Metabolic messengers from the gut to the joint: Toward precision management of osteoarthritis (Review)

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Abstract. Osteoarthritis has evolved from a mechanical concept to a metabolic whole-organ disease driven by systemic inflammation. The 'gut-joint axis' represents a 'biological highway' where intestinal dysbiosis permits the translocation of microbial metabolites into synovial joints. This review focuses on three pivotal metabolite classes with opposing roles: Short-chain fatty acids (SCFAs), which function as anti-inflammatory guardians; trimethylamine N-oxide (TMAO), which acts as a pro-inflammatory aggressor; and bile acids (BAs), which serve as complex regulators that balance homeostasis and catabolism. This review further proposes a novel 'metabolite homeostasis imbalance' theoretical framework, which posits that osteoarthritis pathogenesis is driven by the disruption of the dynamic equilibrium between protective (SCFAs), destructive (TMAO) and context-dependent regulatory (BAs) microbial metabolites. This integrative 'metabolite homeostasis imbalance' model deconstructs the 'biological highway' metaphor into a three-tier mechanistic schema encompassing intestinal barrier integrity, systemic metabolite trafficking and tissue-specific effector functions in the joint microenvironment, thereby providing a unifying conceptual foundation bridging scattered single-metabolite research and mechanism-targeted precision OA management. Additionally, the potential of sports medicine interventions, including exercise and probiotics, to modulate this axis is evaluated. This synthesis provides a comprehensive theoretical basis for novel clinical strategies targeting gut-derived metabolic networks to preserve joint health and mitigate disease progression.

Contents

1. Introduction

Osteoarthritis (OA) has historically been categorized within orthopedics and sports medicine as a localized condition resulting from 'wear and tear' or mechanical overload. However, this hemodynamic and biomechanical perspective fails to explain the prevalence of joint degeneration in non-weight-bearing joints or the accelerated progression observed in patients with metabolic comorbidities. Contemporary epidemiological data indicate that OA is a leading cause of global disability, with its incidence rising in parallel with the obesity epidemic (1,2). Consequently, the paradigm has shifted toward defining OA as a whole-organ disease characterized by low-grade systemic inflammation, often termed 'metabolic OA', a clinical phenotype defined by the co-occurrence of OA with components of metabolic syndrome (obesity, dyslipidemia, hypertension and/or insulin resistance) in the absence of overt mechanical trauma. This phenotype is distinct from posttraumatic etiologies and is intricately linked with metabolic syndrome components such as dyslipidemia, hypertension and insulin resistance (3). Recent evidence suggests that the chronic low-grade inflammation associated with aging, known as 'inflammaging', which is as the age-related, low-grade, sterile systemic inflammation

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Abbreviations: OA, osteoarthritis; SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide; BAs, bile acids; FXR, farnesoid X receptor; TGR5, Takeda G-protein-coupled receptor 5; PXR, pregnane X receptor; TLR4, Toll-like receptor 4; NF-κB, nuclear factor κB; NLRP3, NLR family pyrin domain containing 3; HDAC, histone deacetylase; ROS, reactive oxygen species; LPS, lipopolysaccharides; BEVs, bacterial extracellular vesicles; ADAMTS, A disintegrin and metalloproteinase with thrombospondin motifs; DCA, deoxycholic acid; LCA, lithocholic acid; Sirt6, sirtuin 6; MICT, moderate-intensity continuous training

Key words: osteoarthritis, gut microbiota, gut-joint axis, short-chain fatty acids, trimethylamine n-oxide, bile acids, systemic inflammation, sports medicine

that drives cellular senescence and tissue dysfunction, acts as a critical driver of chondrocyte senescence and synovial dysfunction (4,5). Therefore, understanding the systemic origins of this inflammation is paramount for developing non-surgical interventions that go beyond symptomatic pain relief.

The gastrointestinal tract has emerged as a primary candidate for the origin of this systemic inflammation. The 'gut-joint axis' hypothesis posits that the intestinal ecosystem communicates with articular tissues through complex immunological and metabolic pathways. Under physiological conditions, the gut barrier prevents the translocation of luminal pathogens; however, dysbiosis (an imbalance in microbial composition) can compromise this barrier, leading to a 'leaky gut' phenomenon (6,7). Systematic reviews have consistently identified distinct microbial signatures in patients with OA compared to healthy controls, often characterized by a reduction in diversity and an alteration in the Firmicutes to Bacteroidetes ratio (8,9). Furthermore, recent Mendelian randomization studies have provided causal evidence suggesting that gut microbiota dysbiosis is not merely a consequence of OA or analgesic use but a potential initiating factor in the disease pathogenesis (10,11). This bidirectional relationship suggests that the joint is susceptible to inflammatory signals originating from the gut, challenging the traditional dogma that the articular cavity is a sterile and isolated environment.

While the presence of bacterial DNA in synovial fluid has been documented, the primary mediators of the gut-joint crosstalk are small-molecule metabolites produced by the fermentation of dietary substrates. These metabolites enter the systemic circulation and act as signaling molecules that regulate bone extracellular matrix homeostasis and immune responses in distal tissues (12,13). This 'biological highway' explains how dietary inputs directly influence joint health. Recent multi-omics analyses have revealed that specific alterations in the serum metabolome, driven by gut microbial shifts, correlate strongly with the severity of synovitis and cartilage degradation (14,15). Unlike short-lived cytokines, these metabolites can induce epigenetic changes in chondrocytes and osteoblasts, thereby modulating the gene expression profiles responsible for tissue repair or degradation. Thus, the gut microbiota functions as a 'forgotten organ' with endocrine capabilities, secreting bioactive molecules that dictate the metabolic fate of the musculoskeletal system (14,15).

Among the myriad of microbial byproducts, three classes of metabolites have garnered significant attention due to their opposing roles in joint homeostasis: Short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO) and bile acids (BAs). SCFAs, such as butyrate and propionate, are generally regarded as 'protective guardians' that suppress inflammation and promote regulatory T-cell differentiation (16). Conversely, TMAO, a product of dietary choline metabolism, has been identified as a 'pro-inflammatory aggressor' linked to oxidative stress and the newly described gut-microbiota-ferroptosis axis in OA (17). BAs occupy a complex middle ground; while they are essential for nutrient absorption, dysregulated BA metabolism has been associated with symptomatic hand and knee OA through the modulation of the farnesoid X receptor (FXR) and inflammatory pathways (18,19). The delicate balance between these metabolite classes may determine whether the joint microenvironment remains in a state of homeostasis or progresses toward catabolism.

As sports medicine evolves toward precision health and lifestyle medicine, unraveling these metabolic networks offers novel therapeutic avenues. Current management strategies largely rely on analgesics and eventual arthroplasty, but targeting the gut-joint axis presents an opportunity for disease modification through diet, exercise and microbiome modulation (20,21). Exercise, a cornerstone of OA rehabilitation, has been shown to independently improve gut microbial diversity and serum metabolomics, potentially mitigating the effects of a high-fat diet (20,22). Furthermore, the integration of multi-omics data allows for the identification of personalized metabolic phenotypes, paving the way for targeted interventions such as prebiotics, probiotics or postbiotics (21,23). Thus, a significant unmet cognitive need remains: No existing framework systematically integrates the opposing yet complementary roles of SCFAs, TMAO and BAs to guide the transition from generalized microbiome modulation toward stratified, mechanism-driven interventions.

This review aims to synthesize the current state of knowledge regarding the crosstalk between gut microbiota-derived metabolites and OA, specifically focusing on the mechanistic roles of SCFAs, TMAO and BAs, to provide a theoretical basis for novel clinical strategies in the preservation of joint health. Furthermore, this review deconstructs the conventional 'biological highway' metaphor into a more precise three-tier mechanistic schema. This hierarchical schema provides a structured framework for identifying therapeutic targets at each level of the gut-joint axis and directly addresses the identified cognitive gap by translating the conceptual model of metabolic equilibrium into testable mechanistic hypotheses. A dedicated conceptual schematic (Fig. 1) is placed below this paragraph to systematically visualize the proposed 'metabolite homeostasis imbalance' theoretical framework and three-tier gut-joint axis mechanistic hierarchy. This diagram hierarchically divides gut-joint communication into intestinal barrier integrity, systemic trafficking and local joint effector tiers, and graphically demonstrates how disrupted balance among protective SCFAs, detrimental TMAO and bidirectionally regulated BAs initiates metabolic OA lesions (10,18).

2. The biological highway: The gut-joint axis

The concept of the 'gut-joint axis' represents a paradigm shift in understanding OA pathogenesis, transforming it from a localized disorder of wear and tear into a complex systemic condition driven by metabolic and inflammatory mediators. This bidirectional communication channel facilitates the transit of gut-derived molecules to distal musculoskeletal tissues via the systemic circulation. Consistent with the three-tier mechanistic schema proposed in the introduction, the gut-joint axis operates through a sequential cascade of molecular events that can be precisely delineated at the barrier, trafficking and effector levels. Recent evidence suggests that the integrity of the intestinal barrier and the subsequent translocation of microbial products or metabolites constitute the 'biological highway' through which intestinal dysbiosis exacerbates articular degeneration. Fig. 2

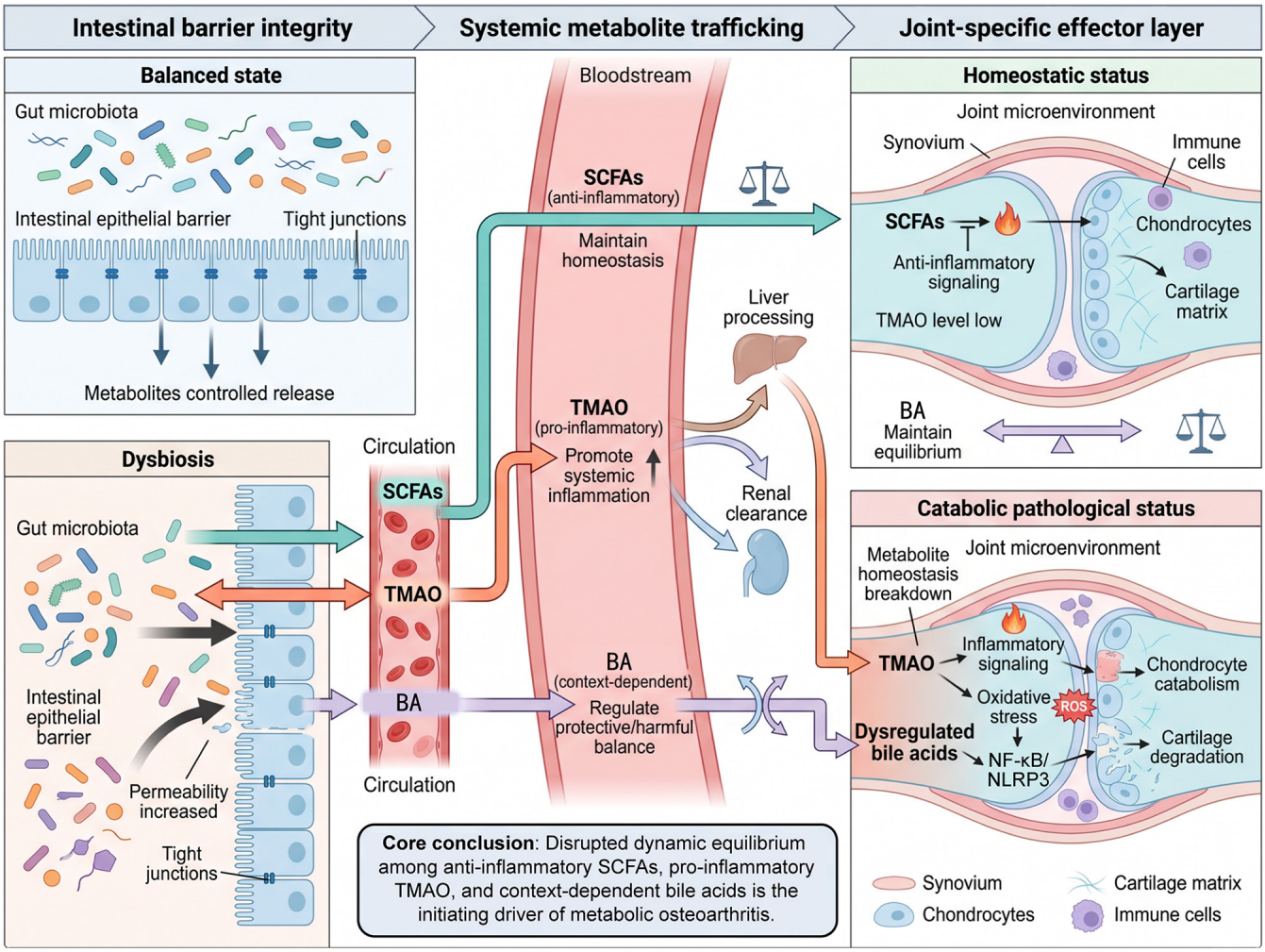

Figure 1. Schematic illustration of the proposed 'metabolite homeostasis imbalance' theoretical framework and three-tier mechanistic gut-joint axis schema. The figure stratifies the whole pathological cascade into intestinal barrier integrity, systemic metabolite trafficking and joint-specific effector three tiers, and demonstrates that disrupted dynamic equilibrium between anti-inflammatory SCFAs, pro-inflammatory TMAO and context-dependent bile acids is the core initiating driver of metabolic osteoarthritis. SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide; BA, bile acid; OA, osteoarthritis; FXR, farnesoid X receptor; TGR5, Takeda G-protein-coupled receptor 5; NLRP3, NLR family pyrin domain containing 3; NF-κB, nuclear factor κB.

centrally illustrates the complete mechanistic cascade of the gut-joint axis in OA pathogenesis. As shown in the schematic, gut dysbiosis disrupts intestinal barrier integrity and increases gut permeability, allowing microbial metabolites and bacterial extracellular vesicles (BEVs) to enter systemic circulation (24). These gut-derived bioactive substances translocate to joint tissues, activate TLR4-mediated inflammatory signaling and chondrocyte pyroptosis and ultimately drive cartilage degeneration and OA progression (25). This graphical model intuitively validates the three-tier gut-joint axis mechanism proposed in this review.

The 'leaky gut' hypothesis. The primary initiation point of this pathological axis lies in the disruption of the intestinal epithelial barrier, a phenomenon clinically termed 'leaky gut'. Under physiological conditions, the intestinal epithelium serves as a selective barrier, regulated by complex apical junctional complexes including tight junctions (zona occludens1, occludin) and adherens junctions. However, dysbiosis induced by Western diets, aging or obesity can impair these junctional proteins, leading to increased intestinal permeability. Guido *et al* (26) conducted a systematic review highlighting that increased intestinal permeability is significantly associated with the severity of OA symptoms and radiographic progression, suggesting that barrier dysfunction is a prerequisite for gut-derived inflammation to reach the joint. Furthermore, Escalante *et al* (7) recently elucidated that age-related deterioration of the gastrointestinal tract exacerbates this permeability, thereby permitting the paracellular leakage of luminal antigens into the lamina propria.

Once the physical barrier is compromised, the immune tolerance of the gut is breached. Jiang *et al* (27) identified that the mechanosensitive channel Piezo1 plays a critical role in regulating intestinal inflammation and barrier function. This offers a novel molecular explanation for how mechanical signals in the gut might influence systemic immunity (27). The breakdown of these defense mechanisms allows for the influx of pathogen-associated molecular patterns, such as lipopolysaccharides (LPS), into the portal circulation. This phenomenon, known as metabolic endotoxemia, triggers a low-grade systemic inflammatory state. Such a state is highly characteristic of metabolic OA phenotypes (21).

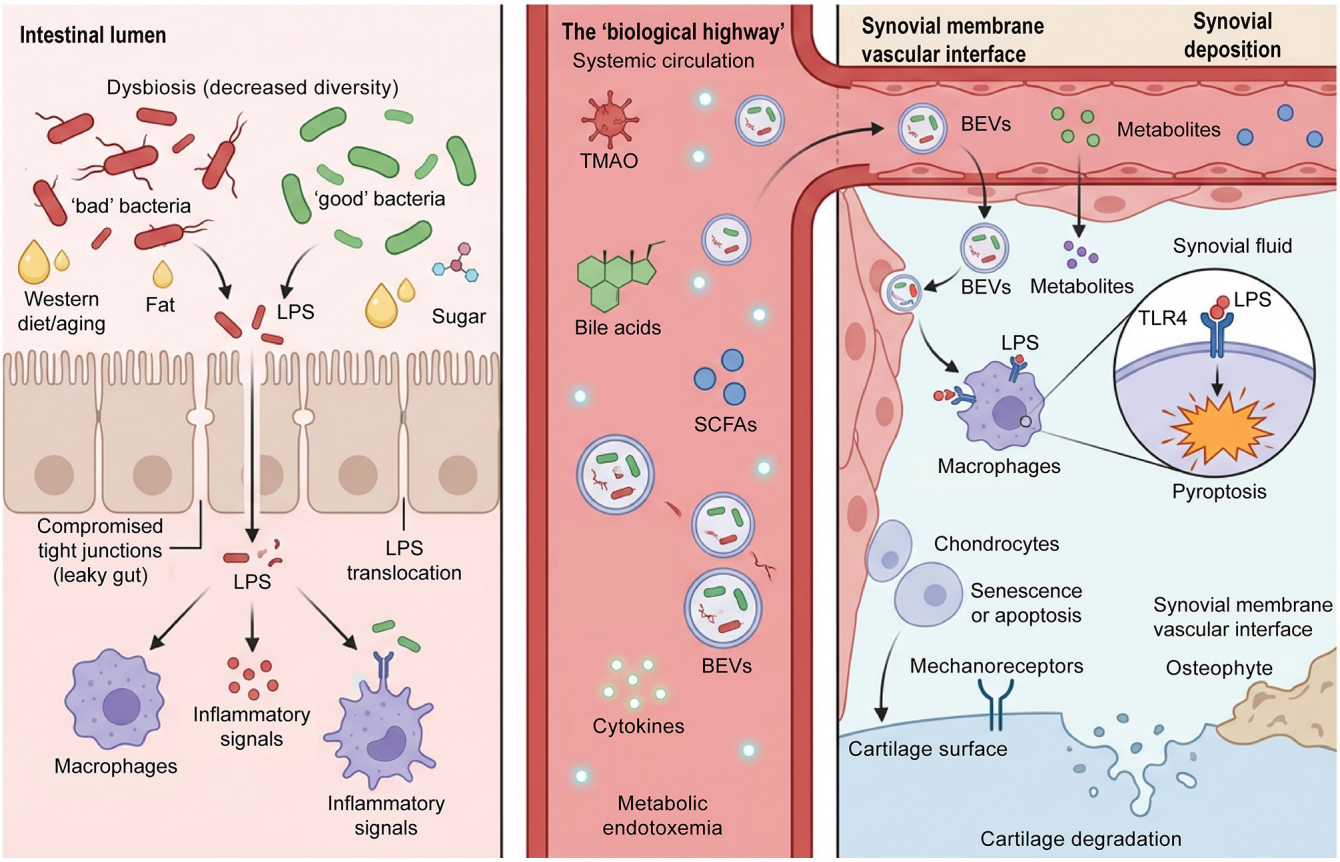

Figure 2. The 'biological highway' of the gut-joint axis. Western diet-induced dysbiosis and barrier disruption enable the influx of metabolites and BEVs. These 'Trojan horses' traverse the circulation to the synovium, activating TLR4 signaling and pyroptosis, which accelerates cartilage degradation and osteoarthritis development. OA, osteoarthritis; BEVs, bacterial extracellular vesicles; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; NLRP3, NLR family pyrin domain containing 3; NF-κB, nuclear factor κB; ROS, reactive oxygen species.

Translocation to the joint. The second segment of this biological highway involves the physical translocation of microbial components and metabolites from the circulation into the synovial fluid and cartilage matrix. Historically, the joint was considered a sterile environment; however, the application of next-generation sequencing has challenged this dogma. Bardi *et al* (28) performed a systematic review of synovial fluid microbiota characterization, confirming the presence of bacterial DNA signatures in OA patients that closely resemble intestinal microbial profiles. This suggests that bacterial genetic material or dormant bacteria can traverse the endothelial barrier of the synovial microvasculature. He *et al* (29) further proposed the concept of 'joint dysbiosis', where the local accumulation of translocated microbial products directly alters the homeostasis of the joint microenvironment.

A critical mechanism facilitating this transport involves BEVs. Niu *et al* (24) demonstrated that BEVs act as a 'Trojan horse', encapsulating bioactive bacterial components and protecting them from degradation in the bloodstream until they reach the target joint tissue. Upon arrival, these vesicles can fuse with synoviocytes or chondrocytes, delivering their cargo. Consequently, the presence of LPS and other bacterial metabolites in the joint activates Toll-like receptors (TLRs), particularly TLR4, on the surface of macrophages and chondrocytes. Yang *et al* (25) detailed how this activation triggers pyroptosis, a highly inflammatory form of programmed cell death, thereby accelerating cartilage matrix degradation and osteophyte formation.

Furthermore, the translocation process is not limited to pro-inflammatory agents but also includes metabolic regulators. Li *et al* (30) discussed how gut microbiota-derived metabolites, once translocated, directly regulate bone extracellular matrix homeostasis through specific signaling pathways. This implies that the 'biological highway' is a dual-use route, transporting both destructive endotoxins and potentially therapeutic metabolites depending on the state of the gut microbiome. Zhang *et al* (31) provided recent evidence that this microbial regulation extends to the Wnt/β-catenin signaling pathway, which is pivotal for joint remodeling and cartilage repair. Therefore, the gut-joint axis functions as a continuous feedback loop where intestinal permeability determines the load of systemic trafficking, ultimately dictating the metabolic and inflammatory fate of the OA joint.

3. The anti-inflammatory guardians

The integrity of the gut-joint axis, as previously described, determines the systemic dissemination of microbial metabolites, with their biological impact contingent upon their specific chemical nature (16). In contrast to pro-inflammatory agents like TMAO, SCFAs, primarily acetate, propionate and butyrate, emerge as a crucial class of gut-derived metabolites

with demonstrated anti-inflammatory and tissue-protective properties (16). Synthesized from dietary fiber fermentation, SCFAs are now recognized as essential signaling molecules that modulate joint homeostasis and combat OA progression through multifaceted mechanisms (32,33). The multifaceted protective mechanisms of SCFAs, spanning receptor signaling, epigenetic regulation and immunomodulation, are supported by a growing body of experimental and clinical evidence, as summarized in Table I, which is organized to highlight the receptor target, molecular mechanism and biological outcome in joint health for each key study. Most of the detailed mechanistic insights into SCFA actions, such as G-protein coupled receptor (GPCR) engagement, histone deacetylase (HDAC) inhibition and autophagy regulation, derive from preclinical models (cell cultures and animal studies) (34,35). Where available, human translational evidence is explicitly noted. The following subsections first summarize the preclinical mechanistic framework and then highlight clinically validated findings.

Biosynthesis and systemic distribution of SCFAs. SCFAs are primarily generated in the cecum and colon through the anaerobic fermentation of indigestible carbohydrates by commensal bacteria such as *Faecalibacterium prausnitzii*, *Roseburia spp*. and *Eubacterium rectale* (32). The levels and ratios of individual SCFAs are dynamically influenced by host diet, with high-fiber intake robustly promoting their production, whereas Western-style diets are linked to reduced SCFA levels and gut dysbiosis (33). Following production, SCFAs are absorbed through the colonic epithelium. Butyrate is preferentially metabolized by colonocytes, while acetate and propionate enter the portal circulation. A significant proportion evades hepatic clearance, achieving systemic bioavailability and enabling these metabolites to reach peripheral tissues, including synovial joints and bone marrow (36,37). This distribution establishes a direct biochemical link between colonic microbial ecology and musculoskeletal tissue metabolism, positioning SCFAs as systemic mediators of the gut-joint axis.

SCFAs as regulators of inflammatory signaling pathways. A primary mechanism of SCFA action involves activation of specific G protein-coupled receptors, namely GPR41 (FFAR3), GPR43 (FFAR2) and GPR109A, expressed on immune cells, chondrocytes and synoviocytes (38). Ligand binding to these receptors initiates intracellular signaling that suppresses key inflammatory cascades. Li *et al* (38) demonstrated that in endothelial cells, SCFAs inhibit LPS or TNF-α-induced inflammation via G protein-coupled receptor 41/43 activation and concurrent HDAC inhibition. In chondrocytes, this receptor-mediated action is particularly relevant. Pirozzi *et al* (34) provided pivotal evidence that butyrate mitigates IL-1β-induced inflammation and matrix degradation predominantly through GPR43. This effect frequently involves the suppression of the nuclear factor-kappa B (NF-κB) pathway, a central driver of OA pathology. For instance, sodium butyrate reduces inflammatory responses in bovine mammary epithelial cells by inactivating NF-κB signaling (39). Sun *et al* (40) further showed that butyrate ameliorates high-fat-diet-induced inflammation partly by activating peroxisome proliferator-activated receptor α. Thus, through GPCR engagement, SCFAs directly interfere with pro-inflammatory signaling hubs within joint tissues.

Epigenetic modulation and autophagy regulation by SCFAs. Beyond receptor activation, SCFAs function as potent endogenous inhibitors of HDAC, leading to histone hyperacetylation and altered gene transcription (41). This epigenetic regulation promotes an anti-inflammatory and pro-reparative cellular state. In the context of OA, this mechanism is critical for maintaining cellular homeostasis. Zhou *et al* (35) elucidated that sodium butyrate attenuates cartilage degradation by restoring impaired autophagy and autophagic flux in chondrocytes. Autophagy is a vital cellular clearance process and its dysregulation contributes to OA progression. The HDAC inhibitory activity of butyrate is central to this effect, influencing the expression of autophagy-related genes. This epigenetic action extends to bone metabolism, where SCFAs promote osteoblast function and inhibit osteoclastogenesis. Tang *et al* (42) demonstrated that sodium butyrate prevents osteoporosis in rats by promoting the osteal glycogen synthase kinase-3β/nuclear factor erythroid 2-related factor 2 signaling axis and improving mitochondrial function. Furthermore, Duscha *et al* (43) reported that propionic acid beneficially modulates osteoporosis biomarkers in patients with multiple sclerosis, indicating a translatable systemic bone-protective effect via similar mechanisms.

Direct protective effects on chondrocytes and cartilage matrix. SCFAs exert direct cytoprotective effects on articular chondrocytes, preserving their phenotype and inhibiting catabolism. Bo *et al* (44) showed that sodium butyrate abolishes the degradation of type II collagen in human chondrocytes, a hallmark of OA cartilage destruction. This protection involves the downregulation of matrix-degrading enzymes such as Matrix metalloproteinases and a disintegrin and metalloproteinase with thrombospondin motifs. Furthermore, SCFAs can counteract cellular senescence and apoptosis in chondrocytes exposed to inflammatory stress. Cho *et al* (45) demonstrated that *Lactobacillus* and butyrate inhibit OA by controlling autophagy and inflammatory cell death (pyroptosis) of chondrocytes. This direct cellular protection is synergistic with their anti-inflammatory actions, creating a comprehensive defense for cartilage matrix integrity against the degradative OA microenvironment.

Immunomodulatory effects in the synovial microenvironment. The synovial inflammation in OA is characterized by immune cell infiltration and cytokine production. SCFAs play a decisive role in modulating this synovial immune landscape. They promote the polarization of macrophages from a pro-inflammatory M1 phenotype towards an anti-inflammatory, tissue-reparative M2 phenotype (46,47). Wu *et al* (48) confirmed that propionate and butyrate attenuate macrophage pyroptosis and osteoclastogenesis induced by wear particles. This modulation is crucial for reducing synovitis and subchondral bone resorption. SCFAs also regulate other immune cells; for example, butyrate has been shown to ameliorate allergic inflammation by limiting eosinophil trafficking and survival (49), and to constrain neutrophil functions

Table I. Summary of key preclinical and clinical evidence elucidating the protective roles of SCFAs in OA and associated musculoskeletal disorders.

Authors, year	Study model/subjects	Specific metabolite/ intervention	Target receptor/ signaling node	Molecular mechanism	Biological outcome involved in joint health	(Refs.)
Pirozzi *et al*, 2018	Human OA chondrocytes	Butyrate	GPR43 (FFAR2)	Inhibition of NF-κB nuclear translocation and reduction of inflammatory cytokines	Attenuation of IL-1β-induced inflammation and cartilage matrix degradation	(34)
Zhou *et al*, 2021	Rat OA model (ACLT)/ chondrocytes	Sodium butyrate	HDAC/PI3K/Akt/ mTOR	Restoration of impaired autophagic flux (LC3II/p62 modulation)	Inhibition of chondrocyte apoptosis and attenuation of cartilage destruction	(35)
Tang *et al*, 2020	Ovariectomized rats/ osteoblasts	Sodium butyrate	GSK-3β/Nrf2	Enhancement of mitochondrial function and antioxidant defense	Prevention of subchondral bone loss and promotion of osteoblastic activity	(42)
Duscha *et al*, 2022	Human cohort (n=290)/ *in vitro*	Propionic acid	Tregs	Enhancement of Treg functionality and suppression of Th1/Th17 axis	Improvement of systemic bone health biomarkers and immunomodulation	(43)
Bo *et al*, 2018	Human OA chondrocytes	Sodium butyrate	MMPs/ADAMTSs	Downregulation of catabolic enzymes expression (MMP-13, ADAMTS-5)	Prevention of type II collagen degradation and preservation of chondrocyte phenotype	(44)
Cho *et al*, 2022	Rat OA model (MIA)/ chondrocytes	*Lactobacillus* (SCFA producer)/ butyrate	AMPK/mTOR	Suppression of NLRP3 inflammasome-mediated pyroptosis	Reduction of inflammatory cell death and relief of OA pain behaviors	(45)
Wu *et al*, 2022	Murine macrophages (RAW264.7)	Propionate/butyrate	GPR43/NLRP3	Inhibition of ROS production and caspase-1 activation	Attenuation of wear particle-induced macrophage pyroptosis and osteoclastogenesis	(48)
Korsten *et al*, 2024	Human OA patients (RCT)	Sustained-release butyrate tablet	T helper cells	Systemic immunomodulation of effector T-cell responses	Suppression of *ex vivo* T-cell activation, demonstrating translational potential	(51)

ACLT, anterior cruciate ligament transection; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AMPK, AMP-activated protein kinase; GPR, G-protein coupled receptor; GSK-3β, glycogen synthase kinase-3β; HDAC, histone deacetylase; IL, interleukin; MIA, monosodium iodoacetate; MMP, matrix metalloproteinase; NF-κB, nuclear factor κB; NLRP3, NLR family pyrin domain containing 3; Nrf2, nuclear factor erythroid 2-related factor 2; OA, osteoarthritis; RCT, randomized controlled trial; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; TLR, Toll-like receptor; Treg, regulatory T cell.

in inflammatory settings (50). Korsten *et al* (51) provided clinical translational evidence, showing that a sustained-release butyrate tablet suppresses *ex vivo* T helper cell activation in patients with OA. By reshaping the immune response within the joint towards a more regulatory state, SCFAs effectively dampen the chronic low-grade inflammation that fuels OA progression.

In conclusion, SCFAs serve as fundamental anti-inflammatory guardians within the gut-joint axis. Their pleiotropic mechanisms, which span GPCR signaling, epigenetic regulation, direct chondroprotection and immunomodulation, establish them as critical metabolites for maintaining joint homeostasis. Strategies aimed at augmenting SCFA levels, such as dietary fiber supplementation, prebiotics, probiotics or even postbiotic administration, therefore represent promising, multi-targeted approaches for the prevention and management of OA. This perspective resonates strongly with the holistic principles of contemporary sports and regenerative medicine.

4. The pro-inflammatory aggressor

In stark contrast to the protective and reparative nature of SCFAs, TMAO has emerged as a potent pro-inflammatory metabolite that exacerbates musculoskeletal degeneration. While originally identified as a cardiovascular risk factor, accumulating evidence suggests that TMAO acts as a systemic 'aggressor' affecting cartilage viability, subchondral bone architecture and muscle function. Elevated serum TMAO levels are increasingly recognized as a metabolic link connecting dietary habits, gut dysbiosis and the low-grade systemic inflammation (inflammaging) observed in metabolic OA phenotypes. As depicted in the accompanying conceptual framework, TMAO operates through a multi-hit mechanism involving oxidative stress induction, inflammasome activation and the disruption of the gut-kidney-joint axis. The molecular mechanisms linking TMAO to joint and bone pathology, including NLRP3 inflammasome activation, NF-κB signaling and Piezo1 upregulation, have been primarily established in cellular and rodent models. However, corroborating clinical evidence exists for associations between circulating TMAO levels and adverse musculoskeletal outcomes, as detailed in this chapter. The following discussion distinguishes preclinical mechanistic findings from human observational data.

The diet-microbe-host axis. The biosynthesis of TMAO is a classic example of co-metabolism between the host and the gut microbiome. It begins with the dietary intake of quaternary amine precursors such as choline, L-carnitine and phosphatidylcholine, which are abundant in red meat, eggs and dairy products. Alisson-Silva *et al* (52) reviewed the human risk associated with high red meat intake, noting that unabsorbed precursors reach the cecum and colon. Here, specific bacterial clostridia possess the cutC/D gene cluster (choline utilization) or cntA/B genes (carnitine monooxygenase), converting these substrates into trimethylamine (TMA).

TMA is a volatile gas that traverses the intestinal barrier and enters the portal circulation to reach the liver. In hepatocytes, flavin-containing monooxygenases (FMOs), specifically the FMO3 isoform, oxidize TMA into TMAO. Thomas and Fernandez (53) highlighted that this conversion is highly variable and influenced by host genetics, hormonal status and the extent of gut dysbiosis. Crucially, this axis is bidirectional; studies indicate that TMAO itself can further alter the gut microbiota composition. For instance, sports nutrition reviews such as that by Sawicka *et al* (54) have scrutinized L-carnitine supplementation, noting that while it aids performance, chronic high-dose ingestion in the presence of a dysbiotic gut may inadvertently fuel TMAO production. Furthermore, since TMAO is primarily cleared by the kidneys, renal function plays a gatekeeping role. Lau *et al* (55) and Lei *et al* (56) described a 'gut-kidney-vascular-bone axis', suggesting that even mild renal insufficiency, which is common in elderly OA populations, can lead to the accumulation of uremic toxins like TMAO, thereby amplifying systemic osteotoxicity.

Molecular mechanisms of joint and tissue damage. Once in the systemic circulation, TMAO translocates to synovial joints and skeletal muscles, where it exerts deleterious effects through several converging molecular pathways. The most prominent mechanism involves the induction of mitochondrial dysfunction and oxidative stress.

Oxidative stress and senescence. TMAO has been shown to impair mitochondrial electron transport, leading to an excessive production of reactive oxygen species (ROS). In the context of bone and cartilage, Li *et al* (57) demonstrated that TMAO promotes oxidative stress, which in turn suppresses Sirtuin 6 (Sirt6), a longevity gene essential for DNA repair and genomic stability. The downregulation of Sirt6 accelerates cellular senescence in chondrocytes and osteoblasts, impairing their ability to maintain the extracellular matrix. Similarly, Zou *et al* (58) utilized metabolomic analysis on C2C12 myoblasts to show that TMAO treatment exacerbates oxidative damage in muscle cells, providing a metabolic basis for the sarcopenia often comorbid with OA.

Inflammasome activation and NF-κB signaling. Beyond direct oxidative damage, TMAO is a potent activator of the innate immune system. Zhang *et al* (59) provided pivotal evidence that TMAO triggers the activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome. This multiprotein complex is responsible for the cleavage and secretion of the pro-inflammatory cytokines IL-1β and IL-18. In the OA joint, IL-1β is the 'master cytokine' driving cartilage catabolism. Notably, this activation often occurs in parallel with the NF-κB pathway. Wang *et al* (60) and Zhao *et al* (61) independently confirmed that TMAO enhances osteoclast differentiation and bone resorption via the ROS-dependent NF-κB signaling cascade. This leads to an uncoupling of bone remodeling, characterized by increased osteoclast activity and suppressed osteoblast function, ultimately resulting in subchondral bone loss and fragility.

Mechanosensitivity and the 'mechanical-metabolic' interface. Perhaps the most intriguing mechanism for sports medicine is the interaction between TMAO and mechanotransduction. Zhuang *et al* (62) recently reported that TMAO sensitizes chondrocytes to mechanical loading through the upregulation of Piezo1, a mechanosensitive ion channel. Under physiological loading, Piezo1 maintains homeostasis; however, in a TMAO-rich environment, the channel becomes hypersensitive, converting normal mechanical signals into

pro-inflammatory responses and calcium influx overload. This finding suggests that metabolic dysregulation (high TMAO) makes the joint more susceptible to mechanical injury, fundamentally linking the 'wear and tear' theory with metabolic pathology.

Clinical correlations: Bone, muscle and cartilage. The mechanistic toxicity of TMAO translates into observable clinical outcomes across the musculoskeletal spectrum. High circulating levels of TMAO are no longer viewed solely as cardiovascular markers but are now implicated in 'osteosarcopenic obesity'.

Osteoporosis and bone quality. Several clinical studies have established a negative correlation between serum TMAO and bone mineral density. Elam *et al* (63), in a large-scale analysis of the Cardiovascular Health Study, found that elevated TMAO levels were associated with a higher risk of hip fractures in older adults, independent of traditional risk factors. This is supported by Lin *et al* (64), who observed that TMAO impairs the functional capacity of bone marrow mesenchymal stem cells, diverting their differentiation away from osteogenesis and towards adipogenesis. This 'fatty marrow' conversion compromises bone quality and structural support for the overlying cartilage.

Sarcopenia and muscle function. Given the close functional unit of the muscle and joint, muscle wasting (sarcopenia) significantly accelerates OA progression by reducing joint stability. Mo *et al* (65) elucidated a 'gut-TMAO-muscle' axis, demonstrating that high-fat diet-induced TMAO accumulation drives sarcopenic obesity by impairing muscle protein synthesis and promoting proteolysis. Furthermore, Lin *et al* (66) found an association between uremic toxins (including TMAO precursors) and reduced skeletal muscle mass in patients with compromised renal function. This suggests that TMAO-mediated myopathy may precede or exacerbate articular pathology.

Synovial inflammation. In the specific context of joint disease, Murillo-Saich *et al* (67) performed metabolomic profiling of synovial tissue, identifying distinct metabolic signatures associated with inflammation. While direct synovial TMAO quantification is an emerging field, the presence of its downstream effectors and the strong association between gut dysbiosis and hand OA severity, as noted by Silvestre *et al* (68), supports the hypothesis that this metabolite is a key driver of synovitis. Additionally, Huang *et al* (69) showed in animal models that periodontal inflammation (another source of systemic bacterial burden) aggravates TMAO metabolism, further linking oral-gut dysbiosis to systemic inflammatory loads that burden the joint. Collectively, these data position TMAO as a critical therapeutic target, where reducing its generation could simultaneously benefit cardiovascular, renal and musculoskeletal health. Key experimental and clinical findings linking TMAO to musculoskeletal dysfunction are consolidated in Table II, which categorizes evidence by tissue/cell type, molecular pathway and translational outcome to help readers trace the mechanistic chain from TMAO elevation to bone, muscle or synovial pathology. Before translating these findings into clinical strategies, it is essential to examine how well the mechanistic evidence from model systems aligns with human OA pathophysiology.

Translational considerations for TMAO-mediated pathogenesis. The translational relevance of TMAO-induced pathogenic mechanisms in human OA is supported by several lines of clinical evidence. Large-scale epidemiological studies have established that elevated serum TMAO levels are associated with increased risk of hip fractures 63 and reduced bone mineral density (57), consistent with the osteoclastogenic effects observed in murine models. Synovial tissue metabolomic profiling of patients with OA has identified TMAO-related metabolic signatures that correlate with synovitis severity (67), suggesting that TMAO accumulates in human joint tissues and contributes to local inflammation. Furthermore, the observation that periodontal treatment reduces systemic TMAO levels and inflammatory burden provides indirect evidence that modulating TMAO metabolism can alter systemic inflammation in humans (69). However, direct evidence that TMAO activates the NLRP3 inflammasome or induces chondrocyte senescence in human OA joints remains limited, and it is unclear whether the concentrations of TMAO achieved in the human circulation are sufficient to replicate the robust effects observed in cell culture studies. Future human studies should measure TMAO levels in synovial fluid and correlate them with local expression of NLRP3 inflammasome components and chondrocyte senescence markers to validate these mechanistic pathways *in vivo*.

5. The complex regulators

BAs are historically viewed merely as digestive surfactants required for lipid absorption; however, contemporary research has redefined them as potent signaling steroid hormones that regulate systemic metabolic homeostasis. Following synthesis in the liver as primary BAs, these molecules undergo significant modification by gut microbiota into secondary BAs, such as deoxycholic acid (DCA) and lithocholic acid (LCA). These metabolites re-enter the systemic circulation and reach distant organs, including the synovial joints, where they interact with specific nuclear and membrane receptors. In the context of OA, BAs exhibit a dual nature, functioning as either protective agents or destructive proinflammatory mediators depending on their hydrophobicity and concentration, and the specific receptor activated. Preclinical studies [e.g., FXR agonist studies in murine OA models, Takeda G-protein-coupled receptor 5 (TGR5) activation in chondrocyte cultures and DCA-induced pyroptosis in hepatocytes] have defined the core BA signaling pathways. Recent human metabolomic profiling and interventional trials have started to validate these pathways in patients with OA (18,19). The following subsections clearly separate preclinical mechanistic evidence from clinical translational data.

Microbiota-driven alterations in the BA pool. The composition of the systemic BA pool is dictated by the metabolic activity of the intestinal microbiome. Dysbiosis, characterized by a reduction in beneficial commensals and an increase in pathogenic strains, fundamentally alters the ratio of primary to secondary BAs. Chen *et al* (70) demonstrated that maintaining gut-liver axis homeostasis through microbiota-mediated secondary BA pathways is essential for systemic health. When this balance is disrupted, there is an accumulation of hydrophobic secondary

Table II. Summary of experimental and clinical evidence linking TMAO to OA pathogenesis and musculoskeletal dysfunction.

Authors, year	Study model/subjects	TMAO-related intervention/exposure	Target tissue/cell type	Molecular mechanism/ signaling pathway	Key biological outcome	(Refs.)
Li *et al*, 2019	Aging mice and osteoblast culture	High TMAO diet	Bone tissue/osteoblasts	Oxidative stress and Sirt6 suppression	Accelerated bone aging, reduced bone quality	(57)
Zou *et al*, 2022	C2C12 myoblasts under oxidative stress	TMAO treatment	Skeletal muscle cells	Mitochondrial dysfunction and ROS overproduction	Exacerbated oxidative damage in muscle cells	(58)
Zhang *et al*, 2020	Vascular smooth muscle cells and calcification models	TMAO treatment	Vascular cells/osteoclast precursors	NLRP3 inflammasome activation and NF-κB signaling	Promotion of vascular calcification and osteogenic differentiation	(59)
Wang *et al*, 2022	Osteoclast precursors (RAW264.7) and ovariectomized mice	TMAO administration	Bone marrow-derived macrophages	ROS-dependent NF-κB activation	Enhanced osteoclast differentiation and bone loss	(60)
Zhao *et al*, 2024	Osteoclast precursors and mouse calvarial osteolysis model	TMAO exposure	Osteoclasts/bone tissue	NF-κB/MAPK pathway activation	Increased osteoclastogenesis and bone resorption	(61)
Zhuang *et al*, 2023	Human chondrocytes and mechanical loading model	TMAO pre-treatment	Articular chondrocytes	Upregulation of Piezo1 mechanosensitive channel	Sensitization to mechanical stress, promoting inflammatory response	(62)
Elam *et al*, 2022	Older adults (cardiovascular health study)	Serum TMAO measurement	Systemic/BMD	Not specified (observational)	Association between high TMAO levels and increased hip fracture risk	(63)
Lin *et al*, 2020	Osteoporotic patients and BMSC culture	TMAO exposure	BMSCs	Impaired osteogenic differentiation	Reduced bone formation and increased adipogenesis in BMSCs	(64)
Mo *et al*, 2025	Aging rats on high-fat diet	Diet-induced TMAO elevation	Skeletal muscle	Gut-muscle axis dysregulation	Promotion of sarcopenic obesity and muscle atrophy	(65)
Murillo-Saich *et al*, 2022	OA patients (synovial tissue metabolomics)	Metabolomic profiling	Synovial tissue	Inflammatory metabolite signature (incl. TMAO-related pathways)	Correlation with synovitis severity and metabolic dysregulation	(67)
Huang *et al*, 2025	ApoE(-/-) mice with periodontitis	Periodontal treatment	Systemic/gut-kidney axis	Modulation of TMAO metabolism	Reduced systemic TMAO and inflammatory burden	(69)

BMSCs, bone marrow mesenchymal stem cells; BMD, bone mineral density; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; NLRP3, NLR family pyrin domain containing 3; OA, osteoarthritis; ROS, reactive oxygen species; Sirt6, sirtuin 6; TMAO, trimethylamine N-oxide.

BAs, which are often cytotoxic at high concentrations. This perturbation is not merely local to the gut; rather, it leads to increased intestinal permeability and the translocation of these metabolites into the blood, eventually accumulating within the synovial fluid of joints. Yu *et al* (71) identified that BA insufficiency and specific metabolic alterations are mechanically linked to oxidative stress-mediated pathology, providing a bridge between metabolic liver diseases and the development of OA. Consequently, the specific profile of BAs circulating in the host serves as a critical determinant of whether the joint microenvironment remains homeostatic or shifts toward a catabolic state.

FXR: The protective guardian. The FXR acts as a nuclear transcription factor and is widely regarded as a protective sensor in joint tissues. Under physiological conditions, FXR activation suppresses inflammatory signaling and maintains metabolic quiescence in chondrocytes. Hu *et al* (72) provided compelling evidence regarding the therapeutic potential of this pathway; they found that an FXR agonist significantly attenuated osteochondral pathologies in an OA model. Their study revealed that FXR activation suppressed the c-Jun N-terminal kinase 1/2/nuclear factor of activated T-cells 1 pathway, thereby inhibiting osteoclast fusion in the subchondral bone (72). This is a crucial finding because it suggests that BAs affect not only the cartilage surface but also the underlying bone remodeling, which is a key driver of OA progression. Furthermore, the anti-inflammatory capacity of FXR is linked to the inhibition of the NLRP3 inflammasome. Sun *et al* (73) reported that regulation of the FXR-NLRP3 signaling pathway could alleviate inflammatory conditions, suggesting a similar mechanism may protect synovial tissues from cytokine-induced degradation. Therefore, strategies that preserve FXR expression or enhance its activation by specific BA ligands represent a promising avenue for halting the structural deterioration of the joint.

The TGR5 and NLRP3 axis: A context-dependent interaction. While FXR generally exerts protective effects, the role of the TGR5 and its interaction with specific secondary BAs is more complex and context-dependent. TGR5 is expressed on chondrocytes and immune cells within the synovium and its activation has been shown to inhibit catabolic enzymes. Huang *et al* (74) demonstrated that activation of TGR5 ameliorates IL-1β induced chondrocyte senescence, indicating a direct anti-aging effect on the cartilage matrix. Similarly, Zhuo *et al* (75) observed that TGR5 activation inhibits the degradation of type II collagen and aggrecan in human chondrocytes, further supporting a chondroprotective role for this receptor.

However, the specific ligands available to bind these receptors can drastically alter the outcome. High levels of hydrophobic secondary BAs, particularly DCA, have been implicated in triggering inflammation rather than resolving it. Mai *et al* (76) highlighted that DCA promotes pyroptosis, a highly inflammatory form of programmed cell death, by inhibiting mitophagy and activating the NLRP3 inflammasome. This aligns with findings by Holtmann *et al* (77), who reported that certain BAs specifically activate the NLRP3 inflammasome to promote inflammation in a cell-type-specific manner.

However, not all secondary BAs are detrimental; Zhong *et al* (78) found that LCA, another secondary BA, could alleviate inflammatory conditions via inhibition of the NLRP3 inflammasome, contrasting with the effects of high-dose DCA. Additionally, Liu *et al* (79) reported that LCA ameliorates inflammation via the pregnane X receptor (PXR)/TLR4/NF-κB/NLRP3 signaling pathway, further illustrating the nuance that different metabolites from the same class can have opposing biological effects. Thus, the 'complex regulator' designation arises from this delicate balance: TGR5 activation is beneficial, but an excess of cytotoxic secondary BAs like DCA can bypass these protective checks to trigger the NLRP3 inflammasome and induce chondrocyte death.

Clinical evidence and translational perspectives. The transition from basic science to clinical reality is supported by recent metabolomic profiling of patients with OA. Li *et al* (18) conducted a comprehensive analysis of BA metabolism in patients with symptomatic hand OA, providing direct clinical evidence of altered BA profiles in human OA populations. Their work validates the hypothesis that systemic metabolic perturbations are reflected in the clinical phenotype of joint disease. Furthermore, the connection between metabolic health and joint integrity is reinforced by broader comorbidity studies. Zemedikun *et al* (80) and Sharafi *et al* (81) utilized latent class analysis to identify comorbidity phenotypes, consistently finding that metabolic clusters (often involving dyslipidemia and liver dysfunction) are high-risk groups for severe OA and mortality.

Collectively, these studies suggest that the 'gut-joint axis' is not a passive system but an active signaling highway mediated by BAs. The presence of specific BA transporters and receptors on joint tissues renders the cartilage and synovium sensitive to microbiome-derived metabolic shifts. In summary, BAs regulate OA pathology through a tripartite mechanism: Protecting subchondral bone via FXR, modulating chondrocyte senescence via TGR5 and potentially driving inflammation via NLRP3 activation when hydrophobic secondary BAs accumulate. Future therapeutic interventions may focus on manipulating the gut microbiota to optimize the BA pool or developing selective receptor modulators that uncouple the anti-inflammatory benefits from the cytotoxic risks. The dual and context-dependent roles of BAs, as elucidated by pivotal preclinical and clinical studies, are detailed in Table III, which separates protective (FXR, TGR5) from detrimental (DCA, NLRP3) pathways and includes recent human validation studies for easier comparison.

Translational validation of BA signaling in human OA. Recent clinical studies have significantly advanced the current understanding of BA signaling in human OA pathophysiology. Li *et al* (18) conducted the first comprehensive metabolomic analysis of BA profiles in patients with symptomatic hand OA, identifying specific alterations in primary and secondary BA levels that correlate with disease severity. Most notably, Yang *et al* (19) demonstrated in a landmark study that glucagon like peptide 1 receptor agonists improve OA outcomes by targeting intestinal FXR signaling, providing direct clinical validation of the therapeutic potential of modulating BA receptors in human OA. This study confirmed that the FXR-NLRP3

Table III. Complex and dual roles of bile acids in OA pathophysiology: A summary of mechanistic insights from preclinical and clinical studies.

Authors, year	Study model/subjects	Specific bile acid/intervention	Target receptor/signaling node	Molecular mechanism	Biological outcome in joint health	(Refs.)
Chen *et al*, 2025	Weaned piglets/ gut-liver axis	Metasilicate water (modulates BA pool)	Microbiota-mediated secondary BA pathway	Maintenance of gut-liver axis homeostasis	Systemic health promotion, implying stabilized joint microenvironment	(70)
Yu *et al*, 2025	PFOS-induced mouse model	Bile acid insufficiency	Oxidative stress pathways	Linking BA insufficiency to oxidative stress	Proposed mechanism connecting metabolic liver disease to OA development	(71)
Hu *et al*, 2022	Mouse OA model	FXR agonist	FXR/JNK1/2/NFATc1	Suppression of JNK1/2/ NFATc1 pathway	Attenuation of subchondral bone osteoclast fusion and osteochondral pathology	(72)
Sun *et al*, 2023	DSS-induced colitis mice	*Bacteroides dorei* BDX-01	FXR-NLRP3 axis	Regulation of intestinal BSH activity and FXR-NLRP3 signaling	Alleviation of systemic inflammation, suggesting potential joint protection	(73)
Huang *et al*, 2018	IL-1β-treated human chondrocytes	TGR5 agonist	TGR5 (GPBAR1)	Activation of TGR5 signaling	Amelioration of IL-1β-induced chondrocyte senescence	(74)
Zhuo *et al*, 2019	IL-1β-treated human chondrocytes	TGR5 agonist	TGR5 (GPBAR1)	Activation of TGR5 signaling	Inhibition of type II collagen and aggrecan degradation	(75)
Mai *et al*, 2023	Steatotic HepG2 cells	DCA	NLRP3 inflammasome	Inhibition of mitophagy, activation of NLRP3	Induction of pyroptosis (pro-inflammatory cell death)	(76)
Holtmann *et al*, 2021	Murine liver inflammation models	Specific bile acids	NLRP3 inflammasome	Cell-type-specific activation of NLRP3	Promotion of inflammation or fibrosis	(77)
Zhong *et al*, 2026	Colitis mouse model	LCA/EGCG	NLRP3 inflammasome	Gut microbiota-derived LCA inhibits NLRP3	Alleviation of colitis inflammation, suggesting anti-inflammatory potential	(78)
Liu *et al*, 2025	Ulcerative colitis mouse model	LCA	PXR/TLR4/NF-κB/ NLRP3	Modulation of PXR/TLR4/ NF-κB/NLRP3 axis and gut microbiota	Amelioration of inflammation, highlighting metabolite-specific effects	(79)
Li *et al*, 2025	Human patients with symptomatic hand OA	Bile acid metabolomics profile	Systemic metabolic perturbation	Altered bile acid metabolism	Direct clinical correlation of BA dysregulation with human OA phenotype	(18)

BA, bile acid; BSH, bile salt hydrolase; DCA, deoxycholic acid; DSS, dextran sulfate sodium; EGCG, epigallocatechin gallate; FXR, farnesoid X receptor; GPBAR1, G protein-coupled bile acid receptor 1; IL-1β, interleukin-1β; JNK, c-Jun N-terminal kinase; LCA, lithocholic acid; NFATc1, nuclear factor of activated T-cells 1; NF-κB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; OA, osteoarthritis; PFOS, perfluorooctane sulfonate; PXR, pregnane X receptor; TGR5, takeda G protein-coupled receptor 5; TLR4, Toll-like receptor 4.

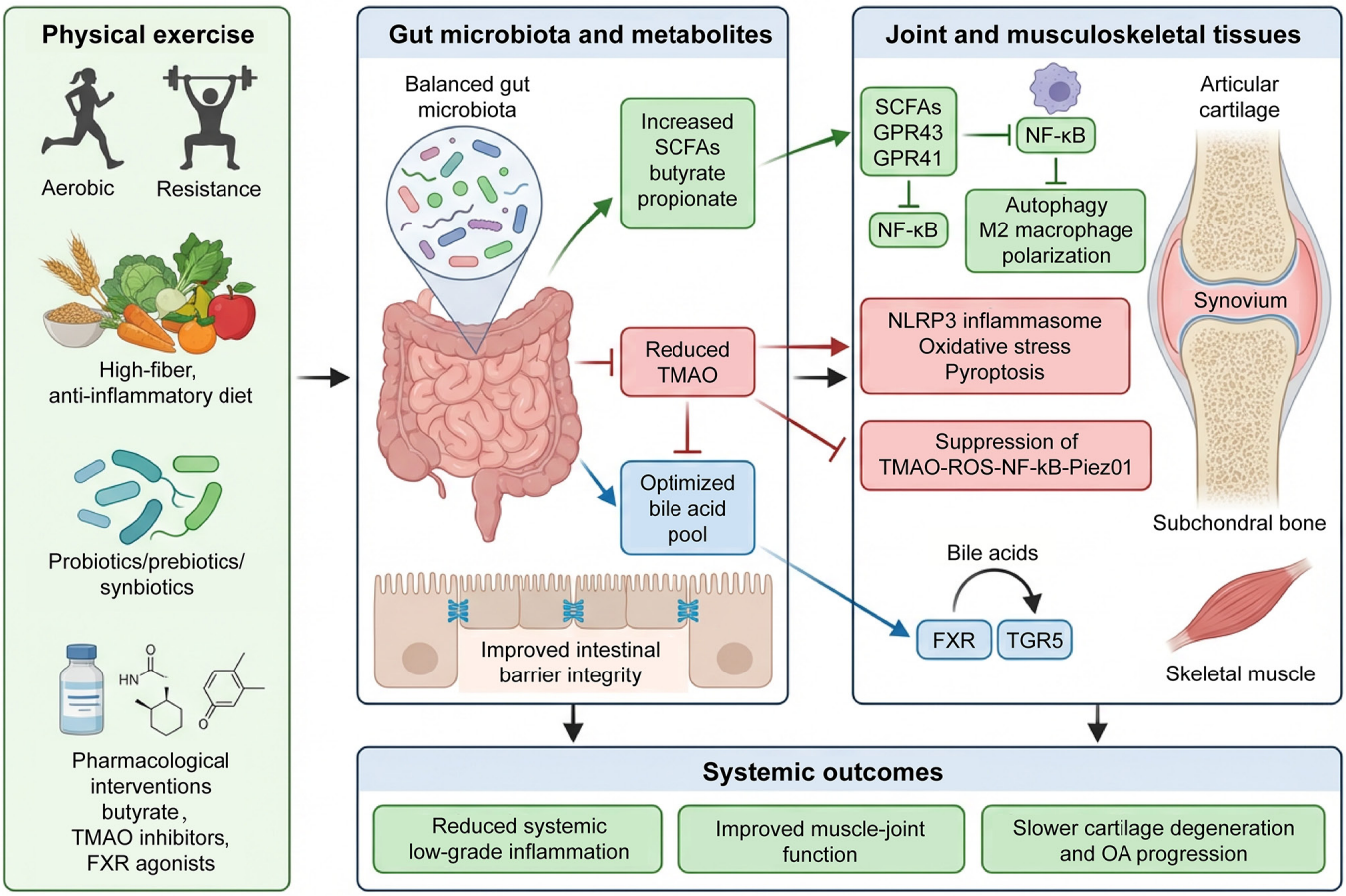

Figure 3. Therapeutic modulation of the gut-joint axis in osteoarthritis: A sports medicine perspective. Scientific diagram illustrating how exercise, diet, probiotics and targeted metabolite-based therapies modulate the gut microbiota-derived metabolites (SCFAs, TMAO, bile acids) to influence the gut-joint axis in osteoarthritis, highlighting anti-inflammatory SCFA signaling, inhibition of TMAO-driven oxidative stress, and bile acid receptor regulation (FXR/TGR5) in cartilage, synovium, bone and muscle. SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide; BAs, bile acids; FXR, farnesoid X receptor; TGR5, Takeda G-protein-coupled receptor 5; NLRP3, NLR family pyrin domain containing 3; NF-κB, nuclear factor κB; ROS, reactive oxygen species; TLR4, Toll-like receptor 4.

signaling axis, previously characterized in preclinical models, plays a critical role in human disease pathogenesis. However, the dual nature of BA signaling presents unique translational challenges. While FXR activation is consistently protective, the effects of TGR5 activation and individual secondary BAs in human OA remain incompletely understood. For example, while DCA induces pyroptosis *in vitro* (76), it is unclear whether the concentrations of DCA present in human synovial fluid are sufficient to trigger this response. Further clinical studies are needed to define the optimal BA profile for joint health and to develop selective receptor modulators that maximize therapeutic benefits while minimizing potential adverse effects.

6. Therapeutic implications: A sports medicine perspective

The delineation of the gut-joint axis, mediated by microbial metabolites such as SCFAs, TMAO and BAs, reframes OA management. It advocates for a systemic strategy targeting underlying metabolic and inflammatory dysregulation, moving beyond local symptom control. This paradigm aligns with the holistic principles of sports medicine, which emphasizes optimizing the whole-body environment for tissue resilience and long-term musculoskeletal health. Consequently, strategic modulation of the gut microbiota and its metabolic output emerge as a compelling therapeutic frontier. To translate these concepts into actionable clinical practice, the following mechanism-guided strategies are proposed. Fig. 3 serves as the core therapeutic schematic of this review, summarizing the multi-modal sports medicine interventions for precision OA management via targeting the gut-joint axis. As illustrated, exercise, dietary regulation, probiotic supplementation and targeted pharmacotherapy collectively remodel gut microbial metabolite profiles, including upregulating protective SCFAs, inhibiting pro-inflammatory TMAO production and balancing BA receptor signaling (20,51,82). This integrated graphical framework systematizes mechanism-based interventions to restore joint metabolic homeostasis and delay OA progression.

Exercise as a microbiome modulator: Towards prescription. Physical activity is a cornerstone of sports medicine and OA management, renowned for its direct benefits on muscle strength and systemic inflammation. Compelling evidence now positions regular exercise as a potent non-pharmacological modulator of the gut ecosystem. Both aerobic and resistance training are associated with increased gut microbial diversity, a hallmark of a stable and functional microbiome often observed in athletes.

This 'athlete's microbiome' is frequently enriched with taxa capable of producing beneficial metabolites, particularly SCFAs. Li *et al* (83) demonstrated that moderate exercise ameliorated OA progression in mice, an effect linked to reduced systemic LPS and a favorable microbial shift. Further reinforcing this link, Hao *et al* (21,84) showed that exercise intervention altered gut microbiome profiles and serum metabolomics in rat models of post-traumatic OA, promoting a less inflammatory state.

Exercise also appears to counteract the detrimental TMAO pathway. Brunt *et al* (85) reported that voluntary wheel running mitigated vascular dysfunction and exercise intolerance induced by a Western diet in mice, with suppression of circulating TMAO implicated as a key mechanism. Furthermore, Pedersini *et al* (86) reviewed the evidence linking physical activity to gut microbiota composition, supporting its role in maintaining gut barrier integrity and microbial homeostasis. Therefore, tailored exercise prescriptions serve a dual purpose: Directly enhancing musculoskeletal function and indirectly cultivating a gut environment that favors protective metabolites while suppressing harmful ones.

From a prescription standpoint, existing evidence supports the use of moderate-intensity continuous training (MICT) performed for 30-45 min per session, at least 3-5 times per week, as a feasible regimen to increase gut microbial diversity and SCFA-producing taxa (20). For patients in whom MICT is limited by joint symptoms, accumulating evidence suggests that resistance training and high-intensity interval training may offer comparable or even superior benefits for specific metabolites. However, data in OA populations remain preliminary (83). Importantly, the gut microbiome responds to exercise in a dose-dependent manner, with responders showing increased *Bifidobacterium* and *Lactobacillus* abundance, whereas non-responders exhibit a resilient microbial profile that may require longer training durations or adjunctive dietary modulation.

Nutritional interventions: Moving from general advice to quantified targets. Dietary patterns are primary determinants of gut microbiota composition and the systemic metabolite profile. From a sports medicine perspective, nutritional strategies can be optimized to foster a joint-protective gut environment. The dichotomy between a Western diet and diets rich in fiber and polyphenols is critical. The former promotes dysbiosis and elevates TMAO production, while high intake of fermentable fibers stimulates SCFA production. Fortuna *et al* (82) conducted a randomized controlled trial demonstrating that prebiotic fiber supplementation in adults with knee OA and obesity improved physical function and shifted gut bacterial taxa beneficially.

Probiotic supplementation represents a direct strategy to introduce beneficial microbes. Substantial evidence supports specific *Lactobacillus* strains such as *L. casei* Shirota (87), *L. acidophilus* (88) and *L. rhamnosus* (89), all of which have been shown to improve knee symptoms, attenuate pain and cartilage damage, or ameliorate OA progression. The efficacy of Bifidobacterium species is also well-documented for OA and bone health (90-92). Henrotin *et al* (91) demonstrated that *Bifidobacterium longum* CBi0703 protected against spontaneous OA in guinea pigs. Synbiotic combinations may offer synergistic effects, as suggested by studies on bone metabolism (93-95). Ishizu *et al* (96) further highlighted the potential in athletes, finding that prebiotic food intake may improve bone resorption markers in Japanese female athletes. Thus, nutritional counseling should prioritize anti-inflammatory, fiber-rich dietary patterns, potentially augmented with evidence-based prebiotic or probiotic supplements.

To operationalize these findings, a daily fermentable fiber intake target of 25-35 g/day is recommended based on data showing that this amount increases circulating acetate and butyrate concentrations and reduces inflammatory markers in patients with OA (82). Furthermore, dietary interventions to lower TMAO should prioritize reducing red meat intake to ≤2 servings per week, given that L-carnitine is a major TMAO precursor (52). In athletic populations requiring higher protein intake for muscle maintenance, alternative protein sources such as plant-based proteins or egg white (which are lower in TMA precursors than red meat) should be emphasized while maintaining total protein goals.

Targeted pharmacotherapy and personalization. Beyond lifestyle modifications, the precise targeting of specific microbial metabolic pathways represents a novel frontier in pharmacotherapy. The concept of 'postbiotics', which involves administering beneficial bacterial metabolites, holds significant promise. Butyrate, a principal SCFA, has demonstrated chondroprotective effects in OA models (45,97). Translating this to humans, Korsten *et al* (51) conducted a double-blind trial showing that a sustained-release butyrate tablet suppressed *ex vivo* T helper cell activation in patients with OA, suggesting direct metabolite supplementation could bypass variable microbial fermentation.

A major therapeutic target is the TMAO-generating pathway. Inhibition of microbial enzymes like trimethylamine (TMA) lyase can block TMA formation. Wang *et al* (98) and Fechtner *et al* (99,100) demonstrated that the inhibitor 3,3-dimethyl-1-butanol and its metabolite attenuated pathology in models of heart failure and arthritis by reducing TMAO levels. Natural compounds also show potential; Baptista *et al* (101) investigated resveratrol's effects on TMAO changes post-exercise in older adults, while Huang *et al* (102) evaluated resveratrol butyrate esters for interrupting TMA metabolism *in vitro*. Furthermore, strategies to modulate BA receptors, such as FXR agonists, have shown promise in preclinical OA models by protecting subchondral bone (103). These approaches underscore the potential for developing interventions that selectively inhibit detrimental metabolites or supplement beneficial ones.

A critical step toward personalization is the integration of multi-omics data to identify patients who are most likely to respond to specific interventions. Machine learning algorithms have recently been employed to associate gut microbiota compositions with physical functioning in patients with OA, enabling the identification of distinct 'metabolic phenotypes' (104). For example, patients with high baseline TMAO may benefit more from TMA lyase inhibitors or dietary red meat restriction, whereas those with low SCFA levels may respond preferentially to prebiotic fiber or butyrate supplementation. Furthermore, genetic factors such as polymorphisms in the flavin-containing FMO3 gene, which encodes the hepatic

enzyme converting TMA to TMAO, can influence individual TMAO responses to dietary choline (53). Screening for such variants could identify patients with genetically determined high TMAO production who would derive the greatest benefit from microbial TMA lyase inhibition rather than dietary modification alone.

In summary, the sports medicine perspective is uniquely equipped to implement a holistic strategy informed by the gut-joint axis. Exercise establishes a foundational pro-homeostatic shift in the gut microbiome. Nutrition provides the necessary substrates to sustain this beneficial environment. Emerging targeted therapies offer precision tools to correct specific metabolic imbalances. The proposed algorithm provides a mechanism-guided, implementable pathway for translating gut-joint axis biology into clinical practice. This integrative, multi-modal framework aligns with the preventive, systems-oriented ethos of sports medicine, addressing the root systemic dysregulation in OA and paving the way for personalized, mechanism-driven preservation of joint health.

7. Challenges and future directions

The proposed 'metabolite homeostasis imbalance' model has important implications for addressing the current challenges in gut-joint axis research. This integrative framework suggests that future studies should move beyond investigating individual metabolites in isolation and instead focus on characterizing the global metabolic profile of patients to determine their specific 'metabolic imbalance phenotype'. Despite the exponential growth in delineating the gut-joint axis, a significant dichotomy remains between the robust causal evidence established in animal models and the largely associative nature of human clinical studies. Most current research relies on cross-sectional sequencing of the microbiome, which captures a static snapshot of dysbiosis rather than the dynamic temporal changes preceding joint degeneration. While recent investigations using fecal microbiota transplantation in germ-free mice have successfully demonstrated that OA susceptibility is transferable and immunologically mediated (105), translating these findings to human cohorts remains complex due to confounding lifestyle variables. Longitudinal studies are scarce but essential to determine whether gut dysbiosis is a precursor to OA or a consequence of disease-related lifestyle changes such as immobility and analgesic use. Recent efforts analyzing gut microbiomics in relation to sustained knee pain represent a positive step toward establishing temporality (106), yet large-scale prospective cohorts integrating multi-omics are required to definitively map the transition from gut dysbiosis to the onset of articular cartilage degradation.

A critical challenge in gut-joint axis research is the translation of mechanistic findings from cellular and animal models to human OA pathophysiology. While reductionist models are essential for defining molecular pathways, such as TMAO activating NLRP3 inflammasomes or SCFAs inhibiting NF-κB signaling, the human joint microenvironment is complex and validation in clinical settings remains limited. Nevertheless, convergent human evidence already supports these mechanisms, including Mendelian randomization studies establishing causal links between gut microbiota and OA risk (10,11), human synovial fluid metabolomics identifying TMAO-related signatures associated with synovitis (67), clinical trials demonstrating butyrate-mediated immunomodulation in patients with OA (51) and large-scale metabolomic and interventional studies validating BA-FXR signaling in human OA (18,19). Future efforts should prioritize direct quantification of these metabolites in human synovial fluid and single-cell analyses of patient-derived joint tissues to further bridge the translational gap.

Furthermore, the influence of sexual dimorphism on the gut-joint axis represents a critical knowledge gap that current literature often overlooks. OA prevalence exhibits a distinct female predominance particularly after menopause, yet many preclinical mechanistic studies utilize male animals to avoid hormonal variability, thereby obscuring potential sex-specific microbial interactions. Recent evidence indicates that sex differences significantly alter how external factors like alcohol or high-fat diets impact the intestinal flora and subsequent bone resorption (107,108). The interplay between estrogen depletion and the microbiome is pivotal, as estrogens regulate both gut barrier integrity and microbial composition (109). Consequently, future investigative frameworks must rigorously stratify data by sex to determine if the 'estrogen-gut-bone axis' requires distinct therapeutic approaches for male vs. female patients, potentially explaining the variable efficacy of metabolic interventions observed in clinical trials.

A second major challenge lies in deciphering the precise molecular mechanisms by which specific metabolites influence joint tissue homeostasis beyond general anti-inflammatory effects. While the protective roles of SCFAs and the detrimental impact of TMAO are broadly categorized, the specific signaling cascades within the chondrocyte and osteoblast microenvironment require further elucidation. Emerging research has begun to map these interactions, such as the regulation of bone extracellular matrix homeostasis by gut-derived metabolites and the modulation of the Wnt/β-catenin signaling pathway in joint remodeling (30,31). However, the interplay is often non-linear and involves complex feedback loops including the 'gut-microbiota-ferroptosis axis', which has been recently proposed as a critical pathogenic pathway (17). Future research must focus on validating specific receptor targets on synovial cells for these metabolites, moving from general observations of 'metabolic shifts' to identifying druggable molecular targets that can halt cartilage senescence and subchondral bone loss. A specific knowledge gap regarding SCFAs concerns the absence of direct quantification in human OA synovial fluid and the unknown relationship between oral supplementation doses and clinically relevant concentration ranges within the joint microenvironment. While serum SCFA levels have been associated with OA severity, direct measurements in synovial fluid remain scarce and existing metabolomic profiling of OA synovial tissue has focused on other metabolite classes rather than systematically quantifying SCFAs (67). Future studies should prioritize paired serum-synovial fluid SCFA quantification in patients receiving SCFA-based interventions to determine whether the butyrate doses shown to improve clinical outcomes (300-600 mg/day) achieve sufficient synovial fluid concentrations to directly modulate chondrocyte and synovial cell functions.

The heterogeneity of OA phenotypes necessitates a shift from a 'one-size-fits-all' probiotic strategy toward

personalized precision medicine based on distinct metabolomic signatures. Current clinical applications are hindered by the lack of reliable biomarkers to predict which patients will respond to microbiome modulation. Advanced analytical techniques are beginning to bridge this gap, with machine learning algorithms now being employed to associate specific gut microbiota compositions with physical functioning in patients with OA (104). Furthermore, distinct metabolic profiles have been identified for specific disease subtypes, such as erosive hand OA (110), suggesting that the gut-joint axis may operate differently depending on the affected joint and systemic metabolic status. Future directions should prioritize the development of 'companion diagnostics' that utilize fecal or serum metabolomics to phenotype patients, thereby enabling clinicians to prescribe targeted prebiotic or postbiotic regimens tailored to the individual's specific dysbiotic profile.

Finally, the clinical translation of microbiome-based therapies faces significant hurdles regarding standardization, delivery and safety. While probiotic supplements are popular, their colonization efficiency is transient and highly variable among individuals. The field is progressively pivoting toward 'postbiotics' or metabolite-based therapies, which offer more predictable pharmacokinetics. For instance, the use of sustained-release butyrate tablets has shown promise in suppressing immune cell activation in patients with OA (51), providing a proof-of-concept for direct metabolite supplementation. However, rigorous Mendelian randomization studies are needed to confirm the causal impact of the microbiota on arthritis outcomes to prevent premature clinical application (111). The ultimate goal for sports medicine and rheumatology is to develop standardized, evidence-based protocols that integrate exercise, which independently modulates the microbiome (21), with targeted metabolic interventions to restore joint homeostasis through the gut-joint axis.

8. Conclusion and future perspectives

The 'gut-joint axis' redefines OA from simple mechanical wear to a systemic metabolic pathology driven by intestinal dysbiosis. This review highlights how microbial metabolites, including protective SCFAs, destructive TMAO and complex BAs, act as critical molecular switches regulating joint homeostasis. Future clinical innovation lies in precision sports medicine where integrating exercise, nutrition and targeted microbiome therapies will transition OA management from symptomatic relief to proactive and mechanism-driven disease modification.

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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