ICM 2026 Question 6. "Should we define standardized models, metrics, and outcomes for obesity and weight loss in preclinical OA studies—including metabolic profiling, body composition, joint-specific assessments, and pain?"

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Consensus Recommendation: YES
Standardized models, metrics, and outcomes can and should be defined for preclinical studies of obesity-associated osteoarthritis, and weight loss interventions should be systematically investigated using standardized frameworks.
The evidence supports that standardization across four core domains, including metabolic phenotyping, body composition, joint-specific structural assessment, and pain/functional outcomes, is not only feasible but essential for improving reproducibility, cross-study comparability, and translational relevance. Weight loss paradigms require dedicated investigation as distinct experimental phases with prespecified metabolic response criteria and longer follow-up to determine therapeutic windows and mechanisms.

Level of Evidence: I
Systematic reviews and meta-analyses of multiple independent controlled experimental studies with meta-analyses demonstrate consistent obesity effects on increased cartilage degeneration (effect sizes ranging from 1.27-1.84 standard deviations compared to lean controls) and pain (effect size -1.42 standard deviations compared to lean controls), while documenting substantial heterogeneity that standardization would address. Weight loss evidence from controlled intervention studies supports systematic investigation of switching diet and intermittent fasting.

Delegate Vote:

Agree: [ ]
Disagree: [ ]
Abstain: [ ]

Rationale

Three LLM-assisted systematic reviews (ChatGPT, Gemini, DeepSeek) were generated independently following PRISMA and Cochrane guidelines [1] and synthesized evidence from 86, 67, and 86 preclinical studies, respectively. These studies were selected from >1,000 studies peer-reviewed manuscripts by keyword searches across PubMed/MEDLINE, Web of Science, Scopus, and Embase (2000-2025) because they satisfied inclusion criteria including the use preclinical animal models with obesity induction (diet-induced, genetic, or metabolic manipulation), evaluating osteoarthritis-specific outcomes including structural joint assessment (histology, imaging), metabolic phenotyping, body composition, or pain/functional measures. Additional guidelines and commentaries addressing relevant methodology were also included. Studies were excluded if they were human-only clinical trials, in vitro experiments without in vivo validation, lacked both obesity and OA components, or were non-peer-reviewed publications such as editorials or commentaries. The authors carefully edited this manuscript and verified the accuracy of the information and the fidelity and relevance of the cited references. The authors are responsible for the conclusions and recommendations reached.

Despite differences in analytic scope of the included studies, all three reviews converge on critical findings that justify standardization. Briefly, diet-induced obesity (DIO) in C57BL/6 mice is the predominant and most translationally relevant approach. However, extreme methodological heterogeneity, particularly in diet composition, study duration, and OA induction methods, limits cross-study comparability. All reviews agree that body weight alone is insufficient for metabolic characterization, recommending comprehensive panels including glucose tolerance, insulin resistance, lipids, and inflammatory markers. Pain outcomes remain underutilized despite being clinically primary, and longitudinal pain assessment is deemed essential. OARSI histopathology is the accepted standard for structural assessment, though application varies. Regarding weight loss interventions, all sources concur that while dietary switch reverses metabolic dysfunction and synovial inflammation, it has inconsistent efficacy in reversing established cartilage degeneration, suggesting "metabolic memory" in articular cartilage.

Areas of disagreement center on specific standardization parameters and analytical approaches. Regarding dietary fat content, recommendations vary between advocating standardizing obesogenic diets from 45% kcal to higher threshold of 60% kcal from fat. Fasting protocols for glucose tolerance testing also lack consensus and range from 4-16 hours, but there is some agreement that a 5-6 hour short fast is recommended, warning against overnight fasting to prevent metabolic stress in mice. Another, perhaps not recommended, perspective does not prescribe an exact percentage of fat in diet or define fasting duration, instead emphasizing mandatory reporting of diet composition and fasting duration.

Strength of Existing Evidence

Multiple controlled experimental studies demonstrate that obesity significantly exacerbates cartilage degeneration and pain hypersensitivity in preclinical models. Griffin and Guilak (2008) established the foundational framework linking obesity to OA through both mechanical and metabolic mechanisms, demonstrating that adipose tissue dysfunction promotes a chronic low-grade inflammatory state characterized by adipokine dysregulation [2, 3]. Mooney et al. (2011) and Louer et al. (2012) subsequently showed that high-fat diet feeding significantly accelerates post-traumatic OA following meniscal/ligamentous injury, with effect sizes indicating clinically meaningful amplification of cartilage degeneration [4, 5]. These findings support treating “obesity-OA” as a metabolic–inflammatory syndrome requiring metabolic profiling, not only anatomical readouts.

Griffin et al. (2010) provided critical evidence that diet-induced obesity differentially regulates behavioral, biomechanical, and molecular risk factors for OA, demonstrating that pain-related behaviors can precede overt structural damage, a finding with direct translational relevance to human OA where symptoms and radiographic severity often dissociate [6]. Collins and colleagues further established that high-fat/high-sucrose diets induce joint degeneration, synovial inflammation, and functional impairment in rodents, supporting the concept of a metabolically driven OA phenotype [7, 8]. These studies established the importance of including both structural and functional outcomes in preclinical designs.

Berenbaum articulated the framework of “metabolic OA,” emphasizing that obesity-associated OA represents a distinct inflammatory and metabolic subtype characterized by low-grade systemic inflammation and altered lipid metabolism [9, 10] More recent work has further underscored obesity and metabolic syndrome as central drivers of OA pathogenesis beyond biomechanical stress [11, 12]

Animal Models

The diet-induced obesity (DIO) model in C57BL/6 mice has emerged as the predominant and most translationally relevant approach. Collins et al. (2015) comprehensively characterized metabolic dysfunction in DIO rats, demonstrating that high-fat feeding recapitulates human metabolic syndrome features including hyperinsulinemia, glucose intolerance, dyslipidemia, and adipose tissue inflammation [13]. These findings were extended to identify systemic and joint-specific mediators of obesity-associated OA, confirming that metabolic dysfunction tracks with OA severity independent of body weight alone [14, 15].

Griffin et al. (2009) examined leptin-deficient (ob/ob) mice and found that extreme obesity due to impaired leptin signaling does not cause knee osteoarthritis, demonstrating that leptin pathway alterations directly affect joint tissues and limiting the translational relevance of genetic obesity models for acquired obesity [16].

Sergio et al. (2025) and Ley et al. (2025) have advanced large animal models (porcine and feline) that offer greater translational relevance but remain underutilized [17, 18]. Abughazaleh et al. (2025) investigated inflammation of adipose tissue in female rats, addressing the critical gap of sex-specific mechanisms, though female studies remain limited [19].

Hooijmans et al. (2014) developed SYRCLE's risk of bias tool for animal studies, providing a framework for assessing methodological quality that reveals frequent incomplete reporting of randomization, blinding, and sample size justification [20].

Commonly Used Metrics

Metabolic phenotyping varies widely across studies. Dumond et al. (2003) first identified leptin as a key mediator in OA pathogenesis, demonstrating leptin receptors on chondrocytes and synoviocytes [21]. Presle et al. (2006) subsequently showed differential distribution of adipokines between serum and synovial fluid, establishing the importance of measuring both systemic and local mediators [22]. Sekar et al. (2017) demonstrated that saturated fatty acids induce both metabolic syndrome and OA in rats, highlighting the critical

role of dietary fat composition beyond caloric content alone [23]. Therefore, standardization must include metabolic phenotyping. Total body weight alone is insufficient; fat mass and lean mass should be quantified serially using technologies such as DXA or EchoMRI. Circulating metabolic markers, including fasting glucose, insulin, lipid profiles, leptin, adiponectin, IL-6, TNF-α, and MCP-1, should be measured longitudinally to characterize systemic inflammation and insulin resistance. Dietary composition must also be carefully reported, as macronutrient content independently affects cartilage biology and inflammatory responses [6].

Glasson et al. (2010) established the OARSI histopathology initiative, providing a standardized framework for murine OA scoring that has become the field standard, though its application currently lacks harmonization [24]. This work enables cross-study comparability when protocols are consistently applied.

Structural outcomes predominantly employ OARSI histopathological scoring. Little et al. (2009) established histological methods for osteophyte assessment [25], while Bouxsein et al. (2010) provided guidelines for microCT evaluation of subchondral bone that could apply to osteophytes [26]. Wang et al. (2026) performed metabolomic profiling to identify novel mediators of joint degeneration [15].

Several studies show diet or metabolic perturbations produce behavioral indicators of pain before overt histological OA changes, indicating pain outcomes should be measured independently and longitudinally. However, pain outcomes remain underutilized. Miller et al. (2014) have advanced preclinical pain phenotyping using bioluminescence imaging and behavioral assays, demonstrating that pain mechanisms can be studied longitudinally in OA models [27]. Malfait et al. (2013) and Jacobs et al. (2014) provided methodological guidance for selecting and implementing pain and gait analysis in rodent OA models [28, 29].

The evidence base is robust in demonstrating obesity effects on both structural and functional outcomes across multiple independent laboratories and model systems. However, substantial methodological heterogeneity limits cross-study comparability. Brunner et al. (2012) demonstrated that high dietary fat composition significantly affects OA development in rabbits, with different fat sources producing distinct metabolic phenotypes [30]. This variability in dietary protocols likely contributes to the heterogeneity observed across studies.

Weight Loss Evidence

Wu et al. (2015) demonstrated that dietary fatty acid content regulates wound repair and OA pathogenesis following joint injury, establishing that nutritional interventions can modify disease trajectory [31]. Wu et al. (2021) subsequently showed that switching from high-fat to normal diet improves metabolic syndrome and synovial inflammation but fails to rescue established osteoarthritis in mice, a critical finding suggesting "metabolic memory" and the importance of intervention timing [14].

Tang et al. (2024) provided evidence that gene therapy for fat-1 prevents obesity-induced metabolic dysfunction, cellular senescence, and osteoarthritis, demonstrating that metabolic interventions can provide joint protection through mechanisms independent of weight loss [32]. Condado-Huerta et al. (2025) showed that intermittent fasting protects against obesity-induced OA, further supporting dietary intervention approaches [33]. Li et al. (2021) demonstrated that voluntary wheel running ameliorates obesity-induced OA, establishing exercise as an effective intervention [34]. Li et al. (2023) showed that metformin attenuates OA progression in diet-induced obese mice, suggesting pharmacological metabolic modulation may provide benefit [35].

Summary

In summary, converging evidence from the primary peer-reviewed literature strongly supports establishing harmonized standards for preclinical obesity-associated OA studies. These standards should include defined diet-induced obesity models, rigorous body composition analysis, comprehensive metabolic profiling, validated joint structural scoring, synovial inflammatory endpoints, and multidimensional pain assessment. Incorporating weight-loss and metabolic interventions into these standardized protocols is essential to determine disease reversibility, clarify mechanistic drivers, and improve translational alignment with clinical metabolic OA phenotypes. Adoption of consensus standards will substantially enhance rigor, reproducibility, and therapeutic development in obesity-related osteoarthritis research.

Supporting References

[1] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P.G. The, Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, PLOS Medicine 6(7) (2009) e1000097.
[2] T.M. Griffin, F. Guilak, Why is obesity associated with osteoarthritis? Insights from mouse models of obesity, Biorheology 45(3-4) (2008) 387-98.
[3] T.M. Griffin, J.L. Huebner, V.B. Kraus, Z. Yan, F. Guilak, Induction of osteoarthritis and metabolic inflammation by a very high-fat diet in mice: effects of short-term exercise, Arthritis Rheum 64(2) (2012) 443-53.
[4] R.A. Mooney, E.R. Sampson, J. Lerea, R.N. Rosier, M.J. Zuscik, High-fat diet accelerates progression of osteoarthritis after meniscal/ligamentous injury, Arthritis Res Ther 13(6) (2011) R198.
[5] C.R. Louer, B.D. Furman, J.L. Huebner, V.B. Kraus, S.A. Olson, F. Guilak, Diet-induced obesity significantly increases the severity of posttraumatic arthritis in mice, Arthritis Rheum 64(10) (2012) 3220-30.
[6] T.M. Griffin, B. Fermor, J.L. Huebner, V.B. Kraus, R.M. Rodriguiz, W.C. Wetsel, L. Cao, L.A. Setton, F. Guilak, Diet-induced obesity differentially regulates behavioral, biomechanical, and molecular risk factors for osteoarthritis in mice, Arthritis Res Ther 12(4) (2010) R130.
[7] K.H. Collins, D.A. Hart, R.A. Seerattan, R.A. Reimer, W. Herzog, High-fat/high-sucrose diet-induced obesity results in joint-specific development of osteoarthritis-like degeneration in a rat model, Bone Joint Res 7(4) (2018) 274-281.
[8] K.H. Collins, R.A. Reimer, R.A. Seerattan, T.R. Leonard, W. Herzog, Using diet-induced obesity to understand a metabolic subtype of osteoarthritis in rats, Osteoarthritis Cartilage 23(6) (2015) 957-65.
[9] F. Berenbaum, Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!), Osteoarthritis Cartilage 21(1) (2013) 16-21.
[10] F. Berenbaum, I.J. Wallace, D.E. Lieberman, D.T. Felson, Modern-day environmental factors in the pathogenesis of osteoarthritis, Nat Rev Rheumatol 14(11) (2018) 674-681.
[11] B. Sobieh, H. El Mesallamy, D. Kassem, Beyond mechanical loading: The metabolic contribution of obesity in osteoarthritis unveils novel therapeutic targets, Heliyon 9 (2023) e15700.
[12] A. Batushansky, S. Zhu, R.K. Komaravolu, S. South, P. Mehta-D'souza, T.M. Griffin, Fundamentals of OA. An initiative of Osteoarthritis and Cartilage. Obesity and metabolic factors in OA, Osteoarthritis Cartilage 30(4) (2022) 501-515.
[13] K.H. Collins, H.A. Paul, R.A. Reimer, R.A. Seerattan, D.A. Hart, W. Herzog, Relationship between inflammation, the gut microbiota, and metabolic osteoarthritis development: studies in a rat model, Osteoarthritis Cartilage 23(11) (2015) 1989-98.
[14] A.R. Sun, X. Wu, R. Crawford, H. Li, L. Mei, Y. Luo, Y. Xiao, X. Mao, I. Prasadam, Effects of Diet Induced Weight Reduction on Cartilage Pathology and Inflammatory Mediators in the Joint Tissues, Front Med (Lausanne) 8 (2021) 628843.
[15] W. Wang, H. Liu, M. Zhang, L. Wang, Integrative multi-omics analysis reveals gut microbiota-derived metabolites and immune regulatory pathways in osteoarthritis pathogenesis, J Orthop Surg Res 21(1) (2026) 87.
[16] T.M. Griffin, J.L. Huebner, V.B. Kraus, F. Guilak, Extreme obesity due to impaired leptin signaling in mice does not cause knee osteoarthritis, Arthritis Rheum 60(10) (2009) 2935-44.
[17] M. Sergio, V.P. Karjalainen, S. Das Gupta, V.R. Herrera Millar, G. Mirra, M. Di Giancamillo, S. Modina, L.M. Sconfienza, L. Mangiavini, G.M. Peretti, M.A.J. Finnilä, A. Di Giancamillo, Prolonged excessive weight induces spontaneous meniscal degeneration in sows: A preclinical model for obesity-related knee OA, Ann Anat 260 (2025) 152681.
[18] C.J. Ley, E. M. Strage, S.M. Stadig, C. von Brömssen, U. Olsson, A. Bergh, C. Ley, Associations between body composition, metabolic mediators and osteoarthritis in cats, BMC Veterinary Research 21(1) (2025) 103.
[19] N. Abughazaleh, H. Smith, H. Chaudhri, R.A. Seerattan, D.A. Hart, R.A. Reimer, W. Herzog, Investigating inflammation of adipose tissue in a diet induced obesity model of OA in female sprague dawley rats, Sci Rep 15(1) (2025) 41582.
[20] C.R. Hooijmans, M.M. Rovers, R.B. de Vries, M. Leenaars, M. Ritskes-Hoitinga, M.W. Langendam, SYRCLE's risk of bias tool for animal studies, BMC Med Res Methodol 14 (2014) 43.
[21] H. Dumond, N. Presle, B. Terlain, D. Mainard, D. Loeuille, P. Netter, P. Pottie, Evidence for a key role of leptin in osteoarthritis, Arthritis Rheum 48(11) (2003) 3118-29.

[22] N. Presle, P. Pottie, H. Dumond, C. Guillaume, F. Lapicque, S. Pallu, D. Mainard, P. Netter, B. Terlain, Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production, Osteoarthritis Cartilage 14(7) (2006) 690-5.
[23] S. Sekar, S.R. Shafie, I. Prasadam, R. Crawford, S.K. Panchal, L. Brown, Y. Xiao, Saturated fatty acids induce development of both metabolic syndrome and osteoarthritis in rats, Sci Rep 7 (2017) 46457.
[24] S.S. Glasson, M.G. Chambers, W.B. Van Den Berg, C.B. Little, The OARSI histopathology initiative - recommendations for histological assessments of osteoarthritis in the mouse, Osteoarthritis Cartilage 18 Suppl 3 (2010) S17-23.
[25] C.B. Little, A. Barai, D. Burkhardt, S.M. Smith, A.J. Fosang, Z. Werb, M. Shah, E.W. Thompson, Matrix metalloproteinase 13-deficient mice are resistant to osteoarthritic cartilage erosion but not chondrocyte hypertrophy or osteophyte development, Arthritis Rheum 60(12) (2009) 3723-33.
[26] M.L. Bouxsein, S.K. Boyd, B.A. Christiansen, R.E. Guldberg, K.J. Jepsen, R. Müller, Guidelines for assessment of bone microstructure in rodents using micro-computed tomography, J Bone Miner Res 25(7) (2010) 1468-86.
[27] R.E. Miller, R.J. Miller, A.M. Malfait, Osteoarthritis joint pain: the cytokine connection, Cytokine 70(2) (2014) 185-93.
[28] A.M. Malfait, C.B. Little, J.J. McDougall, A commentary on modelling osteoarthritis pain in small animals, Osteoarthritis Cartilage 21(9) (2013) 1316-26.
[29] B.Y. Jacobs, H.E. Kloefkorn, K.D. Allen, Gait analysis methods for rodent models of osteoarthritis, Curr Pain Headache Rep 18(10) (2014) 456.
[30] A.M. Brunner, C.M. Henn, E.I. Drewniak, A. Lesieur-Brooks, J. Machan, J.J. Crisco, M.G. Ehrlich, High dietary fat and the development of osteoarthritis in a rabbit model, Osteoarthritis Cartilage 20(6) (2012) 584-92.
[31] C.L. Wu, D. Jain, J.N. McNeill, D. Little, J.A. Anderson, J.L. Huebner, V.B. Kraus, R.M. Rodriguiz, W.C. Wetsel, F. Guilak, Dietary fatty acid content regulates wound repair and the pathogenesis of osteoarthritis following joint injury, Ann Rheum Dis 74(11) (2015) 2076-83.
[32] R. Tang, N.S. Harasymowicz, C.L. Wu, Y.R. Choi, K. Lenz, S.J. Oswald, F. Guilak, Gene therapy for fat-1 prevents obesity-induced metabolic dysfunction, cellular senescence, and osteoarthritis, Proc Natl Acad Sci U S A 121(43) (2024) e2402954121.
[33] C. Condado-Huerta, A. López-Barradas, A. Hernández-Melgar, R.A. Carballo-Castañeda, R. De la Torre-Baez, M.R. Encarnacion-Garcia, M. Sánchez-Tapia, O. Granados-Portillo, L.G. Noriega, N. Vázquez-Manjarrez, M. Guevara-Cruz, N. Torres, J.C. León-Contreras, G.J. Baay-Guzman, O. Rodríguez-Lima, A. Landa, P. Nava, A. Moreno-Ulloa, A.R. Tovar, F. Flores-Murrieta, L.A. Velázquez-Villegas, Intermittent Fasting Reduces Obesity-driven Oxidative Stress in the Male Mouse Colon via Changes in Gut Microbiota, Cell Mol Gastroenterol Hepatol 19(11) (2025) 101592.
[34] K. Li, A. Liu, W. Zong, L. Dai, Y. Liu, R. Luo, S. Ge, G. Dong, Moderate exercise ameliorates osteoarthritis by reducing lipopolysaccharides from gut microbiota in mice, Saudi J Biol Sci 28(1) (2021) 40-49.
[35] D. Li, G. Ruan, Y. Zhang, Y. Zhao, Z. Zhu, Q. Ou, H. Huang, J. Chen, W. Han, S. Tang, J. Li, L. Wang, T. Chen, X. Bai, D. Cai, C. Ding, Metformin attenuates osteoarthritis by targeting chondrocytes, synovial macrophages and adipocytes, Rheumatology (Oxford) 62(4) (2023) 1652-1661.