The Metabolic Basis of Osteoarthritis: Molecular Mechanisms Linking Excessive Sugar Intake to Joint Pathology

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Osteoarthritis (OA) has long been framed as a prototypical "wear-and-tear" disease, with emphasis on biomechanical factors such as cumulative loading, trauma, and the excess joint forces of obesity (Felson & Zhang, 1998; Hamada et al., 2016). During the past two decades, however, convergent epidemiologic, translational, and mechanistic data have reframed OA as a systems-level disorder in which metabolic dysregulation plays a central, load-independent role in disease onset and progression (Eymard et al., 2015; Guss et al., 2019; Louati et al., 2017; Rajitkanok Amy Puenpatom & Victor, 2009). Here I integrate molecular pathways linking chronic excessive sugar intake, operationalized as recurrent hyperglycemia and hyperinsulinemia within insulin-resistant milieus, to catabolic signaling in synovium and cartilage, accelerated matrix damage, and worsening clinical outcomes. The argument proceeds along three interlocking axes:

1. The Maillard reaction (glycation) → AGE–RAGE signaling in joint tissues;
2. A systemic "metaflammatory" state characterized by adipokines, cytokines, and oxidative stress; and
3. Loss of insulin's local protective actions with the emergence of synovial insulin resistance.

I then translate these mechanisms into pragmatic guidance, defining "how much is too much" by metabolic normalization rather than an absolute gram target, and close with therapeutic carbohydrate reduction (TCR) as a unifying dietary strategy that benefits joints, muscle, vasculature, and brain.

Mechanistic Pathways and Clinical Implications

1) The Maillard Reaction: Glycation and the AGE–RAGE Axis ("Toasting" Your Tissues).

The colloquial "toasting your tissues" captures the Maillard reaction, a non-enzymatic sequence in which reducing sugars react with protein amino groups (lysine/arginine residues) to form a reversible Schiff base, then Amadori products, and ultimately a heterogeneous class of advanced glycation end-products (AGEs) that are chemically irreversible (Giri et al., 2018; Steenvoorden et al., 2006; Suzuki et al., 2022). Because articular cartilage is dominated by type II collagen with extremely slow turnover, AGE burden increases with age and is markedly accelerated by chronic hyperglycemia in type 2 diabetes (T2D) and metabolic syndrome (MetS) (Rasheed et al., 2011; Verzijl et al., 2000; Wang et al., 2008).

AGE accumulation injures joints through two coupled mechanisms

(a) Structural cross-linking. AGEs form non-physiologic cross-links that stiffen the collagen network (**Figure 1**), decrease viscoelastic compliance, increase brittleness, and raise susceptibility to microfailure under routine loads (DeGroot et al., 1999; DeGroot et al., 2001; Verzijl et al., 2002). The resulting AGEs are highly problematic because they cannot be removed until the protein they modify is degraded (Steenvoorden et al., 2006; Verzijl et al., 2000). This is why tissues with low protein turnover, such as collagen in articular cartilage, accumulate AGEs abundantly, making the process a hallmark of aging and chronic hyperglycemia (Steenvoorden et al., 2006; Verzijl et al., 2000). This contributes directly to matrix fragility in OA and similarly affects other collagenous tissues, while glycation of neural structural proteins impairs axonal transport, helping explain diabetic neuropathy (Giri et al., 2018).

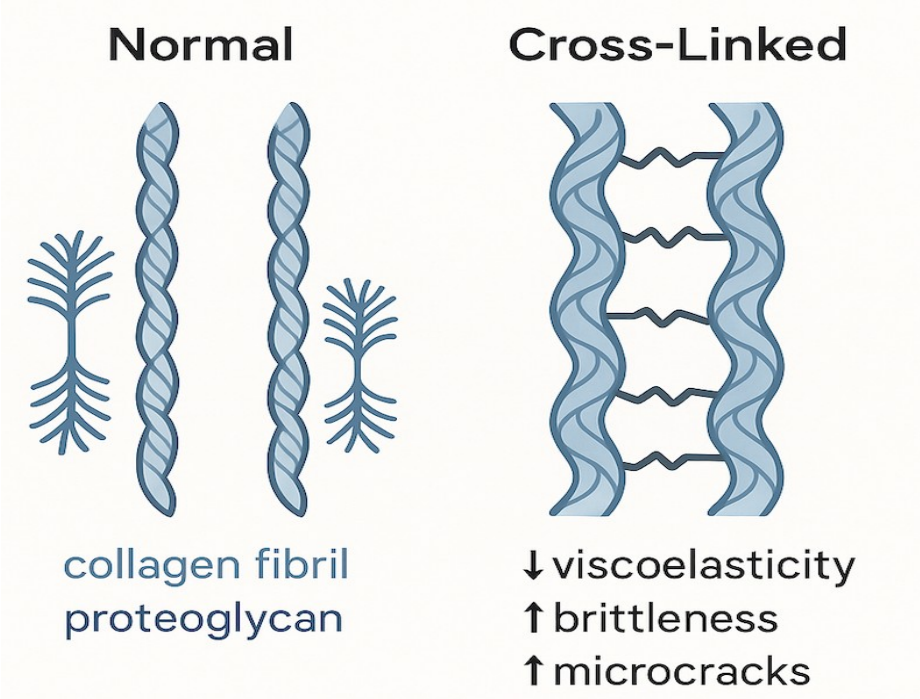

Figure 1. AGE-mediated structural cross-linking. Left: normal type II collagen fibrils with flexible, sliding intermolecular bonds that confer viscoelasticity. Right: AGE cross-links (bridges) tether adjacent collagen molecules, increasing stiffness and brittleness, reducing energy dissipation, and predisposing to micro-failure under everyday loads.

(b) RAGE-mediated inflammatory/catabolic signaling. AGEs ligate the receptor for advanced glycation end-products (RAGE) on chondrocytes, fibroblast-like synoviocytes (FLSs), and endothelial cells, activating redox-sensitive cascades such as NF-κB (nuclear factor kappa-B), MAPKs (mitogen-activated protein kinases: p38, JNK, ERK), and JAK/STAT3 (Janus kinase/signal transducer and activator of transcription 3). These

upregulate MMP-13 and ADAMTS-4/5 (matrix-degrading enzymes), IL-6 and IL-8 (pro-inflammatory cytokines), angiogenic mediators, and adhesion molecules (Chen et al., 2015; Huang et al., 2011; Rasheed et al., 2011; Steenvoorden et al., 2006). Downstream effects include mitochondrial depolarization, reactive oxygen species (ROS) elevation, and caspase-3–dependent apoptosis of chondrocytes (Chen et al., 2015; Wei et al., 2015). In vasculature, RAGE activation drives NADPH-oxidase–derived ROS and endothelial dysfunction (Giri et al., 2018), including increased VCAM-1 expression. In short, high-glycemic dietary patterns foster a biochemical environment in which cartilage becomes stiffer and less reparative, while joint cells adopt catabolic, pro-apoptotic phenotypes.

2) Systemic Meta-inflammation and Oxidative Stress

Excess sugar consumption also acts systemically through meta-inflammation and oxidative stress that do not require excessive joint loading to drive OA pathology. Nutrient excess and adipocyte hypertrophy recruit and polarize adipose macrophages toward an M1 profile, raising circulating TNF-α, IL-1β, and IL-6 (de Mello et al., 2018; Longo et al., 2019). These cytokines then act on synovium and cartilage to amplify catabolic gene expression; in elegant diet-induced models, genetic or pharmacologic TNF suppression blunts osteophyte formation, demonstrating that systemic inflammatory tone is sufficient to modulate early OA changes independent of load per se (Hamada et al., 2016).

Concurrently, chronic hyperglycemia and lipid oversupply overload mitochondria, increasing superoxide generation; inflammatory cues upregulate NOX2/NOX4 (NADPH oxidases), producing ROS that act as second messengers to activate NF-κB and p38/JNK (Han et al., 2022; Lepetsos & Papavassiliou, 2019; Reed et al., 2014). Consequences include enhanced MMP-13/ADAMTS-5 transcription, DNA damage, respiratory dysfunction, and chondrocyte senescence with a senescence-associated secretory phenotype (SASP) that sustains tissue-destructive inflammation (Han et al., 2022; Kang et al., 2024; Reed et al., 2014). Importantly, NOX inhibition prevents experimental OA development, underscoring the causal role of oxidative signaling (Han et al., 2022).

Mechanical Loading: Dose Matters for Cartilage Anabolism and Protection

Evidence also shows a protective role for moderate activity and detrimental effects from underloading. Moderate, physiologic cyclic loading is the optimal stimulus for maintaining articular cartilage (AC) health and quality, promoting an anabolic response through maintenance and expansion of proteoglycan (PG) content (Jørgensen et al., 2011; Loeser et al., 2008). Mechanistically, moderate loading inhibits inflammation and protects against cartilage degradation by activating anabolic factors

(e.g., IL-4, IL-10), which suppress NF-κB signaling and reduce expression of matrix-degrading enzymes (matrix metalloproteinases [MMPs] and a disintegrin and metalloproteinase with thrombospondin motifs [ADAMTS]) (Leong et al., 2011; Nam et al., 2009; Torzilli et al., 2008; Urban, 1994).

Conversely, unloading or immobilization worsens AC condition—producing atrophy, softening, and thinning via reductions in PG content, particularly in the superficial zone (SZ) (Haapala et al., 2015; Leong et al., 2011; Vanwanseele et al., 2002). Lack of mechanical stimulation increases catabolic enzyme expression (e.g., MMP-13, ADAMTS-5), promoting matrix breakdown and heightening susceptibility to inflammatory stress (Leong et al., 2011; Urban, 1994). Clinically, individuals with low body mass index (BMI) and low daily walking (underloading) show an increased risk of worsening medial tibiofemoral cartilage damage (Voinier et al., 2017).

3) Insulin Signaling: From Protection to Pathology

Insulin signaling sits at the crossroads of protection and pathology. Under physiological conditions, insulin exerts anti-inflammatory effects in joint tissues, restraining TNF-α–induced catabolic transcription in FLSs and chondrocytes (Hamada et al., 2016; Lee et al., 2022). In insulin-resistant states typical of MetS and early T2D, this protective brake fails locally ("synovial insulin resistance"), permitting cytokine-driven matrix degradation to proceed unchecked (Hamada et al., 2016; Lee et al., 2022). Compensatory hyperinsulinemia can itself become pro-inflammatory: high insulin concentrations activate PI3K/Akt/mTOR and NF-κB in FLSs, increasing proliferation and secretion of MMP-9 and MMP-13 while inhibiting autophagy (Qiao et al., 2023). Thus, recurrent high-sugar intake that drives both hyperglycemia and hyperinsulinemia removes an endogenous anti-catabolic safeguard and replaces it with signaling that potentiates inflammation and matrix loss. These joint-intrinsic events unfold within a whole-body network that includes hepatic responses to fructose. Excess fructose is preferentially metabolized in the liver, promoting de novo lipogenesis, hepatic triglyceride accumulation, and non-alcoholic fatty liver disease (NAFLD), changes that worsen systemic insulin resistance and thereby further degrade joint homeostasis (Guss et al., 2019; Lee et al., 2022). Importantly, epidemiological data link high dietary glycemic index (GI) to symptomatic knee OA, implicating the magnitude and rapidity of post-prandial glycemic excursions—not merely total calories—as clinically relevant drivers of disease (So et al., 2018).

These mechanistic strands—AGE-mediated matrix cross-linking and RAGE signaling; adipose-derived cytokine flux; mitochondrial and NOX-derived ROS; and the transition from insulin's protection to insulin-resistant permissiveness—together explain why OA risk concentrates in metabolically unhealthy phenotypes, including those with OA in non–load-bearing joints where mechanical

explanations falter (Eymard et al., 2015; Louati et al., 2017; Rajitkanok Amy Puenpatom & Victor, 2009). They also clarify why clinical outcomes in arthroplasty patients with MetS are poorer even after mechanical correction: the catabolic biochemical milieu persists (Gandhi et al., 2010). Conceptually, the dose-toxicity relation is Maillard chemistry writ large across tissues: repeated glucose spikes accelerate AGE formation and redox injury; it is the chronicity of exposure that renders damage progressively irreversible (DeGroot et al., 2001; Giri et al., 2018; Suzuki et al., 2022).

4) The Gut–Joint Axis: Microbiome, Endotoxemia, and OA Progression

Diet shapes the gut microbiome, which in turn modulates obesity, MetS, and OA (Guss et al., 2019; Rogero & Calder, 2018). Obesity-associated microbiota can increase energy harvest and are transferable: transplantation from obese donors to germ-free mice increases adiposity and impairs metabolic health, even with identical caloric intake (Lee et al., 2020; Rogero & Calder, 2018).

A key mechanism is metabolic endotoxemia: dysbiosis and increased intestinal permeability allow lipopolysaccharide (LPS) translocation, activating TLR4 (Toll-like receptor 4) and driving systemic low-grade inflammation that worsens insulin resistance and OA pathogenesis (Rogero & Calder, 2018; Wang & He, 2018; Zhang et al., 2021). In elegant work, TLR5-deficient (Toll-like receptor 5) mice spontaneously develop MetS due to altered microbiota; disrupting the microbiome with chronic antibiotics prevents the MetS phenotype and reduces cartilage damage after mechanical loading (Guss et al., 2019). Diet patterns that improve microbiome-metabolic health, e.g., Mediterranean-style eating, associate with lower OA prevalence (Riera-Escamilla et al., 2021).

5) From Mechanism to Practice: Defining “Too Much Sugar”

Mechanistically, repeated glucose spikes accelerate Maillard chemistry, AGE accumulation, and redox injury. Because only ~4 g of glucose circulate at any moment in a 70-kg adult (Wasserman, 2009), the system is tightly regulated; it is the chronicity and amplitude of excursions—not an arbitrary per-meal gram cap—that drive injury. Practically, “too much sugar” is the intake that prevents metabolic homeostasis. Clinically meaningful thresholds include fasting glucose ≥110 mg/dL (≈6.1 mmol/L) or frequent post-prandial values >180 mg/dL (≈10.0 mmol/L), states that predict accelerated AGE accrual/oxidative stress and track with OA prevalence and progression (Eymard et al., 2015; Giri et al., 2018; Rajitkanok Amy Puenpatom & Victor, 2009).

On the intake side, dietary quality and glycemic dynamics matter. High-GI patterns associate with symptomatic knee OA (So et al., 2018), whereas Mediterranean-style patterns correlate with lower OA prevalence (Riera-Escamilla et al., 2021). Acute modulation with viscous fibers (e.g., oat β-glucans [beta-glucans]) blunts post-prandial glucose/insulin (Hossain et al., 2025). In established knee OA, a therapeutic low-carbohydrate diet (LCD) of ~20 g/day—liberalized to ~40 g/day based on tolerance—

reduced oxidative stress markers, leptin, and both self-reported and functional pain within 12 weeks (Strath et al., 2019). For individuals with MetS/T2D not pursuing intensive LCDs, even “moderate” intakes (~50–100 g/day) may be excessive if they fail to prevent hyperglycemia/hyperinsulinemia; the target is normalizing glycemic indices and restoring insulin sensitivity to re-engage insulin’s local anti-inflammatory effects (Hamada et al., 2016; Lee et al., 2022; Wang & He, 2018). Adjuncts may include weight reduction to decompress cytokine-active adipose depots and redox-targeted strategies that interrupt NOX-driven signaling (Han et al., 2022; Longo et al., 2019).

6) Therapeutic Carbohydrate Reduction (TCR): An Integrative Strategy

Therapeutic carbohydrate reduction (TCR) refers to dietary patterns that restrict total carbohydrate intake. TCR is increasingly recognized as a viable strategy for managing and, in some cases, achieving remission of T2D (Wheatley et al., 2021). In Australia, TCR principles have moved into mainstream clinical guidance and implementation efforts (Gunatillaka et al., 2025), and national materials from the Australian Diabetes Society now present TCR as an evidence-based option. International position statements (e.g., the American Diabetes Association, Diabetes Canada, and Diabetes UK) likewise emphasize that reducing overall carbohydrate intake has among the strongest evidence for improving glycemia when matched to individual preferences and delivered with clinical supervision (Diabetes Canada, 2020; Evert et al., 2019). In practice, many therapeutic protocols use stricter carbohydrate targets (e.g., ≤50 g/day) to maximize glycemic impact, while more moderate low-carbohydrate diets (LCDs; <130 g/day) also improve HbA1c (glycated hemoglobin) and can reduce medication burden (Evert et al., 2019; Wheatley et al., 2021). Very low-carbohydrate ketogenic diets (VLCKDs) are a subset of LCDs that typically restrict carbohydrate to ~20–50 g/day.

Evidence from LCD/VLCKD interventions shows improvements in HbA1c, body weight, blood pressure, and medication burden (Brinkworth et al., 2022; Dening et al., 2023; Wheatley et al., 2021). mHealth (mobile-health) LCD education programs produce clinically meaningful HbA1c reductions and improved systolic blood pressure with medication de-intensification (Kolivas et al., 2025). In clinician-delivered programs, many participants with baseline HbA1c ≥6.5% achieve HbA1c <6.5% by follow-up—commonly used as a remission threshold (Brinkworth et al., 2022). Structured DiRECT-style pathways (Diabetes Remission Clinical Trial) typically begin with VLEDs (very-low-energy diets) to induce substantial weight loss, then transition to supported maintenance; remission is often defined as HbA1c <6.5% sustained ≥3 months without glucose-lowering medications (Gunatillaka et al., 2025).

Mechanistically, TCR reduces substrate for Maillard/AGE formation, attenuates RAGE–NF-κB/MAPK signaling, lowers oxidative stress, and re-sensitizes insulin pathways—benefits that extend beyond

glycemia to joints, muscle, endothelium, and the nervous system/brain (Chen et al., 2015; Giri et al., 2018; Hamada et al., 2016; Suzuki et al., 2022). Safety data suggest well-designed LCDs are comparable or superior to other strategies when diet quality is prioritized (Wheatley et al., 2021), with core features including minimizing ultra-processed, high-GI foods, adequate protein, healthy fats, and micronutrient density (Evert et al., 2019). Because TCR can rapidly lower glucose, clinical supervision is essential—especially for proactive down-titration of insulin and sulfonylureas to avoid hypoglycemia (Brinkworth et al., 2022).

Conclusion

OA is not merely mechanical "wear-and-tear." It is also metabolic chemistry: chronic sugar excess accelerates Maillard-driven AGE accumulation and RAGE signaling; adipose- and gut-derived meta-inflammation and oxidative stress drive chondrocyte catabolism and senescence; and insulin resistance removes an endogenous anti-inflammatory brake. These mechanisms explain OA clustering with cardiometabolic disease, even in non–load-bearing joints, and poorer outcomes after purely mechanical correction.

Therapeutic carbohydrate reduction addresses these upstream drivers by stabilizing glycemia, lowering insulin exposure, and reducing the substrates and signals that damage cartilage, synovium, muscle, endothelium, and neural tissue. Practically, "too much sugar" is whatever intake prevents metabolic normalization. Success should be measured by restored fasting and post-prandial glycemia, improved insulin sensitivity, lower inflammatory tone (including LPS/TLR signaling), and pain/function gains—outcomes predicted by the underlying biochemistry and increasingly supported by clinical trials.

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