

Precision Medicine in Osteoarthritis: A Paradigm Shift toward Phenotype-Driven Targeted Interventions

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Received: 3 April 2026; Accepted: 28 April 2026; Published: 24 May 2026

Abstract:

Background: Osteoarthritis (OA) is traditionally viewed as a biomechanical “wear-and-tear” disease, leading to a monolithic treatment approach that has largely failed in disease-modifying osteoarthritis drug (DMOAD) clinical trials. This archaic, cartilage-centric perspective has significantly hindered the evolution of targeted therapeutics by systematically ignoring the profoundly complex, multifaceted metabolic, genetic, and immunological drivers that continuously interact within the whole-joint ecosystem. The repeated failure of broad-spectrum interventions underscores the urgent need for a more granular understanding of OA pathophysiology. **Objective:** This review highlights the paradigm shift from a joint-centric mechanical model to a precision medicine framework driven by distinct OA phenotypes, aiming to provide a comprehensive roadmap for future clinical trial designs and individualized patient management. This archaic, cartilage-centric perspective has significantly hindered the evolution of targeted therapeutics by systematically ignoring the profoundly complex, multifaceted metabolic, genetic, and immunological drivers that continuously interact within the whole-joint ecosystem. The repeated failure of broad-spectrum interventions underscores the urgent need for a more granular understanding of OA pathophysiology. **Methods:** We systematically distilled a large corpus of recent literature (3,000+ initial records) down to four high-resolution phenotypic subsets. By employing advanced data parsing and algorithmic filtering, we pinpointed the 30 most impactful studies mapping specific biomarkers to targeted molecular interventions. **Results:** Each phenotype presents unique biomarkers and targetable pathways. The metabolic phenotype is heavily influenced by systemic adipokines and meta-inflammation, with GLP-1 receptor agonists showing dual efficacy in both systemic weight reduction and localized chondroprotection. The inflammatory endotype, characterized by synovitis, benefits from targeted anti-cytokine therapies like IL-1 β inhibitors when properly stratified using high-sensitivity C-reactive protein (hs-CRP) thresholds and advanced imaging. The subchondral bone-driven phenotype highlights the Wnt/ β -catenin pathway and bone marrow lesions (BMLs), with lorecivivint demonstrating Phase III promise. Finally, the senescence-driven phenotype introduces “inflammaging” and the senescence-associated secretory phenotype (SASP), which are targetable by emerging senolytics. **Conclusion:** Transitioning from subjective clinical phenotyping to objective, multi-omic endotyping and AI-assisted patient stratification will bypass the historical “dilution effect” in trials, paving the way for personalized OA therapeutics and significantly improving the long-term prognosis of patients suffering from structural joint decay.

Keywords:

Osteoarthritis, Precision Medicine, Phenotypes, Disease-Modifying Osteoarthritis Drugs (DMOADs), Multi-omics, Senolytics

1. Introduction

Osteoarthritis (OA) remains a leading cause of chronic disability worldwide, imposing a staggering socioeconomic burden on global healthcare systems. Recent epidemiological models estimate that over 500 million individuals globally currently suffer from symptomatic OA, a figure projected to escalate dramatically due to the dual demographic pressures of rapidly aging populations and the global obesity epidemic. The indirect costs associated with lost productivity, coupled with the direct medical expenditures of joint replacement surgeries and chronic pain management, have elevated OA from a localized orthopedic issue to a paramount global public health crisis.

For decades, OA has been simplistically conceptualized as an inevitable, age-related “wear-and-tear” disease centered solely on the mechanical degradation of articular cartilage. This monolithic view has heavily constrained therapeutic development, restricting the clinical arsenal primarily to palliative care, such as non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroids. Despite extensive financial and academic investment, the development of disease-modifying osteoarthritis drugs (DMOADs) has faced a notorious string of failures in late-stage clinical trials [1,2,3].

A critical retrospective appraisal reveals that these structural failures were not necessarily due to ineffective molecular targets, but rather a profound methodological flaw: the “dilution effect” [3,4]. By enrolling highly heterogeneous, undifferentiated patient populations into broad-spectrum clinical trials, the therapeutic efficacy of targeted agents in specific responsive sub-cohorts was completely masked. For instance, an agent designed to inhibit bone resorption would inevitably fail to demonstrate statistical significance if administered to a patient whose primary pathology is synovitis rather than subchondral sclerosis.

To break this clinical impasse, the field must undergo a radical paradigm shift toward precision medicine, recognizing OA as a heterogeneous organ-level disease consisting of distinct molecular and clinical phenotypes [4,5,6]. This heterogeneous nature necessitates an intra-organ classification framework that incorporates genetic predisposition, environmental influences, and mechanical triggers. Historically, reliance on a singular structural end-point, such as joint space narrowing (JSN) on plain radiographs, has failed to capture the highly dynamic molecular changes within the joint ecosystem. Consequently, redefining therapeutic success by matching stratified patient cohorts to mechanistically tailored compounds represents the only viable path forward to rescue promising DMOAD candidates from clinical termination.

2. Methodology: From Literature Search to Evidence Synthesis

To ensure a highly rigorous, phenotype-driven selection of evidence, this review utilized a systematic “funnel” approach to identify and curate the most impactful recent literature (primarily focusing on the years 2023–2026). The detailed workflow,

illustrated in Figure 1, proceeded through four distinct stages: Broad Evidence Pool Generation, Algorithmic Refinement & Stratification, Critical Appraisal & Core Selection, and Narrative Synthesis.

During Stage 1, comprehensive multi-database electronic searches were initiated across PubMed, Embase, and the Cochrane Library. To ensure reproducibility, advanced Boolean search strings were deployed: (Osteoarthritis[Mesh] OR “osteoarthritis”) AND (“precision medicine” OR “phenotype” OR “endotype” OR “stratification”) AND (“DMOAD” OR “targeted therapy”). This initial sweeping phase intentionally favored inclusivity to establish a broad overview of the structural landscape. We further manually cross-referenced the bibliographies of major international rheumatology consensus guidelines (such as OARSI and EULAR recommendations) to guarantee that no seminal phenotypic classification frameworks were inadvertently omitted during the automated database queries. In Stage 2, candidate references were subjected to algorithmic text-mining and natural language processing filters to classify papers into specialized sub-phenotypic conceptual categories. Stage 3 applied strict quality appraisal checklists, prioritizing double-blind randomized controlled trials (RCTs), prospective cohort assessments, and multi-omic preclinical datasets. Papers with a high risk of bias, insufficient sample sizes, or poorly defined clinical endpoints were systematically eliminated.

Crucially, the extracted molecular mechanisms, diagnostic biomarkers, and targeted clinical outcomes from these select studies were integrated and synthesized into a comprehensive multi-phenotype therapeutic framework, which is systematically compiled and summarized in Table 1.

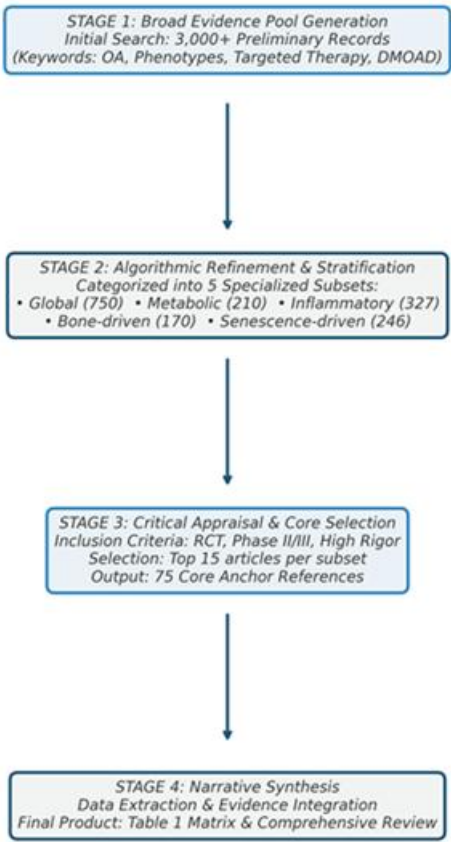


Figure 1. Methodology Workflow: From comprehensive literature retrieval to final synthesis of 30 core references.

3. The Evolving Paradigm of Osteoarthritis Phenotyping

Recent advances in high-resolution imaging, genomics, and biochemical profiling have redefined the joint as an integrated organ system where the cartilage, subchondral bone, synovium, meniscus, and infrapatellar fat pad exist in constant metabolic and mechanical crosstalk. Pathological disruption in any single tissue can ripple across the entire joint ecosystem, driving distinct progression trajectories [5,6].

The historical failure to recognize this multi-tissue interconnectivity explains why single-tissue therapeutic strategies often fell short. For example, a drug designed solely to stimulate chondrocyte matrix production cannot succeed if the underlying subchondral bone is undergoing aggressive catabolic remodeling, or if the synovium is flooded with macrophage-derived inflammatory cytokines. By transitioning toward an organ-level diagnostic baseline, we acknowledge that different tissue components drive the disease at different stages or within different patient subgroups. This conceptual transformation forms the modern definition of endotypes—functional pathogenic pathways defined by distinct, quantifiable molecular biomarkers—thereby replacing historical macroscopic descriptions with actionable therapeutic axes.

Consequently, modern rheumatology classifies OA into multiple distinct subtypes based on the primary driver of joint failure: the metabolic, inflammatory, subchondral bone-driven, and senescence-driven phenotypes. Shifting from a joint-centric, one-size-fits-all model to an endotype-guided stratification strategy provides a robust clinical framework, allowing investigators to precisely match novel biological agents to the patients who harbor the corresponding molecular pathology [6].

4. Phenotype-Specific Targeted Interventions

To address the inherent clinical and biological heterogeneity of OA, targeted therapeutic interventions must be precisely tailored to the dominant driving sub-pathology. A systematic cross-examination of these phenotype-specific parameters—including distinguishing biomarkers, underlying molecular mechanisms, primary candidate drugs, and verified clinical endpoints—is detailed in Table 1.

4.1. The Metabolic Phenotype: Bridging Systemic Dysmetabolism and Chondrocyte Homeostasis

The metabolic phenotype of osteoarthritis (OA) is no longer simplified as a mere consequence of excessive mechanical loading. It is now defined as a distinct clinical entity driven by metabolic syndrome (MetS), including obesity, dyslipidemia, and impaired glucose metabolism [7,8]. Epidemiological evidence indicates that obesity is significantly associated with OA in non-weight-bearing joints, such as the hand, suggesting that systemic metabolic mediators—rather than biomechanical stress alone—play a decisive role in joint degeneration [8,9]. At the molecular level, this phenotype is characterized by ‘meta-inflammation,’ a state of chronic low-grade systemic inflammation mediated by adipokines. Pro-inflammatory adipokines, particularly leptin and resistin, have been shown to trigger the expression of matrix metalloproteinases (MMPs) and ADAMTS-5 in chondrocytes via the NF- κ B and MAPK signaling pathways [9,10]. Concurrently, a downregulation of adiponectin impairs the protective, anabolic functions typically maintained in healthy cartilage tissue, disrupting the crucial balance of extracellular matrix (ECM) synthesis. The infrapatellar fat pad (IFP) acts as a local endocrine organ, continuously secreting these

adipokines directly into the synovial fluid, thereby creating a highly toxic microenvironment that accelerates chondrocyte apoptosis.

The clinical validation of this phenotype has been markedly advanced by the repurposing of metabolic-targeting pharmacotherapies. High-quality, randomized controlled trials, notably the landmark STEP 9 (semaglutide) and LOSEIT (liraglutide) trials, have robustly demonstrated that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) deliver exceptional dual benefits [10,11]. Patients achieved profound, sustained weight reduction coupled with dramatic improvements in knee OA-related pain and physical function (measured via WOMAC scores). Beyond GLP-1 RAs, emerging evidence suggests that metformin may confer chondroprotective effects by activating the AMPK pathway, thereby reducing oxidative stress and inhibiting chondrocyte apoptosis [11]. Metformin-mediated activation of AMPK serves as a critical biological energy sensor, downregulating the catabolic mammalian target of rapamycin (mTOR) signaling axis. This AMPK/mTOR metabolic rewiring enhances autophagy within compromised chondrocytes, allowing them to clear dysfunctional organelles and survive under metabolic stress. However, a critical mechanistic debate remains unresolved within the field: it is currently unclear whether the profound symptomatic relief observed with GLP-1 RAs is exclusively secondary to the mechanical offloading of weight-bearing joints, or if these agents also exert direct, structure-modifying (DMOAD) and anti-inflammatory effects on chondrocytes and synovial tissue via localized adipokine modulation [11,12]. Preclinical intra-articular models strongly suggest that GLP-1 receptors are functionally expressed on human articular chondrocytes, and their activation directly suppresses IL-1 β -induced catabolic gene expression. To settle this debate, ongoing and future clinical trials must decouple weight loss from structural preservation by integrating mandatory magnetic resonance imaging (MRI) or biochemical biomarker tracking (such as serum COMP and CTX-II levels) to definitively isolate the local joint-specific therapeutic contributions of GLP-1 RAs.

4.2. The Inflammatory Phenotype: Unmasking the Driver of Joint Flare and Structural Decay

The inflammatory phenotype, often referred to as ‘synovitis-driven OA’, is characterized by persistent synovial membrane hypertrophy and fluctuating intra-articular effusion [13,14]. Unlike the traditional mechanical model, this phenotype is fueled by a maladaptive innate immune response. Damage-associated molecular patterns (DAMPs), such as S100 proteins and extracellular matrix fragments, activate Toll-like receptors (TLRs) on synovial macrophages and fibroblasts, triggering a catabolic cascade dominated by IL-1 β , TNF- α , and IL-6 [14,15]. This continuous activation promotes a state of persistent macrophage M1 polarization, shifting the synovial environment toward a highly degradative state while inhibiting the tissue-repairing M2 macrophage populations. The resulting cytokine storm not only upregulates degrading enzymes like MMP-13 but also sensitizes peripheral nociceptors, explaining the acute, throbbing pain often reported by these patients. Histological and histopathological studies have confirmed that even in early-stage OA, a significant proportion of patients exhibit lymphocyte infiltration and pro-inflammatory cytokine profiles akin to, though less intense than, rheumatoid arthritis [15,16].

Clinically, the identification of this phenotype relies heavily on advanced imaging. Dynamic contrast-enhanced MRI (DCE-MRI) and musculoskeletal ultrasound have

established ‘effusion-synovitis’ as a robust imaging biomarker, which correlates strongly with both acute pain flares and long-term cartilage loss [16,17]. However, the clinical translation of anti-inflammatory biologics has been historically inconsistent. Early trials of the IL-1 receptor antagonist anakinra failed to meet primary endpoints in undifferentiated OA populations, a setback now attributed to the lack of precision in patient recruitment [17]. A pivotal shift in evidence emerged from the CANTOS trial sub-analysis, which revealed that in a subgroup of patients with elevated systemic inflammation (hs-CRP ≥ 2 mg/L), the IL-1 β neutralizer canakinumab significantly reduced the rates of total hip and knee arthroplasty [17,18]. Similarly, targeted therapies for hand OA with active synovitis, such as those investigated in the HERCULES study, have shown promise when patients are stratified by baseline inflammatory activity [18]. These data conclusively demonstrate that broad anti-inflammatory therapy is highly inefficient unless directed exclusively at patients undergoing an active, molecularly confirmed inflammatory phase. Future clinical diagnostic models should incorporate multiplex synovial fluid cytokine profiling alongside ultrasound imaging to construct a composite ‘Inflammatory Score,’ ensuring that powerful biological agents are reserved for patients with a documented immune-mediated pathology.

4.3. The Subchondral Bone-Driven Phenotype: Subchondral Remodeling and Wnt Pathway Modulation

The prevailing paradigm of OA as exclusively a ‘cartilage surface disease’ has been definitively challenged by the identification of the bone-driven phenotype. This phenotype underscores the mechanical and biochemical crosstalk within the ‘osteochondral unit’ [19,20]. In a distinct subset of patients, localized biomechanical overload induces micro-trabecular fractures and aberrant subchondral bone remodeling, preceding macroscopic cartilage loss. The radiographic hallmarks of this endotype are subchondral sclerosis and MRI-detected bone marrow lesions (BMLs)—regions of edema, fibrosis, and high bone turnover that strongly correlate with unremitting nocturnal and weight-bearing pain [20,21].

At the molecular core of this aberrant remodeling is the dysregulation of the Wnt/ β -catenin signaling pathway. Over-activation of Wnt signaling in the subchondral bone drives osteoblast hyper-proliferation while concurrently triggering the release of catabolic factors that traverse the calcified cartilage zone to degrade the overlying cartilage [21,22]. Targeting this axis has yielded one of the most promising pharmaceutical breakthroughs in recent years. Lorecivivint (SM04690), an intra-articular CLK/DYRK1A inhibitor that modulates the Wnt pathway, has demonstrated profound disease-modifying potential. Building upon successful Phase IIa data, the landmark Phase III trial (OA-10) confirmed that a single injection of lorecivivint provides significant, sustained symptomatic relief and mitigates structural progression in moderately to severely symptomatic knee OA [22,23]. Furthermore, this phenotype has revitalized the investigation into anti-resorptive agents. Historically, broad-spectrum trials of bisphosphonates (e.g., zoledronic acid) yielded negative results. However, recent phenotype-stratified analyses reveal that patients with concurrent osteoporosis and robust baseline BMLs represent a responsive sub-population where bisphosphonates effectively reduce bone attrition [23,24]. For patients with persistent BMLs unresponsive to pharmacotherapy, minimally invasive structural augmentations, such as Subchondroplasty (SCP), have recently demonstrated durable 12-month clinical efficacy [24]. By infusing a biomimetic calcium phosphate bone substitute

directly into the weakened subchondral trabecular network under fluoroscopic guidance, SCP structurally reinforces the architecture. This immediate stabilization drastically reduces mechanical shearing forces and interrupts the chronic nociceptive signaling originating from stressed bone tissue, bridging the gap between conservative management and total joint arthroplasty.

4.4. The Senescence-Driven Phenotype: Eradicating the Source of “Inflammaging”

The senescence-driven phenotype challenges the traditional dogma that osteoarthritis is an inevitable consequence of chronological aging. Instead, it identifies cellular senescence as an active, a targetable pathology [25,26]. In response to oxidative stress, mechanical trauma (such as in post-traumatic OA), or telomere shortening, a subset of chondrocytes and synovial fibroblasts enter an irreversible state of cell-cycle arrest, characterized by the upregulation of p16INK4a and p21 [26,27]. Rather than undergoing apoptosis, these 'zombie cells' remain metabolically active and secrete a toxic cocktail of pro-inflammatory cytokines, chemokines, and matrix-degrading proteases, collectively known as the Senescence-Associated Secretory Phenotype (SASP) [27,28]. This localized SASP not only degrades the extracellular matrix but also induces a bystander effect, propagating an insidious state of ‘inflammaging’ throughout the joint organ [28].

The translation of this biological mechanism into precision medicine has birthed a novel class of therapeutics: senolytics—agents designed to selectively induce apoptosis in senescent cells while sparing healthy tissue [28,29]. Early clinical exploration generated immense enthusiasm, notably with UBX0101, an intra-articular MDM2/p53 interaction inhibitor. Although UBX0101 failed to meet its primary pain endpoints in a highly anticipated Phase II trial, this outcome has been critically reappraised as an issue of drug retention and the need for stricter patient stratification, rather than a failure of the senolytic concept itself [29]. Concurrently, there is growing clinical interest in repurposed and natural senolytics, such as the flavonoid fisetin, which are currently undergoing clinical trials to evaluate their efficacy in mitigating OA progression [29]. Fisetin and other naturally occurring polyphenols operate by selectively downregulating anti-apoptotic networks (such as the Bcl-2 protein family and PI3K/AKT pathways), which senescent chondrocytes heavily rely upon for their abnormal survival. By severing these lifelines, senolytics facilitate the rapid clearance of senescent cells by local macrophages. Moving forward, the true potential of senolytics hinges on advanced diagnostic modalities. Emerging technologies, such as high-resolution spatial transcriptomics, are now being deployed to accurately map the senescence burden within the joint [30]. By tracking the precise spatial coordinates of SASP expression across different cartilage layers, clinicians can understand when the senescence burden transforms from a localized acute injury response into a widespread chronic joint pathology. This spatial intelligence will be absolutely vital to optimizing the dosing schedules of senolytics, shifting clinical application from continuous, non-specific administration to timed, pulse-like therapies that “clear out” senescent cell populations during peak windows of disease acceleration.

5. Future Perspectives: Multi-Omics and Artificial Intelligence in Patient Stratification

The future of OA precision medicine hinges on transitioning from subjective clinical phenotyping to objective, multi-omic endotyping [4,30]. Integrating spatial transcriptomics, synovial fluid proteomics, and metabolomics will yield a granular

molecular map of joint degradation, allowing for the discovery of novel surrogate biomarkers. Concurrently, artificial intelligence (AI) and deep learning algorithms are revolutionizing patient stratification by automatically quantifying bone marrow lesions, synovitis volume, and subchondral bone length from magnetic resonance imaging (MRI) datasets. These digital biomarkers will enable real-time tracking of therapeutic response, eliminating the diagnostic delays inherent in conventional radiography and ensuring optimal clinical trial design that completely bypasses the historic pitfalls of the dilution effect.

Moreover, the integration of wearable biosensors and digital health platforms offers unprecedented opportunities to monitor dynamic biomechanical loads and systemic inflammatory flares in real-time. By coupling these continuous data streams with machine learning models, clinicians may soon be able to predict individual flare-ups and deploy targeted therapies precisely during the “window of opportunity” before irreversible structural damage occurs.

By coupling these continuous biomechanical data streams with machine learning predictive algorithms, clinicians may soon be able to forecast individual acute flare-ups and deploy targeted therapies precisely during the critical “window of opportunity” before irreversible structural damage crystallizes. Ultimately, the convergence of clinical, imaging, and multi-omic data streams will culminate in a cloud-based ‘Joint Digital Twin’ model for individual patients. These sophisticated predictive computational models will simulate personal joint degeneration trajectories in response to specific molecular interventions. For example, a clinician could virtually model whether an obese patient with high baseline inflammation would respond more favorably to a systemic GLP-1 receptor agonist or an intra-articular anti-cytokine injection, completely revolutionizing OA management from reactive palliation to proactive disease eradication. This ‘Digital Twin’ paradigm represents the ultimate zenith of precision medicine, effectively transitioning orthopedics from an observational and reactionary discipline into a highly predictive, computationally driven medical science.

6. Conclusions

The era of viewing osteoarthritis as a uniform, untreatable degenerative disease of aging has drawn to a close. By dismantling the monolithic classification of OA and embracing a phenotype-driven approach, precision medicine offers a clear path toward the approval of the first generation of DMOADs [1,30]. Translating these phenotypic insights into clinical trial design and clinical practice will ultimately safeguard joint longevity, personalize patient care, and drastically reduce the global burden of musculoskeletal joint failure. The integration of objective multi-omic profiling, AI-assisted imaging biomarkers, and mechanistically tailored pharmacotherapy stands as a beacon of hope, promising to definitively rewrite the clinical trajectory for millions of patients currently suffering from this debilitating condition.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Appendix

Table 1. Characteristics and Targeted Therapies of Osteoarthritis Phenotypes.

Target Phenotype	Defining Biomarkers	Key Pathological Mechanisms	Primary Target / Pathway	Investigational Drugs (Phase)	Key Clinical Outcomes	Limitations & Future Directions
Metabolic-driven	BMI >30, MetS, High Leptin/Adiponectin ratio, Systemic low-grade inflammation[7, 8]	Meta-inflammation, AMPK inactivation, Adipokine-mediated cartilage matrix degradation[9,10]	GLP-1 Receptor, AMPK pathway[10,11]	Semaglutide (Phase III) Liraglutide (Phase III) Metformin (Exploratory) [10-12]	Sustained weight loss (>10%), dramatic improvements in WOMAC pain and physical function[10].	Unresolved debate: mechanical offloading vs. direct DMOAD effect. Requires joint-specific structural assessment[11,12].
Inflammatory Endotype	Synovial hypertrophy & Effusion (via DCE-MRI/US), Systemic hs-CRP ≥ 2 mg/L[13,14]	DAMPs-TLR activation, Macrophage M1 polarization, Pro-inflammatory cytokine cascade[14,15]	IL-1 β , TNF- α , IL-6 [15]	Canakinumab (Phase III sub-analysis) Anakinra (Phase II) Tocilizumab (Phase II)[17,18]	Significantly reduced TJR rates in high-CRP subgroups (CANTOS); decreased morning stiffness [17].	Failed in broad undifferentiated OA cohorts (dilution effect). Demands precision stratification via proteomics [17, 18].
Subchondral Bone-driven	Bone Marrow Lesions (BMLs), Subchondral sclerosis, Elevated bone turnover (CTX-II)[19, 20]	Wnt/ β -catenin overactivation, Micro-trabecular fractures, Osteoblast-osteoclast uncoupling [21, 22]	Wnt signaling, Osteoclastic resorption [21]	Lorecivint (Phase III OA-10) Zoledronic acid (Targeted subgroup) Subchondroplasty[22-24]	Sustained pain relief, reduced BML volume, and delayed joint space narrowing (JSN) [22, 24].	Bisphosphonates are only effective in high-BML/osteoporotic subgroups. Structural restoration takes time [23].
Senescence-driven	Elevated p16INK4a & p21, SA- β -gal activity, Telomere	"Inflammaging", Senescence-Associated Secretory	Apoptosis in senescent cells (MDM2/p53),	UBX0101 (Phase II) Fisetin (Phase II) Dasatinib + Quercetin	Potential clearance of 'zombie cells' and suppression of localized	Efficacy limited by short joint retention and poor patient

	shortening [26]	Phenotype (SASP) induced bystander effect[27, 28]	SASP suppressi on[28, 29]	(Phase II) [29]	catabolic SASP microenviron ment[28, 29].	selection. Needs spatial transcripto mics for precise timing[29, 30].
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Table 2. List of Abbreviations Used in the Study.

Abbreviation	Full Name
BML	Bone Marrow Lesion
CTX-II	C-Terminal Telopeptide of Type II Collagen
DCE-MRI	Dynamic Contrast-Enhanced MRI
DMOAD	Disease-Modifying Osteoarthritis Drug
hs-CRP	High-Sensitivity C-Reactive Protein
MetS	Metabolic Syndrome
SASP	Senescence-Associated Secretory Phenotype
TJR	Total Joint Replacement
US	Ultrasound

References

- [1] Liang, Y.C.; Wang, K.; Yang, C.Q.; Huang, J.K.; Huang, Z.L.; Chen, Y. Pathogenesis of osteoarthritis: mechanisms of action of disulfidptosis and targeted therapeutic strategies. *Drug Design Development and Therapy*. 2026.
- [2] Afshari, A.; Khorramdelazad, H.; Abbasifard, M. Breaking the cycle: How immune reprogramming and modulation are redefining Osteoarthritis care. *European journal of pharmacology*. 2026.
- [3] Zhu, N.; Lin, H.M.; Yu, J.; Yang, R.; Tao, D.H.; Huang, G.X.; Qian, D.; Liu, Y.; Chen, B.Q. Exploring the association between frailty index and knee osteoarthritis in middle-aged and older chinese adults: a cross-sectional analysis of data from the China health and retirement longitudinal study. *PLOS One*. 2026.
- [4] Shi, X.W.; Tang, L.M.; Li, M.J.; Wei, M.J.; Wu, Y.P.; Xu, Y.Q. Comprehensive multi-omics and mendelian randomization reveal the key role of monocytes in aging and osteoarthritis. *Molecular Biotechnology*. 2026.
- [5] Tung, K.M.; Pan, P.H.; Lin, Y.T.; Nhu, N.T.; Wu, J.L.; Hu, C.C.; Chen, C.F.; Hou, W.H Effects of cetylated fatty acids on knee osteoarthritis: a systematic review and meta-analysis of real-world evidence. *Clinical and Experimental Rheumatology*. 2026.
- [6] Barreto, R.B.; Barreto, André de Jesus.; do Nascimento.; Abel, L.M.; Carvalho, D.M.B.; Queiroz, B. Efficacy and safety of genicular nerve ablation techniques for knee osteoarthritis: a systematic review and meta-analysis of sham-controlled randomized trials. *Pain Medicine (Malden, Mass.)*. 2026.
- [7] Wu, J.N.; Xu, J.W.; Zhang, M.H.; Zhong, J.H.; Gao, W.J.; Wu, M.J. Chondrocyte mitochondrial quality control: a novel insight into osteoarthritis and cartilage regeneration. *Advances in Wound Care*. 2026.

- [8] Liang, Y.C.; Wang, K.; Yang, C.Q.; Huang, J.K.; Huang, Z.L.; Chen, Y. Pathogenesis of Osteoarthritis: Mechanisms of Action of Disulfidptosis and Targeted Therapeutic Strategies. *Drug design, development and therapy*. 2026.
- [9] Guan, S.Q.; Mei, Y.F. Biomechanics and Obesity in Osteoarthritis: From Mechanism to Precision Medicine. *International journal of rheumatic diseases*. 2026.
- [10] Wu, J.N.; Xu, J.W.; Zhang, M.H.; Zhong, J.H.; Gao, W.J.; Wu, M.J. Chondrocyte Mitochondrial Quality Control: A Novel Insight into Osteoarthritis and Cartilage Regeneration. *Advances in wound care*. 2026.
- [11] Lu, Y.; Liu, J.K.; Wang, S.S.; Gan, J.P.; Cao, W.F.; Wu, B. Identification and validation of a glutamine metabolism-related gene signature as a diagnostic and therapeutic target in osteoarthritis through integrated multi-omics analysis. *PeerJ*. 2026.
- [12] Guan, S.Q.; Mei, Y.F. Biomechanics and obesity in osteoarthritis: from mechanism to precision medicine. *International Journal of Rheumatic Diseases*. 2026.
- [13] Xie, W.B.; Song, C.; Yang, L.; Chen, C.Q.; He, Y.H.; Zeng, L.L.; Liu, Z.C.; Peng, L. The common pathological network of inflammation, extracellular matrix imbalance, and senescence in intervertebral disc degeneration and osteoarthritis. *Molecular Biology Reports*. 2026.
- [14] Zhou, L.; Ju, S.H.; Wang, K.; Fu, Z.B.; Wu, R.C.; He, B.X.; Hu, Y.S. Research progress on the mechanism of chondrocyte ferroptosis in osteoarthritis. *Frontiers in immunology*. 2026.
- [15] Kamau, V.N.; Kim, J.H.; Lee, G.Y. The NLRP3 inflammasome in osteoarthritis: a systematic review of traditional, complementary, and integrative medicine efficacy and underlying mechanisms. *Daru: journal of Faculty of Pharmacy, Tehran University of Medical Sciences*. 2026.
- [16] Zhou, H.D.; Luo, H.; Hu, L.S.; Zhang, F.T.; Hu, W.T.; Xie, J.F.; Lu, Y.H.; Shan, J.C.; Fan, S.Y.; Chen, Y.W. [Mechanisms of miRNA in osteoarthritis and research advances in traditional Chinese medicine intervention]. *Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China journal of Chinese materia medica*. 2026.
- [17] Patusco, R.; Gyasi, K.; Kaufmann, A. Exploring the nexus between inflammation and mobility through the lens of healthy aging: current scenario and future perspectives. *Aging Clinical and Experimental Research*. 2026.
- [18] Xie, W.B.; Song, C.; Yang, L.; Chen, C.Q.; He, Y.H.; Zeng, L.L.; Liu, Z.C.; Peng, L. The common pathological network of inflammation, extracellular matrix imbalance, and senescence in intervertebral disc degeneration and osteoarthritis. *Molecular biology reports*. 2026.
- [19] Zhou, L.; Ju, S.H.; Wang, K.; Fu, Z.B.; Wu, R.C.; He, B.X.; Hu, Y.S. Research progress on the mechanism of chondrocyte ferroptosis in osteoarthritis. *Frontiers in Immunology*. 2026.
- [20] Dan, J.; Ding, H.; Li, L.T.; Wu, Q. Immunonutritional biomarkers in osteoarthritis: mechanistic insights and prognostic potential. *Frontiers in Immunology*. 2026.

- [21] Madry, H.N. Structural relationship between articular cartilage and subchondral bone - A critical frontier in joint homeostasis and osteoarthritis. *Annals of anatomy = Anatomischer Anzeiger: official organ of the Anatomische Gesellschaft*. 2026.
- [22] E, J.P.; E, Q.; Zhou, G.S. Targeting senescent cells in post-traumatic osteoarthritis: mechanisms, microenvironment remodeling, and translational prospects. *PeerJ*. 2026.
- [23] Ahmed, S.; Comolli, N.K. Delivery of potential natural disease-modifying osteoarthritis drugs: beyond polyphenols and flavonoids. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*. 2026.
- [24] Madry, H.N. Structural relationship between articular cartilage and subchondral bone - a critical frontier in joint homeostasis and osteoarthritis. *Annals of Anatomy = Anatomischer Anzeiger: Official Organ of the Anatomische Gesellschaft*. 2026.
- [25] Abbas, M.; Tamargo, Javier, A.; Cruz, C.J.; Zhang, Y.T.; Wohlgemuth, S.; Wu, K.; Chen, L.; Staud, R.; Fillingim, R.B.; Leeuwenburgh, C.; Cruz-Almeida, Y. Circulating cellular senescence biomarkers in persons with chronic knee osteoarthritis pain: an exploratory study. *Molecular Pain*. 2026.
- [26] Silawal, S.; Schulze-Tanzil, G. Perspectives on intrinsic articular cartilage interfaces. *Annals of Anatomy = Anatomischer Anzeiger : Official Organ of the Anatomische Gesellschaft*. 2026.
- [27] E, J.P.; E, Q.; Zhou, G.S. Targeting senescent cells in post-traumatic osteoarthritis: mechanisms, microenvironment remodeling, and translational prospects. *PeerJ*. 2026.
- [28] He, C.P.; Huang, G.W.; Bi, J.W.; Fu, W.Y.; Liu, C.J. cPLA2 in musculoskeletal and autoimmune diseases: molecular mechanisms and therapeutic insights. *Cytokine & Growth Factor Reviews*. 2026.
- [29] Ji, X.X.; He, X.Z.; Cai, H.L.; Tang, P.; Zhou, H.; Wang, J.J.; Wu, Y.F.; Zhou, J.F.; Lin, Z.; Xu, K.C.; Lin, C.J.; Wu, X.Y.; Wang, K.B.; Liu, W.M.; Feng, G.; Yan, Shigui; Jiang, G.Y.; Qu, Z.H.; Qi, Y.Y. Recycling senescent cell lipids for targeted senotherapy. *Nature Communications*. 2026.
- [30] Hsu, J.E.; Wang, B.S.; Hwang, Y.H.; Cheng, W.Q.; Zhao, Q.Y.; Si, Y.C.; Xu, M.; Kang, H.M.; Lee, J.H. Fluorescence-guided spatial mapping of p21-expressing senescent cells in aged liver at single-cell resolution. *Biomolecules*. 2026.



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