. PubMed PMID: 29917100; PMCID: PMC6199417.

20. Wong W, Huang Y, Wichienwantana N, Sun H, Pang J, Shi Y. Efficacy and safety of methotrexate in osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. Osteoarthritis Cartilage. 2025;33(6):680–91. Epub 20250409. doi: 10.1016/j.joca.2025.02.786. PubMed PMID: 40203990.
21. Zhu R, Fang H, Wang J, Ge L, Zhang X, Aitken D, Cai G. Inflammation as a therapeutic target for osteoarthritis: A literature review of clinical trials. Clin Rheumatol. 2024;43(8):2417–33. Epub 20240703. doi: 10.1007/s10067-024-07042-y. PubMed PMID: 38961031; PMCID: PMC11269414.
22. Kloppenburg M, Ramonda R, Bobacz K, Kwok WY, Elewaut D, Huizinga TWJ, Kroon FPB, Punzi L, Smolen JS, Vander Cruyssen B, Wolterbeek R, Verbruggen G, Wittoek R. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2018;77(12):1757–64. Epub 20181003. doi: 10.1136/annrheumdis-2018-213202. PubMed PMID: 30282670.
23. Aitken D, Laslett LL, Pan F, Haugen IK, Otahal P, Bellamy N, Bird P, Jones G. A randomised double-blind placebo-controlled crossover trial of HUMira (adalimumab) for erosive hand OsteoaRthritis - the HUMOR trial. Osteoarthritis Cartilage. 2018;26(7):880–7. Epub 20180302. doi: 10.1016/j.joca.2018.02.899. PubMed PMID: 29499287.
24. Chevalier X, Ravaud P, Maheu E, Baron G, Rialland A, Vergnaud P, Roux C, Maugars Y, Mulleman D, Lukas C, Wendling D, Lafforgue P, Loeuille D, Foltz V, Richette P, French section of o. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. Ann Rheum Dis. 2015;74(9):1697–705. Epub 20140509. doi: 10.1136/annrheumdis-2014-205348. PubMed PMID: 24817417.
25. Verbruggen G, Wittoek R, Vander Cruyssen B, Elewaut D. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. Ann Rheum Dis. 2012;71(6):891–8. Epub 20111129. doi: 10.1136/ard.2011.149849. PubMed PMID: 22128078; PMCID: PMC3371224.
26. Wang J. Efficacy and safety of adalimumab by intra-articular injection for moderate to severe knee osteoarthritis: An open-label randomized controlled trial. J Int Med Res. 2018;46(1):326–34. Epub 20170825. doi: 10.1177/0300060517723182. PubMed PMID: 28840750; PMCID: PMC6011328.
27. Cohen SB, Proudman S, Kivitz AJ, Burch FX, Donohue JP, Burstein D, Sun YN, Banfield C, Vincent MS, Ni L, Zack DJ. A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL-1R1) in patients with osteoarthritis of the knee. Arthritis Res Ther. 2011;13(4):R125. Epub 20110729. doi: 10.1186/ar3430. PubMed PMID: 21801403; PMCID: PMC3239365.
28. Schieker M, Conaghan PG, Mindeholm L, Praestgaard J, Solomon DH, Scotti C, Gram H, Thuren T, Roubenoff R, Ridker PM. Effects of Interleukin-1beta Inhibition on Incident Hip and Knee Replacement : Exploratory Analyses From a Randomized, Double-Blind, Placebo-Controlled Trial. Ann Intern Med. 2020;173(7):509–15. Epub 20200804. doi: 10.7326/M20-0527. PubMed PMID: 32744862; PMCID: PMC8503784.
29. Chevalier X, Goupille P, Beaulieu AD, Burch FX, Bensen WG, Conrozier T, Loeuille D, Kivitz AJ, Silver D, Appleton BE. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2009;61(3):344–52. doi: 10.1002/art.24096. PubMed PMID: 19248129.
30. Fleischmann RM, Bliddal H, Blanco FJ, Schnitzer TJ, Peterfy C, Chen S, Wang L, Feng S, Conaghan PG, Berenbaum F, Pelletier JP, Martel-Pelletier J, Vaeterlein O, Kaeley GS, Liu W, Kosloski MP, Levy G, Zhang L, Medema JK, Levesque MC. A Phase II Trial of Lutikizumab, an Anti-Interleukin-1alpha/beta Dual Variable Domain Immunoglobulin, in Knee Osteoarthritis Patients With Synovitis. Arthritis Rheumatol. 2019;71(7):1056–69. Epub 20190607. doi: 10.1002/art.40840. PubMed PMID: 30653843.
31. Fuggle NR, Chapurlat R, Laslop A, Al-Daghri N, Alokail M, Thiyagarajan JA, Balkowiec-Iskra E, Berenbaum F, Bemden AB, Borg JJ, Bruyere O, Burlet N, Cavalier E, Rosa MM, Conaghan PG, Cooper C, Dennison EM, Englund M, Im GI, Haugen IK, Hiligsmann M, Kurth A, Lane N, Lories R, Marlovits S, Matijevic R, Mobasheri A, Ormarsdottir S, Yerro MCP, Radermecker RP, Rannou F, Sepodes B, Silverman S, Torre C, Veronese N, Rizzoli R, Reginster JY, Harvey NC. Novel approaches to the stratified management of knee osteoarthritis. Nat Rev Rheumatol. 2025;21(11):684–95. Epub 20251003. doi: 10.1038/s41584-025-01305-x. PubMed PMID: 41044417.
32. De la Vega RE, Sellon JL, Smith J, Wisniewski SJ, Jurisson ML, Frick MA, Scrabeck TL, Block JB, Mills CJ, Pohlkamp ZW, Coenen MJ, Hawse GP, Abdul TY, Conaghan P, Keravala A, Chalberg TW, Robbins PD, Ghivizzani SC, Evans CH. A phase 1 clinical trial shows safe, sustained, AAV-mediated expression of IL-1Ra in the human osteoarthritic knee joint. Sci Transl Med. 2025;17(801):eadu9804. Epub 20250604. doi: 10.1126/scitranslmed.adu9804. PubMed PMID: 40465688.
33. Cohen S CP, Hochberg M, Kivitz A, Kim M, Joy N, Jiang S, DiGiorgi M, Slonin J, Slonin D. PCRX-201 High-Capacity Adenovirus Serotype 5 Gene Therapy Demonstrates Sustained Clinical Efficacy and Safety in Patients With Knee Osteoarthritis [abstract]. Arthritis Rheumatol2025.
34. Rannou F, Desallais L, Nguyen C, Daste C, Kirren Q, Lefevre-Colau MM, Launay O, Mouhsine H, Ruiz B, Moreau G, Langenfeld F, Dolimier E, Do H, Azoulai R, Berenbaum F, Boissier MC, Salles JP, Zagury JF. Safety and

immunogenicity of PPV-06, an active anti-IL-6 immunotherapy targeting low-grade inflammation against knee osteoarthritis: a randomized, double-blind, placebo-controlled, clinical phase 1 study. Nat Commun. 2025;16(1):9767. Epub 20251105. doi: 10.1038/s41467-025-64710-6. PubMed PMID: 41193416; PMCID: PMC12589542.
35. Zhang Q, Zhao YX, Li LF, Fan QQ, Huang BB, Du HZ, Li C, Li W. Metabolism-Related Adipokines and Metabolic Diseases: Their Role in Osteoarthritis. J Inflamm Res. 2025;18:1207–33. Epub 20250125. doi: 10.2147/JIR.S499835. PubMed PMID: 39886385; PMCID: PMC11780177.
36. Xie C, Chen Q. Adipokines: New Therapeutic Target for Osteoarthritis? Curr Rheumatol Rep. 2019;21(12):71. Epub 20191207. doi: 10.1007/s11926-019-0868-z. PubMed PMID: 31813080; PMCID: PMC7291783.
37. Conaghan PG, Cook AD, Hamilton JA, Tak PP. Therapeutic options for targeting inflammatory osteoarthritis pain. Nat Rev Rheumatol. 2019;15(6):355–63. doi: 10.1038/s41584-019-0221-y. PubMed PMID: 31068673.
38. Liu Y, Wang Y, Yan P, Cui N, Xu K, Liu D, Tian Y, Cao L. NLRP3 Inflammasome-Mediated Osteoarthritis: The Role of Epigenetics. Biology (Basel). 2025;14(1). Epub 20250114. doi: 10.3390/biology14010071. PubMed PMID: 39857301; PMCID: PMC11761621.
39. Zhu X, Lee CW, Xu H, Wang YF, Yung PSH, Jiang Y, Lee OK. Phenotypic alteration of macrophages during osteoarthritis: a systematic review. Arthritis Res Ther. 2021;23(1):110. Epub 20210410. doi: 10.1186/s13075-021-02457-3. PubMed PMID: 33838669; PMCID: PMC8035781.
40. Wang W, Chu Y, Zhang P, Liang Z, Fan Z, Guo X, Zhou G, Ren W. Targeting macrophage polarization as a promising therapeutic strategy for the treatment of osteoarthritis. Int Immunopharmacol. 2023;116:109790. Epub 20230201. doi: 10.1016/j.intimp.2023.109790. PubMed PMID: 36736223.
41. Paulissen G, Malaise O, Deroyer C, Charlier E, Neuville S, Plener Z, Thirion T, Daniel C, Ribbens C, de Seny D. JAK inhibitors alleviate metabolic dysregulation, inflammation and fibrosis in osteoarthritis: insights from human joint cells and synovium. Rheumatology (Oxford). 2025;64(10):5539–50. doi: 10.1093/rheumatology/keaf298. PubMed PMID: 40459905.
42. Jimi E, Fei H, Nakatomi C. NF-kappaB Signaling Regulates Physiological and Pathological Chondrogenesis. Int J Mol Sci. 2019;20(24). Epub 20191212. doi: 10.3390/ijms20246275. PubMed PMID: 31842396; PMCID: PMC6941088.
43. Choi MC, Jo J, Park J, Kang HK, Park Y. NF-kappaB Signaling Pathways in Osteoarthritic Cartilage Destruction. Cells. 2019;8(7). Epub 20190717. doi: 10.3390/cells8070734. PubMed PMID: 31319599; PMCID: PMC6678954.
44. Shkhyan R, Flynn C, Lamoure E, Sarkar A, Van Handel B, Li J, York J, Banks N, Van der Horst R, Liu NQ, Lee S, Bajaj P, Vadivel K, Harn HI, Tassey J, Lozito T, Lieberman JR, Chuong CM, Hurtig MS, Evseenko D. Inhibition of a signaling modality within the gp130 receptor enhances tissue regeneration and mitigates osteoarthritis. Sci Transl Med. 2023;15(688):eabq2395. Epub 20230322. doi: 10.1126/scitranslmed.abq2395. PubMed PMID: 36947594; PMCID: PMC10792550.
45. Liao Y, Ren Y, Luo X, Mirando AJ, Long JT, Leinroth A, Ji RR, Hilton MJ. Interleukin-6 signaling mediates cartilage degradation and pain in posttraumatic osteoarthritis in a sex-specific manner. Sci Signal. 2022;15(744):eabn7082. Epub 20220726. doi: 10.1126/scisignal.abn7082. PubMed PMID: 35881692; PMCID: PMC9382892.
46. Tassey J, Lee Y, Sarkar A, Yang J, Lee S, Stevic U, Liu NQ, Lu J, Drake AC, Jabbour V, Vergel M, Maretti-Mira AC, Golden- Mason L, Lu R, Evseenko D. GP130 Y814 SIGNALING IS REQUIRED FOR THE DYNAMIN-MEDIATED ENDOCYTOSIS, MAPK/P38 ACTIVATION AND PERSISTENCE OF CHRONIC SYSTEMIC INFLAMMATION INDUCED BY HIGH FAT DIET. bioRxiv. 2026:2026.02.06.704505. doi: 10.64898/2026.02.06.704505.
47. JAK Inhibitor Dose TAPering Strategy Study (JAK-TAP) [Internet]. ClinicalTrials.gov 2024. Available from: https://clinicaltrials.gov/study/NCT06687551.
48. Evaluation of Intra-articular CX-011 to Treat Moderate to Severe Pain From Knee Osteoarthritis [Internet]. ClinicalTrials.gov 2025. Available from: https://clinicaltrials.gov/study/NCT07308834?intr=CX-011&rank=1&tab=study.
49. Schott EM, Farnsworth CW, Grier A, Lillis JA, Soniwala S, Dadourian GH, Bell RD, Doolittle ML, Villani DA, Awad H, Ketz JP, Kamal F, Ackert-Bicknell C, Ashton JM, Gill SR, Mooney RA, Zuscik MJ. Targeting the gut microbiome to treat the osteoarthritis of obesity. JCI Insight. 2018;3(8). Epub 20180419. doi: 10.1172/jci.insight.95997. PubMed PMID: 29669931; PMCID: PMC5931133.
50. Liu Y, Ding W, Wang HL, Dai LL, Zong WH, Wang YZ, Bi J, Han W, Dong GJ. Gut microbiota and obesity-associated osteoarthritis. Osteoarthritis Cartilage. 2019;27(9):1257–65. Epub 20190527. doi: 10.1016/j.joca.2019.05.009. PubMed PMID: 31146016.
51. Yang Y, Hao C, Jiao T, Yang Z, Li H, Zhang Y, Zhang W, Doherty M, Sun C, Yang T, Li J, Wu J, Zhang M, Wang Y, Xie D, Wang T, Wang N, Huang X, Li C, Gonzalez FJ, Wei J, Xie C, Zeng C, Lei G. Osteoarthritis treatment via the GLP-1-mediated gut-joint axis targets intestinal FXR signaling. Science. 2025;388(6742):eadt0548. Epub 20250404. doi: 10.1126/science.adt0548. PubMed PMID: 40179178.

52. Binvignat M, Sokol H, Mariotti-Ferrandiz E, Berenbaum F, Sellam J. Osteoarthritis and gut microbiome. Joint Bone Spine. 2021;88(5):105203. Epub 20210504. doi: 10.1016/j.jbspin.2021.105203. PubMed PMID: 33962035.
53. Mocanu V, Timofte DV, Zara-Danceanu CM, Labusca L. Obesity, Metabolic Syndrome, and Osteoarthritis Require Integrative Understanding and Management. Biomedicines. 2024;12(6). Epub 20240606. doi: 10.3390/biomedicines12061262. PubMed PMID: 38927469; PMCID: PMC11201254.
54. Liu X, Zheng Y, Li H, Ma Y, Cao R, Zheng Z, Tian Y, Du L, Zhang J, Zhang C, Gao J. The role of metabolites in the progression of osteoarthritis: Mechanisms and advances in therapy. J Orthop Translat. 2025;50:56–70. Epub 20250107. doi: 10.1016/j.jot.2024.10.003. PubMed PMID: 39868350; PMCID: PMC11762942.
55. Aziz A, Ganesan Nathan K, Kamarul T, Mobasheri A, Sharifi A. The interplay between dysregulated metabolites and signaling pathway alterations involved in osteoarthritis: a systematic review. Ther Adv Musculoskelet Dis. 2024;16:1759720X241299535. Epub 20241125. doi: 10.1177/1759720X241299535. PubMed PMID: 39600593; PMCID: PMC11590150.
56. Wang C, Fang L, Shi M, Niu X, Li T, Li X, Cho K, He Y, Liu S, Lu A, Xing X, Lukowski J, Goo YA, Speakman JR, Chen D, O'Keefe RJ, Patti GJ, Zuscik MJ, Zhang B, Shen J. NFIA regulates articular chondrocyte fatty acid metabolism and joint homeostasis. Sci Transl Med. 2025;17(809):eadm9488. Epub 20250730. doi: 10.1126/scitranslmed.adm9488. PubMed PMID: 40737429.
57. Pan F, Wang Y, Lim YZ, Urquhart DM, Estee MM, Wluka AE, Wolfe R, Cicuttini FM. Metformin for Knee Osteoarthritis in Patients With Overweight or Obesity: A Randomized Clinical Trial. JAMA. 2025;333(20):1804–12. doi: 10.1001/jama.2025.3471. PubMed PMID: 40274279; PMCID: PMC12022862.
58. Zhu H, Zhou L, Wang Q, Cai Q, Yang F, Jin H, Chen Y, Song Y, Zhang C. Glucagon-like peptide-1 receptor agonists as a disease-modifying therapy for knee osteoarthritis mediated by weight loss: findings from the Shanghai Osteoarthritis Cohort. Ann Rheum Dis. 2023;82(9):1218–26. Epub 20230531. doi: 10.1136/ard-2023-223845. PubMed PMID: 37258065; PMCID: PMC10423473.
59. Cheng J, Solomon T, Estee M, Cicuttini FM, Lim YZ. Effect of glucagon-like peptide-1 receptor agonists in osteoarthritis: A systematic review of pre-clinical and human studies. Osteoarthr Cartil Open. 2025;7(1):100567. Epub 20250128. doi: 10.1016/j.ocarto.2025.100567. PubMed PMID: 39995585; PMCID: PMC11849622.
60. Kuswanto W, Baker MC. Repurposing drugs for the treatment of osteoarthritis. Osteoarthritis Cartilage. 2024;32(8):886–95. Epub 20240529. doi: 10.1016/j.joca.2024.05.008. PubMed PMID: 38821468.
61. Meurot C, Martin C, Sudre L, Breton J, Bougault C, Rattenbach R, Bismuth K, Jacques C, Berenbaum F. Liraglutide, a glucagon-like peptide 1 receptor agonist, exerts analgesic, anti-inflammatory and anti-degradative actions in osteoarthritis. Sci Rep. 2022;12(1):1567. Epub 20220128. doi: 10.1038/s41598-022-05323-7. PubMed PMID: 35091584; PMCID: PMC8799666.
62. Berenbaum F. Beyond weight loss: GLP-1 emerges as a disease-modifying signal in osteoarthritis. Osteoarthritis Cartilage. 2025;33(8):918–20. Epub 20250620. doi: 10.1016/j.joca.2025.06.011. PubMed PMID: 40544946.
63. Chen L, Zhang Z, Liu X. Role and Mechanism of Mechanical Load in the Homeostasis of the Subchondral Bone in Knee Osteoarthritis: A Comprehensive Review. J Inflamm Res. 2024;17:9359–78. Epub 20241121. doi: 10.2147/JIR.S492415. PubMed PMID: 39600681; PMCID: PMC11590007.
64. Chang SH, Mori D, Kobayashi H, Mori Y, Nakamoto H, Okada K, Taniguchi Y, Sugita S, Yano F, Chung UI, Kim-Kaneyama JR, Yanagita M, Economides A, Canalis E, Chen D, Tanaka S, Saito T. Excessive mechanical loading promotes osteoarthritis through the gremlin-1-NF-kappaB pathway. Nat Commun. 2019;10(1):1442. Epub 20190329. doi: 10.1038/s41467-019-09491-5. PubMed PMID: 30926814; PMCID: PMC6441020.
65. Buckwalter JA, Anderson DD, Brown TD, Tochigi Y, Martin JA. The Roles of Mechanical Stresses in the Pathogenesis of Osteoarthritis: Implications for Treatment of Joint Injuries. Cartilage. 2013;4(4):286–94. doi: 10.1177/1947603513495889. PubMed PMID: 25067995; PMCID: PMC4109888.
66. Reyes C, Leyland KM, Peat G, Cooper C, Arden NK, Prieto-Alhambra D. Association Between Overweight and Obesity and Risk of Clinically Diagnosed Knee, Hip, and Hand Osteoarthritis: A Population-Based Cohort Study. Arthritis Rheumatol. 2016;68(8):1869–75. doi: 10.1002/art.39707. PubMed PMID: 27059260; PMCID: PMC4966641.
67. Chu IJH, Lim AYT, Ng CLW. Effects of meaningful weight loss beyond symptomatic relief in adults with knee osteoarthritis and obesity: a systematic review and meta-analysis. Obes Rev. 2018;19(11):1597–607. Epub 20180727. doi: 10.1111/obr.12726. PubMed PMID: 30051952.
68. Wallis JA, Webster KE, Levinger P, Taylor NF. What proportion of people with hip and knee osteoarthritis meet physical activity guidelines? A systematic review and meta-analysis. Osteoarthritis Cartilage. 2013;21(11):1648–59. Epub 20130812. doi: 10.1016/j.joca.2013.08.003. PubMed PMID: 23948979.
69. Verhagen AP, Ferreira M, Reijneveld-van de Vendel EAE, Teirlinck CH, Runhaar J, van Middelkoop M, Hermsen L, de Groot IB, Bierma-Zeinstra SMA. Do we need another trial on exercise in patients with knee osteoarthritis?: No new

trials on exercise in knee OA. Osteoarthritis Cartilage. 2019;27(9):1266–9. Epub 20190617. doi: 10.1016/j.joca.2019.04.020. PubMed PMID: 31220609.
70. Kitagawa T, Isaji Y, Sasaki D, Onishi K, Hayashi M, Okuyama W. Effectiveness of exercise therapy in patients with knee osteoarthritis: an overview of systematic reviews. BMJ Open. 2025;15(7):e093163. Epub 20250716. doi: 10.1136/bmjopen-2024-093163. PubMed PMID: 40669904; PMCID: PMC12273085.
71. Cicuttini FM, Proietto J, Lim YZ. Our biology working against us in obesity: A narrative review on implications for management of osteoarthritis. Osteoarthr Cartil Open. 2023;5(4):100407. Epub 20230909. doi: 10.1016/j.ocarto.2023.100407. PubMed PMID: 37744021; PMCID: PMC10514453.
72. Stanczak M, Swinnen B, Surmacz J, Bielenda B, Febbi M, Trybulski R, Hagner-Derengowska M. Knee Joint Response to Mechanical Loading: Bounding Mechanotransduction with Rehabilitation. Cell Physiol Biochem. 2025;59(5):666–729. doi: 10.33594/000000818. PubMed PMID: 41196605.
73. Lohberger B, Kaltenegger H, Weigl L, Mann A, Kullich W, Stuendl N, Leithner A, Steinecker-Frohnwieser B. Mechanical exposure and diacerein treatment modulates integrin-FAK-MAPKs mechanotransduction in human osteoarthritis chondrocytes. Cell Signal. 2019;56:23–30. Epub 20181221. doi: 10.1016/j.cellsig.2018.12.010. PubMed PMID: 30583016.
74. Lu M, Zhu M, Wu Z, Liu W, Cao C, Shi J. The role of YAP/TAZ on joint and arthritis. FASEB J. 2024;38(10):e23636. doi: 10.1096/fj.202302273RR. PubMed PMID: 38752683.
75. Wang N, Lu Y, Rothrauff BB, Zheng A, Lamb A, Yan Y, Lipa KE, Lei G, Lin H. Mechanotransduction pathways in articular chondrocytes and the emerging role of estrogen receptor-alpha. Bone Res. 2023;11(1):13. Epub 20230303. doi: 10.1038/s41413-023-00248-x. PubMed PMID: 36869045; PMCID: PMC9984452.
76. Nims R, Palmer DR, Kassab J, Zhang B, Guilak F. The chondrocyte "mechanome": Activation of the mechanosensitive ion channels TRPV4 and PIEZO1 drives unique transcriptional signatures. FASEB J. 2024;38(13):e23778. doi: 10.1096/fj.202400883R. PubMed PMID: 38959010; PMCID: PMC11327906.
77. Zhu Q, Yin F, Qin J, Shi W, Liu Y, Zhao Y, Wang J, Zhang L, Fan A, Cao D, Peng Q, Zhou B, Wang L, Zou W, Yue R. Procr(+) chondroprogenitors sense mechanical stimuli to govern articular cartilage maintenance and regeneration. Cell. 2025;188(19):5194–211 e16. Epub 20250721. doi: 10.1016/j.cell.2025.06.036. PubMed PMID: 40695281.
78. Lee W, Nims RJ, Savadipour A, Zhang Q, Leddy HA, Liu F, McNulty AL, Chen Y, Guilak F, Liedtke WB. Inflammatory signaling sensitizes Piezo1 mechanotransduction in articular chondrocytes as a pathogenic feed-forward mechanism in osteoarthritis. Proc Natl Acad Sci U S A. 2021;118(13). doi: 10.1073/pnas.2001611118. PubMed PMID: 33758095; PMCID: PMC8020656.
79. Wang S, Li W, Zhang P, Wang Z, Ma X, Liu C, Vasilev K, Zhang L, Zhou X, Liu L, Hayball J, Dong S, Li Y, Gao Y, Cheng L, Zhao Y. Mechanical overloading induces GPX4-regulated chondrocyte ferroptosis in osteoarthritis via Piezo1 channel facilitated calcium influx. J Adv Res. 2022;41:63–75. Epub 20220111. doi: 10.1016/j.jare.2022.01.004. PubMed PMID: 36328754; PMCID: PMC9637484.
80. Du J, Sun X, Ao L, Zhou X, Shi H, Yong Q, Zhang X, Guan T. Impact of Abnormal Mechanical Stress on Chondrocyte Death in Osteoarthritis. Med Sci Monit. 2025;31:e948290. Epub 20250610. doi: 10.12659/MSM.948290. PubMed PMID: 40493524; PMCID: PMC12166663.
81. Zhang H, Shao Y, Yao Z, Liu L, Zhang H, Yin J, Xie H, Li K, Lai P, Zeng H, Xiao G, Zeng C, Cai D, Bai X. Mechanical overloading promotes chondrocyte senescence and osteoarthritis development through downregulating FBXW7. Ann Rheum Dis. 2022;81(5):676–86. Epub 20220120. doi: 10.1136/annrheumdis-2021-221513. PubMed PMID: 35058228.
82. Shao Y, Zhang H, Guan H, Wu C, Qi W, Yang L, Yin J, Zhang H, Liu L, Lu Y, Zhao Y, Zhang S, Zeng C, Wang G, Bai X, Cai D. PDZK1 protects against mechanical overload-induced chondrocyte senescence and osteoarthritis by targeting mitochondrial function. Bone Res. 2024;12(1):41. Epub 20240717. doi: 10.1038/s41413-024-00344-6. PubMed PMID: 39019845; PMCID: PMC11255281.
83. Koike M, Nojiri H, Ozawa Y, Watanabe K, Muramatsu Y, Kaneko H, Morikawa D, Kobayashi K, Saita Y, Sasho T, Shirasawa T, Yokote K, Kaneko K, Shimizu T. Mechanical overloading causes mitochondrial superoxide and SOD2 imbalance in chondrocytes resulting in cartilage degeneration. Sci Rep. 2015;5:11722. Epub 20150625. doi: 10.1038/srep11722. PubMed PMID: 26108578; PMCID: PMC4480010.
84. Jiang W, Liu H, Wan R, Wu Y, Shi Z, Huang W. Mechanisms linking mitochondrial mechanotransduction and chondrocyte biology in the pathogenesis of osteoarthritis. Ageing Res Rev. 2021;67:101315. Epub 20210305. doi: 10.1016/j.arr.2021.101315. PubMed PMID: 33684550.
85. Miller RE, Miller RJ, Malfait AM. Osteoarthritis joint pain: the cytokine connection. Cytokine. 2014;70(2):185–93. Epub 20140724. doi: 10.1016/j.cyto.2014.06.019. PubMed PMID: 25066335; PMCID: PMC4254338.

86. Miller RE, Ishihara S, Tran PB, Golub SB, Last K, Miller RJ, Fosang AJ, Malfait AM. An aggrecan fragment drives osteoarthritis pain through Toll-like receptor 2. JCI Insight. 2018;3(6). Epub 20180322. doi: 10.1172/jci.insight.95704. PubMed PMID: 29563338; PMCID: PMC5926921.
87. Denk F, Bennett DL, McMahon SB. Nerve Growth Factor and Pain Mechanisms. Annu Rev Neurosci. 2017;40:307–25. Epub 20170424. doi: 10.1146/annurev-neuro-072116-031121. PubMed PMID: 28441116.
88. Wise BL, Seidel MF, Lane NE. The evolution of nerve growth factor inhibition in clinical medicine. Nat Rev Rheumatol. 2021;17(1):34–46. Epub 20201120. doi: 10.1038/s41584-020-00528-4. PubMed PMID: 33219344.
89. Mobasheri A, Rannou F, Ivanavicius S, Conaghan PG. Targeting the TRPV1 pain pathway in osteoarthritis of the knee. Expert Opin Ther Targets. 2024;28(10):843–56. Epub 20241025. doi: 10.1080/14728222.2024.2416961. PubMed PMID: 39450875.
90. Zhou R, Hu W, Waxman SG, Liu CJ. Ion channels as therapeutic targets in osteoarthritis. Trends Pharmacol Sci. 2025;46(8):792–813. Epub 20250710. doi: 10.1016/j.tips.2025.06.003. PubMed PMID: 40645849.
91. Obeidat AM, Wood MJ, Adamczyk NS, Ishihara S, Li J, Wang L, Ren D, Bennett DA, Miller RJ, Malfait AM, Miller RE. Piezo2 expressing nociceptors mediate mechanical sensitization in experimental osteoarthritis. Nat Commun. 2023;14(1):2479. Epub 20230429. doi: 10.1038/s41467-023-38241-x. PubMed PMID: 37120427; PMCID: PMC10148822.
92. Suri S, Gill SE, Massena de Camin S, Wilson D, McWilliams DF, Walsh DA. Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. Ann Rheum Dis. 2007;66(11):1423–8. Epub 20070419. doi: 10.1136/ard.2006.063354. PubMed PMID: 17446239; PMCID: PMC2111605.
93. Aso K, Shahtaheri SM, Hill R, Wilson D, McWilliams DF, Nwosu LN, Chapman V, Walsh DA. Contribution of nerves within osteochondral channels to osteoarthritis knee pain in humans and rats. Osteoarthritis Cartilage. 2020;28(9):1245–54. Epub 20200526. doi: 10.1016/j.joca.2020.05.010. PubMed PMID: 32470596.
94. Obeidat AM, Miller RE, Miller RJ, Malfait AM. The nociceptive innervation of the normal and osteoarthritic mouse knee. Osteoarthritis Cartilage. 2019;27(11):1669–79. Epub 20190725. doi: 10.1016/j.joca.2019.07.012. PubMed PMID: 31351964; PMCID: PMC7020657.
95. Zhu S, Zhu J, Zhen G, Hu Y, An S, Li Y, Zheng Q, Chen Z, Yang Y, Wan M, Skolasky RL, Cao Y, Wu T, Gao B, Yang M, Gao M, Kuliwaba J, Ni S, Wang L, Wu C, Findlay D, Eltzschig HK, Ouyang HW, Crane J, Zhou FQ, Guan Y, Dong X, Cao X. Subchondral bone osteoclasts induce sensory innervation and osteoarthritis pain. J Clin Invest. 2019;129(3):1076–93. Epub 20190204. doi: 10.1172/JCI121561. PubMed PMID: 30530994; PMCID: PMC6391093.
96. Blackler G, Lai-Zhao Y, Klapak J, Philpott HT, Pitchers KK, Maher AR, Fiset B, Walsh LA, Gillies ER, Appleton CT. Targeting STAT6-mediated synovial macrophage activation improves pain in experimental knee osteoarthritis. Arthritis Res Ther. 2024;26(1):73. Epub 20240320. doi: 10.1186/s13075-024-03309-6. PubMed PMID: 38509602; PMCID: PMC10953260.
97. Kraus VB, McDaniel G, Huebner JL, Stabler TV, Pieper CF, Shipes SW, Petry NA, Low PS, Shen J, McNearney TA, Mitchell P. Direct in vivo evidence of activated macrophages in human osteoarthritis. Osteoarthritis Cartilage. 2016;24(9):1613–21. Epub 20160412. doi: 10.1016/j.joca.2016.04.010. PubMed PMID: 27084348; PMCID: PMC4992586.
98. Moulin D, Sellam J, Berenbaum F, Guicheux J, Boutet MA. The role of the immune system in osteoarthritis: mechanisms, challenges and future directions. Nat Rev Rheumatol. 2025;21(4):221–36. Epub 20250313. doi: 10.1038/s41584-025-01223-y. PubMed PMID: 40082724.
99. Geraghty T, Winter DR, Miller RJ, Miller RE, Malfait AM. Neuroimmune interactions and osteoarthritis pain: focus on macrophages. Pain Rep. 2021;6(1):e892. Epub 20210309. doi: 10.1097/PR9.0000000000000892. PubMed PMID: 33981927; PMCID: PMC8108586.
100. Raoof R, Martin Gil C, Lafeber F, de Visser H, Prado J, Versteeg S, Pascha MN, Heinemans ALP, Adolfs Y, Pasterkamp J, Wood JN, Mastbergen SC, Eijkelkamp N. Dorsal Root Ganglia Macrophages Maintain Osteoarthritis Pain. J Neurosci. 2021;41(39):8249–61. Epub 20210816. doi: 10.1523/JNEUROSCI.1787-20.2021. PubMed PMID: 34400519; PMCID: PMC8482866.