The Metabolic Basis of Osteoarthritis: Molecular Mechanisms Linking Refined Carbohydrates, Glycaemic Dysregulation, and Gut Dysbiosis to Joint Pathology

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Abstract

Osteoarthritis (OA) has traditionally been framed as a "wear-and-tear" disease driven by biomechanical overload. Over the past two decades, epidemiologic, translational, and mechanistic evidence has reframed a substantial subset of OA as a metabolically driven disorder. This narrative review develops the argument that chronic excess of refined and high-glycaemic carbohydrate that is absorbed and metabolized as glucose and fructose, and distinct from fibre-rich whole-food carbohydrate and contributes to joint pathology through several converging pathways that are at least partly independent of mechanical load. Four mechanisms are integrated: (1) non-enzymatic glycation (the Maillard reaction) and advanced glycation end-product (AGE)–RAGE signaling in cartilage and synovium, where the slow turnover of type II collagen makes it a preferential glycation target; (2) fructose-specific hepatic and vascular effects, including de novo lipogenesis, non-alcoholic fatty liver disease, and a uric-acid pathway that impairs endothelial nitric oxide, together with the observation that hyperglycemia itself generates fructose endogenously through the polyol pathway; (3) systemic low-grade inflammation and oxidative stress from dysfunctional adipose tissue, mitochondria, and the endothelial glycocalyx; and (4) a gut–joint axis in which a Western dietary pattern promotes dysbiosis, intestinal barrier dysfunction, and metabolic endotoxemia, driving insulin resistance and systemic inflammation. Insulin signaling is considered as a hinge that shifts from locally protective to permissive as synovial insulin resistance develops. The evidence is graded honestly by link: the upstream metabolic and vascular steps are supported in humans, the tissue-level steps are largely preclinical, and the final step to clinical OA is supported only by observational association and, for the gut arm, by animal-manipulation studies and human associations rather than any trial with a structural endpoint. Therapeutic carbohydrate reduction is well established for glycemic control and type 2 diabetes remission; its benefit for joints is biologically plausible but unproven. The model is best read as a well-grounded, testable hypothesis that complements the mechanical understanding of OA.

Introduction

Osteoarthritis has long been described as a prototypical mechanical disease, with emphasis on cumulative loading, trauma, and the excess joint forces associated with obesity (Felson & Zhang, 1998; Hamada et al., 2016). That framing remains valid and important. Mechanical factors are central to how and where OA develops. During the past two decades, however, converging epidemiologic, translational, and mechanistic data have shown that metabolic dysregulation also participates in disease onset and progression, in some cases independently of load (Eymard et al., 2015; Guss et al., 2019; Louati et al., 2015; Puenpatom & Victor, 2009). The clearest clinical signal is that OA clusters with the components of metabolic syndrome (MetS) and type 2 diabetes (T2D), and that OA occurs in non–load-bearing joints

such as the hands, an observation a purely mechanical model does not fully explain (Hamada et al., 2016; Puenpatom & Victor, 2009).

This review focuses on dietary carbohydrate as a modifiable exposure. From a biochemical standpoint, the digestible carbohydrate that reaches the circulation resolves almost entirely into two monosaccharides, glucose and fructose, while non-digestible carbohydrate (fiber) is not absorbed and instead feeds the gut microbiota (Craciun et al., 2022; Zhang et al., 2022). The physiologically relevant exposure is therefore the glycemic and fructose load a diet imposes, not carbohydrate mass as such. Refined starches, added sugars, and high-glycemic-index foods are consequently not metabolically equivalent to fiber-rich, minimally processed carbohydrates, and the argument that follows concerns the former. There is also no absolute dietary requirement for carbohydrate, since the modest glucose the body needs can be produced endogenously through gluconeogenesis. I integrate the pathways that plausibly link a chronically high glycemic and fructose load to catabolic signaling in synovium and cartilage: glycation and AGE–RAGE signaling; fructose-specific hepatic and vascular effects; systemic meta-inflammation and oxidative stress, including microvascular injury; and a gut–joint axis operating through dysbiosis and metabolic endotoxemia. Insulin signaling is treated as a hinge between protection and pathology. Throughout, I distinguish mechanistic plausibility from demonstrated clinical effect and calibrate each conclusion to the strength and directness of the evidence.

Mechanistic Pathways

1. Glycation and the AGE–RAGE Axis

The Maillard reaction is a non-enzymatic sequence in which reducing sugars react with protein amino groups (lysine and arginine residues) to form a reversible Schiff base, then Amadori products, and ultimately a heterogeneous class of advanced glycation end-products (AGEs) that are effectively 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, its half-life estimated at roughly 117 years in one biochemical analysis, AGEs accumulate over decades, and carboxymethyl-lysine, carboxyethyl-lysine, and pentosidine all rise with age in human cartilage collagen (Verzijl et al., 2000a, 2000b). This accumulation is accelerated under chronic hyperglycemia, as in T2D and MetS (Steenvoorden et al., 2006; Suzuki et al., 2022). The result makes the structural proteins of the joint a preferential target: the very longevity that gives collagen its mechanical role also gives glycation chemistry decades in which to act.

AGE accumulation affects joint tissue through two coupled mechanisms.

(a) Structural cross-linking. AGEs form non-physiologic cross-links that stiffen the collagen network (Figure 1) below, reduce viscoelastic compliance, increase brittleness, and raise susceptibility to microfailure under routine loads. Experimental glycation of human cartilage produces a dose-dependent stiffening that reduces instantaneous deformation by as much as 40%, an effect attenuated by glycation inhibitors (Verzijl et al., 2002). Once formed, AGEs cannot be removed until the modified protein is degraded, so tissues with low protein turnover accumulate them progressively, making AGE accrual a

hallmark of both aging and chronic hyperglycemia (Steenvoorden et al., 2006; Verzijl et al., 2000a). Independent of cross-linking, glycation also impairs chondrocyte-mediated matrix synthesis and turnover, further limiting repair (DeGroot et al., 1999; DeGroot et al., 2001). Glycation of long-lived proteins in other tissues contributes to the broader complications of chronic hyperglycemia, including diabetic neuropathy (Giri et al., 2018; Suzuki et al., 2022).

(b) RAGE-mediated inflammatory and catabolic signaling. AGEs ligate the receptor for advanced glycation end-products (RAGE) on chondrocytes and fibroblast-like synoviocytes (FLSs), activating redox-sensitive cascades including NF-κB (nuclear factor kappa-B), the MAPKs (mitogen-activated protein kinases: p38, JNK, ERK), and JAK/STAT3 (Chen et al., 2016; Huang et al., 2011; Rasheed et al., 2011; Steenvoorden et al., 2006). These pathways upregulate matrix-degrading enzymes (MMP-13 and ADAMTS-4/5), pro-inflammatory cytokines (IL-6 and IL-8), and angiogenic mediators such as VEGF. RAGE expression is itself greater in aged and osteoarthritic cartilage (Loeser et al., 2005), and AGE stimulation of human OA chondrocytes raises COX-2, iNOS, prostaglandin E2, and nitric oxide—responses blunted by soluble RAGE (Nah et al., 2008). AGE exposure can also provoke mitochondrial dysfunction and caspase-3–dependent apoptosis in chondrocytes (Yang et al., 2015). In broad terms, high-glycemic dietary patterns foster a biochemical environment in which cartilage becomes stiffer and less reparative while joint cells adopt catabolic phenotypes.

Beyond cell and explant systems, glycation modifies OA in vivo. Raising cartilage AGE content roughly fivefold in dogs, by intra-articular ribose, increased collagen damage, proteoglycan loss, and histological OA severity after cruciate transection (DeGroot et al., 2004), and in mice, enhancing matrix cross-linking aggravated post-traumatic OA while suppressing it reduced disease and matrix-degrading enzyme expression (Kim et al., 2015). Human tissue links the chemistry to disease: cartilage and bone from people with diabetes contain more pentosidine than tissue from people without (Oren et al., 2011), and in the Osteoarthritis Initiative, participants with diabetes showed faster progression of cartilage and meniscal damage over four years (Neumann et al., 2019). These findings move glycation from a plausible mechanism to one experimentally capable of worsening OA, at least in the setting of aging and sustained hyperglycemia—though they demonstrate that glycation can amplify disease, not that dietary carbohydrate is its cause.

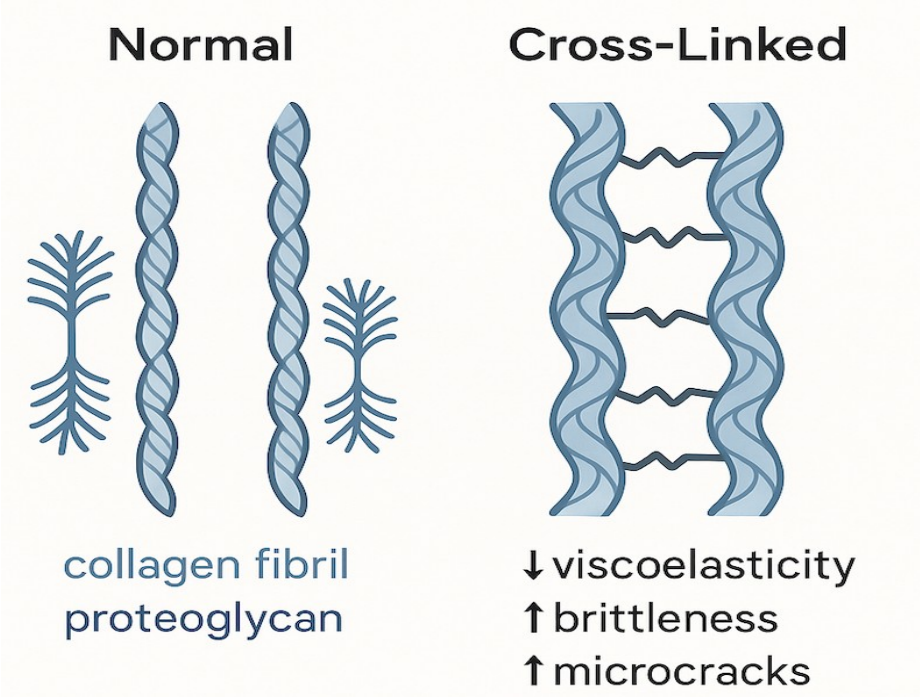

Figure 1. AGE-mediated structural cross-linking. Left: normal type II collagen fibrils with flexible, sliding intermolecular bonds that confer viscoelasticity. Right: AGE cross-links tether adjacent collagen molecules, increasing stiffness and brittleness, reducing energy dissipation, and predisposing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

2. Fructose-Specific Pathways: Liver, Uric Acid, and Endogenous Fructose

Although glucose and fructose enter as a pair, fructose has distinct metabolism with its own consequences. Fructose is preferentially cleared by the liver, where it drives de novo lipogenesis, hepatic triglyceride accumulation, and non-alcoholic fatty liver disease—changes that worsen systemic insulin resistance and thereby degrade joint homeostasis (Ahmed et al., 2021; Hannou et al., 2018; Lee et al., 2022). Fructose phosphorylation by ketohexokinase is not feedback-inhibited and transiently depletes hepatic ATP, generating AMP that is catabolized to uric acid (Hannou et al., 2018). Uric acid, in turn, can impair endothelial nitric oxide and endothelial function (Khosla et al., 2005), and lowering uric acid ameliorates features of fructose-induced metabolic syndrome in rodents (Nakagawa et al., 2006). This uric-acid mechanism should be presented as plausible rather than settled: Mendelian-randomization data do not strongly support uric acid as a direct causal mediator of cardiometabolic disease in humans (Hannou et al., 2018).

A less familiar point unifies the two sugars. Under sustained hyperglycemia, glucose is increasingly diverted through the polyol pathway, where aldose reductase produces sorbitol and sorbitol dehydrogenase then yields fructose—so the body manufactures fructose endogenously from glucose. Flux through this pathway is small under normal glucose concentrations (on the order of 3% of glucose metabolism) but rises substantially—to more than 30%—under hyperglycemia (Tang et al., 2012). In mice, endogenous fructose produced this way contributes to hepatic fat and metabolic syndrome, and blocking the pathway is protective (Lanaspa et al., 2013). The implication is that chronic hyperglycemia can drive fructose-type injury even without dietary fructose, and that glucose and fructose toxicity converge rather than acting in isolation. These flux and endogenous-fructose data come from liver, nerve, and vascular tissue rather than cartilage, so extension to the joint is a mechanistic extrapolation.

3. Systemic Meta-inflammation, Oxidative Stress, and the Microvasculature

Excess energy intake also acts systemically, through low-grade inflammation and oxidative stress that do not require excess joint loading. Adipocyte hypertrophy and nutrient excess recruit and polarize adipose-tissue macrophages toward a pro-inflammatory (M1) profile, raising circulating TNF-α, IL-1β, and IL-6 (Longo et al., 2019). These cytokines act on synovium and cartilage to amplify catabolic gene expression. In diet-induced obesity models, genetic deletion of TNF blunts osteophyte formation and synovial hyperplasia even in the uninjured joint, indicating that systemic inflammatory tone can modulate early OA changes independently of load (Hamada et al., 2016).

Oxidative stress is a well-established driver of chondrocyte catabolism. Reactive oxygen species (ROS) from mitochondria and from NADPH oxidases (NOX2/NOX4) act as second messengers that engage redox-sensitive signaling and increase expression of matrix-degrading enzymes; chronic oxidative load also promotes DNA damage, mitochondrial respiratory dysfunction, and chondrocyte senescence with a senescence-associated secretory phenotype (SASP) (Kang et al., 2022; Lepetsos & Papavassiliou, 2016; Lepetsos et al., 2019; Reed et al., 2014). In a murine model, pharmacologic NADPH-oxidase inhibition reduced ROS, DNA damage, and cartilage degradation and attenuated experimental OA, supporting a causal contribution of NOX-derived oxidative signaling (Han et al., 2022). In humans, systemic markers of oxidative stress correlate with adiposity in cross-sectional data (Furukawa et al., 2004); this supports the upstream premise that metabolic excess raises oxidative tone but does not by itself demonstrate that dietary carbohydrate drives joint-level oxidative injury.

A microvascular strand may also connect hyperglycemia to tissue injury. The endothelial glycocalyx, a carbohydrate-rich layer lining the vasculature that regulates permeability and nitric-oxide –dependent perfusion, is acutely vulnerable to high glucose: in human studies, acute hyperglycemia reduces glycocalyx volume by roughly half and coincides with endothelial dysfunction, an effect attenuated by antioxidant co-infusion (Nieuwdorp et al., 2006), and glycocalyx degradation is implicated in the microvascular complications of diabetes (Dogné et al., 2018). Whether this contributes to OA is unknown: no study has examined the glycocalyx of the subchondral or synovial microcirculation, so any link to joint tissue is at present an extrapolation from the systemic vasculature rather than a demonstrated joint mechanism.

4. Mechanical Loading: Dose Matters for Cartilage Health

A metabolic model does not displace mechanics. The two interact. Moderate, physiologic cyclic loading is the optimal stimulus for maintaining articular cartilage, supporting proteoglycan content and an anabolic chondrocyte phenotype (Jørgensen et al., 2017). Mechanistically, moderate loading restrains inflammatory signaling, in part through anabolic mediators such as IL-4 and IL-10 and through mechanotransduction pathways (e.g., CITED2) that suppress NF-κB and reduce expression of matrix-degrading enzymes (Leong et al., 2011; Nam et al., 2009; Torzilli et al., 2010; Urban, 1994).

Conversely, unloading and immobilization worsen cartilage condition, producing softening, thinning, and proteoglycan loss, particularly in the superficial zone, and upregulating catabolic enzymes such as MMP-3 (Haapala et al., 2000; Leong et al., 2010; Vanwanseele et al., 2002; Urban, 1994).

Clinically, individuals with low body mass index and low daily walking (relative underloading) show an increased risk of worsening medial tibiofemoral cartilage damage (Voinier et al., 2020). Both overload and underload are thus harmful. The metabolic pathways described here are best understood as shifting the loading dose at which damage occurs, so that joints of metabolically unhealthy individuals tolerate less mechanical stress before catabolism predominates (Issa & Griffin, 2012).

5. Insulin Signaling: From Protection to Pathology

Insulin sits at the crossroads of protection and pathology in the joint. Under physiological conditions, insulin exerts anti-inflammatory effects on synovial tissue. In human OA FLS, insulin suppresses TNF-α–induced expression and release of catabolic enzymes (MMP-1, MMP-13, ADAMTS-4) by roughly half, and synovium from patients with T2D shows blunted insulin signaling consistent with local insulin resistance (Hamada et al., 2016). In insulin-resistant states typical of MetS and early T2D, this protective brake fails locally, a state that can be described as synovial insulin resistance, permitting cytokine-driven matrix degradation to proceed (Hamada et al., 2016; Lee et al., 2022).

At the same time, compensatory hyperinsulinemia may itself become deleterious. In cultured FLS, high insulin concentrations activate PI3K/Akt/mTOR and NF-κB signaling, increase proliferation and secretion of MMP-9 and MMP-13, and inhibit autophagy. Notably, these effects were observed at supraphysiologic insulin concentrations, a caveat that limits direct extrapolation to human tissue (Qiao et al., 2020). Taken together, a chronically high carbohydrate load that drives both hyperglycemia and hyperinsulinemia may remove an endogenous anti-catabolic safeguard while adding signals that favor inflammation and matrix loss. Epidemiologically, higher dietary glycemic index is associated with symptomatic knee OA in cross-sectional data, however, the association was significant only in women, applied to symptomatic rather than radiographic-only disease, and was seen for glycemic index but not glycemic load (So et al., 2018).

6. The Gut–Joint Axis: Dysbiosis, Endotoxemia, and Osteoarthritis

Diet is among the strongest determinants of gut microbial composition, and a Western pattern high in refined carbohydrate and fat is associated with dysbiosis and a depletion of fiber-fermenting, short-chain-fatty-acid (SCFA)–producing taxa (Craciun et al., 2022; Liu et al., 2021; Tilg et al., 2020; Zhang et al., 2022). Sugar may also drive dysbiosis through glycation itself. In rats, high-fructose feeding glycates intestinal proteins and favors bacteria able to adhere to and utilize glycated substrates, provoking dysbiosis, elevated TNF-α and IFN-γ, and insulin resistance, a mechanism that ties the glycation and gut arms of this review together, though only in a preclinical model (Patil & Arvindekar, 2021). SCFAs, especially butyrate, nourish the colonic epithelium and help maintain tight-junction integrity, and their loss is one proposed route to a more permeable intestinal barrier (Craciun et al., 2022; Saad et al., 2016; Zhang et al., 2022). Human data on barrier dysfunction are, however, mixed, and more consistently described in T2D than in obesity. Shotgun-metagenomic profiling of European women shows reproducible T2D-associated compositional and functional shifts in the microbiome (Karlsson et al., 2013), yet a direct causal role for dysbiosis in metabolic disease has not been established in humans, so

this arm is best stated as association and mechanism rather than proof (Salazar et al., 2020; Tilg et al., 2020).

The better-supported node is metabolic endotoxemia. When the barrier is compromised, lipopolysaccharide (LPS) from Gram-negative bacteria translocates into the circulation, binds LPS-binding protein and CD14, and activates Toll-like receptor 4 (TLR4), triggering NF-κB, and JNK-dependent inflammation and serine phosphorylation of IRS-1 that impairs insulin signaling (Al Bander et al., 2020; Salazar et al., 2020; Saad et al., 2016). Several lines of evidence anchor this chain. Colonizing germ-free mice with a conventional microbiota markedly increases body fat despite reduced feeding, establishing that the microbiota regulates host energy storage (Bäckhed et al., 2004), and transplanting cultured microbiota from human twins discordant for obesity transmits the donor's adiposity and metabolic phenotype to recipient mice (Ridaura et al., 2013). High-fat feeding raises circulating LPS and induces obesity and insulin resistance in mice, an effect abolished by antibiotics—the original demonstration of metabolic endotoxemia (Cani et al., 2007). Most importantly for human relevance, experimental low-grade endotoxemia induced by infusing LPS into healthy volunteers produces adipose inflammation and systemic insulin resistance, providing a genuine human causal link for the LPS-to-insulin-resistance step (Mehta et al., 2010). Mouse studies in which TLR4 or CD14 is genetically disabled confirm the receptor's necessity for diet-induced insulin resistance (Saad et al., 2016).

Whether these metabolic events actually reach the joint is a separate question, and a substantial body of OA-specific evidence has now accumulated, strongest in animals, suggestive in humans. The most direct causal evidence comes from animal manipulation. Germ-free mice subjected to surgical destabilization of the medial meniscus develop less cartilage damage, less proteoglycan loss, and smaller osteophytes than conventionally colonized mice, showing that microbial exposure modifies OA severity (Ulici et al., 2018). Earlier work established the same principle from the metabolic side. TLR5-deficient mice, which develop a microbiota-dependent metabolic syndrome, sustain more load-induced cartilage damage, and disrupting the microbiome with chronic antibiotics both prevents the metabolic phenotype and reduces cartilage damage, with LPS burden tracking damage more closely than adiposity (Guss et al., 2019). Conversely, transplanting fecal microbiota from metabolically compromised human OA donors into germ-free mice increases intestinal permeability, systemic IL-1β and IL-6, synovitis, and post-injury cartilage damage relative to microbiota from healthier donors (Huang et al., 2020). Targeting the microbiome is protective: in obese mice the prebiotic oligofructose expands *Bifidobacterium pseudolongum*, lowers systemic and synovial inflammation, and protects against obesity-associated OA (Schott et al., 2018), and in a high-fat/high-sucrose rat model, prebiotic fiber and exercise each prevent knee damage while normalizing microbiota, endotoxemia, insulin resistance, dyslipidemia, and leptin (Rios et al., 2019). A "double-hit" model combining antibiotic- and *E. coli*–induced dysbiosis with joint destabilization reproduces the whole sequence in one experiment with reduced tight-junction proteins, elevated serum LPS, M1 macrophage polarization, and accelerated cartilage loss (Wu et al., 2025). These experiments establish, at least in rodents, that the microbiome is a genuine modifier of OA rather than a bystander, and the magnitude and the precise mediator, however, are model-dependent, and protection has been clearer in developing than in established obesity.

Human data are more limited and characteristically associative. In the Rotterdam Study, higher intestinal *Streptococcus* abundance was associated with greater knee pain, an association independently replicated in a second cohort and attributable to local joint inflammation rather than cartilage structure (Boer et al., 2019). Systemic and synovial-fluid LPS burden correlates with activated joint macrophages, osteophytes, joint-space narrowing, and symptom severity after adjustment for age, sex, and body mass (Huang et al., 2016). Bacterial products are demonstrably present within the joint. Peptidoglycan was detected in the synovium of a majority of knee-replacement patients and correlated with synovitis and synovial IL-6, which cultured synovial fibroblasts secreted on exposure to it (Holub et al., 2024). Because hand OA cannot be explained by weight-bearing load, its association with altered microbial tryptophan metabolism, lower indole-3-lactic acid, replicated in a second cohort—is a particularly relevant human signal (Wei et al., 2023). Against these positive findings stands an important negative study: among obese adults, OA cases had higher serum LPS than obese controls but showed no distinct gut-diversity or genus-level signature, and transplanting case versus control microbiota into germ-free mice produced no difference in OA severity (Loeser et al., 2022). Reports of an OA-associated taxonomic profile, for example, expanded Proteobacteria with depleted *Roseburia* and *Lactobacillus does* exist but have not reproduced consistently (Wang et al., 2023). The reasonable reading is that barrier function and LPS handling may matter more than any recognizable "OA microbiome," consistent with endotoxemia-driven inflammation being implicated in OA on broader grounds (Wang & He, 2018; Zhang et al., 2021).

Interventional human trials suggest symptomatic and inflammatory benefit but stop short of structural proof. A six-month randomized trial of *Lactobacillus casei* Shirota in knee OA improved WOMAC and pain scores and lowered hs-CRP (Lei et al., 2017). A triple-blind trial of *Saccharomyces boulardii* in overweight or obese knee-OA patients improved pain, hs-CRP, and oxidative-stress markers over twelve weeks (Dolatkhah et al., 2024). A prebiotic-fiber trial improved physical performance and reduced trunk fat, though its between-group pain difference narrowly missed significance ($p = 0.059$) (Fortuna et al., 2024); and a probiotic (Probio-M8) added to chondroitin improved WOMAC scores with corresponding immune and microbiome shifts (Wang et al., 2025). These benefits are strain-specific rather than general. A randomized trial of a heat-killed *Clostridium butyricum* postbiotic found no benefit over placebo (Lee et al., 2026), and a meta-analysis of the eligible trials concluded that the apparent effect was driven almost entirely by *L. casei* Shirota, with other preparations ineffective (Moyseos et al., 2024). No trial has used a structural (imaging) endpoint or shown that microbiome change prevents cartilage loss. A recent systematic review spanning roughly ten human and twenty-one animal studies reached the same balanced conclusion and that is dysbiosis, permeability, and inflammation probably influence OA, but that high-quality prospective human evidence is lacking and bacterial findings are inconsistent (S. Liu et al., 2023).

Where insulin resistance fits in this arm deserves particular care, because it is central to the thesis of this review and its position as the required intermediary is weaker than the LPS–inflammation route. That gut changes can cause insulin resistance is well supported in animals (Cani et al., 2007) and has limited human support, and transferring lean-donor microbiota transiently improved insulin sensitivity in men with metabolic syndrome (Vrieze et al., 2012). But a subsequent double-blind trial achieved microbial engraftment without improving insulin sensitivity (Yu et al., 2020). Crucially, the human

insulin-resistance transfer studies did not measure OA, and the human OA microbiome trials did not rigorously measure insulin sensitivity, so the complete pathway from dysbiosis through insulin resistance to joint damage remains untested in humans. On current evidence, the LPS–innate-immune-inflammation pathway is better supported than insulin resistance as the necessary link between the gut and the joint.

The strength of evidence therefore differs sharply by claim, and it is worth stating each grade explicitly. That gut microbiota can modify experimental OA is supported by moderate-to-strong animal evidence; that gut permeability and LPS are associated with human OA inflammation and severity is moderate associative evidence; that a consistent OA-specific microbial signature exists is weak; that dysbiosis causes human insulin resistance is plausible but mixed; that insulin resistance mediates microbiome-related human OA is of very low certainty; and that probiotics or prebiotics prevent cartilage loss is not demonstrated. Accordingly, commercial stool testing, fecal transplantation, and generic probiotic use cannot yet be recommended to diagnose or structurally treat OA, and any effect appears highly strain-, diet-, and patient-dependent. The most defensible conclusion is that the microbiome is probably an OA modifier, particularly in the obese, metabolically unhealthy phenotype, and that a fiber-rich Mediterranean-style pattern—associated with lower OA prevalence in observational data (Veronese et al., 2017)—remains a reasonable general recommendation on broad grounds rather than as a proven joint-specific therapy.

Human Dietary Evidence and Limitations

Human evidence is consistent with, but does not establish, a pathogenic role for refined and rapidly absorbed carbohydrate in knee OA. The most informative studies are prospective and use structural endpoints. In an Osteoarthritis Initiative (OAI) cohort of 2,149 adults with radiographic knee OA, men consuming at least five sugar-sweetened soft drinks per week showed greater 48-month joint-space loss (0.60 versus 0.31 mm) and faster radiographic progression (hazard ratio 2.05, 95% CI 1.32–3.19), with no association in women (Lu et al., 2013). In a separate OAI cohort of 2,842 participants, the highest versus lowest quartile of a Western dietary pattern predicted incident radiographic knee OA (hazard ratio approximately 1.6–1.7), with roughly 30% of the association mediated through BMI (Xu et al., 2021). Cross-sectionally, higher dietary glycemic index was associated with symptomatic knee OA among women in a Korean survey of 9,203 adults (odds ratio 1.77, 95% CI 1.20–2.60), while glycemic load, radiographic-only OA, and all outcomes in men were null (So et al., 2018).

Interventional data are sparse but directionally supportive. The only randomized trial in knee OA, a 12-week pilot in 21 non-diabetic older adults, found that carbohydrate restriction improved several pain measures and lowered oxidative stress (TBARS) and leptin relative to low-fat and usual diets—though its size and duration preclude any conclusion about cartilage or disease progression (Strath et al., 2020). A larger, non-randomized two-year study of 242 adults with type 2 diabetes and knee pain reported that carbohydrate restriction within a continuous-care model improved knee function (total KOOS), with nearly half of participants meeting the minimal clinically important difference, versus no significant change under usual care; participants self-selected treatment and OA was not radiographically confirmed (Lyman et al., 2022).

A related line of evidence implicates ultra-processed foods, which are typically refined-carbohydrate-dense but not carbohydrate-specific. In the UK Biobank (163,987 participants), the highest quartile of ultra-processed-food intake was associated with incident knee—but not hip—OA (hazard ratio 1.10, 95% CI 1.03–1.18) (Wei et al., 2024), and in 4,403 OAI participants, greater ultra-processed-food consumption was cross-sectionally associated in women with worse symptoms, slower gait, and roughly 13 μm thinner knee cartilage per standard-deviation increase (Akkaya et al., 2025). Higher added-sugar intake has likewise been associated with self-reported OA (odds ratio 1.40, 95% CI 1.09–1.81), though both exposure and outcome were self-reported and temporality is indeterminate (S. Liu et al., 2024).

The counter-evidence is equally important and points to carbohydrate quality rather than quantity. Fiber-rich carbohydrate appears protective: in the OAI and Framingham cohorts, the highest fiber quartile was associated with lower symptomatic knee-OA risk (odds ratios 0.70 and 0.39, respectively) (Dai et al., 2017), and higher whole-grain and cereal-fiber intake predicted lower incident radiographic knee OA in the OAI (hazard ratios 0.66 and 0.61) (T. Liu et al., 2023). Because whole-grain and refined-starch foods can carry similar total carbohydrate yet opposite risk associations, the operative distinction is not "complex versus simple" carbohydrate—a categorization that misclassifies high-glycemic starches such as white bread—but the degree of refinement, the glycemic response, and the fiber content of the food. Taken together, the human data support a hypothesis centered on refined, high-glycemic, and ultra-processed dietary patterns; they do not demonstrate that carbohydrate intake per se causes OA, and the strongest structural signal is confined to men and to a single beverage exposure (Lu et al., 2013).

From Mechanism to Practice: Defining "Too Much Carbohydrate"

Because only about 4 g of glucose circulate at any moment in a 70-kg adult, glycemia is tightly regulated (Wasserman, 2009); it is the chronicity and amplitude of glycemic excursions, rather than any single per-meal gram count, that plausibly drive glycation, endogenous fructose production, and oxidative injury over time. A practical definition follows: "too much carbohydrate" is the intake that prevents metabolic homeostasis for a given individual. Standard clinical reference values—impaired fasting glucose at ≥110 mg/dL (≈6.1 mmol/L) and post-prandial values above roughly 180 mg/dL (≈10.0 mmol/L)—identify chronic hyperglycemia, but they are general glycemic markers rather than validated OA-specific thresholds; what the joint literature supports is that diabetes and metabolic syndrome, as sustained hyperglycemic states, are associated with knee-OA prevalence and progression (Eymard et al., 2015; Puenpatom & Victor, 2009).

Dietary quality and glycemic dynamics matter on the intake side, as reviewed above: Mediterranean-style patterns are associated with lower OA prevalence (Veronese et al., 2017), and fiber-rich rather than refined carbohydrate is the relevant distinction (Dai et al., 2017; T. Liu et al., 2023). Viscous fibers such as oat β-glucans acutely blunt post-prandial glucose and insulin responses in healthy adults (Hossain et al., 2025), and fermentable fiber is also the principal substrate for the SCFA-producing bacteria that support the gut barrier (Zhang et al., 2022). The type of sweetener may matter as much as the amount: in a controlled murine study, non-nutritive sweeteners (sucralose and steviol glycosides) produced the lowest microbial diversity, and refined sucrose combined with saturated fat produced the

most metabolic endotoxemia, whereas unrefined caloric sweeteners such as honey and brown sugar produced none—consistent with the refined-versus-whole-food distinction drawn here, although this has been shown so far only in mice (Sánchez-Tapia et al., 2020). As reviewed above, the interventional human evidence in OA remains limited to a small non-diabetic pilot and a non-randomized diabetes study, so intake guidance is anchored in metabolic normalization rather than trial-proven OA benefit (Lyman et al., 2022; Strath et al., 2020).

For individuals with MetS or T2D, the target is metabolic: normalizing fasting and post-prandial glycemia and restoring insulin sensitivity, which would be expected to re-engage insulin's local anti-inflammatory actions and reduce the substrates and signals implicated above (Hamada et al., 2016; Lee et al., 2022; Wang & He, 2018). Weight reduction, which decompresses cytokine-active adipose depots, is an established adjunct (Longo et al., 2019).

Therapeutic Carbohydrate Reduction (TCR)

Therapeutic carbohydrate reduction (TCR) refers to dietary patterns that restrict total carbohydrate intake, and it is increasingly recognized as a viable strategy for managing T2D and, in some cases, supporting remission (Wheatley et al., 2021). In Australia, TCR has been formalized in a clinical statement endorsed by the Australian Diabetes Society, which presents it as an evidence-based option and defines its subtypes: low-carbohydrate diets at less than 130 g/day and very-low-carbohydrate (ketogenic) diets at roughly 20–50 g/day (Stranks & Lawlor-Smith, 2023). International bodies including the American Diabetes Association and Diabetes Canada likewise conclude that reducing overall carbohydrate intake has among the strongest supporting evidence for improving glycemia, when individualized and clinically supervised (Diabetes Canada, 2020; Evert et al., 2019).

Evidence from low-carbohydrate interventions shows improvements in HbA1c (glycated hemoglobin), body weight, blood pressure, and medication burden (Brinkworth et al., 2022; Dening et al., 2023; Wheatley et al., 2021). In a single-arm, clinician-delivered program, among participants with baseline HbA1c ≥6.5%, most improved and about half reached HbA1c <6.5% at follow-up, a commonly used remission threshold (Brinkworth et al., 2022). A 6-month mobile-health low-carbohydrate program produced a clinically meaningful HbA1c reduction (approximately 1.0 percentage point) and medication de-intensification, although its blood-pressure benefit was not sustained at 6 months (Kolivas et al., 2025).

The durability and specificity of these benefits warrant caution. In head-to-head comparisons, the glycemic advantage of carbohydrate restriction over balanced-carbohydrate diets is clearest in the short term—up to roughly six months—and attenuates by 12 to 24 months; a 2022 systematic review found little to no difference in weight, HbA1c, or LDL cholesterol at up to two years (South, 2025). Remission, likewise, appears to track with the degree of weight loss and energy deficit rather than with carbohydrate restriction per se, and meta-analytic data do not show higher remission rates for low- or very-low-carbohydrate diets than for other energy-reduced approaches (Diabetes Australia, 2021). Structured programs such as DiRECT and its Australian implementation begin with very-low-energy total diet replacement to induce weight loss before transitioning to supported maintenance, with remission defined

as HbA1c <6.5% sustained for at least 3 months without glucose-lowering medication (Gunatillaka et al., 2025). Carbohydrate reduction also carries safety considerations beyond hypoglycemia, including euglycemic ketoacidosis in patients taking SGLT2 inhibitors; it is contraindicated or requires specialist supervision in type 1 diabetes, pregnancy, childhood, advanced renal or hepatic disease, and disordered eating (Diabetes Australia, 2018; South, 2025).

Mechanistically, sustained carbohydrate reduction would be expected to lower the substrate for Maillard/AGE formation, attenuate RAGE-driven inflammatory signaling, reduce oxidative stress, and improve insulin sensitivity—benefits that are plausible for joint tissue and are established for glycemic control (Chen et al., 2016; Giri et al., 2018; Hamada et al., 2016; Suzuki et al., 2022). Very-low-carbohydrate (ketogenic) intake may add a distinct anti-inflammatory action: the ketone β-hydroxybutyrate directly inhibits the NLRP3 inflammasome and lowers IL-1β in preclinical models, independent of glucose lowering (Youm et al., 2015)—although this has not yet been tested in joint tissue. Well-designed low-carbohydrate diets appear comparable or superior on safety when diet quality is prioritized—minimizing ultra-processed, high-glycemic foods while ensuring adequate protein, healthy fats, fiber, and micronutrient density (Evert et al., 2019; Wheatley et al., 2021).

Discussion

The evidence assembled here supports a coherent, biologically plausible model in which a chronically high carbohydrate load contributes to OA through glycation, fructose-specific metabolism, meta-inflammation, oxidative and microvascular injury, and the loss of insulin's protective actions, reinforced by a gut–joint axis. Three features make the model persuasive rather than merely speculative. It explains the clustering of OA with cardiometabolic disease; it accounts for OA in non–load-bearing joints, which pure mechanics cannot; and it is supported by a convergent chain of mechanistic experiments in which manipulating individual nodes such as TNF, NADPH oxidase, insulin signaling, the microbiome, alters joint outcomes in animal models (Guss et al., 2019; Hamada et al., 2016; Han et al., 2022). At the population level, a synthesis of human observational data reports that type 2 diabetes is associated with OA independently of body mass index (odds ratio ≈1.25), predicts radiographic progression, and roughly doubles the likelihood of joint replacemen, while its authors emphasize that a causal relationship is not established and that some studies are null (Veronese et al., 2019). A clinical corollary is that patients with metabolic syndrome derive less functional benefit from hip and knee arthroplasty, consistent with a catabolic milieu that persists after the mechanical problem is surgically corrected (Gandhi et al., 2010).

The evidence should not be overstated, and several counterpoints deserve explicit weight. First, most mechanistic findings come from in vitro systems and rodent models and thus extrapolation to human joints is reasonable but unproven, and some key experiments used stimuli other than dietary carbohydrate, chemical oxidants, IL-1β, or supraphysiologic insulin, rather than glucose or fructose exposure itself (Qiao et al., 2020; Reed et al., 2014). Second, several strands are indirect to the joint by their nature: the endothelial-glycocalyx and uric-acid pathways are documented in the systemic vasculature and liver but have not been demonstrated in cartilage or synovium, and the uric-acid

mechanism is itself contested by Mendelian-randomization data (Dogné et al., 2018; Hannou et al., 2018; Nieuwdorp et al., 2006). Third, the gut–joint arm is well supported up to the level of metabolic endotoxemia and insulin resistance in humans (Mehta et al., 2010) and is now backed at the joint by multiple animal-manipulation experiments and replicated human associations (Boer et al., 2019; Ulici et al., 2018). But no human trial has used a structural endpoint, probiotic benefit is strain-dependent and includes clear negatives (Loeser et al., 2022; Moyseos et al., 2024), and the specific step from dysbiosis through insulin resistance to OA remains untested in humans. Fourth, human associations between metabolic disease and OA are partly confounded by adiposity and load. In one meta-analysis the association between diabetes and OA is attenuated—though not always eliminated—after adjustment for body mass index and age (Louati et al., 2015), and some cohorts show diabetes predicting knee-OA progression predominantly in men (Eymard et al., 2015). A larger systematic review of 31 studies and roughly 295,000 people went further, concluding that diabetes is not an independent risk factor for OA once BMI is adequately accounted for and identifying adiposity as the dominant confounder (Khor et al., 2020)—a direct challenge to the causal reading that must be weighed against the positive syntheses. Animal models are not uniformly supportive either. A mouse study that independently varied dietary sucrose and fat found less cartilage pathology in the high-sucrose group, a paradoxical result its authors attributed in part to control-diet composition (Donovan et al., 2018). Fifth, and most important for clinical framing, efforts to treat OA by targeting systemic pathways have a mixed-to-negative record. Anti-TNF trials in OA have been inconsistent (Hamada et al., 2016), and antioxidant and nitric-oxide-synthase–inhibitor strategies that protect cartilage in animals have failed to translate, including a negative two-year trial of the iNOS inhibitor cindunistat (Bolduc et al., 2019).

Read as the causal chain it implies, the model's evidence is uneven and can be graded link by link. The upstream link that excess carbohydrate promoting energy surplus, insulin resistance, systemic oxidative stress, and endotoxemia, is supported in humans, including cross-sectional correlations between adiposity and oxidative-stress markers (Furukawa et al., 2004), the reproducible glycemic effects of carbohydrate manipulation, and a human endotoxin-infusion study linking LPS to insulin resistance (Mehta et al., 2010). The middle link thats insulin resistance, oxidative stress, glycation, and microvascular injury altering cartilage, synovium, and subchondral bone, rests largely on in vitro and animal work and is therefore mainly mechanistic and preclinical (Han et al., 2022; Qiao et al., 2020), a status underscored by the failure of antioxidant interventions in human OA (Bolduc et al., 2019). The glycation arm is the best-developed of these, adding in vivo animal evidence that raising cartilage AGEs or matrix cross-linking worsens OA (DeGroot et al., 2004; Kim et al., 2015) and human-tissue evidence of more cartilage pentosidine and faster structural progression in diabetes (Neumann et al., 2019; Oren et al., 2011); even so, the specific human chain from dietary carbohydrate through cartilage AGE accumulation to incident OA has not been demonstrated, and the broader diabetes–OA association is itself contested once adiposity is controlled (Khor et al., 2020). The downstream link that these tissue changes producing clinical OAis supported in humans only at the level of observational association: diabetes and metabolic syndrome track with OA prevalence, progression, and arthroplasty need, at times independently of body mass (Veronese et al., 2019), while the sole low-carbohydrate dietary trial in OA remains a small pilot (Strath et al., 2020) and the gut-specific evidence, though spanning many animal-

manipulation studies and replicated human associations, still lacks any trial with a structural endpoint (S. Liu et al., 2023; Ulici et al., 2018). Proof-of-concept that a metabolic intervention can alter OA comes from the insulin-sensitizer metformin, which limits cartilage degradation and synovitis in mouse and non-human-primate models, though its human evidence is confined to conflicting observational cohorts (Li et al., 2020). No link in the chain is yet supported by human causal evidence from randomized trials or Mendelian randomization; the model is therefore best read as a well-grounded, testable hypothesis rather than an established causal sequence.

Several limitations of this review should be acknowledged. It is a narrative synthesis rather than a systematic review, so study selection was not exhaustive and formal risk-of-bias appraisal was not performed. The mechanistic literature is heterogeneous in model system, exposure, and outcome, which constrains quantitative comparison. Causal language has been avoided where only associations exist, but residual confounding in the observational data cannot be excluded. Finally, "excess carbohydrate" is not a single standardized exposure across the cited studies, and the practical thresholds discussed are individualized rather than empirically derived OA cutoffs.

Conclusion

Osteoarthritis is not only a mechanical disease. A substantial and internally consistent body of mechanistic and observational evidence indicates that a chronically high load of refined, high-glycaemic carbohydrate, delivered as glucose and fructose, can contribute to joint pathology through Maillard-driven AGE accumulation and RAGE signaling, fructose-specific hepatic and vascular effects, adipose-, microvascular-, and gut-derived inflammation, oxidative stress, and the loss of insulin's local anti-inflammatory actions. This metabolic model complements the mechanical one and helps explain why OA clusters with cardiometabolic disease and appears in non–load-bearing joints. At the same time, the human clinical evidence that reducing dietary carbohydrate improves OA outcomes remains preliminary, the gut–joint link, though now supported by multiple animal-manipulation studies and replicated human associations, still lacks any trial showing that microbiome-directed treatment preserves cartilage, insulin resistance as the mediating step remains largely untested in humans, and interventions targeting metabolic pathways have a mixed record in the joint.

For patients with metabolic syndrome or type 2 diabetes, restoring metabolic health and normalizing glucose, improving insulin sensitivity, supporting a fiber-fed microbiome, and reducing inflammatory tone, is worthwhile on its own strong merits, and therapeutic carbohydrate reduction is a well-supported means to those ends under clinical supervision. Whether these metabolic gains translate into slower OA progression or less pain is a promising hypothesis that now needs to be tested directly rather than assumed. Framed this way, the metabolic view of OA is both scientifically defensible and clinically responsible and it broadens the differential of modifiable risk without promising more than the current evidence can support.

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