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REVIEW

Diabetes-Related Metabolic Osteoarthritis: Advanced Glycation–Collagen Axis, Cartilage Stiffening, and Biomaterials-Based Therapeutic Strategies

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Abstract: Diabetes mellitus, particularly type 2 diabetes, has been associated in some studies with increased osteoarthritis (OA) risk, greater symptom burden, and structural progression; however, epidemiological evidence remains heterogeneous, and the extent to which diabetes independently contributes to OA after accounting for obesity, adiposity, physical inactivity, and other metabolic confounders remains debated. In metabolically susceptible patients, chronic hyperglycemia, insulin resistance, carbonyl stress, and low-grade inflammation may contribute to disruption of the joint microenvironment. One proposed mechanism involves the accumulation of advanced glycation end products (AGEs), which can cross-link with type I/II collagen and may increase extracellular matrix crosslinking and stiffness. Through these biochemical and biomechanical effects, the AGE–collagen axis may influence chondrocyte mechanotransduction, inflammatory signaling, matrix turnover, and cell survival, thereby providing a plausible but not yet fully validated link between systemic metabolic dysfunction and OA-relevant structural degeneration. Recent advances in biomaterials may offer experimental and translational strategies to modulate the glycated, inflamed, and mechanically altered joint microenvironment. These approaches include stiffness-tunable and stimuli-responsive hydrogels, nanocarriers designed to deliver anti-AGE agents or AGE-cleaving enzymes, osteochondral gradient scaffolds that mimic native tissue transitions, and immunomodulatory materials that may attenuate local inflammation. At present, these interventions should be viewed primarily as preclinical or early translational strategies rather than established disease-modifying therapies. This review discusses the potential molecular and biomechanical implications of the AGE–collagen axis in diabetes-related OA, critically evaluates emerging biomaterials-based therapeutic approaches, and highlights preclinical evaluation models and outcome measures. Finally, we outline key translational challenges—including targeted delivery, long-term safety of degradation products, metabolic heterogeneity, patient stratification, and integration with systemic therapies—and propose methodological frameworks to support the future development of clinically testable biomaterials interventions.

Keywords: advanced glycation end products, cartilage-bone scaffolds, collagen glycation, diabetes, drug delivery, osteoarthritis, smart hydrogels

Introduction

Osteoarthritis (OA) is a chronic joint disease with a steadily rising global burden of disability. According to the latest Global Burden of Disease (GBD) analyses, approximately 528 million people were living with OA in 2019, with

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substantial growth over the past three decades—an increase that reflects the combined impact of population aging and the obesity epidemic on disease prevalence and health-care demand.[1] In parallel, the high prevalence and improved survival of type 2 diabetes mellitus (T2DM) have made the coexistence of diabetes and OA a common yet complex comorbidity spectrum in routine practice.[2] A systematic review and meta-analysis reported a statistically significant association between diabetes and OA, supporting the use of "diabetes-related OA" as an emerging clinical and translational concept rather than a definitively established phenotype.[3] Longitudinal cohorts further suggest that patients with OA and concomitant diabetes may experience greater pain, faster declines in physical function and activity, and more pronounced functional limitation; however, the extent to which these associations reflect an independent effect of disordered glucose metabolism, or are partly confounded or mediated by obesity, adiposity, physical inactivity, and other metabolic factors, remains an important question.[4]

In this review, we distinguish three related but non-identical concepts. "Diabetes-related OA" refers to OA discussed in the context of diabetes-associated hyperglycemia, insulin resistance, carbonyl stress, AGE accumulation, and inflammatory–matrix alterations. "Metabolic OA" is a broader phenotype involving systemic metabolic dysfunction, including but not limited to diabetes, obesity, dyslipidemia, adipokine imbalance, and low-grade inflammation.[5,6] "Obesity-associated OA" emphasizes the combined contribution of excess mechanical loading and adipose-driven inflammatory/metabolic signaling. These concepts overlap biologically and clinically, but they should not be used interchangeably.

Within this conceptual framework, the advanced glycation–collagen (AGE–COL) axis provides a plausible molecular and biomechanical link between diabetes-associated metabolic stress and OA-relevant joint degeneration. Chronic hyperglycemia and oxidative/carbonyl stress promote non-enzymatic AGE crosslinking with type I/II collagen, which may increase matrix crosslink density and stiffness; in parallel, AGE engagement of the receptor for AGEs (RAGE) activates NF-κB and pro-inflammatory mediators, potentially contributing to aberrant chondrocyte mechanosensing, matrix degradation, and apoptosis.[7,8] Foundational and translational studies indicate that AGE accumulation can alter cartilage material properties, including elastic modulus and energy dissipation, and may amplify a sterile-inflammation-like joint phenotype through inflammatory and oxidative pathways—distinct from rheumatoid arthritis but potentially relevant to OA progression in metabolically stressed joints.[9–11]

Therapeutically, current OA care remains largely palliative. Guideline-endorsed non-surgical strategies, including education and exercise, weight management, analgesics, and anti-inflammatory treatments, are broadly effective at the population level, but durability and efficacy can be limited in metabolically complicated OA subgroups. No disease-modifying OA drug (DMOAD) has been approved to date, and repeated trial failures highlight challenges spanning target selection, phenotypic stratification, and pharmacokinetics/delivery.[12,13] These realities are shifting research from pain control alone toward microenvironment remodeling and matrix homeostasis modulation. Materials-based interventions—such as tunable/stimuli-responsive injectable hydrogels, targeted nanocarriers, osteochondral gradient scaffolds, and immunomodulatory interfaces—may achieve high local exposure with programmable spatiotemporal release in the joint cavity, offering potential strategies to modulate glycation-associated matrix stiffening and inflammatory imbalance while complementing systemic metabolic therapy.[14–16]

Scope and aims. Within the paradigm of metabolic OA, this review integrates a three-tier framework of mechanisms, countermeasures, and translation: (1) we synthesize epidemiologic and clinical evidence for diabetes-related OA, using the AGE–COL axis as a central thread to explain how diabetes-associated metabolic dysregulation may reshape molecular signaling and biophysical properties in joint tissues; (2) we appraise recent materials-science strategies—including injectable hydrogels, stimuli-responsive drug-delivery systems, osteochondral composite scaffolds, and immunomodulatory materials—focusing on how they may enable targeted "deglycation/anti-re-glycation—anti-inflammation—matrix homeostasis modulation"; and (3) we discuss translational routes and practical hurdles across preclinical models and endpoints, early-phase clinical design, and regulatory/manufacturing feasibility, while considering coordination with systemic metabolic interventions such as weight reduction and improved insulin sensitivity. Collectively, these discussions aim to support more precise stratification of metabolically complicated OA and integrated local-to-systemic intervention strategies. The overall conceptual framework of diabetes-related metabolic osteoarthritis and its local-to-systemic therapeutic implications are summarized in Figure 1.

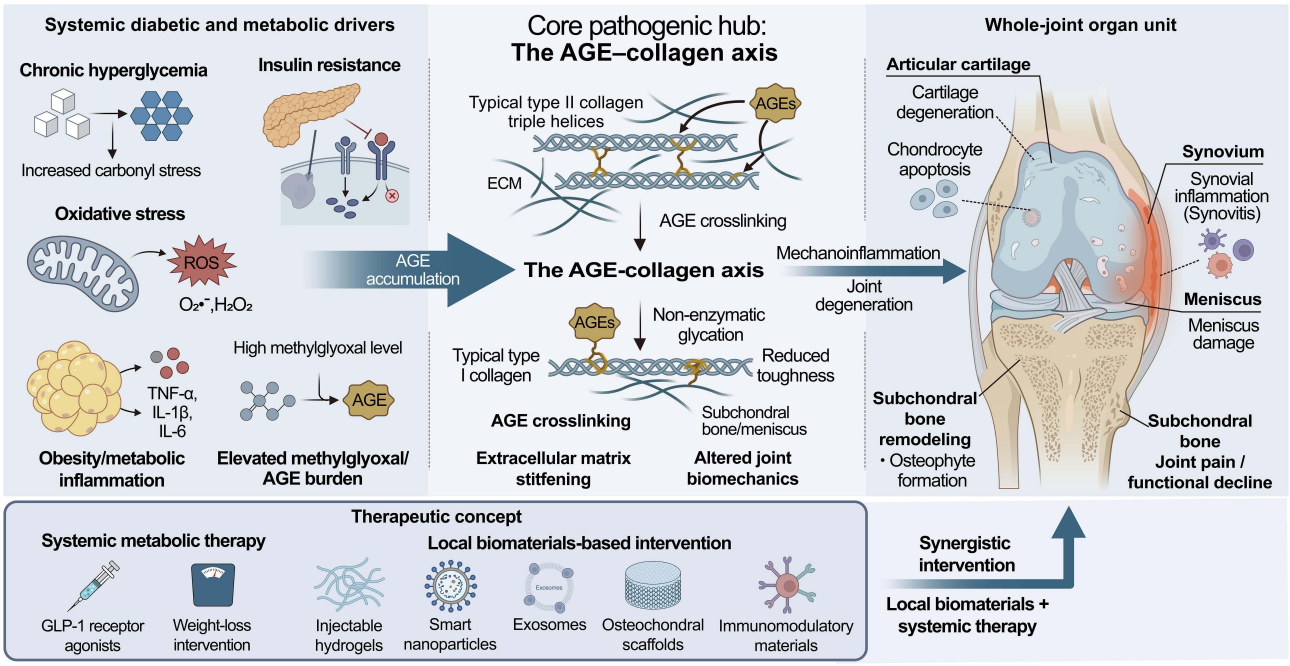

Figure 1 Overall conceptual framework of diabetes-related metabolic osteoarthritis centered on the AGE–collagen axis. Systemic diabetic and metabolic drivers, including chronic hyperglycemia, insulin resistance, oxidative/carbonyl stress, obesity-associated inflammation, and elevated methylglyoxal/AGE burden, may promote AGE accumulation in joint tissues. AGE-mediated collagen crosslinking may stiffen the extracellular matrix, reduce tissue toughness, alter joint biomechanics, and amplify mechanoinflammation, thereby contributing to whole-joint degeneration involving cartilage, synovium, meniscus, and subchondral bone. The lower panel presents a conceptual local–systemic therapeutic strategy combining systemic metabolic therapy with local biomaterials-based interventions. This proposed strategy remains exploratory and requires further validation.

Abbreviations: AGEs, advanced glycation end products; ECM, extracellular matrix; GLP-1, glucagon-like peptide-1; IL, interleukin; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha.

The AGE–Collagen Axis: Molecular Mechanisms and Biomechanical Consequences

Biological Basis of AGEs

Advanced glycation end products (AGEs) arise in the late stages of the Maillard reaction: reducing sugars or reactive dicarbonyls first form Schiff base–Amadori intermediates with lysine/arginine residues on proteins, which then undergo oxidation, dehydration, and rearrangement to yield irreversible AGE structures. Representative species include Nε-carboxymethyl-lysine (CML), Nε-carboxyethyl-lysine (CEL), and pentosidine, the latter capable of forming intermolecular crosslinks. This chemistry is markedly amplified under chronic hyperglycemia and oxidative/carbonyl stress and constitutes a fundamental driver of tissue stiffening and functional impairment in diabetes.[8,17,18]

Endogenous AGE burden derives primarily from spontaneous glucose glycation and accumulation of dicarbonyls such as methylglyoxal (MGO)—generated largely from glycolytic triose intermediates—which directly modify proteins to form MGO-AGEs while increasing reactive oxygen species and overwhelming anti-glycation repair systems.[19] Exogenous inputs include dietary AGEs produced by high-temperature dry cooking (frying, grilling, roasting) and glycation products in cigarette smoke; these compounds are absorbed and accumulate in the circulation and tissues, augmenting systemic inflammation/oxidative stress and overall AGE load.[20]

Within the joint, the collagen networks of articular cartilage (COL2-dominant) and of meniscus/subchondral bone matrix (COL1-dominant) are characterized by low turnover and long lifespan. When exposed to sustained hyperglycemia and dicarbonyl stress, this slow remodeling renders them particularly susceptible to AGE accumulation and crosslinking, laying the material foundation for subsequent increases in network stiffness and for imbalances in cellular responses.[21]

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AGEs–Collagen Crosslinking: From Molecules to Tissues

Within joint collagens (COL1/COL2), AGEs such as pentosidine and CML form irreversible covalent crosslinks both within and between fibrils, directly altering the mechanical response of the collagen network. Classic experiments on human articular cartilage first established this principle: ex vivo threose-induced glycation of adult human cartilage markedly increased collagen-network stiffness, implicating non-enzymatic crosslinking as a key driver of the age- and hyperglycemia-related decline in cartilage damage tolerance.[21,22] Subsequently, Chen et al[23] elevated AGE levels in bovine cartilage to approximate those of aged tissue and observed an increased tensile modulus accompanied by reduced failure strain and extensibility—ie, the mechanical fingerprint of "stiffness↑/toughness↓". This provided direct evidence for a structure–function causal chain whereby increased AGE burden yields a material that is stiffer yet more brittle.

At the level of matrix turnover, DeGroot et al[24] showed in explant cartilage that AGE accumulation suppresses proteoglycan synthesis and diminishes degradative renewal, thereby lowering overall matrix turnover and repair capacity —mechanistic support for a dual imbalance of "materials hardening" coupled to "biologic under-renewal". Functional animal data align with these findings: in a rat knee immobilization model, tissue accumulation of AGEs accelerates the development and severity of arthrogenic contracture, indicating that AGE load not only remodels fibrillar microstructure but also magnifies organ-level passive biomechanical deterioration.[25,26] Multiscale experimental and computational studies further illuminate the micromechanical basis: AGE crosslinks restrict collagen fibril "sliding" and energy-dissipation pathways, precipitating earlier instability and brittle failure in regions of high strain and, at the macroscopic level, amplifying the shift toward higher elastic modulus and reduced toughness.[27]

RAGE-Mediated Signaling and Cellular Effects

Articular chondrocytes express a ligand-responsive receptor for advanced glycation end products (RAGE), with up-regulated expression in OA cartilage. Binding of AGEs to RAGE can trigger MAPK/NF-κB-centered inflammatory signaling and amplify oxidative stress in chondrocytes, thereby promoting matrix breakdown and cellular injury, as demonstrated in human articular chondrocyte/cartilage studies.[28] At the pathway level, RAGE-driven NF-κB activation and ROS accumulation induce a catabolic transcriptional program typified by up-regulation of matrix-degrading enzymes: MMP-13, a key collagenase for type II collagen, is strongly induced in OA under the control of NF-κB and upstream inflammatory signals; ADAMTS-5, the principal aggrecanase, is likewise activated in inflammatory settings and drives aggrecan loss.[29–31] In parallel with inflammatory amplification, the AGE–RAGE axis elicits mitochondrial and lysosomal stress, leading to increased apoptosis and impaired autophagy. Because autophagy generally confers cytoprotection in chondrocytes, its disruption further undermines matrix homeostasis and stress resilience.[2,32,33]

Notably, the inflammation initiated by AGE–RAGE is coupled to, and reciprocally amplified by, mechanotransduction pathways. Matrix stiffening elevates focal-adhesion tension and augments the integrin–FAK–RhoA axis, facilitating maintenance and escalation of the catabolic phenotype; under compressive and shear loading, NF-κB target genes are induced in chondrocytes, indicating that mechanical forces can directly promote the inflammation–degradation linkage.[34] Moreover, the mechanosensitive Hippo–YAP/TAZ pathway and inflammatory signaling cross-regulate one another: reduced YAP/TAZ activity relieves repression of NF-κB, enhancing expression of MMPs/ADAMTS, whereas preserving or augmenting YAP/TAZ activity can suppress NF-κB–driven inflammatory transcription and slow OA progression—identifying a transcriptional intersection between "inflammation" and "mechanics".[35–37]

Taken together, these data indicate that AGE–RAGE–NF-κB/ROS–driven inflammatory and catabolic programs are interwoven with mechanotransduction networks such as integrin–FAK–RhoA and Hippo–YAP/TAZ, collectively sustaining a vicious cycle of "inflammation amplification → matrix degradation → cell death/autophagy impairment → exacerbated mechanical abnormalities", thereby propagating glycation load from cellular to tissue-level OA pathology.[7,38] Evidence from rheumatoid arthritis (RA) suggests that hypoxic synovial/cartilage microenvironments can stabilize HIF-1α and interact with NF-κB signaling, thereby promoting inflammatory and matrix-degrading mediators such as IL-6, IL-8, and MMPs.[39] However, whether this hypoxia–HIF-1α–NF-κB mechanism directly cooperates with AGE–RAGE signaling in diabetes-related OA remains to be validated. We therefore regard this pathway as a potential extrapolative mechanism rather than an established component of diabetes-related OA pathogenesis. For a tissue-level overview of pathogenic routes and evidence types linked to AGE burden, see Table 1.

Table 1 Roles of AGEs in Joint Tissues and Key Evidence

Tissue	Primary Mechanisms	Evidence Type/Model	Key Observations and Conclusions	Ref.
Hyaline cartilage (COL2)	AGE-mediated crosslinking ↑ → collagen-network stiffness ↑ and toughness ↓; MMP/ADAMTS and NF-κB signaling ↑	Ex vivo + human	Threose-induced glycation stiffened human articular cartilage, supporting "AGE-mediated crosslinking → tissue embrittlement" as an OA-relevant risk mechanism.	[22]
Hyaline cartilage (COL2)	AGE accumulation associated with cartilage aging and end-stage OA	Human end-stage OA cartilage	Cartilage PEN measured by HPLC indicates AGE accumulation as a histological surrogate of aging- and damage-related burden.	[18]
Synovium (FLS)	AGE–RAGE-associated pro-inflammatory changes in FLS	Human OA synovium-derived FLS	AGEs induce RAGE expression and pro-inflammatory/osteoclastogenic marker changes in OA-derived FLS, suggesting that synovial cells may participate in AGE-related metabolic–inflammatory amplification.	[22,31]
Meniscus/joint capsule (COL1-dominant)	AGE accumulation → passive biomechanical deterioration and contracture	Rat knee immobilization/AGE-accumulation model	Accelerated arthrogenic contracture reflects parallel "stiffening–embrittlement–functional decline" of soft tissues and the joint complex.	[26]
Subchondral bone	AGE–RAGE signaling perturbs osteoblast function and material properties; intraosseous PEN ↑ with skeletal fragility	Review; human bone	AGE–RAGE signaling is associated with skeletal fragility; hip-fracture patients show higher bone/serum PEN than OA controls, with a serum–bone PEN correlation.	[40]

Notes: Symbols used in this table: ↑ indicates increased, elevated, or upregulated; ↓ indicates decreased or reduced; → indicates a proposed or observed downstream effect or sequence.

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AGEs, advanced glycation end products; COL1, type I collagen; COL2, type II collagen; FLS, fibroblast-like synoviocyte; HPLC, high-performance liquid chromatography; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; OA, osteoarthritis; PEN, pentosidine; RAGE, receptor for advanced glycation end products.

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How Mechanical Microenvironment Changes Drive Disease Progression

Glycation-induced matrix stiffening first alters chondrocyte adhesion and force distribution: integrin clustering and focal adhesion kinase (FAK) phosphorylation are persistently enhanced, traction forces propagate along the integrin–FAK–RhoA/ROCK axis, and actin stress fibers together with nucleus–cytoskeleton linkages are remodeled. These shifts push cells from an anabolic steady state toward a catabolism-biased mechanobiologic phenotype—a sequence delineated in mechanotransduction reviews and demonstrated in human and animal cartilage studies.[41,42] The multiscale pathogenic cascade linking diabetic metabolic stress, collagen glycation, mechanotransduction dysregulation, and tissue-level joint degeneration is summarized in Figure 2.

The nuclear mechanosensors YAP/TAZ are key termini of stiffness signaling: the stiffer the matrix, the more readily YAP/TAZ translocate into the nucleus and couple to transcriptional networks, whereas inflammatory mediators can promote YAP/TAZ degradation via TAK1, releasing their restraint on NF-κB. This establishes a transcriptional crossroads where "stiffness" and "inflammation" exert bidirectional pull. In human and murine OA models, augmenting YAP activity suppresses NF-κB–driven inflammatory transcription and attenuates cartilage damage, indicating that mechanical and inflammatory programs can antagonize—or be converted into—one another at the transcriptional level.[35,43]

Tunable-stiffness models provide direct causal support: on 2D/3D hydrogels with programmable elasticity, increasing stiffness concomitantly alters chondrocyte morphology, cytoskeletal organization, and intrinsic mechanical modulus, eliciting a suite of stretch and stress-adaptation responses; conversely, restoring the microenvironment to a "cartilage-like" modulus window partially re-establishes homeostatic signaling and phenotype.[44–46] These materials-level observations align with histologic evidence of the "crosslinking → stiffening → catabolism" trajectory and echo the mechanoinflammatory coupling provoked by matrix crosslinking enzymes (eg, lysyl oxidase) in OA.[47]

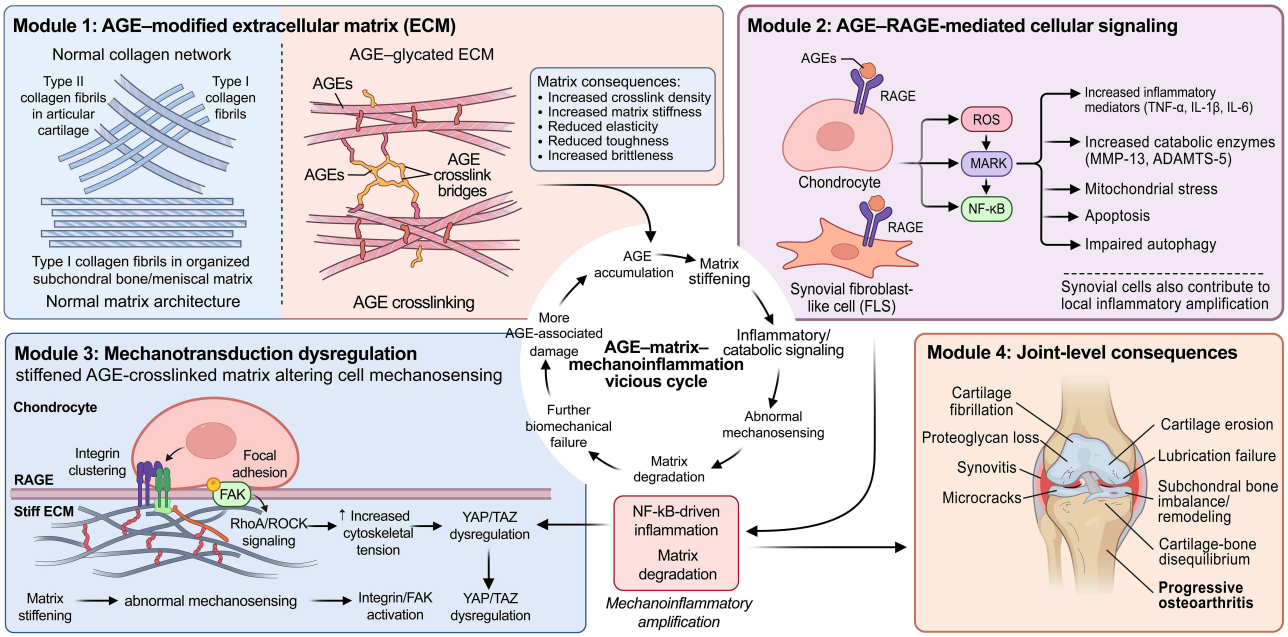

Figure 2 Cellular and mechanotransductive mechanisms linking AGE–collagen crosslinking to inflammatory–catabolic signaling in diabetes-related osteoarthritis. AGE-mediated collagen crosslinking may convert the normal extracellular matrix into an AGE-glycated and mechanically stiffened matrix, with increased crosslink density, reduced toughness, and greater brittleness. In chondrocytes and synovial fibroblast-like cells, AGE–RAGE signaling can activate ROS-, MAPK-, and NF-κB-related pathways, thereby increasing inflammatory mediators, catabolic enzymes, mitochondrial stress, apoptosis, and impaired autophagy. In parallel, matrix stiffening may disturb cellular mechanosensing through integrin clustering, FAK activation, RhoA/ROCK signaling, increased cytoskeletal tension, and YAP/TAZ dysregulation. These biochemical and biomechanical changes may reinforce an AGE–matrix mechanoinflammatory vicious cycle, contributing to cartilage fibrillation, proteoglycan loss, synovitis, lubrication failure, subchondral bone imbalance/remodeling, cartilage–bone disequilibrium, and progressive osteoarthritis.

Abbreviations: ADAMTS-5, a disintegrin and metalloproteinase with thrombospondin motifs-5; AGE, advanced glycation end product; AGEs, advanced glycation end products; ECM, extracellular matrix; FAK, focal adhesion kinase; FLS, fibroblast-like cell; IL, interleukin; MAPK, mitogen-activated protein kinase; MMP-13, matrix metalloproteinase-13; NF-κB, nuclear factor kappa B; RAGE, receptor for advanced glycation end products; ROCK, Rho-associated coiled-coil-containing protein kinase; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha.

At tissue and joint-organ scales, stiffening and embrittlement render load-bearing surfaces more prone to microcracking, fibrillar misalignment, and boundary-lubrication failure under everyday loads. Elevated shear and contact stresses then amplify inflammatory–catabolic signaling while blunting the cartilage's anabolic mechanoresponses, scaling a cell-level mechanical bias into measurable tribological dysfunction and structural degeneration.[48]

Clinical and Epidemiological Evidence: Does Diabetes Independently Worsen OA?

Evidence regarding whether diabetes (DM) independently aggravates osteoarthritis (OA) is not fully concordant: earlier and more recent systematic reviews/meta-analyses have reached conflicting conclusions, largely owing to differences in cohort design (cross-sectional vs. longitudinal), OA definition (self-report vs. radiographic vs. symptomatic), population structure (age, sex, ethnicity), and the rigor of controlling for confounders such as body weight/obesity and physical activity.[49,50] In more methodologically robust longitudinal work, a 20-year population cohort published in *Diabetes Care* reported that type 2 diabetes was independently associated with "severe OA" defined by total knee/hip replacement; after adjustment for age, BMI, and other factors, the hazard ratio remained ≈2.1, with a duration–response relationship, suggesting a metabolic OA signal beyond mechanical loading (observable across sex and BMI strata).[51] At the level of overall association, an earlier multi-region meta-analysis found higher OA risk in people with DM than in non-DM counterparts (OR ≈1.46). Among the 12 studies that at least adjusted for BMI, 7 still indicated an independent association while 5 did not, implying the presence of metabolic pathways only partially overlapping with obesity.[3] By contrast, an updated 2020 meta-analysis in *BMJ RMD Open*—with stricter consideration of BMI—concluded that "DM is not an independent risk factor for OA", highlighting BMI as the dominant confounder. This stance echoes Global Burden of Disease findings that high BMI is a major modifiable risk factor for OA and underscores the need to prioritize confounding and mediation by adiposity/body-fat distribution in study design.[52] Accordingly, throughout this review, "diabetes-related OA" is used as an emerging mechanistic and translational framework, not as a definitively validated clinical phenotype, and the AGE–COL axis is discussed as a biologically plausible contributor whose disease-modifying relevance requires further validation in metabolically stratified cohorts.

Focusing on "disease progression" rather than incidence/prevalence, an analysis of the SEKOIA cohort in *Osteoarthritis and Cartilage* showed that, among patients with established knee OA, type 2 diabetes predicted annualized medial joint-space narrowing, with a more stable association in men—suggesting sex-specific metabolic–cartilage vulnerability pathways in structural worsening.[53] Regarding symptoms and function, longitudinal analyses from the Osteoarthritis Initiative and other clinical studies indicate that knee OA patients with coexisting DM report greater pain, poorer physical/mental health scores, and steeper declines in objective performance over time, providing evidence of "clinical worsening" that complements structural progression findings.[54]

At the biomarker level, noninvasive skin autofluorescence (SAF) and circulating/synovial analytes indexing "AGE burden" offer readouts aligned with imaging and functional outcomes. In a large Rotterdam sample, each unit increase in SAF in women corresponded to greater overall radiographic burden (Kellgren–Lawrence), and in an MRI subcohort SAF positively associated with full- or partial-thickness cartilage defects; results in men were inconsistent, suggesting that sex and endpoint definitions modulate association strength.[55] In another prospective Osteoarthritis Initiative subcohort, "skin AGEs (sAGE)" quantified by intrinsic skin fluorescence independently associated—with adjustment for age and BMI—with 4-year knee joint-space loss in men but not women, reinforcing the biological link between AGE load and structural progression while revealing sex specificity.[56,57] For circulating molecules, multiple studies report elevated serum/synovial AGEs (eg, pentosidine) in OA, correlating with cartilage degradation markers (eg, COMP). Over longer follow-up, higher baseline pentosidine shows a suggestive association with subsequent joint-space loss or radiographic worsening, although consistency and effect size remain limited across cohorts—calling for standardized assays and careful control of renal function and dietary AGE intake.[58] Conversely, soluble RAGE (sRAGE), a decoy receptor, is often reduced in plasma and synovial fluid in knee OA and inversely correlates with Kellgren–Lawrence grade, implying that down-titration of this antagonistic node in the AGE–RAGE axis may accompany greater disease severity and offers a measurable window into "inflammation–metabolism–structure" coupling.[59]

In sum, population-level evidence for the DM–OA relationship unfolds along two parallel threads: one emphasizes an "independent metabolic signal" that persists after rigorous BMI adjustment (eg, severe OA/replacement endpoints, selected structural progression, and worse pain/function); the other underscores potent confounding/mediation by adiposity and physical activity, which can attenuate or even nullify the statistical association under stricter modeling. For identifying "metabolic OA" subgroups and advancing disease-modifying interventions, these lines are not mutually exclusive. Future studies should, within a unified analytic framework, concurrently address (1) decomposition of confounding and mediation by obesity, (2) biomarker stratification by AGE burden and the RAGE axis, and (3) heterogeneity by sex and age—while deploying radiographic (JSN/MRI cartilage volume), symptomatic (pain), and objective performance measures as linked endpoints—to more precisely answer whether, in whom, and through which pathways DM independently worsens OA.[52]

Materials-Based Strategies: From "Repairing" to "Rewriting" the Glycated Matrix

Under conditions of diabetes and OA, AGE–collagen crosslinking may contribute to a joint microenvironment that is stiffer, more brittle, and more inflamed. Accordingly, intra-articular materials are increasingly being explored not only as structural repair tools but also as platforms to modulate the interacting loop of glycation, mechanics, inflammation, and cellular stress responses. On one front, deglycation and prevention of re-glycation are being investigated as potential approaches to reduce pathological crosslinking and recalibrate matrix mechanics; on the other, programmable delivery and immune reshaping may help attenuate low-grade inflammation and support tissue repair. However, most of these strategies remain experimental, and their efficacy in diabetes-related OA has not yet been established clinically.

In recent years, intra-articular (IA) platforms for OA—injectable hydrogels, microsphere/nanoparticle delivery systems, and stimuli-responsive materials—have rapidly emerged. These platforms enable high local exposure at the lesion site with minimal systemic burden, and they allow stage-specific interventions that are temporally and spatially programmable ("right time–right place–right dose"). Multiple systematic reviews and methodological papers now regard such approaches as key levers for translating foundational mechanisms into clinically actionable pathways.[60,61]

Below, we delineate the major material modalities in a modular fashion. For a concise overview of platform composition, payloads, and triggering mechanisms, see Table 2.

Vectorizing Chemical and Enzymatic Anti-AGE Strategies

A dual-track concept— "breaking existing crosslinks + preventing re-glycation"—has been proposed as a potential anti-AGE strategy, although its relevance to diabetes-related OA remains largely exploratory. On the chemical side, thiazolium AGE-crosslink breakers such as alagebrium (ALT-711) have shown compliance-improving or collagen-softening effects mainly in non-joint settings, including vascular studies in elderly participants, obese/diabetic animal models, and vascular graft models.[66,67] Materials-biology studies further suggest that ALT-711 can reduce AGE accumulation, lower collagen-matrix stiffness, and attenuate stiffness-linked pathogenic cell behaviors in engineered or non-OA matrix systems.[68] Together, these data support the physicochemical plausibility that AGE-modified collagen networks may be pharmacologically modifiable, but they should not be interpreted as direct evidence that ALT-711 reverses glycation-associated cartilage stiffening or modifies OA progression. Joint-specific studies are still needed to test cartilage penetration, intra-articular pharmacodynamics, matrix viscoelasticity/toughness, AGE–RAGE-associated signaling, and safety under metabolically relevant OA conditions.

Enzymatic deglycation/decarbonylation represents a complementary but similarly early-stage approach. The combination of fructosamine-3-kinase (FN3K) and fructosyl-amino acid oxidase (FAOD) has been reported to lower autofluorescence and improve elasticity in skin/scar models, while mass spectrometry and in vitro substrate profiling suggest activity against several early glycation adducts.[69,70] However, these findings derive largely from non-joint tissues and should be treated as extrapolative rather than direct OA evidence. Intra-articular translation would require validation of enzyme stability, activity retention in synovial fluid, cartilage penetration, perimatrix localization, immunogenicity, and compatibility with the pH, ionic, and protease-rich milieu of OA.

Table 2 Materials-Based Intervention Strategies (At-a-Glance)

Strategy	Composition	Payload	Release/Trigger	Intended Action	Pros/limits (Summary)	Ref.
Cartilage-targeting nanoplatform (WYRGRL-peptide)	MPDA@MOF core–shell NPs with COL2-targeting peptide (WYRGRL)	Rapamycin + bilirubin (dual)	NIR-triggered sequential release; pH/temperature-tunable	Antioxidation + pro-autophagy; suppress MMP/ADAMTS; metabolic rescue	Cartilage targeting, imageable, prolonged intra-articular residence; requires external NIR device.	[62]
Multiresponsive hydrogel microspheres (MMP-13/hypoxia/ROS)	HA-MA with azo-calixarene monomer; MMP-13-cleavable peptide-crosslinked microspheres	HCQ (etc).	MMP-13-degradation release + hypoxia-promoted release + intrinsic ROS scavenging	Anti-inflammation/ROS clearance; cartilage protection	Matches OA microenvironment (MMP-13/hypoxia/ROS) for on-demand delivery; complex formulation—scale-up/QC need validation.	[30]
Injectable rapamycin hydrogel (immuno-materials)	Injectable polymer/physical gel	Rapamycin	pH/thermo-controlled sustained release	Polarize synovial macrophages (M1→M2); reduce synovitis	Single IA dose reduces inflammation and improves cartilage; low systemic AEs with rapamycin, but long-term regimen needs evaluation.	[63]
Exosome-adhesive hydrogel (Exo-Hydrogel)	Oxidized chondroitin-sulfate /gelatin adhesive hydrogel	BMSC-Exos	Dynamic Schiff-base self-healing/adhesion → sustained release	Promote M2, anti-inflammation, lubrication + regeneration	Adhesive + long residence; improves histology and inflammatory indices; source/batch consistency and regulatory class need standardization.	[64]
Osteochondral gradient composite scaffold (3D-printed/continuous gradient)	Multimaterial zonation or continuous mineralization gradient (eg, PCL/HAp/gelatin)	Optional TGF-β/VEGF/anti-AGE agents	Structural–mineral–pore continuous gradients	Concurrent cartilage + subchondral bone repair; optimized stress transfer	Strong mechanics and interfacial integration; high customization and surgical coordination required.	[65]
Stimuli-responsive nano/hydrogels (review exemplars)	Natural/synthetic polymer systems (various)	Multiple anti-inflammatory/antioxidant/anti-AGE agents	pH/enzymes/ROS/light/ultrasound, etc.	Microenvironment-sensing, on-demand release	Recent 3-year strategies and limitations summarized—useful for platform selection and combinatorial design.	[61]

Notes: "Anti-AGE" may act via (i) anti-reglycation (carbonyl scavenging/MGO clearance/GLO-1 activation), and/or (ii) loading AGE-breakers (eg, ALT-711)—mostly extra-articular evidence to date; requires materials-enabled targeting/amplification.

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AGEs, advanced glycation end products; BMSC, bone-marrow stromal cell; COL2, type II collagen; Exos, exosomes; GLO-1, glyoxalase-1; HA-MA, hyaluronic acid-methacrylate; HAp, hydroxyapatite; HCQ, hydroxychloroquine; IA, intra-articular; MGO, methylglyoxal; MMP-13, matrix metalloproteinase-13; MOF, metal–organic framework; MPDA, mesoporous polydopamine; NIR, near-infrared; PCL, poly(ε-caprolactone); ROS, reactive oxygen species; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; WYRGRL, COL2-binding peptide.

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Overall, chemical and enzymatic anti-AGE approaches provide mechanistic inspiration for biomaterials design, especially when paired with targeted or stimuli-responsive hydrogels, microspheres, or nanocarriers.[14,71,72] However, future studies should clearly distinguish biochemical deglycation, cartilage-matrix mechanical modulation, and true disease modification in metabolically relevant OA models.

Tunable-Stiffness and Biomimetic Hydrogels

Because glycation can increase collagen-network crosslink density and shift cartilage-like tissues toward a "stiffer but more brittle" state, approximating a cartilage-like viscoelastic window has become an important design goal for injectable hydrogels. This window includes appropriate elasticity, viscoelasticity, lubrication, and energy-dissipation capacity, rather than simple stiffness reduction alone. Injectable hydrogels, with controllable crosslinking and dynamic networks, such as reversible covalent bonds and supramolecular interactions, can gel in situ after minimally invasive administration and distribute over damaged cartilage surfaces and joint spaces. These systems may function both as drug depots and as mechanical microenvironment modulators by combining programmable modulus, lubrication, and energy dissipation.[73] However, whether such mechanical modulation can durably alter disease progression in metabolically complicated OA remains an open translational question.

Recent reviews synthesize structure–function principles for HA-, PEG-, and composite hydrogel systems in OA. These include dual chemical/physical networks, dynamic covalent chemistries such as Schiff base and boronate ester bonds, ionic or hydrogen bonding, and host–guest interactions, all of which allow tunable control over modulus, toughness, injectability, degradation, and payload release. In the context of diabetes-related OA, these design features may be particularly relevant because they provide an experimental platform to examine whether local modulation of the glycated and mechanically altered matrix can attenuate inflammatory–catabolic signaling and support cartilage homeostasis.[14]

HA-based dynamic hydrogels are widely adopted for their affinity to joint ECM and their mild crosslinking under physiological conditions. Network "remodelability" helps disperse peak stresses, reduce crack propagation, and provide reversible niches for cells/exosomes or small molecules. Methodological and applications-focused appraisals emphasize that, through molecular-weight selection, degree-of-substitution, and crosslink-site design, one can obtain a cartilage-like viscoelastic spectrum without sacrificing injectability, and further incorporate adhesive/targeting motifs for lesion enrichment.[74] In self-healing HA hydrogels, reinforcement via nanoclay/phenolic hydroxyls or dual dynamic bonds enables resistance to repeated in vivo shear while maintaining lubrication and anti-inflammatory effects; animal studies show attenuation of wear and restoration of anabolic chondrocyte phenotypes, substantiating an integrated effect of "mechanical re-normalization + microenvironment reprogramming".[75]

To improve in vivo localization and evaluability, a new generation of radiopaque, self-healing HA hydrogels integrates iodine-bearing groups or nano-contrast agents into the network, enabling in situ tracking by X-ray/CT while preserving mechanical and delivery performance under cyclic loading. Preclinical intra-articular studies in small and large animals suggest that such "visualizable hydrogels" could bring dose–position–time information into the clinical translation loop.[76] In parallel, lubrication- and dissipation-oriented designs are evolving from "single-function" to "multifunctional": boundary-lubricating composites, shear-responsive lubricating mesh works, and double-network architectures can maintain low friction under high loads and suppress inflammatory amplification—complementary to modulus-tuning strategies.[76]

Within PEG/protein/peptide systems, in situ gelling via Diels–Alder cycloaddition, click chemistry, and enzymatic crosslinking expands the operative window of "injectable → set-in-place → degradable" intra-articular workflows. These platforms facilitate parallel integration of anti-AGE modules—anti-inflammatory, carbonyl/ROS scavenging—with mechanical regulation. Reviews and methods papers across Wiley and Elsevier emphasize that tunable modulus, enhanced toughness, and network dynamics are pivotal for in vivo durability and load accommodation, and they serve as essential building blocks for coordinating "systemic metabolic therapy + local biomaterials" strategies.[73]

Smart, Stimuli-Responsive Carriers: PH/Enzyme/Redox-Triggered Anti-Inflammatory and Anti-AGE Delivery

Lesions in diabetes-related OA exhibit mild acidification (lowered synovial/joint-fluid pH), heightened protease activity (notably MMP-13/ADAMTS), and elevated ROS burden. These microenvironmental shifts both drive inflammation–catabolism and furnish programmable triggers for on-demand release. pH-, enzyme-, and ROS-responsive hydrogels and nanosystems built around these cues can raise effective intra-articular exposure during mechanical or inflammatory peaks while reducing systemic exposure and adverse effects. Methodological and systematic reviews increasingly regard these platforms as pivotal for transitioning local IA therapy toward disease modification.[77]

pH-Responsive Designs

HA/PEG composite networks that gel in situ after injection can accelerate drug efflux under the mildly acidic conditions of OA, achieving dynamic provisioning— "high delivery during inflammatory flares, low baseline during remission". Using rapamycin (an mTOR inhibitor) as a model payload, pH-sensitive hydrogels reduced synovitis and improved histologic cartilage scores in knee-OA animals, validating an acid-triggered anti-inflammatory loop. Earlier gelatin–rapamycin micelles likewise showed that IA delivery can significantly restrain OA progression, laying a reference point for subsequent pH/multiresponsive platforms.[63]

ROS-Responsive Systems

These exploit excess peroxides/free radicals in OA tissues as "switches", using oxidizable linkages (eg, boronate esters, thioethers) or antioxidant networks to couple on-demand release with in situ ROS scavenging. Recent work encapsulated MMP-13 siRNA nanocarriers within ROS-responsive hydrogels, markedly mitigating cartilage degeneration, osteophyte formation, and pain behaviors in DMM mice. In temporomandibular-joint OA, ROS-responsive self-healing hydrogels likewise reduced inflammation and promoted repair, illustrating synergy among antioxidation, anti-catabolism, and pro-regeneration. Reviews further highlight macrophage-polarization remodeling as a key mechanism of action for such materials.[78]

Enzyme-Responsive Platforms

Leveraging overexpressed MMP-13/ADAMTS-5 in OA, one approach embeds small-molecule inhibitors within hydrogels that release cargo upon MMP-13 cleavage, yielding highly selective, durable IA exposure. Another deploys MMP-13-responsive microspheres to match inhibitory intensity to lesion spatiotemporal dynamics, slowing structural progression without increasing systemic burden. Integrative assessments of enzyme-linked materials for inflammatory–oxidative arthropathies also emphasize pairing with antioxidant enzymes/scavenging systems.[79]

Targeting the AGE/RAGE Axis Locally

Stimuli-responsive carriers can sustain the release of RAGE inhibitors or anti-carbonyl/antioxidant polyphenols to dampen AGE–RAGE-driven NF-κB activation and downstream catabolism. In vitro/cellular studies show polyphenols such as EGCG down-regulate RAGE and suppress ROS and NF-κB; small-molecule RAGE antagonists (eg, azeliragon/TTP488) already have human safety data and are conceptually suited for low-dose IA reformulation to limit systemic exposure, though this indication awaits clinical validation.[80]

Dual Metabolic–Inflammatory Targeting

Agents such as GLP-1 receptor agonists—shown in preclinical studies and reviews to inhibit NF-κB and reduce ROS and MMP-3/13/ADAMTS-4/5—and metformin—which improves the OA microenvironment via AMPK–mTOR/autophagy and antioxidant pathways—can be incorporated into responsive networks to achieve "local low dose, lower systemic load". Because metformin clears rapidly from the joint, sustained residence and controlled release require injectable hydrogels or DNA supramolecular gels. Loading these molecules into pH/ROS/enzyme-responsive matrices enables "adaptive" up-titration of local concentration during inflammatory or oxidative surges, balancing efficacy with safety.[81]

Nanoparticle and Exosome Delivery Systems

Articular cartilage is dense, avascular, and enriched with a highly sulfated, negatively charged glycosaminoglycan network—features that contribute to short intra-articular residence and poor tissue penetration for many therapeutic agents. Engineering strategies may partly convert this barrier into a local drug reservoir through two complementary routes: charge-driven transport and ligand-directed targeting.

On the charge-driven route, cationic carriers undergo reversible electrostatic partitioning and electro-diffusive co-transport with the fixed negative charges of cartilage, enabling rapid intratissue ingress and prolonged retention without overt disruption of tissue architecture. Multi-arm cationic nanostructures such as multi-arm avidin (mAv) show ≥7-day tissue–joint distribution and programmable kinetics in rat knees, achieving single-dose, cartilage-entering intra-articular delivery, for example using kartogenin as a model payload, with histological benefit in preclinical OA settings. Earlier foundational studies using avidin/cationic proteins as charge-driven models demonstrated long-lived, weakly reversible binding within cartilage, providing a biophysical basis for such platforms.[82] In parallel, cartilage-penetrating cationic peptides (CPCs) tuned for net charge, hydrophobicity, and spatial distribution exhibit enhanced trans-tissue transport and binding in both healthy and arthritic cartilage, supporting the general strategy of using charge to improve cartilage penetration and retention.[83]

On the ligand-directed route, cartilage- or collagen-homing peptides further improve on-target efficiency and tissue selectivity. The phage-display-derived sequence WYRGRL binds specifically to the α1 chain of type II collagen and has been used to deliver inhibitors or antioxidant nanomedicines to articular cartilage, achieving deeper penetration and longer retention. Recent cerium oxide nanoformulations modified with this ligand, such as WY–PEG–CeO, prolonged intra-articular residence, enhanced cartilage penetration, and alleviated cartilage degeneration in preclinical OA models.[62,84] These findings suggest that combining charge-based penetration with ligand-directed targeting may strengthen local delivery performance, although its specific advantages in glycation-stiffened or diabetes-related OA cartilage remain to be directly tested. Addressing the engineering trade-offs among charge, size, and density, systematic reviews and methodological studies provide parameterized guidance: within safety limits, moderately increasing positive charge density and compactness may improve penetration, binding, and intra-articular half-life, offering design principles for subsequent composites with hydrogels or microspheres.[85]

In parallel with inorganic and polymeric nanocarriers, exosomes—natural vesicles carrying proteins, lipids, and nucleic acids—are being investigated as immunomodulatory and pro-regenerative delivery platforms for OA. OA-specific reviews and preclinical meta-analyses suggest that stem-cell-derived exosomes can promote cartilage matrix synthesis, attenuate inflammatory signaling, modulate synovial and subchondral bone responses, and improve histological OA severity in animal models.[85] However, the current evidence remains predominantly preclinical, and clinical disease-modifying efficacy in OA has not yet been established. Broader musculoskeletal-regeneration literature on stem-cell-derived exosomes and gene-vector systems, including intervertebral disc degeneration, may inform platform design, cargo engineering, and local delivery concepts, but should be cited only as cross-tissue translational background rather than as direct OA efficacy evidence.[86]

Materials engineering may further improve exosome retention and spatial control within the joint. Exosome–hydrogel or exosome–microsphere hybrids can reduce passive clearance and enable more sustained or directional release. Photo-crosslinkable or thermosensitive spherical hydrogels encapsulating ligand-modified engineered exosomes have shown cartilage-protective and anti-inflammatory effects in preclinical OA models.[64,87] These systems suggest that coupling exosome bioactivity with materials-controlled delivery may help overcome the short intra-articular half-life of vesicle therapies, but dose, source, purification, potency assays, biodistribution, and long-term safety still require standardization.

Overall, cationic/ligand-directed nanocarriers and exosome–material hybrids represent two complementary delivery strategies: the former are engineered platforms designed to improve cartilage penetration and local retention, whereas the latter are bio-derived platforms with immunomodulatory and regenerative potential. Against a background of glycation-associated matrix stiffening and inflammatory imbalance, both may serve as modular carriers for anti-AGE/RAGE, antioxidant, anti-inflammatory, or pro-regenerative payloads. Nevertheless, their application to diabetes-related OA should be considered exploratory until validated in metabolically relevant OA models with standardized pharmacokinetic, biomechanical, histological, and functional endpoints.[88]

Osteochondral Gradient Composite Scaffolds

In diabetes-related OA, abnormal subchondral bone remodeling, including reduced mineral density and increased porosity, may disturb bone–cartilage coupling and aggravate cartilage degeneration even after adjustment for body weight.[89] Therefore, repair strategies should address not only cartilage defects but also the cartilage–calcified cartilage–subchondral bone interface. Osteochondral gradient composite scaffolds provide a materials-based approach by integrating mechanical gradients and bioactive zonation. By varying composition, porosity, mineralization, elastic modulus, and factor distribution, these constructs can approximate the layered transition from hyaline cartilage to calcified cartilage and subchondral bone, thereby supporting interfacial integration, stress transfer, and osteochondral repair.[40,90]

For diabetes-related OA, the relevance of such scaffolds lies not only in structural reconstruction but also in their potential to incorporate microenvironment-modulating components. Cartilage-side phases may be designed to carry antioxidant, anti-carbonyl, or RAGE-inhibitory modules, whereas bone-side phases may provide osteogenic or angiogenic cues under metabolically stressed conditions. This structural–biochemical dual-gradient concept could support coordinated chondrogenic and osteogenic repair while allowing local modulation of AGE-related stress. However, direct evidence in diabetes-related OA remains limited, and future studies should validate scaffold performance in metabolically relevant OA models with attention to interface mechanics, degradation behavior, local inflammatory responses, and long-term osteochondral integration.[65]

Immunomodulatory Materials

Diabetes-associated low-grade chronic inflammation keeps the synovium–cartilage interface in an M1-skewed immune disequilibrium. Materials can "push back" the local milieu toward an M2 bias through surface chemistry and controlled release of immunoregulatory factors. For example, intra-articular delivery of mTOR inhibitors such as rapamycin via injectable hydrogels polarizes synovial macrophages toward M2, down-regulates TNF-α/IL-1β/IL-6, and attenuates synovitis and structural deterioration in rat knee OA—supporting the notion that combining immune biasing with sustained exposure helps stabilize anti-inflammatory programs.[63]

ECM-functionalized hydrogels provide mesenchymal stem cell (MSC)-derived metabolic and adhesion cues capable of reprogramming synovial macrophages without added drugs. By improving mitochondrial function and cellular bioenergetics, these matrices suppress inflammatory pathways and promote expression of cartilage homeostasis–related genes; in rodent OA models, they reduce inflammatory cytokines and improve histologic scores.[91]

Cytokine-driven immune skewing is also feasible. Bilayer microspheres enabling controlled release of IL-4 achieve temporally staged delivery ("outer anti-inflammatory layer, inner M2-polarizing layer"), thereby enhancing COL2/proteoglycan expression and suppressing intra-articular inflammation. Local administration of IL-10 or an IL-4/IL-10 fusion protein likewise yields analgesic and chondroprotective signals in rodent arthritis models, indicating platform compatibility between anti-inflammatory cytokines and delivery carriers.[92]

Adaptive antioxidant/ROS-scavenging gels can actively "adsorb" radicals during inflammatory flares while releasing therapeutics, thereby lowering oxidative stress and steering macrophages toward M2 polarization. Thermosensitive gels containing copper nanodots and redox-responsive gels employing oxidizable linkages have demonstrated an in vivo cascade of ROS removal → M2 promotion → cartilage protection.[93,94]

Exosomes, as natural vesicular carriers, combine immunomodulatory and pro-regenerative attributes. Multiple high-quality reviews synthesize evidence that MSC-derived exosomes suppress NF-κB, promote M2 polarization, and support cartilage repair; embedding exosomes in hydrogels significantly extends intra-articular residence and enables directional, on-demand release. Exosomes derived from M2 macrophages (M2-Exos), loaded into adhesive/self-healing gels, further reduce inflammation and pathology in OA animal models.[95]

For clinical translation, immuno-materials can operate synergistically with anti-AGE strategies and mechanical re-normalization. On one hand, microenvironment-responsive carriers provide long-acting, localized, low–systemic exposure delivery platforms for rapamycin, antioxidant components, and inhibitors of the RAGE axis; on the other, ECM functionalization and exosome–hydrogel hybrids can durably recalibrate the immune ecosystem without altering joint-scale mechanics. Overall, these pathways align with prevailing consensus in "materials-for-regeneration" and "materials-for-drug-delivery" directions.[96]

Synergy with Systemic Metabolic Interventions

Systemic metabolic interventions may create a more favorable biological and mechanical background for local biomaterial strategies in selected patients with OA complicated by obesity or metabolic dysfunction. Weight reduction can decrease joint loading and may attenuate systemic inflammatory tone, but these effects do not by themselves establish diabetes as an independent driver of OA progression. In the STEP-9 randomized controlled trial (N=407; 68 weeks), once-weekly semaglutide 2.4 mg produced greater weight loss than placebo (−13.7% vs −3.2%) and significantly reduced WOMAC pain (−41.7 vs −27.5 points), with concomitant improvement in the SF-36 physical component. Rates of drug-related serious adverse events were similar, although discontinuation due to gastrointestinal effects was more common with semaglutide (6.7% vs 3.0%).[97] These findings support the clinical relevance of semaglutide-associated weight reduction in obesity-associated knee OA, and are consistent with current OA guidelines that prioritize weight management as a core non-pharmacological intervention.[98,99] However, STEP-9 does not directly establish a mechanistic pathway linking systemic metabolic correction to reduced local mechanical/inflammatory stress or structural disease modification, nor does it validate biomaterials-based interventions in diabetes-related OA. Rather, it supports the need to consider metabolic status and weight management in future stratified studies of local biomaterial therapies.

Mechanistically, GLP-1 receptor agonists (GLP-1RAs) may have effects that extend beyond weight loss, although the clinical relevance of these mechanisms for OA disease modification remains uncertain. Anti-inflammatory and antioxidant signaling, including AMPK activation, NF-κB inhibition, and CRP reduction, has been reported in clinical and experimental studies, providing a rationale for exploring possible interactions between metabolic therapy and local microenvironment-modulating materials. Systematic reviews and meta-analyses suggest that semaglutide can reduce CRP levels across different formulations and populations.[100] At the joint level, preclinical studies indicate that GLP-1R is expressed in chondrocytes and synovial macrophages; liraglutide has been reported to suppress iNOS, MMP-13, and ADAMTS-5 and to attenuate hypersensitivity in inflammatory pain models, suggesting potential anti-inflammatory and anti-catabolic effects.[101] In addition, in vitro AGE-induced chondrocyte models suggest that liraglutide may inhibit RAGE-related signaling, reduce inflammatory and apoptotic responses, and partially preserve matrix-related markers.[102] These findings are mechanistically consistent with the AGE–COL framework, but they remain insufficient to establish GLP-1RAs as disease-modifying therapies for diabetes-related OA.

Accordingly, a cautious and testable combination framework can be proposed. Systemically, GLP-1RAs and lifestyle-based weight management may reduce body weight, improve metabolic status, and lower the inflammatory baseline in selected patients. Locally, injectable, modulus-tunable, and microenvironment-responsive materials could be used to deliver anti-inflammatory, antioxidant, or anti-AGE payloads, or to integrate RAGE-inhibition and immune-modulating modules such as M2-polarizing designs and exosome-based systems. Rather than assuming a direct "systemic metabolic correction → local joint restoration" pathway, future studies should evaluate whether systemic metabolic improvement enhances the retention, pharmacodynamics, and structural or symptomatic efficacy of local biomaterials. Practical issues also require attention, including GLP-1RA-related gastrointestinal adverse effects and discontinuation rates, as well as the need for imaging-visible constructs, intra-articular pharmacokinetic monitoring, and patient stratification by obesity, glycemic control, AGE burden, and inflammatory phenotype.[97] The overall biomaterials-based therapeutic framework for diabetes-related osteoarthritis, including local matrix-modulating strategies and their potential interaction with systemic metabolic intervention, is summarized in Figure 3.

Animal Models, Endpoints, and Methodological Standardization

Along the translation chain linking "diabetes → AGE–COL axis → osteoarthritis", in vivo designs must model both metabolic burden and joint injury as converging causal threads, and apply a cross-scale, reproducible endpoint framework that connects molecular, tissue, biomechanical, and functional readouts. To ensure external comparability and reporting quality, we recommend strict adherence to ARRIVE 2.0 (randomization, blinding, sample-size justification, preregistration, exclusion criteria, etc), and explicit reporting of strain, sex, age, diet, and procedures for validating glycemic/insulinemic phenotypes in the Methods.[103]

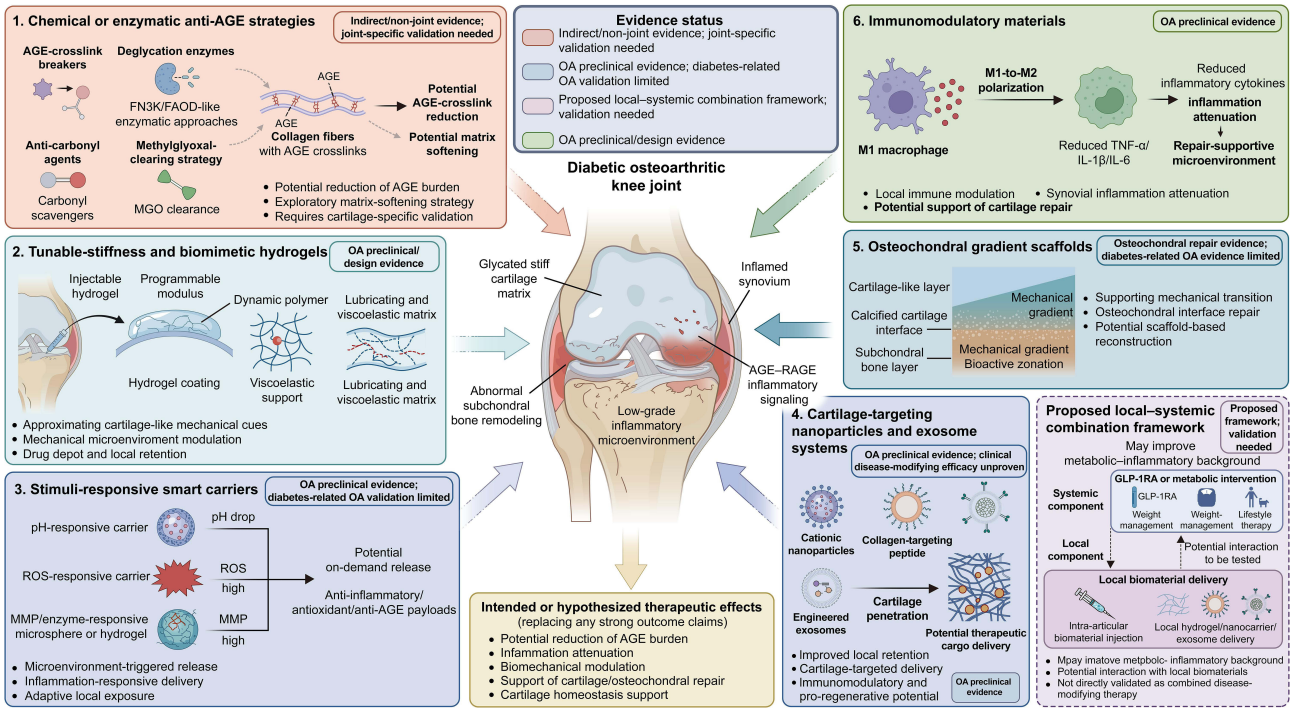

Figure 3 Emerging biomaterials-based strategies for diabetes-related osteoarthritis. The central panel depicts a diabetes-related osteoarthritic knee joint characterized by a glycated stiff cartilage matrix, inflamed synovium, abnormal subchondral bone remodeling, a low-grade inflammatory microenvironment, and AGE–RAGE inflammatory signaling. Surrounding modules present candidate biomaterial strategies, including chemical or enzymatic anti-AGE approaches, tunable-stiffness hydrogels, stimuli-responsive carriers, cartilage-targeting nanoparticles or exosome systems, osteochondral gradient scaffolds, and immunomodulatory materials. The intended effects include potential reduction of AGE burden, inflammation attenuation, biomechanical modulation, cartilage/osteochondral repair support, and cartilage homeostasis support; these should be regarded as hypothesized or preclinical effects rather than confirmed clinical outcomes. The lower-right panel presents a proposed local–systemic combination framework integrating systemic metabolic intervention with local biomaterial delivery, which remains to be validated.

Abbreviations: AGE, advanced glycation end product; AGEs, advanced glycation end products; FAOD, fructosyl-amino acid oxidase; FN3K, fructosamine-3-kinase; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; IL, interleukin; MGO, methylglyoxal; MMP, matrix metalloproteinase; OA, osteoarthritis; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha.

Models and Induction Strategies

Diabetes Modeling and Validation

Common approaches include streptozotocin (STZ) to induce type 1–like hyperglycemia, high-fat diet (HFD) plus STZ or genetic obesity/insulin-resistance models (db/db, ob/ob) to simulate type 2–like metabolic derangement. Joint phenotypes are not uniform across models: the literature indicates that HFD accelerates cartilage degeneration in post-traumatic OA settings beyond what can be explained by body weight alone, whereas some db/db studies report no marked cartilage differences—implying that "metabolic composition", rather than mechanical load per se, determines joint susceptibility. Accordingly, eligibility criteria should prespecify fasting/postprandial glucose, insulin, HOMA-IR, body composition, and activity level as confounders for baseline control and stratification.[104]

OA Induction and Indication Alignment

Destabilization models (eg, DMM) recapitulate the common clinical trajectory of meniscal/ligament injury leading to PTOA, with predictable time courses for cartilage damage, osteophytes, and subchondral sclerosis. Chemical mono-iodoacetate (MIA) models hinge on glycolytic inhibition in chondrocytes and are better suited to analgesia/behavioral pharmacodynamics. ACL/meniscal resection and joint immobilization model high-load and disuse contexts. Model selection should match the research question: for "metabolic burden + mechanical instability", a sequential "metabolic priming → DMM" design is appropriate; for pain-pathway and analgesic materials, MIA is preferable.[105]

Combined Designs and Timeline Recommendations

In composite "DM→OA" models, we recommend first establishing a ≥8–12-week metabolic-phenotype stabilization period (according to model type and glucose/insulin readouts), followed by DMM and 2–12 weeks of follow-up to span

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the critical windows of "inflammatory surge → cartilage degradation → subchondral bone remodeling". Controls should include OA-only, DM-only, and sham/vehicle groups. Within the 2–12-week DMM interval, literature shows progressive increases in cartilage degeneration and synovitis scores; subchondral morphometrics (BV/TV, Tb.Th, Tb.Sp) can be longitudinally tracked by μCT to evaluate coupled intra-articular remodeling.[106]

Endpoint Framework and Standardization

A tiered endpoint framework should connect structural, molecular, biomechanical, imaging, and functional readouts, while avoiding reliance on any single outcome measure. For structural assessment, histology should use standardized OARSI scoring with species-specific criteria, compartmental evaluation, and transparent reporting of section depth and sampling planes. Subchondral bone changes should be quantified by μCT according to established reporting standards, including voxel size, thresholding strategy, and predefined VOIs, with outputs such as BV/TV, Tb.Th, Tb.Sp, SMI, and pore connectivity. Where feasible, quantitative MRI approaches such as T2/T1ρ/dGEMRIC can complement histology and μCT by providing cartilage compositional and clinically translatable imaging readouts.[107,108]

Mechanical and molecular endpoints are particularly important for studies targeting the AGE–COL axis. Cartilage indentation or compressive testing should report both instantaneous and equilibrium responses, because these parameters reflect collagen-network stiffness and proteoglycan-associated matrix properties, respectively. Friction and lubrication testing may further capture surface failure and material performance, especially for self-lubricating hydrogels or interfacial coatings; therefore, lubricant, normal load, sliding speed, contact geometry, and hydration conditions should be specified.[109,110] In parallel, molecular readouts should assess AGE–RAGE–NF-κB activation, oxidative stress, and catabolic/anabolic balance, including RAGE, p-p65, NOX/ROS, MMP-13, ADAMTS-5, COL2A1, ACAN, COL10A1, and RUNX2. Immune and synovium–cartilage crosstalk can be evaluated using macrophage markers such as CD68, iNOS, and CD206, together with cytokine panels including IL-1β, TNF-α, IL-6, and IL-10.[111]

Functional and reproducibility endpoints should be integrated into the same experimental design. Pain and function are best assessed with complementary behavioral measures, including static/dynamic weight-bearing, mechanical allodynia, gait profiling, and spontaneous activity assays; reporting should include acclimation, circadian timing, device settings, and assessor blinding.[112,113] Time-point selection should match disease kinetics: weeks 2–4 generally capture inflammatory and early compositional changes, weeks 6–8 reflect structural damage, and later time points can assess osteophyte formation and subchondral remodeling. Studies should include a priori sample-size calculations based on expected differences and variance in OARSI scores, μCT parameters, or other primary endpoints.[114] Cross-center harmonization further requires blinded histological scoring with inter-rater reliability, μCT phantom calibration and threshold locking, standardized mechanical testing parameters, preregistered behavioral analysis pipelines, and retention of raw images or trajectories for auditability.[115] A detailed endpoint panel is summarized in Table 3.

Translational Challenges and Regulatory Considerations

For prolonged intra-articular residence and sustained release, the first priority is to build an auditable chain of evidence for biocompatibility and degradative safety. The FDA's latest application guidance on ISO 10993–1 specifies that, within a risk-management framework, conventional biological evaluations (cytotoxicity, sensitization, pyrogenicity, genotoxicity, implantation, etc.) must be paired with rigorous chemical characterization of materials, assessment of extractables/leachables and degradation products, and clear descriptions of in vivo metabolism and clearance. These elements directly support consistency and comparability in 510(k)/IDE/PMA submissions.[118]

For natural polymers and their composites—exemplified by hydroxyapatite (HA), collagen, and chitosan—batch-to-batch consistency remains a key regulatory "hard point". Under the ICH Q8/Q9/Q10 paradigm of Quality by Design (QbD) and Quality Risk Management (QRM), the Chemistry, Manufacturing, and Controls (CMC) dossier should define and continually monitor critical quality attributes (CQAs)—such as molecular weight, degree of substitution, crosslinking density, and impurity profile—together with the corresponding critical process parameters (CPPs).

For products in drug–device combination (DDC) form, compliance with EU/EMA quality and compatibility expectations is also required, including compatibility with syringes or introducer devices, extractables/leachables analyses, and both accelerated and long-term stability studies, to ensure overall product safety and performance control.[119]

Table 3 Preclinical and Clinical Endpoints with Recommended Methods

Evaluation tier	Indicator/Tool	Recommended Method/Standard	Recommended Time Points	Ref.
Molecular (AGE burden)	PEN, CML	Cartilage/tissue or biofluid PEN: HPLC with fluorescence; CML: ELISA or LC–MS; report intra-/inter-batch CV	Baseline; 4–8 and 12 weeks post-surgery/dosing; terminal histology in parallel	[18]
Molecular (inflammation/catabolism)	MMP-13, ADAMTS-5, IL-1β, TNF-α	qPCR, WB, ELISA on synovial fluid/tissue	Same as above; pair with carrier PK sampling	[18]
Histology	OARSI scoring (mouse/rat/rabbit)	OARSI Histopathology Initiative standardized scoring (mouse 0–6 scale; whole-joint human–mouse schema also used)	Terminal (6–12 weeks); for DMM/ACLT include 4/8/12-week longitudinal reads	[107]
Mechanics	Cartilage compression/indentation modulus; friction coefficient	Follow systematic reviews and automated indentation mapping; record sample hydration/thickness	Parallel with histology; add in vivo tribology substudies as needed	[110]
Imaging	μCT (subchondral plate thickness/ trabecular metrics); MRI T2*/ dGEMRIC	Quantitative structure–function; paired with histology	Baseline and end-of-follow-up; add mid-course scan in live animals if feasible	[108]
Animal function	Joint nociception/gait/activity	Published quantitative nociception and gait methods; treadmill/spontaneous activity monitoring	Every 2–4 weeks (matched to dosing cadence)	[113]
Human (if translational)	WOMAC, KOOS, SF-36	Use validated WOMAC/KOOS references; ensure version and linguistic validation	Baseline; 12/24/52 weeks; consider pairing with SAF as an AGE surrogate	[99,116,117]
Cutaneous AGE surrogate	SAF (AGE-Reader)	Noninvasive SAF; validated as reflecting systemic AGE burden	Baseline; 12/24/52 weeks; analyze alongside weight/glucose/lipid metrics	[57]

Abbreviations: ACLT, anterior cruciate ligament transection; ADAMTS-5, a disintegrin and metalloproteinase with thrombospondin motifs-5; CML, Nε-carboxymethyl-lysine; CV, coefficient of variation; DMM, destabilization of the medial meniscus; dGEMRIC, delayed gadolinium-enhanced MRI of cartilage; ELISA, enzyme-linked immunosorbent assay; HPLC, high-performance liquid chromatography; IL-1β, interleukin-1 beta; KOOS, Knee injury and Osteoarthritis Outcome Score; LC–MS, liquid chromatography–mass spectrometry; MMP-13, matrix metalloproteinase-13; MRI, magnetic resonance imaging; OARSI, Osteoarthritis Research Society International; PEN, pentosidine; qPCR, quantitative polymerase chain reaction; SAF, skin autofluorescence; SF-36, 36-Item Short Form Health Survey; T2*, transverse relaxation time (star); TNF-α, tumor necrosis factor alpha; WB, Western blot; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; μCT, micro-computed tomography.

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With respect to immunogenicity and local reactions, intra-articular dosing confers low systemic exposure, yet source materials and crosslinking chemistries can modify immune responses and the synovial irritation threshold. Study designs should therefore prioritize monitoring of local adverse events (acute synovitis, effusion, fever), with prespecified criteria for drug interruption/rescue, synovial-fluid cytology, and inflammatory panels. For materials containing bioactive protein/exosome components, release testing should follow biologics pathways, reinforcing sterility, endotoxin, residual DNA/protein, and stability controls. Regarding exosomes per se, the FDA has clarified in safety communications and warning letters that no exosome products are currently approved; such products fall under drug/biologic regulation, and prior "regenerative therapy" marketing has led to serious adverse event alerts. Any IA-EV program must proceed via compliant IND/BLA routes and adhere to ISEV's MISEV2023 technical standards for preparation/characterization and reproducibility.[120]

Concomitant therapy and population selection should make interaction with systemic metabolic interventions explicit. STEP-9 showed that once-weekly semaglutide 2.4 mg over 68 weeks yielded greater weight loss and significantly reduced WOMAC pain, underscoring the real-world basis for "upstream weight loss/metabolic correction → downstream reductions in load and inflammatory pressure". Early IA-materials trials should therefore preplan GLP-1RA/metformin use as stratified subgroups and monitor gastrointestinal adverse events, hypoglycemia, and the impact of rapid weight change on joint loading. For inclusion/stratification, we recommend a four-axis scheme—HbA1c (glycemic control), adiposity/body composition, complications (eg, neuropathy, nephropathy), and AGE-burden surrogates (skin autofluorescence[SAF] or serum AGEs)—to reduce metabolic heterogeneity and its confounding of efficacy readouts.[97]

Early-phase clinical pathways should prioritize "safety first, with sensitive endpoints in parallel". Phase I/Ib should emphasize single/multiple IA dose escalation, focusing on local/systemic adverse events, synovial fluid and plasma exposure, and imaging safety signals. Phase IIa/IIb should incorporate the OMERACT–OARSI core domains (pain, function, quality of life, patient global assessment) and add structural/compositional MRI (T2/T1ρ/dGEMRIC) as sensitive secondary endpoints. Symptom, function, and health-related quality-of-life outcomes may be captured using validated instruments such as WOMAC for hip/knee OA, KOOS for knee-related symptoms and function, and SF-36 as a generic quality-of-life measure in OA trials.[99,116,117] Proposals to employ "structural endpoints" must be cross-referenced to the FDA guidance on OA structural endpoints, detailing the evidence bridge to clinical benefit or, for accelerated approval, post-marketing follow-up commitments.[121]

Unresolved Questions and Future Directions

Measurement Standardization

A comparable, multi-tiered metric system linking "AGE quantification → mechanical readouts → symptoms/function" is needed. Beyond harmonizing assay methodology for tissue/fluids CML, pentosidine, and SAF, we recommend moving materials-science readouts—instantaneous indentation modulus, friction coefficient, fiber orientation/instantaneous strain—into fixed panels for animal studies and early clinical trials, to delineate the true effect size and dose–response of "deglycation/anti-reglycation" strategies.[55]

Feasibility of in vivo Selective AGE-Cleaving

Crosslink breakers typified by alagebrium (ALT-711) suggest improvements in tissue stiffness and vascular compliance in animals and select clinical contexts, yet overall human evidence remains inconsistent. For joint applications, a more pragmatic breakthrough may lie in "perimatrix-targeted delivery + chemical/enzymatic synergy + imaging visibility", validated in large animals with chained readouts spanning "dose → tissue mechanics → function".[122]

Timing of Synergy with Systemic Metabolic Agents

STEP-9 provides Level-1 evidence for positioning GLP-1RAs as "upstream unloading", but the extent to which weight loss mediates pain improvement—and the optimal timing of IA materials ("metabolic first, then local" vs. concurrent initiation)—requires prospective trials using interaction-term modeling and integrated PK/PD monitoring.[97]

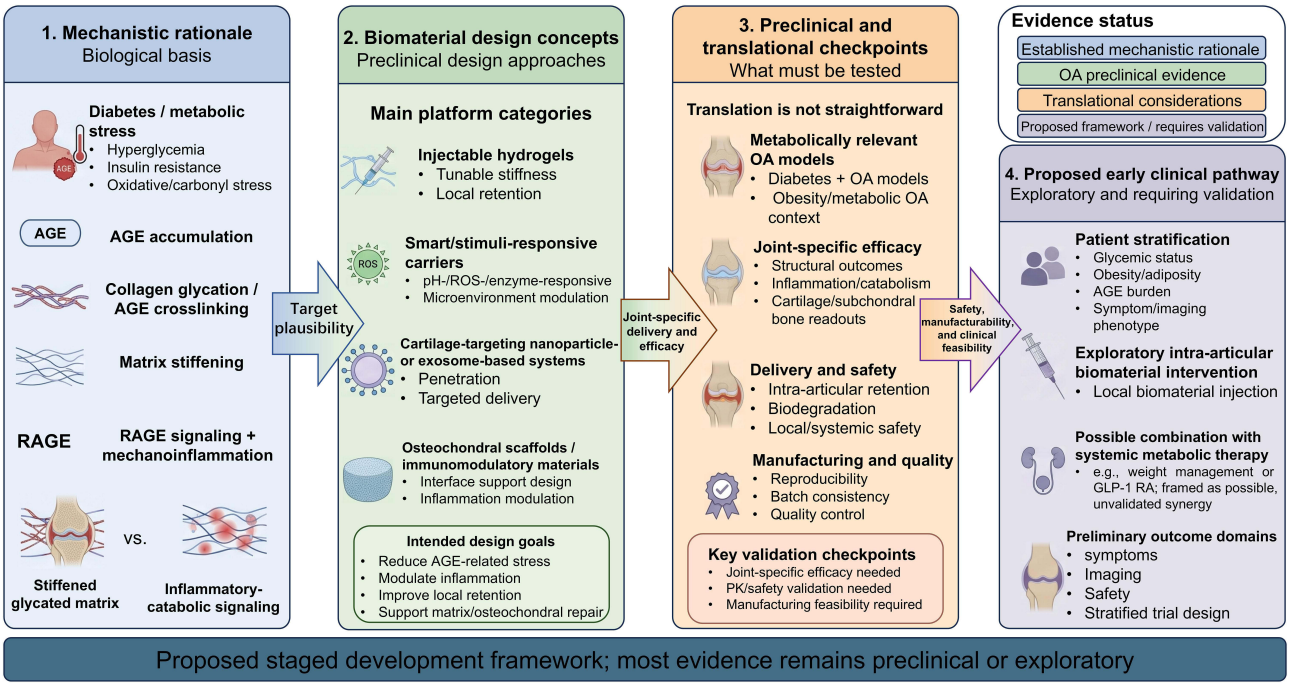

Figure 4 Proposed translational framework for AGE–COL axis-targeted biomaterials in diabetes-related osteoarthritis. This figure summarizes a staged framework for developing AGE–COL axis-targeted biomaterials in diabetes-related osteoarthritis, moving from mechanistic rationale to biomaterial design, preclinical/translational checkpoints, and a proposed early clinical pathway. The framework highlights diabetes-related metabolic stress, AGE accumulation, collagen glycation, matrix stiffening, RAGE signaling, and representative biomaterial strategies including injectable hydrogels, stimuli-responsive carriers, cartilage-targeting nanoparticle or exosome-based systems, osteochondral scaffolds, and immunomodulatory materials. Key translational checkpoints include metabolically relevant OA models, joint-specific efficacy, intra-articular delivery and safety, biodegradation, PK/safety validation, manufacturing reproducibility, and quality control. The clinical pathway is presented as exploratory and requiring validation, with emphasis on patient stratification, local biomaterial intervention, possible systemic metabolic therapy, and preliminary safety, symptom, and imaging outcomes.
Abbreviations: AGE, advanced glycation end product; COL, collagen; GLP-1RA, glucagon-like peptide-1 receptor agonist; OA, osteoarthritis; PK, pharmacokinetics; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species.

Long-Term and "Stress-Ecology" Assessments

Most preclinical follow-up is ≤12–24 weeks, insufficient to capture chronic trajectories of material degradation, interfacial integration, and osteochondral coupling. We advocate ≥6–12-month studies incorporating gait/activity spectra and combined imaging–mechanics endpoints as hard outcomes, aligning with clinical natural history and regulatory priorities.[123]

Regulatory Alignment and CQAs for Exosome/EV Products

EV development must proceed in lockstep with research standards: adhere to MISEV2023 characterization/reporting, and establish release specifications and inter-batch consistency for size/ζ-potential, purity, potency bioassays, impurity profile, and stability, alongside sterile and viral-safety validation under IND/BLA pathways.[124]

Evidence Bridging for Drug–Device Combinations

Plan early for bridging among CMC, clinical, and real-world evidence. Prioritize composite endpoints integrating "imaging/compositional improvement + symptom/function response + medication reduction", and align statistical plans with FDA guidance on structural endpoints and the OMERACT–OARSI core domains, thereby creating a verifiable path toward registration and reimbursement.[125] The overall translational roadmap for advancing AGE–COL axis-targeted biomaterials from mechanistic rationale to early clinical testing in diabetes-related osteoarthritis is summarized in Figure 4.

Conclusion

The AGE–COL axis provides a biologically plausible framework linking diabetes-associated hyperglycemia/carbonyl stress with OA-relevant matrix and cellular changes. AGE-mediated collagen crosslinking may increase matrix stiffness and alter

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mechanotransduction, while AGE–RAGE–NF-κB/ROS signaling may amplify inflammation, catabolism, apoptosis, and impaired stress adaptation. However, the extent to which diabetes independently worsens OA remains debated after accounting for obesity, adiposity, physical inactivity, and other metabolic confounders. Thus, diabetes-related OA should be regarded as an emerging mechanistic and translational construct rather than a fully established clinical phenotype. Biomaterials—including anti-AGE systems, modulus-tunable hydrogels, responsive carriers, nanoparticle/exosome platforms, osteochondral scaffolds, and immunomodulatory materials—may provide promising experimental tools for probing and potentially modulating the glycated, inflamed, and mechanically altered joint microenvironment. Future studies should test these strategies in metabolically relevant models, standardized endpoint systems, and stratified clinical designs to clarify whether targeting the AGE–COL axis can contribute to OA disease modification.

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Author Contributions

Jiayao Li contributed to literature collection, data curation, and manuscript revision. Binhao Cao contributed to literature screening, reference organization, and manuscript revision. Shuxia Yu contributed to evidence collection, content organization, and language polishing. Chengjin Li contributed to figure refinement, reference checking, and manuscript revision. Mengen Xue contributed to literature analysis, data organization, and manuscript editing. Qiqi Xie contributed to literature retrieval, information extraction, and manuscript revision. Cheng Luo contributed to content discussion, figure review, and manuscript editing. Chengzheng Duan contributed to critical revision of the manuscript and academic discussion. Zhipeng Li conceived and designed the review, organized the manuscript framework, performed the core literature analysis, prepared the figures, and drafted the manuscript. Chongqiang Jin supervised the study, provided overall academic guidance, critically revised the manuscript for important intellectual content, and approved the final version for publication.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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