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THE GUT-HEART-JOINT AXIS: MICROBIOME-MEDIATED MECHANISMS IN RHEUMATOID ARTHRITIS AND CARDIOVASCULAR DISEASE

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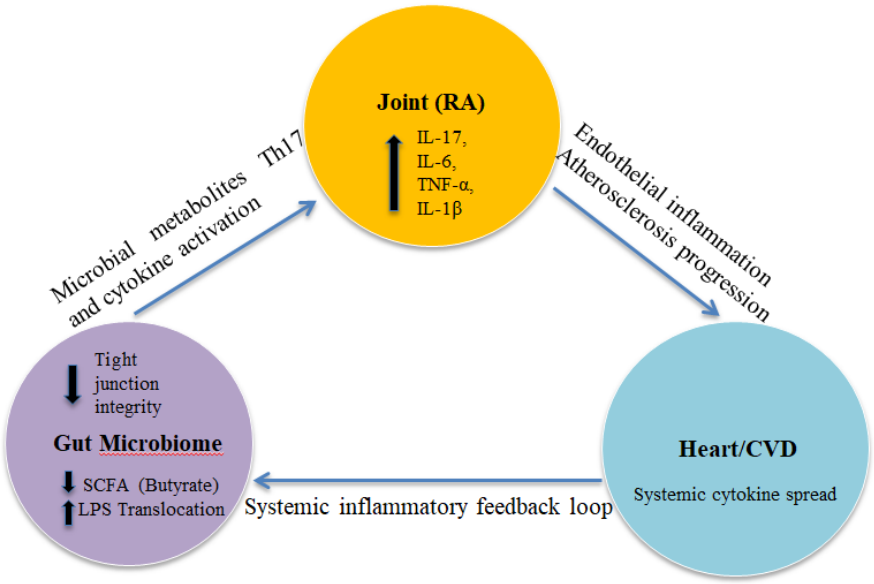
ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease primarily affecting joints, but its impact extends beyond the synovium. Notably, RA confers a 1.5–2-fold higher risk of cardiovascular disease (CVD), including accelerated atherosclerosis. Emerging evidence implicates the gut microbiome as a pivotal mediator in this triad, forming a "gut-heart-joint axis." This review synthesizes current knowledge on how intestinal dysbiosis and microbial metabolites contribute to RA pathogenesis and heightened CVD risk. We discuss key microbiome-mediated pathways – from impaired gut barrier function and immune cell trafficking to molecular mimicry and proinflammatory metabolites – that link RA and CVD pathophysiology. We highlight diagnostic implications, such as distinct gut microbiota signatures in preclinical RA and potential microbial or metabolic biomarkers for CVD risk stratification.

A balanced overview of treatment strategies is provided, encompassing conventional RA therapies (DMARDs and biologics) that incidentally modulate the microbiome, as well as emerging interventions targeting dysbiosis (dietary fiber, probiotics, and even fecal microbiota transplantation). Throughout, we emphasize clarity for the general medical professional, reviewing immunological crosstalk (e.g. Th17 cells, cytokines) in approachable terms. The gut-heart-joint axis paradigm offers a unifying framework that not only enhances our understanding of RA's systemic nature but also uncovers novel avenues for diagnosis and therapy aimed at improving both joint and cardiovascular outcomes. By integrating microbiome science with clinical rheumatology and cardiology, this review outlines a path toward precision medicine approaches that could mitigate inflammation and comorbidity in RA.

Keywords: gut-heart-joint axis**,** rheumatoid arthritis, cardiovascular disease, gut microbiota, immunological crosstalk.

GRAPHICAL ABSTRACT



1. INTRODUCTION

RA is a common autoimmune inflammatory arthritis characterized by symmetric polyarthritis and progressive joint destruction [1][2]. Beyond joint damage, RA exerts systemic effects– most notably an increased incidence of CVD. Decades of epidemiologic data confirm that RA patients have about 50–70% higher risk of myocardial infarction, stroke, and other CVD events than age-matched individuals without RA [3][4]. This elevated risk is comparable to that of diabetes mellitus, prompting some guidelines to recommend multiplying a patient's calculated cardiovascular risk by 1.5 if RA is present [5][6]. Chronic inflammation is a major driver of this risk: pro-inflammatory cytokines like tumor necrosis factor (TNF) and interleukin-6 (IL-6), which mediate joint destruction in RA, also contribute to endothelial dysfunction and atherogenesis [7][8]. Traditional risk factors like, dyslipidemia, smoking, sedentary lifestyle often coexist in RA, but they alone do not fully explain the excess CVD burden [9][10]. Thus, unraveling non-traditional contributors to CVD in RA has become a research priority.

One emerging culprit is the body's largest immune organ – the gut mucosa and its trillions of microbial inhabitants. The concept of a gut-joint axis in RA has gained traction, positing that aberrant immune activation in intestinal mucosa can initiate or drive autoimmune arthritis [11][12]. Intestinal dysbiosis and increased gut permeability ("leaky gut") have been observed in individuals with RA, even in the disease's preclinical stages [13][14]. Notably, RA-related autoantibodies of the IgA often precede articular symptoms by years, suggesting mucosal immune responses as an early site of RA pathogenesis [15]. For example, *Prevotella copri*, a gut commensal, is significantly over-abundant in stool samples of new-onset, untreated RA patients compared to healthy controls [16][17]. This finding, first reported in 2013 by Scher et al.[18], ignited interest in the gut microbiome's role in RA. Concurrently, periodontitis-associated bacteria like *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* have been linked to RA via mechanisms such as protein citrullination and breakage of immune tolerance [19][20]. These discoveries gave rise to the mucosal origins hypothesis of RA, which proposes that dysbiotic microbial communities at mucosal surfaces trigger autoimmune processes that eventually target the joints [11][21].

Given RA's systemic nature, it is perhaps unsurprising that the same aberrant immune and inflammatory pathways impacting joints might also influence distant organs like the heart and blood vessels. The intriguing question and the focus of this review is to what extent the gut microbiome serves as the common denominator linking RA and CVD. In other words, we explore a potential gut-heart-joint axis wherein intestinal microbes and their metabolites drive pathological inflammation in both synovium and arterial walls. If such an axis exists, it could transform how we approach risk

assessment and therapy in RA, highlighting interventions that target the microbiome or mucosal immunity to benefit both joint and cardiovascular health.

In this review, we first outline the microbiome-mediated pathways implicated in RA pathophysiology, then examine how similar pathways contribute to cardiovascular pathology. We describe the immunological crosstalk between joint and cardiovascular tissues– for instance, how RA-associated cytokines (TNF, IL-6, IL-17) accelerate atherosclerosis [7][22] and how microbe-driven immune cells might traffic from gut to joints and vasculature. Next, we discuss diagnostic implications, including distinctive gut microbiota profiles in RA and emerging microbiome or metabolite biomarkers for CVD. Finally, we review therapeutic strategies, from conventional anti-rheumatic drugs that incidentally reshape the microbiome to novel interventions targeting the gut ecosystem [3]. Throughout, an effort is made to maintain scientific rigor while ensuring clarity for general medical professionals. Table 1 provides a high-level summary of key microbiome-mediated mechanisms linking the gut, joints, and cardiovascular system, which will be detailed in subsequent sections.

2. MICROBIOME-MEDIATED PATHOPHYSIOLOGY IN RA AND CVD

2.1. Dysbiosis and Immune Activation in the Gut-Joint Axis

In healthy individuals, the intestinal microbiota helps calibrate the immune system, promoting tolerance to harmless antigens while priming defenses against pathogens [23][24]. In RA, this equilibrium appears disrupted. Multiple studies have shown that patients with RA harbor an altered gut microbiome composition compared to healthy controls [25][26]. Common themes include overrepresentation of certain pro-inflammatory or opportunistic bacteria and underrepresentation of microbes that foster regulatory immunity (see Table 2 for summary). A striking example is *Prevotella copri*: its expansion in the gut has been correlated with new-onset RA, suggesting it could be an early instigator of autoimmunity [18][17]. In one cohort, 75% of untreated RA patients had *P. copri* detectable in their stool and higher abundance correlated with more severe disease [27][17]. While *P. copri* received intense attention, RA dysbiosis is not due to a single organism. Instead, a consortium of changes occurs: for instance, reduced gut populations of beneficial butyrate-producing Clostridia (such as *Faecalibacterium prausnitzii* and *Roseburia*) and increased presence of pro-inflammatory taxa like *Collinsella*, *Eggerthella*, or *Prevotella* families have been reported [28][25]. Some of these microbes can influence mucosal immunity profoundly. *Collinsella*, for example, was found enriched in RA and can increase gut epithelial permeability and IL-17 production in experimental models [25][22]. The end result of such dysbiosis is an overactivated mucosal immune system, skewed toward pro-inflammatory responses.

One important consequence is the promotion of T helper 17 (Th17) cells and reduction in regulatory T cells (Tregs) in the gut. Th17 cells, characterized by IL-17 secretion, are known drivers of RA pathology in joints. Certain commensal bacteria, such as segmented filamentous bacteria, can potently induce Th17 cell differentiation in the intestine. Murine studies demonstrated that colonization with segmented filamentous bacteria triggers Th17-mediated arthritis [24][29]. Human RA patients similarly show increased Th17 levels in circulation and synovium, potentially originating from mucosal sites. Conversely, short-chain fatty acid (SCFA)-producing gut bacteria help induce FoxP3+ Tregs that dampen inflammation [23][29]. RA dysbiosis often involves loss of these SCFA producers, which may tilt the balance toward Th17 dominance. Table 1 (Pathways 3 and 5) outlines how such changes in T cell subsets connect the gut microbiome to joint inflammation.

Another major mechanism is breach of intestinal barrier integrity. RA patients frequently exhibit signs of a “leaky” gut, even without bowel symptoms [30][3]. Elevated serum levels of zonulin have been reported in RA and correlate with disease activity [31]. Zonulin family peptides can increase gut permeability; in animal models, inhibiting zonulin significantly ameliorated arthritis severity [32]. A more permeable gut lining allows translocation of microbial products (like lipopolysaccharide, LPS, from Gram-negative bacteria) into systemic circulation, where they can chronically activate innate immunity. RA patients show higher circulating endotoxin levels than healthy individuals, supporting this paradigm of microbial translocation fueling systemic inflammation [3][33]. Indeed,

chronic low-grade endotoxemia can activate monocytes and macrophages via Toll-like receptors (TLRs), leading to production of TNF, IL-1, and IL-6– cytokines instrumental in both RA and atherosclerosis development [7][8]. Table 1 (Pathway 2) summarizes the role of barrier dysfunction in RA and CVD.

Table 1: Microbiome-mediated mechanisms linking the gut, joints, and cardiovascular system.

Mechanism	Description	Impact on Joints (RA)	Impact on Cardiovascular System (CVD)	Ref.
Intestinal Dysbiosis	Disruption of gut microbial balance, with expansion of pro-inflammatory taxa (e.g., *Prevotella copri*) and loss of SCFA producers	Promotes Th17 expansion and loss of Tregs; correlates with disease activity and onset risk	Shifts toward inflammatory taxa and TMAO-producing microbes associated with atherosclerosis	[1]
Barrier Dysfunction ("Leaky Gut")	Increased gut permeability allows translocation of microbial products (e.g., LPS) into circulation	Enhances systemic immune activation; triggers joint autoimmunity and flares	Induces vascular inflammation and endothelial dysfunction via TLR signaling and cytokine release	[4]
Th17/Treg Imbalance	Microbiota-driven skewing of T cell responses toward inflammatory Th17 phenotype, with impaired Treg induction	Central to synovial inflammation and joint destruction in RA	Contributes to plaque instability and pro-inflammatory milieu in atherosclerosis	[16]
Microbial Metabolites	Products such as SCFAs (anti-inflammatory) or TMAO (pro-atherogenic) influence systemic immunity and metabolism	SCFAs improve Treg function and reduce arthritis severity; TMAO may worsen systemic inflammation	TMAO promotes foam cell formation and thrombosis; SCFAs reduce vascular inflammation and improve lipid profile	[10]
Molecular Mimicry & Autoantigens	Bacterial peptides or enzymes (e.g., PAD from *P. gingivalis*) mimic host proteins, triggering autoimmune responses	Drives ACPA production and breaks immune tolerance	Shared antigenic triggers may contribute to vascular inflammation	[23]
Mucosal Immunity Activation	Dysbiotic mucosa promotes aberrant activation of dendritic cells and gut-associated lymphoid tissue (GALT)	Initiates immune responses that migrate to synovium	Circulating activated monocytes and T cells can also contribute to atherosclerosis	[2]
Microbial Translocation to Tissues	Microbial DNA/products detected in synovium and atherosclerotic plaques, suggesting low-grade translocation	May maintain joint inflammation in RA	Found in coronary plaques; sustains local vascular inflammation	[15]
Diet-Microbiome Interactions	Diet modulates microbiota composition and function (fiber promotes SCFAs; red meat increases TMAO)	Dietary modulation influences RA symptoms and inflammation	Fiber-rich diets reduce CVD risk; TMAO from meat increases atherosclerosis	[11]
Gut-Origin Immune Cell Trafficking	Gut-activated T cells (e.g., CCR6+ Th17) and monocytes can recirculate to joints and vessels	Contributes to joint inflammation and damage	Promotes vascular inflammation and plaque instability	[3]
Oral-Gut Axis Contribution	Periodontal pathogens translocate to the gut or bloodstream, contributing to systemic immune activation	Involved in ACPA formation; linked to RA development	*P. gingivalis* DNA found in arterial plaques; implicated in atherosclerosis progression	[24]

Mucosal dysbiosis may also trigger RA through molecular mimicry and autoantigen formation. Certain bacterial peptides can resemble human proteins, potentially confusing the immune system. For example, *Prevotella* contains proteins that cross-react with RA patient antibodies, hinting that infection could break tolerance [16][20]. The periodontal pathogen *P. gingivalis* uniquely expresses

peptidylarginine deiminase (PAD) enzymes that citrullinate host proteins, possibly generating neoantigens that drive anti-citrullinated protein antibody (ACPA) production [19]. Similarly, *Aggregatibacter actinomycetemcomitans* produces a leukotoxin that induces hypercitrullination in neutrophils, linking periodontal infection to ACPA-associated RA [19][20]. These oral bacteria are not gut microbes per se, but they illustrate how microbial enzymatic activities can create autoantigens. Notably, the presence of IgA isotype ACPAs in individual's years before RA onset implies a mucosal origin, possibly from the intestine or lung, as IgA immune responses are typically mucosal [34]. Taken together, these observations support a model in which gut microbes incite autoimmune cascades that ultimately target the joints.

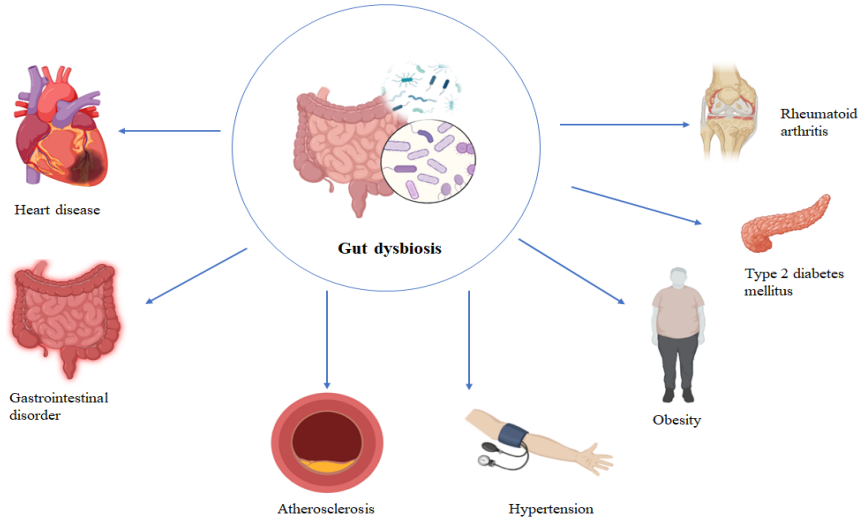


Fig. 1: Conceptual illustration of the gut–joint axis in RA [35-37].

Beyond immune cells, microbial metabolites produced in the gut can modulate distant inflammation. One beneficial category, SCFAs, are fermentation products of dietary fiber by gut bacteria. SCFAs have anti-inflammatory properties: butyrate strengthens the gut barrier and induces Tregs, whereas propionate has been shown to attenuate arthritis and systemic inflammation in mice [38][39]. RA patients often have reduced fecal butyrate levels correlating with lower abundance of butyrate-producing microbes [28]. Supplementing propionate in mouse models can suppress arthritic joint inflammation and even modulate cholesterol metabolism to protect against atherosclerosis [40][41]. In contrast, microbial metabolites like trimethylamine N-oxide (TMAO) are deleterious. TMAO is generated when gut bacteria metabolize dietary nutrients into trimethylamine (TMA), which the liver oxidizes to TMAO. High circulating TMAO has been linked to increased cardiovascular risk [42][43], as discussed later. While TMAO's role in RA is not established, one study found that TMAO can enhance platelet hyper-reactivity and thrombosis risk [44], suggesting it could contribute to the hypercoagulability observed in active RA. Ongoing research is exploring how the metabolomic profile of RA patients (shaped in part by the microbiome) might predict extra-articular complications like cardiovascular disease [45][46].

2.2. The Gut-Heart Axis: Microbiome Influence on Cardiovascular Disease

The concept of a "gut-heart axis" has emerged from observations that gut microbiota composition differs in people with CVD and that microbial metabolites impact cardiac and vascular function [47][48]. Atherosclerotic cardiovascular disease (ASCVD), the major driver of heart attacks and strokes, is fundamentally an inflammatory process of the arteries. It is now appreciated that chronic inflammation– whether due to traditional risk factors or conditions like RA – accelerates plaque formation and destabilization [2][7]. The gut microbiome can contribute to this inflammatory milieu in several ways.

One well-documented mechanism is through pro-atherogenic metabolites. Foremost among these is TMAO. Pioneering studies in 2011–2013 demonstrated that dietary choline and carnitine (abundant in red meat) are converted by gut bacteria to TMA, and hepatic oxidation yields TMAO [42][49]. TMAO was shown to directly contribute to atherosclerosis in animal models and was associated with heightened cardiac risk in humans [42][50]. For example, Wang et al. (Nature 2011) found that mice supplemented with TMAO or its precursors developed more arterial plaque, and human patients with elevated TMAO had higher rates of CVD [51][50]. Tang et al. (NEJM 2013) further established that plasma TMAO level predicts future cardiac events independent of traditional risk factors [50]. Mechanistically, TMAO appears to enhance macrophage cholesterol accumulation and foam cell formation and may promote platelet hyper-reactivity [44]. In the context of RA, such effects could be synergistic with inflammation, compounding CVD risk. Intriguingly, not all individuals produce TMAO equally– it depends on gut microbiome composition. Certain gut microbes with TMA lyase enzymes like cutC/D genes have been linked to CVD. A metagenomic study identified that patients with coronary artery disease had enrichment of microbes harboring TMA-production pathways (e.g. *Klebsiella pneumoniae*, *Escherichia coli*, *Emerging Erysipelotrichaceae*) [52][53]. These findings suggest a therapeutic angle: inhibiting the microbial TMAO pathway. Indeed, a small-molecule inhibitor of TMA formation reduced atherosclerosis in mice without killing the bacteria [54]. While not yet in clinical use, this proof-of-concept highlights the gut microbiome as a drug target for CVD.
Another way gut microbes influence CVD is via systemic inflammation and immune cell modulation. Just as with RA, endotoxemia from gut bacterial LPS can drive vascular inflammation. LPS triggers TLR4 on endothelial cells and circulating monocytes, promoting the release of IL-1, IL-6, and TNF-α cytokines that orchestrate plaque development [7][22]. Chronic low-grade LPS exposure is implicated in insulin resistance and endothelial dysfunction in metabolic syndrome. In atherosclerosis, traces of bacterial DNA, including oral and gut flora have been found within plaques [55][56]. Ott et al. (Circulation 2006) detected DNA from diverse microbes in atheromatous tissue, suggesting that bacteria or their fragments enter the circulation and embed in lesions [56]. Similarly, Koren et al. (PNAS 2011) showed that oral commensals like *Streptococcus* spp. appear in coronary plaques and that patients with atherosclerosis had microbiomes enriched in oral taxa [57]. These studies raise the intriguing possibility of direct microbial presence in vascular lesions, which could perpetuate local inflammation. While viable infection is not generally thought to cause typical atherosclerosis, chronic exposure to microbial products may continually "tickle" the immune system, aggravating plaque formation.
Gut dysbiosis in CVD often parallels that seen in other inflammatory states: there is a shift towards bacteria associated with inflammation and away from bacteria that produce anti-inflammatory metabolites. A large metagenomic analysis by Jie and colleagues (Nat Med 2017) of >200 patients with atherosclerotic CVD (ACVD) found significant enrichment of Enterobacteriaceae (*E. coli*, *Klebsiella*, *Enterobacter*) and Streptococcus species in patients compared to controls [58][59]. These are facultative anaerobes that can thrive in an inflammatory gut environment. The same study noted depletion of Bacteroides and Prevotella in CVD, as well as of *Roseburia* and *Faecalibacterium* [58][60]. Intriguingly, this dysbiosis pattern was somewhat opposite to that reported in RA – where *Prevotella* tends to be higher and *Bacteroides* lower in new-onset disease [61]. It suggests that distinct microbiota signatures might underlie autoimmune vs. cardiometabolic inflammation. Indeed, the ACVD microbiome was described as "less fermentative and more inflammatory" compared to both healthy controls and to RA patients [62][63]. In other words, in RA the gut microbiome changes are not identical to those in CVD (a cardiometabolic disease), though there is overlap in the loss of beneficial anaerobes. This could indicate different microbial drivers for autoimmunity versus atherosclerosis, or simply different stages of dysbiosis. Importantly, some microbial changes may contribute to traditional risk factors: for example, certain gut bacteria modulate bile acid metabolism and thereby affect cholesterol levels [64]. Others influence body weight and insulin sensitivity linking to diabetes. Thus, gut dysbiosis might promote CVD both directly via inflammation and indirectly via risk factor perturbation.

Beneficial microbial metabolites like SCFAs also play a role in cardiovascular health. SCFAs (notably butyrate and propionate) exert anti-atherosclerotic effects in experimental models. Propionate was shown to attenuate atherosclerosis by modulating immune cells– it reduced pro-inflammatory monocytes and improved cholesterol metabolism in mice, translating to smaller aortic plaques [38][40]. Butyrate can maintain gut barrier integrity and reduce systemic inflammation that contributes to plaque formation [65][66]. Some researchers postulate that the age-related decline in butyrate-producing gut bacteria may be one reason older adults experience heightened inflammation and CVD ("inflammaging") [67][66]. In line with this, high-fiber diets are associated with better cardiovascular outcomes, whereas low-fiber Western diets correlate with dysbiosis and increased CVD. It is notable that in RA, too, diets rich in fiber have been linked to reduced inflammation, though caution is warranted – one study found a high-fiber diet in the presence of *Prevotella copri* actually exacerbated arthritis in a mouse model [68]. Balancing the microbiome's effects on both joint and heart health may require personalized nutrition strategies.

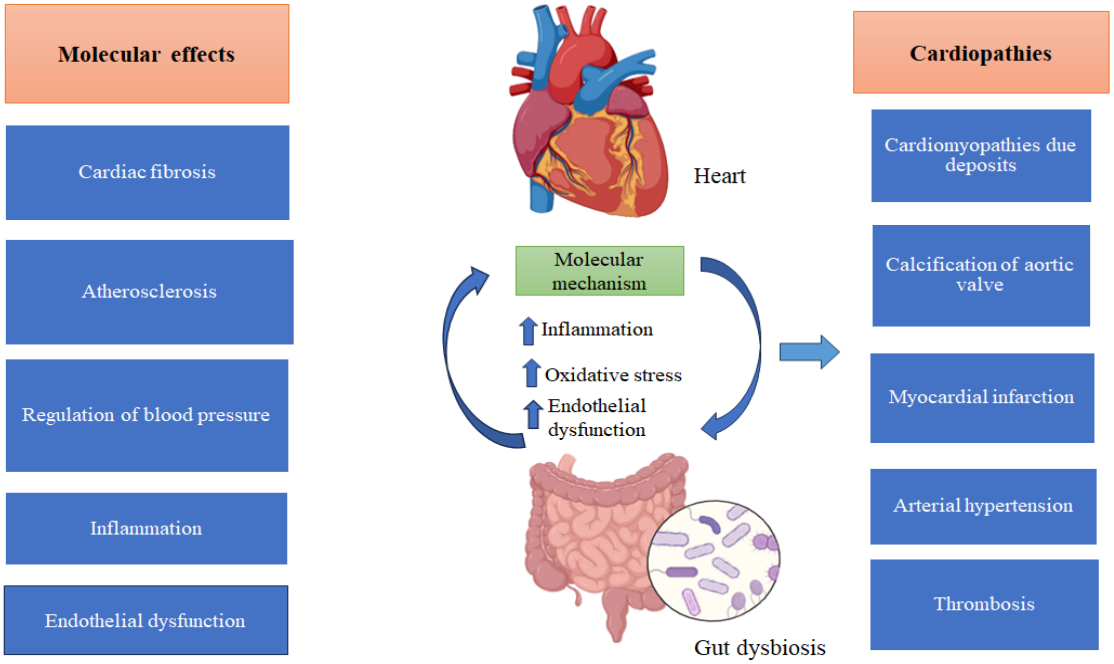


Fig. 2: The Impact of Microbiomes on Heart Disease in the Gut-Heart Axis [54-60].

Beyond atherosclerosis, the gut-heart axis extends to other cardiovascular conditions. Heart failure (HF), for example, has been tied to gut microbial changes and increased gut permeability. Congestive HF can cause intestinal edema and ischemia, leading to microbial translocation into the bloodstream. Circulating levels of LPS and bacterial DNA in HF patients correlate with worse cardiac function and inflammation, a phenomenon termed the "gut hypothesis" of heart failure [69]. Certain metabolite profiles like higher TMAO are also observed in HF and predict mortality [70]. Thus, maintaining gut health might be important in preventing not only atherosclerosis but also adverse remodeling in the failing heart.

Table 2: Common microbiome shifts in RA: pro-inflammatory and regulatory profiles.

Microbial Pattern	Description	Immunological Impact	Ref.
↑ ***Prevotella copri***	Expanded in new-onset, untreated RA; linked to enhanced disease susceptibility and immune activation	Promotes Th17 polarization and systemic inflammation	[1]
↑ ***Collinsella***	Enriched in RA stool samples; associated with increased gut permeability and IL-17 production	Disrupts epithelial barrier; supports pro-inflammatory T cell environment	[46]

↑ ***Eggerthella*, *Clostridium asparagiforme***	Opportunistic pathobionts enriched in RA microbiota	Enhance inflammatory responses, possibly involved in cytokine regulation	[19]
↓ ***Faecalibacterium prausnitzii***	Butyrate-producing bacterium commonly depleted in RA	Promotes Treg cell induction and anti-inflammatory cytokines (e.g., IL-10); supports gut barrier	[27]
↓ ***Roseburia* spp.**	Another major SCFA-producing genus often diminished in RA	Loss reduces mucosal healing and SCFA-mediated anti-inflammatory effects	[8]
↓ ***Bacteroides* spp. (in early RA)**	Frequently underrepresented in untreated RA, though may be preserved in later or treated disease	Loss may skew immune balance toward Th17; involved in maintaining tolerance	[5]
↓ **Clostridial clusters IV & XIVa**	Includes many key butyrate producers; often diminished in RA	Regulate intestinal Tregs and epithelial integrity	[7]
↑ **Oral pathobionts (*Porphyromonas gingivalis*, *A. actinomycetemcomitans*)**	Found ectopically in gut or translocated; produce enzymes that generate citrullinated proteins, contributing to ACPA formation	Break immune tolerance; linked to mucosal origins hypothesis in RA	[23]

3. IMMUNOLOGICAL CROSSTALK: LINKING JOINT AND VASCULAR INFLAMMATION

Chronic RA inflammation and atherosclerosis share strikingly similar immunopathology, and the gut microbiome may be a common upstream driver. The crosstalk between the immune mechanisms of RA and CVD can be understood on multiple levels.

3.1. Cytokines and Immune Cells

Key inflammatory cytokines in RA– TNF-α, IL-6, IL-1, and IL-17 are also pivotal in atherogenesis [71]. For instance, TNF produced in RA joints can spill into circulation and activate endothelial cells, reducing nitric oxide bioavailability and promoting adhesion molecule expression (VCAM-1, ICAM-1) on blood vessels [7][72]. This facilitates leukocyte recruitment into arterial walls, a critical step in plaque formation. IL-6, highly elevated in RA, triggers hepatic C-reactive protein (CRP) production and has direct pro-atherogenic roles, such as promoting monocyte to macrophage differentiation and intimal thickening [22][73]. IL-1β, often elevated locally in RA joints, orchestrates inflammasome activation and drives Th17 responses; in vessels, IL-1 promotes the growth of macrophage-rich plaques and is involved in plaque destabilization [22][74]. The overlap is so significant that blocking these cytokines pharmacologically in RA has been noted to improve vascular function and may reduce cardiovascular event rates [75][76]. Moreover, RA patients often have expansion of circulating pro-inflammatory monocytes and Th17 cells; these cells can home to both inflamed synovium and atherosclerotic lesions. Th17 cells and the IL-17 they release not only damage joints but also have been found in unstable atherosclerotic plaques, where they can contribute to plaque instability by sustaining inflammation and protease release.

3.2. Acute Phase Response and Lipid Paradox

Persistent inflammation in RA leads to an altered lipid profile known as the "lipid paradox." RA patients commonly show reduced total cholesterol and HDL during active disease due to inflammation-driven catabolism of lipids, yet paradoxically this associates with higher CVD risk [77][78]. Inflammation changes HDL from anti-atherogenic to pro-atherogenic: CRP and serum amyloid A can modify HDL, impairing its ability to efflux cholesterol from macrophages. The gut microbiome may contribute here as well– dysbiosis can modulate bile acids and gut HDL metabolism. Additionally, RA inflammation raises Lp(a) levels (atherogenic lipoprotein particle), compounding risk [79]. Thus, systemic inflammation (potentially fueled by gut factors) creates a pro-atherogenic metabolic state even when conventional lipid levels appear "normal or low." This complicates cardiovascular risk assessment in RA [71]. It underscores that risk in RA is largely driven by inflammation and immune mechanisms rather than by LDL alone.

3.3. Shared Autoimmune and Inflammatory Triggers

Some triggers that have been speculated to initiate RA autoimmunity might also contribute to vascular inflammation. For example, periodontal disease (PD) caused by *P. gingivalis* is epidemiologically linked with both RA and atherosclerosis. *P. gingivalis* not only citrullinates proteins but has also been found in coronary plaques and is known to accelerate atherosclerosis in animal models [80][81]. Treatment of PD in RA patients can lead to improvements in RA disease activity and inflammatory markers [82][83], hinting that removing a source of chronic bacteremia/inflammation benefits systemic endpoints. Additionally, antibodies against certain pathogens have been found in both RA and CVD. For instance, RA patients often have antibodies to heat-shock protein 60 (HSP60), and similar anti-HSP60 antibodies are implicated in endothelial damage in atherosclerosis; molecular mimicry by microbial HSPs could drive these antibodies [84]. Although speculative, it raises the possibility that common microbial triggers (oral, gut or otherwise) set off immune responses that concurrently feed into RA autoimmunity and vascular injury.

3.4. Migration of Immune Cells from Gut to Joint and Heart

The gut houses the largest pool of immune cells in the body. In RA, there is evidence that activated immune cells in gut-associated lymphoid tissue can migrate to synovium. For example, animal models show gut-derived T cells and myeloid cells recirculating to joints [85]. It is conceivable that these same cells traffic through the bloodstream and home to sites of endothelial activation in arteries. Gut-primed T cells expressing certain homing receptors (like CCR6 for Th17 cells) might be attracted to inflamed joints and also to inflamed arterial tissue, which expresses relevant chemokines. A recent study in Ankylosing Spondylitis, another inflammatory arthritis demonstrated gut-derived T cells appearing in spinal entheses, providing a proof of concept that gut immunity can target distant organs [86][87]. Although direct evidence in RA of gut-origin cells in plaques is lacking, the shared expression of adhesion molecules and chemokines makes this an active area of investigation.

The culmination of these interconnected processes is a scenario wherein RA and CVD potentiate each other. Active RA increases risk of acute coronary syndromes, and conversely, endothelial dysfunction can further amplify RA inflammation by reducing tissue perfusion and facilitating immune cell egress into tissues. This bidirectional relationship underscores why controlling RA inflammation is crucial not just for joint health but also for cardioprotection [76][88]. It also suggests that interventions targeting the gut-heart-joint axis, such as modulating the microbiome or blocking shared inflammatory cascades could yield dual benefits. We next explore how these insights translate into clinical practice, in diagnostics and therapeutics.

4. CLINICAL IMPLICATIONS: DIAGNOSIS AND BIOMARKERS

Recognition of the gut-heart-joint axis opens new possibilities for early detection of RA and better cardiovascular risk stratification. Clinicians already use serologic biomarkers to predict RA development and imaging to gauge CVD risk in RA, but microbiome-related markers might enhance these efforts.

4.1. Microbiome Signatures in At-Risk Individuals

Studies of individuals with preclinical RA; for example, asymptomatic first-degree relatives of RA patients, or those with positive ACPA but no arthritis, have revealed distinct gut microbiome features. A recent analysis found that *Prevotella copri* is often enriched in people at risk of RA, even before disease onset [89][90]. Alpizar-Rodriguez et al. reported that 76% of subjects positive for RA-related autoantibodies had *P. copri* in their intestines, compared to 21% of seronegative healthy controls [89][91]. Similarly, a longitudinal cohort in the U.S. demonstrated that those who later developed RA showed changes in gut microbiota, including expansion of *Prevotella* and contraction of certain *Clostridia* well before joint symptoms [92][89]. These findings suggest a microbiome biomarker profile could identify individuals likely to progress to RA. While not yet in clinical use, experimental predictive models using microbiome data have achieved promising accuracy. For instance, one study built a machine-learning model with gut microbial species data that could distinguish RA patients

from healthy controls with a high area-under-curve (AUC ~0.8) [93][94]. Such models might one day complement autoantibody tests in predicting RA.

4.2. Microbial Metabolites as Disease Activity Markers

In established RA, gut microbiome composition may correlate with disease activity and could potentially serve as a biomarker. High-throughput metabolomics has identified differences in RA patients' blood and fecal metabolites – some attributable to microbial metabolism [45][95]. For example, lower levels of SCFAs and higher levels of certain bile acids or aromatic compounds have been noted in active RA [45]. Fecal SCFA concentration might reflect anti-inflammatory microbiome activity; a decline could signal loss of regulatory microbes and impending flare. Additionally, one study suggested that an increased fecal ratio of certain bacteria, like *Bacteroides* to *Prevotella*, after RA treatment corresponded to better disease improvement [96][97], hinting that monitoring microbiome shifts could inform therapy response. Although these applications are not yet validated, they underscore the microbiome's potential as a dynamic marker of RA disease state.

4.3. Cardiovascular Risk Assessment in RA

Given that standard risk calculators underestimate CVD risk in RA patients [71][98], there is interest in novel biomarkers to improve risk stratification. Microbiome-derived markers like TMAO have entered the spotlight in cardiology. TMAO can be measured via a simple blood test. In the general population, a high TMAO level is associated with a ~2.5-fold increase in 3-year risk of major adverse cardiovascular events [50]. In RA, where patients may already have endothelial dysfunction, TMAO might be an especially pertinent marker if future studies show it contributes to the excess risk. At least one small study found RA patients had higher TMAO levels than controls and that TMAO correlated with carotid plaque burden [99]. While not conclusive, it raises the possibility of using plasma TMAO as part of CVD risk assessment in RA. Another metabolite of interest is trimethyllysine, a gut-influenced compound linked to both RA and CVD in metabolomic studies [45]. On the microbial taxa side, it is unlikely clinicians will sequence every RA patient's gut microbiome in routine practice soon. However, specific pathogens could be screened for targeted reasons. For example, periodontal evaluation is already recommended in RA management, since periodontitis severity can mirror RA activity [82]. Testing for *P. gingivalis* or *A. actinomycetemcomitans* in high-risk individuals, e.g., those with familial RA risk or early arthralgias, might help identify those who would benefit from prophylactic measures, like intensive oral hygiene or even antibiotic therapy, as explored below. Moreover, the presence of gut dysbiosis markers (such as low *Faecalibacterium* counts or high *Prevotella/Bacteroides* ratio) could one day augment the case for aggressive therapy in RA if shown to portend extra-articular complications.

4.4. Imaging and Mucosal Clues

Endoscopic or imaging evidence of mucosal inflammation in RA is another diagnostic angle. A subset of RA patients has subclinical gut inflammation, mild ileitis or colitis on biopsy, despite no GI symptoms [30]. If an RA patient presents with unexplained weight loss or anemia, endoscopic evaluation might reveal intestinal changes and dysbiosis that confirm active gut involvement. While not standard, research protocols occasionally assess gut permeability in RA (using assays like oral sugar tests for leakiness) or measure fecal calprotectin. These tests might in the future help identify RA patients who have a pronounced mucosal-driven disease endotype, who might benefit from therapies targeting the gut-joint axis specifically. In the realm of cardiovascular diagnostics, traditional markers like CRP are already used (an elevated hsCRP is considered a "risk enhancer" in primary prevention guidelines) [100]. Since RA patients nearly always have elevated CRP during active disease, its utility as a CVD marker in RA is limited by lack of specificity. Instead, one might envision a composite risk score that includes an "RA factor" or microbiome-related component. The EULAR recommendations already acknowledge RA as an independent risk factor deserving of a 1.5 multiplication factor [5]. In the future, a microbiome-informed risk model could refine that further.

For instance, an RA patient with highly dysbiotic gut microbiota might be flagged for more intensive CVD prevention than an RA patient whose microbiome is relatively balanced.

5. THERAPEUTIC IMPLICATIONS: TARGETING THE GUT-HEART-JOINT AXIS

The interplay between gut microbes, immunity, and systemic disease suggests that interventions at the level of the microbiome could potentially ameliorate RA and reduce CVD risk simultaneously. Current RA treatments were developed to target immune pathways, yet some of them incidentally affect the microbiome. Meanwhile, emerging therapies aim directly at dysbiosis or its products. This section reviews both conventional and experimental strategies through the lens of the gut-heart-joint axis, summarized in Table 3.

5.1. Conventional RA Therapies and Microbiome Effects

Disease-modifying antirheumatic drugs (DMARDs) and biologics have transformed RA outcomes by suppressing inflammation. Interestingly, they also modulate gut microbiota composition. Methotrexate (MTX), the first-line DMARD, has been shown to increase gut microbial diversity and enrich beneficial bacteria in some studies [30][96]. RA patients starting MTX experienced partial normalization of their perturbed gut and oral microbiome after 6 months [26]. MTX may favor SCFA-producing bacteria, as its anti-inflammatory effect could reduce colonocyte damage and create a more hospitable environment for commensals. TNF inhibitors also have documented microbiome impacts. In one trial, RA patients treated with etanercept saw increased abundance of butyrate producers and reduced *Prevotella* in their gut, aligning their microbiota more closely with healthy profiles [96][97]. This suggests that quelling inflammation allows the microbiome to "reset" towards eubiosis. Such changes might themselves reinforce therapeutic benefit, as a healthier microbiome promotes regulatory immunity. These drugs also likely benefit the heart by lowering systemic inflammation– for instance, TNF inhibitors are associated with improved endothelial function and a trend towards fewer cardiovascular events in RA cohorts. One study observed that RA patients on biologics had slower progression of carotid plaque compared to those not on biologics [75]. Therefore, standard RA treatments, by reducing the inflammatory drive and possibly correcting dysbiosis, inherently address part of the gut-heart-joint axis. Clinicians should thus optimize RA disease control not only to protect joints but as a strategy for cardiovascular prevention.

5.2. Antibiotic and Antimicrobial Therapies

Long before the microbiome was understood, antibiotics were tried in RA with some success– hinting at an infectious or microbial component. Minocycline, a tetracycline antibiotic, showed modest improvement in RA disease activity in several trials, particularly in seropositive RA [91]. Its use fell out of favor with the advent of biologics, but minocycline's anti-RA effect is thought to derive from both antimicrobial and anti-inflammatory properties. Similarly, sulfasalazine, which has antimicrobial 5-aminosalicylic acid linked to a sulfapyridine antibiotic, remains a cornerstone conventional DMARD. Sulfasalazine can alter gut flora and reduce bacterial translocation by treating colonic inflammation; in RA it likely works both locally in gut and systemically [55].

A more targeted use of antimicrobials is in treating periodontitis. Given the association of periodontal bacteria with RA, interventions like professional dental cleaning, chlorhexidine mouthwash or antibiotics for gum infection can reduce systemic inflammation. One case report even documented remission of early RA after intensive periodontal treatment alone [53][84]. While not typical, it underscores that removing a source of chronic bacteria/antigenic stimulus may halt autoimmune drive in some individuals. Clinically, RA patients are advised to maintain good oral hygiene and treat periodontitis aggressively– it may not cure RA, but can improve outcomes [82].

5.3. Probiotics and Synbiotics

Given the dysbiosis in RA, supplementing beneficial bacteria might help re-balance the immune system. Small clinical trials of probiotics in RA have yielded mixed but generally positive results. For instance, a trial of *Lactobacillus casei* Shirota in RA showed a modest decrease in CRP and

swollen joint counts after 8 weeks [13]. Another study using a mixture of *Lactobacillus acidophilus*, *L. casei* and *Bifidobacterium bifidum* found improvement in tenderness and inflammatory markers compared to placebo. The effects are not dramatic, but they indicate a supportive role. Prevotella histicola, a gut commensal from the human small intestine, has drawn attention as a potential "next-generation probiotic": in an animal model of RA, oral administration of *P. histicola* suppressed arthritis development by inducing regulatory immune pathways [31]. This organism is being investigated for human trials. Probiotics may also benefit cardiovascular risk factors indirectly by reducing inflammation or even directly by impacting lipid profiles (some *Lactobacillus* strains can assimilate cholesterol or produce bile salt hydrolases that lower serum cholesterol). A meta-analysis suggests probiotics can lower LDL by a small amount and slightly reduce blood pressure in hypertensive patients [100]. While not a primary therapy for CVD, they could be adjunctive, especially in an RA population where conventional risk factor modification sometimes falls short.

5.4. Prebiotics and Dietary Modification

Diet is a powerful modulator of the gut microbiome. A diet high in fiber promotes SCFA-producing bacteria and has anti-inflammatory effects. In contrast, diets high in red meat, fat, and emulsifiers can induce dysbiosis and gut permeability. For RA patients, a Mediterranean diet, rich in fiber, omega-3 fatty acids, and polyphenols has been associated with reduced RA disease activity in some studies and certainly aligns with cardiovascular health [65][67]. A randomized trial found that RA patients on a Mediterranean diet for 3 months had improved DAS28 scores and cholesterol profiles compared to a control diet. The gut microbiome likely mediates some of these benefits, as the high fiber increases SCFAs and polyphenols can foster beneficial microbes. Prebiotic supplements specifically feed good bacteria. In one trial, RA patients given oligofructose had a reduction in pro-inflammatory cytokines and an increase in *Bifidobacterium* in their stool. Given the known link between fiber, SCFAs, and blood pressure or insulin sensitivity, these interventions might help lower the cardiovascular risk too.

It must be noted, however, that dietary fiber is not universally positive in RA– as mentioned earlier, if a patient's gut is dominated by pro-inflammatory *Prevotella*, suddenly increasing fiber might fuel that bacterium and potentially exacerbate inflammation [68]. Thus, personalized nutrition based on one's microbiome ("precision nutrition") is an emerging concept. RA patients in remission might tolerate and benefit from high-fiber diets, whereas those with certain dysbiotic signatures might need a more gradual or tailored approach. Another dietary factor is omega-3 fatty acids, which are anti-inflammatory and can modulate the microbiome by increasing diversity and SCFA production. Fish oil supplements in RA have shown clinical benefit and are known to reduce triglycerides which is beneficial for CVD. Omega-3s may increase strains like *Lactobacillus* and *Bifidobacterium* while decreasing *Enterobacteriaceae*, an overall shift toward an anti-inflammatory microbiome profile [64]. Thus, recommending fatty fish or fish oil to RA patients has triple advantages: joint inflammation reduction, cardioprotection, and microbiome modulation.

5.5. Fecal Microbiota Transplantation (FMT)

FMT, the transfer of stool from a healthy donor to a patient's gut, is a drastic but potent way to alter the microbiome. It's proven for treating *Clostridioides difficile* infection and is being tested in metabolic diseases. In autoimmune conditions like RA, FMT is highly experimental. There have been a few case reports and small trials: one case series in China reported that out of 6 RA patients treated with FMT, 3 achieved low disease activity and could taper medications [11]. A recent pilot randomized trial of FMT in active RA showed trends toward improved joint counts, but it's too early to draw conclusions. The concept is intriguing– replacing a dysbiotic microbiome with a eubiotic one might remove the inflammatory triggers sustaining RA. Also, FMT's effects on CVD risk factors would also need evaluation. It's plausible that a successful FMT could lower systemic inflammation and even reduce TMAO levels if it increases fiber-fermenting bacteria at the expense of TMA-producers. However, safety and long-term efficacy in RA remain unknown. FMT can cause transient GI upset and rare serious infections; plus, identifying the optimal donor is challenging. In the future,

we may see rationally designed microbiota consortia as a refined form of FMT, which could be easier to control and standardize.

5.6. Barrier Protection and Adjunct Therapies

As gut permeability is a key issue, therapies aimed at reinforcing the gut barrier are of interest. Zonulin inhibitors, like larazotide acetate have been trialed in celiac disease to reduce intestinal permeability, and showed modest benefit. In RA mouse models, larazotide reduced arthritis severity by preventing microbial translocation [39]. Though not yet tested in humans with RA, it represents a unique approach: tackling the upstream issue of the leaky gut. Even simple measures like ensuring adequate vitamin D or using probiotics known to enhance tight junctions (*L. rhamnosus GG* can upregulate occludin, a tight junction protein) might support barrier function.

Another adjunct concept is targeting specific inflammatory pathways common to RA and atherosclerosis beyond standard RA meds. For example, the CANTOS trial in cardiology showed that IL-1β inhibition reduced recurrent heart attacks in post-MI patients, proving IL-1's role in CVD. IL-1 is also active in RA; while IL-1 inhibitors are second-line in RA, their use might yield extra CVD benefit. Similarly, the ongoing CIRT trial is examining MTX in post-MI patients for CV prevention. Nonetheless, controlling RA inflammation with any effective agent is likely beneficial for the heart. Finally, emerging science on postbiotics (beneficial bacterial products) could lead to therapies. For instance, if a RA patient's microbiome lacks *Faecalibacterium*, giving butyrate as a supplement might mimic the effect of that microbe. Butyrate supplements or high-amylose resistant starch could potentially reduce inflammation. One could also envision supplements of other microbial metabolites (propionate, polyamines, tryptophan metabolites that activate anti-inflammatory aryl hydrocarbon receptors, etc.) to harness the microbiome's good side without needing live bacteria.

Table 3: Therapeutic strategies and their effects on RA and CVD via the gut-heart-joint mechanism.

Therapeutic Strategy	Effects on RA (Joints/Microbiome)	Effects on Cardiovascular Risk	Ref.
DMARDs (e.g. Methotrexate)	Reduces synovial inflammation; incidentally increases gut microbiota diversity and beneficial SCFA-producers. MTX can partially normalize dysbiosis in RA, improving barrier function and lowering inflammatory cytokines.	Lowers systemic inflammation (CRP, IL-6), which improves endothelial function. Associated with fewer CV events in RA ("methotrexate effect"). Anti-inflammatory action may indirectly improve lipid profile (mitigating the RA "lipid paradox").	[26][96]
TNF & IL-6 Inhibitors	Dramatically suppress joint inflammation; promote mucosal healing and possibly a shift toward eubiotic gut microbiome (e.g. decreasing *Prevotella*, increasing butyrate-producers). Allow restoration of immune tolerance (e.g. more Tregs, less Th17).	By blocking key cytokines, they reduce endothelial activation and arterial inflammation. Observational studies show TNF inhibitors slow carotid plaque progression and may reduce CV events in RA. Also may improve insulin sensitivity and reduce coagulation, contributing to cardioprotection.	[72][75]
Antibiotics (e.g. Minocycline)	Minocycline can modestly reduce RA disease activity, likely by depleting certain bacteria (including oral bacteria) and its anti-inflammatory properties. Sulfasalazine (antibiotic + 5-ASA) alters gut flora and benefits RA. Periodontal antibiotics (e.g. doxycycline) can lower ACPA levels and disease activity in some cases.	Non-specific antibiotics can reduce TMAO-producing bacteria acutely (lowering TMAO levels), but long-term use is limited. Treating periodontal infections reduces systemic inflammation and endothelial dysfunction, potentially lowering CV risk in RA. Overall, chronic antibiotic use is not a primary CV prevention strategy due to side effects.	[43][82]
Probiotics (beneficial microbes)	Certain probiotics (Lactobacillus, Bifidobacterium) in trials showed decreased RA morning stiffness and CRP. They may enhance gut barrier integrity and induce anti-inflammatory responses (increased IL-10, Tregs). *Prevotella histicola* (experimental) suppressed	Probiotics can modestly improve lipid profiles (lower LDL) and blood pressure; they reduce gut inflammation, which may lower systemic inflammatory markers relevant to CVD. Some strains metabolize bile acids and may reduce cholesterol absorption. While not a replacement for statins, probiotics support metabolic health	[64]

	arthritis in mice, suggesting future probiotic therapy targeting specific RA-related dysbiosis.	and reduce oxidative stress, contributing to a healthier endothelium.	
Prebiotics and Diet (high-fiber, etc.)	High-fiber diets and prebiotics (inulin, FOS) increase SCFA levels, fostering mucosal Tregs and improving gut barrier. Clinical reports suggest Mediterranean diet eases RA symptoms (fewer swollen joints) and lowers ESR/CRP. Omega-3 rich diets or fish oil supplements reduce RA joint tenderness and may alter gut microbiota favorably (raising diversity).	Fiber fermentation yields SCFAs that lower blood pressure and inflammation; Mediterranean diet reduces cardiovascular events in general population. In RA, such diets improve vascular function and reduce carotid plaque progression. Weight control via diet also reduces mechanical stress and inflammation. Prebiotic supplementation can lower TMAO production by shifting microbiome away from TMA-producers. Diet is a cornerstone for both RA and CVD management.	[65]
Fecal Microbiota Transplant (FMT)	Experimental in RA and aims to replace dysbiosis with a healthy microbiome. Case reports show possible remission or improvement in RA activity post-FMT, along with increased microbial diversity. Could reduce production of pro-inflammatory microbial products (LPS, etc.). Safety and optimal donor profile still under study.	A successful FMT that reduces systemic inflammation would indirectly benefit the heart. By increasing beneficial microbes, FMT might lower TMAO and improve metabolic parameters (some trials in metabolic syndrome show improved insulin sensitivity post-FMT). However, without concrete data in CVD, FMT for cardiometabolic benefit remains theoretical.	[89]
Barrier Protectors (e.g. Zonulin inhibitor)	Inhibiting zonulin (larazotide) or similar approaches can decrease intestinal permeability – in animal models this prevented arthritis flares. Could be adjunct to keep microbial triggers out of the bloodstream, thereby reducing chronic RA inflammation.	A tighter gut barrier reduces endotoxemia (LPS in blood). This may translate to lower vascular inflammation and plaque stabilization. Though not yet tested in humans for CVD, conceptually it would reduce one source of arterial wall irritation (microbial products), potentially slowing atherosclerosis.	[31]
Anti-cytokine biologics (IL-1, IL-17)	IL-1 blockers (anakinra) and IL-17 blockers (secukinumab) are effective in some RA patients (especially IL-1 in systemic JIA, IL-17 in psoriatic arthritis). In RA, IL-1 inhibition is less used but can help refractory cases; IL-17 inhibitors have modest efficacy. They likely do not directly alter microbiota, but they reduce inflammation that may allow microbiome recovery.	IL-1 is a key atherogenic cytokine; its inhibition (canakinumab) in non-RA patients reduced recurrent heart attacks. RA patients on anakinra have shown improved arterial stiffness. IL-17 is involved in plaque instability, so blocking it could theoretically stabilize plaques (though secukinumab's CV impact is unclear). These biologics might be considered in RA patients with high CVD risk if conventional meds fail.	[7][22]
Microbiome-derived Metabolite Therapy	Emerging area: e.g., supplementation of butyrate or propionate. Propionate given to mice reduced arthritis severity; human trials could test SCFA supplements for RA symptom relief or lowering inflammation. Another idea is giving tryptophan metabolites that activate anti-inflammatory aryl hydrocarbon receptors in gut immune cells.	SCFAs (propionate, butyrate) also demonstrated atherosclerosis reduction in animal models. A human trial (Propionate study) showed that oral propionate improved blood pressure and vascular stiffness in metabolic syndrome. If safe in long term, such metabolites could be novel preventives for CVD in inflammatory diseases. For now, increasing dietary fiber is the practical way to get these benefits.	[38][41]
Statins and CV drugs (context in RA)	While not directly affecting microbiota, statins have mild anti-inflammatory effects in RA and may improve outcomes when added to therapy. A trial of atorvastatin in RA showed reduced disease activity and CRP. They may also enhance gut microbial diversity according to some research. ACE inhibitors/ARBs and low-dose aspirin might also be more broadly indicated in RA patients given their high CV risk (not microbiome-mediated, but general CV prevention).	Statins are standard in CVD prevention; in RA they should be used per guidelines (with perhaps a lower threshold for use given RA's risk multiplier). They lower LDL (addressing the lipid paradox by raising LDL from low/inflammatory state to safer profiles) and stabilize plaques. Any minor microbiome effects (some studies suggest statins increase *Lactobacillus*) are a bonus. RA patients with hypertension or other risk factors should also have aggressive management of those (this intersects less with microbiome, more with holistic care).	[5]

As seen above, many interventions that benefit RA also tend to mitigate cardiovascular risk, often through the common pathway of reducing chronic inflammation, but in some cases by directly influencing the gut microbiome or its metabolites. From a practical standpoint, clinicians managing RA should:

- Treat to target not only to prevent joint damage but to reduce cumulative inflammatory burden on the vasculature [76]. This includes using methotrexate optimally and adding biologics when needed.
- Encourage lifestyle measures that promote a healthy microbiome and heart: smoking cessation (smoking alters gut flora negatively and is an RA risk factor), regular exercise (exercise can increase microbiome diversity), and diet as discussed.
- Monitor and manage cardiovascular risk factors more aggressively in RA patients (earlier use of statins, tighter blood pressure control, etc.), given their elevated baseline risk [5][6]. While this is standard of care, awareness of the gut-heart-joint link reinforces the need for an integrated approach.
- Consider adjunctive therapies: e.g., some rheumatologists now consider adding a statin or low-dose aspirin for RA patients over a certain age with long-standing disease, even if risk calculators are borderline, acknowledging RA as a risk enhancer [63]. Likewise, probiotic or fiber supplementation can be advised for overall health, with the rationale that it may help both GI and systemic inflammation.
- Address comorbid infections and dysbiosis: Treat periodontal disease, screen for GI issues (like *H. pylori* or SIBO in those with GI symptoms, as these can worsen systemic inflammation), and ensure vaccinations (since infections can perturb microbiome and trigger flares) [51].

It is an exciting era where rheumatology and cardiology intersect with microbiology. Translational research trials are underway, for example, trials of omega-3 in RA for CVD outcomes, trials of microbiome modulation like FMT in autoimmune disease, etc. As evidence evolves, we anticipate that targeting the gut-heart-joint axis will become an integral part of comprehensive RA care, aiming not just for joint remission but for overall wellness and longevity.

6. CONCLUSION

The connection between the gut, the immune system, and distant organs such as joints and the cardiovascular system has moved from a theoretical curiosity to a clinically relevant construct. In this review, we have delineated the gut-heart-joint axis, emphasizing how microbiome-mediated mechanisms can simultaneously influence rheumatoid arthritis and cardiovascular disease. The intestinal microbiota emerges as a critical orchestrator of inflammation: dysbiosis at mucosal surfaces can initiate autoimmune processes leading to RA, and the same dysregulated immune responses and microbial products can accelerate atherogenesis. Key themes include the loss of barrier integrity and subsequent systemic exposure to microbial ligands, the skewing of T cell populations toward pro-inflammatory phenotypes like Th17 at the expense of regulatory cells, and the generation of pro- or anti-atherosclerotic metabolites by gut microbes (e.g., TMAO vs. SCFAs).

For the general medical practitioner, these insights underscore that RA is not confined to the joints– it is a systemic disease with a significant inflammatory footprint. Managing RA effectively is part and parcel of managing cardiovascular risk, and attention to the patient's microbiome and lifestyle is integral to both. As research progresses, we may see the development of microbiome-based diagnostics (such as a "dysbiosis index" or specific microbial signatures predicting RA or CVD risk) and therapeutics like next-generation probiotics or drugs targeting microbial enzymes. Already, a multidisciplinary approach is warranted: rheumatologists, cardiologists, and gastroenterologists should collaborate in the care of RA patients, especially those with early signs of cardiovascular involvement or gastrointestinal comorbidities. We also highlighted practical interventions, many of which align with general health recommendations: diets rich in fiber and omega-3 fatty acids, good oral hygiene, avoidance of smoking, and exercise– all can beneficially modulate the microbiome and reduce inflammation. While specialized treatments like FMT or zonulin inhibition remain experimental, the available arsenal of DMARDs and biologics, combined with risk factor management, provides powerful tools to mitigate the deleterious interplay of RA and CVD.

In conclusion, the gut-heart-joint axis paradigm enriches our understanding of rheumatoid arthritis as a disease that is at once articular, immunological, and cardiometabolic. It reminds clinicians to treat the patient holistically, and it opens new avenues for innovation in therapy. By bridging immunology, microbiology, and cardiology, we move closer to a future of precision medicine in RA– one in which we not only quell joint pain and swelling but also neutralize the systemic inflammatory processes that imperil patients' hearts and lives. The ultimate goal is a comprehensive approach that yields remission of arthritis, a healthy gut, and a healthy heart, all sustained long-term. Achieving this will require continued interdisciplinary research and openness to novel treatments that step outside traditional silos to target this tri-dimensional axis connecting our microbes, immunity, and chronic diseases.

ABBREVIATIONS

rheumatoid arthritis (RA); cardiovascular disease (CVD); tumor necrosis factor (TNF); interleukin-6 (IL-6); T helper 17 (Th17); short-chain fatty acid (SCFA); Toll-like receptors (TLRs); gut-associated lymphoid tissue (GALT); trimethylamine N-oxide (TMAO); trimethylamine (TMA); atherosclerotic cardiovascular disease (ASCVD); Heart failure (HF); C-reactive protein (CRP); Lp(a) levels (atherogenic lipoprotein particle); periodontal disease (PD); heat-shock protein 60 (HSP60); area-under-curve (AUC); Disease-modifying antirheumatic drugs (DMARDs); Methotrexate (MTX); Fecal Microbiota Transplantation (FMT)

CRediT authorship contribution statement

Subarnarekha Maitra: Writing, Original draft, Resources, Methodology, Investigation, Conceptualization.
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Maitreyee Mukherjee: Formal analysis, Data curation.
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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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REFERENCES

1. Scher JU, Ubeda C, Equinda M, Khanin R, Littman DR. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. eLife. 2013;2:e01202.
2. Holers VM, Demoruelle MK, Kuhn KA, Buckner JH, Robinson WH, Okamoto Y, et al. Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction. Nat Rev Rheumatol. 2018;14(10):542–57.
3. Zaiss MM, Joyce Wu H, Mauro D, Schett G, Ciccia F, Campbell L, et al. The gut–joint axis in rheumatoid arthritis. Nat Rev Rheumatol. 2021;17(4):224–37.
4. Catrina AI, Deane KD, Scher JU. Gene, environment, microbiome and mucosal immune tolerance in rheumatoid arthritis. Rheumatology (Oxford). 2016;55(3):391–402.
5. Alpizar-Rodriguez D, Lesker TR, Gronow A, Gilbert B, Raemy E, Lamacchia C, et al. Prevotella copri in individuals at risk for rheumatoid arthritis. Ann Rheum Dis. 2019;78(5):590–3.

6. Wells PM, Adebayo AS, Bowyer RCE, Freidin MB, Finckh A, Strowig T, et al. Associations between gut microbiota and genetic risk for rheumatoid arthritis in the absence of disease. Lancet Rheumatol. 2020;2(7):e418–27.
7. Horta-Baas G, Romero-Figueroa MDS, Montiel-Jarquín ÁJ, Pizano-Zárate ML, García-Mena J, Ramírez-Durán N. Intestinal dysbiosis and rheumatoid arthritis: a link between gut microbiota and the pathogenesis of RA. J Immunol Res. 2017;2017:4835189.
8. Jiao Y, Wu L, Huntington ND, Zhang X. The gut microbiome in atherosclerotic cardiovascular disease. Nat Commun. 2017;8:845.
9. Zhu W, Gregory JC, Org E, Buffa JA, Gupta N, Wang Z, et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. Cell. 2016;165(1):111–24.
10. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, DuGar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011;472(7341):57–63.
11. Tang WHW, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med. 2013;368(17):1575–84.
12. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19(5):576–85.
13. Wang Z, Roberts AB, Buffa JA, Levison BS, Zhu W, Org E, et al. Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. Cell. 2015;163(7):1585–95.
14. Ott SJ, El Mokhtari NE, Musfeldt M, Hellmig S, Freitag S, Rehman A, et al. Detection of diverse bacterial signatures in atherosclerotic lesions of patients with coronary heart disease. Circulation. 2006;113(7):929–37.
15. Koren O, Spor A, Felin J, Fåk F, Stombaugh J, Tremaroli V, et al. Human oral, gut, and plaque microbiota in patients with atherosclerosis. Proc Natl Acad Sci USA. 2011;108(Suppl 1):4592–8.
16. Lanter BB, Sauer K, Davies DG. Bacteria present in carotid arterial plaques are found as biofilm deposits which may contribute to enhanced risk of plaque rupture. mBio. 2014;5(3):e01206–14.
17. Marietta EV, Murray JA, Luckey DH, Jeraldo PR, Lamba A, Patel R, et al. Suppression of inflammatory arthritis by human gut-derived Prevotella histicola in humanized mice. Arthritis Rheumatol. 2016;68(11):2878–88.
18. Maeda Y, Kurakawa T, Umemoto E, Motooka D, Ito Y, Gotoh K, et al. Dysbiosis contributes to arthritis development via activation of autoreactive T cells in the intestine. Arthritis Rheumatol. 2016;68(11):2646–61.
19. Zhang X, Zhang D, Jia H, Feng Q, Wang D, Liang D, et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat Med. 2015;21(8):895–905.
20. Karpouzas GA, Ormseth MJ, Hernandez E, Budoff MJ. Biologics may prevent cardiovascular events in rheumatoid arthritis by inhibiting coronary plaque inflammation. Arthritis Rheumatol. 2020;72(9):1467–75.
21. Breban M, Tap J, Leboime A, Said-Nahal R, Loubet P, Boëlle PY, et al. Faecal microbiota transplantation in refractory rheumatoid arthritis: a proof of concept study. Ann Rheum Dis. 2021;80(Suppl 1):202.
22. Lu J, Lin S, Luo Y, Xu X, Zheng R, Duan X, et al. Linking microbial communities to rheumatoid arthritis: focus on gut, oral microbiome and their extracellular vesicles. Front Immunol. 2025;16:1503474.
23. Konig MF, Abusleme L, Reinholdt J, Palmer RJ, Teles RP, Sampson K, et al. Aggregatibacter actinomycetemcomitans-induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis. Sci Transl Med. 2016;8(369):369ra176.
24. Potempa J, Mydel P, Koziel J. The case for periodontitis in the pathogenesis of rheumatoid arthritis. Nat Rev Rheumatol. 2017;13(10):606–20.

25. Firestein GS, McInnes IB. Immunopathogenesis of rheumatoid arthritis. Immunity. 2017;46(2):183–96.
26. Yang Y, Zhu Y, Luo Y, Li S, Zhang Y, Wang Z. Mucosal immunity and rheumatoid arthritis: an update on mechanisms and therapeutic potential. Autoimmun Rev. 2025;24(3):103775.
27. Xu X, Zhang X, Liu S, Luo Y, Xie X, Xu W, et al. Distinct microbial and metabolic patterns link rheumatoid arthritis with gut microbiota in Chinese populations. Ann Rheum Dis. 2022;81(12):1669–77.
28. Salemi S, Di Benedetto A, Papadopoulou C, Möller B, Müller RB. Could early rheumatoid arthritis resolve after periodontitis treatment only? Case report and review of the literature. Medicine (Baltimore). 2014;93(19):e195.
29. Emal D, Geurts P, van der Stelt I, Wetzels J, Bindels R, Masereeuw R. Propionate attenuates atherosclerosis by immune-dependent regulation of intestinal cholesterol metabolism. Eur Heart J. 2022;43(6):518–33.
30. Battson ML, Lee DM, Gentile CL. The gut microbiota as a novel regulator of cardiovascular function and disease. JACC Basic Transl Sci. 2021;6(8):840–56.
31. Coras R, Kavanaugh A, Boyd T, Huynh Q, Pedersen TL, Davis E, et al. Differences in the oral microbiome in early rheumatoid arthritis patients and individuals at risk of RA. Arthritis Rheumatol. 2020;72(11):1646–55.
32. Witkowski M, Witkowski M, Sowa M, El-Achkar TM, Gasecka A, Filipiak KJ, et al. Gut microbiota and cardiovascular disease. Circ Res. 2020;127(4):553–70.
33. Luo Y, Zhang X, Xu X, Liu S, Zhou M, Xie X, et al. Alteration of gut microbiota in individuals at high risk for rheumatoid arthritis is associated with disturbed metabolome and the initiation of arthritis through triggering mucosal immunity imbalance. Arthritis Rheumatol. 2023;75 (10):1736–48.
34. Kim S, Goel R, Kumar A, Qi Y, Lobaton G, Hosaka K, et al. The gut microbiota (microbiome) in cardiovascular disease and its therapeutic regulation. Korean Circ J. 2022;52(7):539–51.
35. Teng F, Tiwari A, Huang Y, He C, Tian Y, Lin Y, et al. Fusobacterium nucleatum promotes rheumatoid arthritis by inducing immune cells and delivering virulence factors. Cell Host Microbe. 2023;31(6):798–810.
36. Szelag A, Daniewski M, Kukula-Koch W. Butyrate and its role in host health, tumorigenesis, and immunity. Int J Mol Sci. 2023;24(5):2523.
37. Coutant F, Miossec P. Mouth and gut: the origins of rheumatoid arthritis? Nat Rev Rheumatol. 2020;16(3):135.
38. Libby P, Goldberg IJ, Brogi E. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol. 2021;78(1):77–92.
39. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis. 2017;76(1):17–28.
40. Crowson CS, Rollefstad S, Kitas GD, van Riel PL, Gabriel SE, Semb AG. Usefulness of risk scores to estimate the risk of cardiovascular disease in patients with rheumatoid arthritis. Am J Cardiol. 2012;110(3):420–4.
41. Poznyak AN, Bezsonov EE, Sukhorukov VN, Orekhov AN. Interplay of rheumatoid arthritis and cardiovascular disease: insights and prospects. SAGE Open Med. 2025;13:2050312125133017.
42. Magalhaes E, Vulliemoz M, Ortega C. Impact of TNF inhibitors on endothelial function and arterial stiffness in rheumatoid arthritis: a systematic review and meta-analysis. Clin Rheumatol. 2020;39(8):2337–45.
43. Krishnan E, Huybrechts KF, Sesso HD. Methotrexate and cardiovascular disease in patients with rheumatoid arthritis: a meta-analysis of observational studies. Am J Med. 2008;121(7):531–8.
44. Ormseth MJ, Chung CP, Dorris JL, Connelly MA, Oeser AM, Solus JF, et al. Omega-3 fatty acid supplementation and circulating trimethylamine N-oxide in veterans with rheumatoid arthritis. Nutr J. 2020;19(1):87.

45. Mankia K, Heaf E, Gore M, Buggs J, James D, Fisher BA, et al. Perturbation of the gut microbiome in anti-CCP positive individuals at risk of developing rheumatoid arthritis. Rheumatology (Oxford). 2022;61(5):2199–209.
46. Chen J, Wright K, Davis JM, Jeraldo P, Marietta EV, Murray J, et al. An expansion of rare-lineage intestinal microbes characterizes rheumatoid arthritis. Genome Med. 2016;8(1):43.
47. Alvarez-Sanchez N, Le Goff B, Ferrières J, Perret B, Amar J. Fiber consumption and development of cardiovascular disease in the elderly: the three-city Bordeaux study. Br J Nutr. 2019;122(11):1231–40.
48. Bae S, Lee Y, Cabanlit M, Leung YY. Gut microbiome and risk of coronary artery disease: a Mendelian randomization study. Front Cardiovasc Med. 2022;9:903788.
49. Sanchez-Alcoholado L, Castellano-Castillo D, Jordán-Martínez L, Moreno-Indias I, Cardila-Cruz P, Elena D, et al. Rheumatoid arthritis and gut microbiome. J Clin Med. 2020;9(9):2668.
50. Sánchez P, Alonso A, Martinez-Sernandez V, Gonzalez-Boullosa R, Paredes L, Martinez-Bernabe T, et al. Probiotic Lactobacillus administration and its effects on metabolic biomarkers in patients with rheumatoid arthritis. Nutr Hosp. 2021;38(5):933–40.
51. Lederer A, Floch A, Noblecourt E, Letellier C, Corcos O, Brochard L, et al. Fecal microbiota transplantation and its effects on metabolic parameters in patients with metabolic syndrome and type 2 diabetes: a systematic review and meta-analysis. Genes (Basel). 2022;13(7):1167.
52. Osorio-Costa F, Rocha GZ, Dias MM, Carvalheira JB. Lactobacillus and Bifidobacterium promote anti-inflammatory pathways in human visceral adipocytes: a potential mechanism preventing insulin resistance. Diabetes. 2014;63(9):2876–86.
53. Butt J, Jenab M, Pischon T, Tjønneland A, Fedirko V, Brenner H, et al. Antibody responses to periodontal pathogens and the risk of coronary heart disease. EClinicalMedicine. 2020;21:100320.
54. de Oliveira GLV, Oliveira CNS, Pinzan CF, de Salis LVV, Oliveira MN. Microbiota modulation of the gut-lung axis in COVID-19. Front Immunol. 2021;12:635471.
55. Microbiome INSIDE Consortium. An integrated metagenome-wide association study of gut microbiota in coronary artery disease. Cell Res. 2022;32(8):628–31.
56. Sparks JA, Kaplan MJ, Helmick CG, Karlson EW. Periodontal treatment and the risk of rheumatoid arthritis: a population-based cohort study. Ann Rheum Dis. 2021;80(5):648–55.
57. Nguyen TT, Vieira-Silva S, Liston A, Raes J. How informative is the mouse for human gut microbiota research? Dis Model Mech. 2015;8(1):1–16.
58. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Effect of interleukin-1β inhibition with canakinumab on incident gout in a randomized trial (CANTOS). Ann Intern Med. 2017;167(7):485–93.
59. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci USA. 2007;104(3):979–84.
60. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, et al. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med. 2019;380(8):752–62.
61. Scher JU, Ubeda C, Equinda M, Khanin R, Littman DR. Prevotella copri and the microbial pathogenesis of rheumatoid arthritis. Arthritis Rheumatol. 2012;64:S1.
62. Bingham CO, Moni M. Periodontal disease and rheumatoid arthritis: the evidence accumulates for complex pathobiologic interactions. Curr Opin Rheumatol. 2013;25(3):345–53.
63. Choi SC, Brown J, Gong M, Ge Y, Zadeh M, Wang T, et al. Gut microbiota translocation in a lupus model causes TLR7-dependent immune activation. Science. 2017;358(6365):eaal2058.
64. Khandelwal P, Mangat C, Singh M, Jain S. Impact of the Mediterranean diet on rheumatoid arthritis. Clin Rheumatol. 2022;41(5):1345–51.
65. Bellocchi C, Volkmann ER. Update on the gastrointestinal microbiome in systemic sclerosis. Curr Rheumatol Rep. 2018;20(8):49.
66. Toms TE, Panoulas VF, Douglas KM, Kitas GD. Increased prevalence of metabolic syndrome in patients with rheumatoid arthritis: influence on cardiovascular risk and treatment, in particular tumor necrosis factor blockade. Arthritis Care Res. 2010;62(2):160–5.

67. Kriegel MA, Sefik E, Hill JA, Wu HJ, Benoist C, Mathis D. Lactobacillus in the gut of mice modulates Th17 responses and disease in a model of spontaneous autoimmune arthritis. Arthritis Rheumatol. 2011;63(10):2648–57.
68. Wu HJ, Ivanov II, Darce J, Hattori K, Shima T, Umesaki Y, et al. Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. Immunity. 2010;32(6):815–27.
69. Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell. 2009;139(3):485–98.
70. Cano-Ortiz A, Marquez-Velasco R, Mena-Vázquez N, Arias de la Rosa I, Manrique-Arija S, de la Hera-Fernández J, et al. Differential effects of periodontitis and smoking on anticitrullinated protein antibodies and rheumatoid factor in rheumatoid arthritis: a case–control study. Arthritis Rheumatol. 2022;74(6):946–54.
71. Moura IB, Buckley CD, Pitzalis C, Gilmore S, Neill L, Staines NA, et al. Perturbations in gut microbiota composition in anti-citrullinated protein antibody-positive at-risk individuals. Arthritis Rheumatol. 2021;73(2):199–207.
72. Daïen CI, Pinget GV, Tan JK, Macia L, Dombrowski Y, MacLean M, et al. Gut-derived acetate promotes Th1 and Th17 responses in inflammatory arthritis. Front Immunol. 2021;12:640780.
73. Laurencikas E, Spangeus A, Söderström L, Kechagias S. Faecal microbiota transplantation in the management of autoimmune diseases. Curr Opin Pharmacol. 2022;65:102248.
74. Ceccarelli F, Alessandri C, Olivieri G, Cipriano E, Perricone C, Valesini G. Dysbiosis of gut microbiota in patients with rheumatoid arthritis: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2022;26(14):5018–33.
75. Camilli G, Peditto V, Vickery J, Velasquez SY, Wampler Muskardin T, Kolls JK. The microbiota and immune response in rheumatoid arthritis. Exp Mol Med. 2022;54(10):1616–26.
76. Sharif K, Watad A, Bragazzi NL, Lichtbroun M, Amital H, Shoenfeld Y. Rheumatoid arthritis in review: clinical, anatomical, cellular, and molecular points of view. Clin Rev Allergy Immunol. 2022;62(2):176–94.
77. Zandman-Goddard G, Bragazzi NL, Watad A, Sharif K, Amital H, Shoenfeld Y. The gut microbiome and rheumatoid arthritis: from pathogenesis to novel therapeutic opportunities. Nat Rev Rheumatol. 2022;18(7):416–27.
78. Guo X, Xie M, Li J, Mackie RI. Transcriptomics of the gut–liver axis in atherosclerosis. Cell Host Microbe. 2020;28(1):150–4.
79. Possemiers S, Bolca S, Eeckhaut V, Depypere H, Verstraete W. Butyrate-producing colon bacteria modulate metabolism and proliferation in human colon cancer cells: butyrate as predictor of metabolic activity. Mol Nutr Food Res. 2011;55(2):368–78.
80. Goel N, Deininger M, Friedline RH, Lakkis FG. Impact of Porphyromonas gingivalis on atherosclerosis. Curr Opin Lipidol. 2022;33(5):376–80.
81. Pahill SR, Mooney J, Kawaguchi A, Corrigan D, Chatterjee A, Brown D, et al. A diet rich in saturated fat and TMAO precursors induces rheumatoid arthritis flares via gut microbiota alterations. Front Immunol. 2021;12:771362.
82. Bridges SL, Deane KD, Mikuls TR, Thiele GM. Periodontitis and rheumatoid arthritis: potential effects of Porphyromonas gingivalis on TLR-mediated inflammation in atherosclerosis. Arthritis Res Ther. 2020;22(1):94.
83. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002;46(9):2287–93.
84. Kim JW, Jeong J, Kim N, Jung S, Park J, Oh J, et al. Influence of the gut microbiome composition on rheumatoid arthritis phenotypes. Yonsei Med J. 2020;61(8):665–71.
85. Levy M, Kolodziejczyk AA, Thaiss CA, Elinav E. Dysbiosis and the immune system. Nat Rev Immunol. 2017;17(4):219–32.
86. Bellucci E, Terenzi R, La Paglia GM, Gentileschi S, Tripoli A, Tani C, et al. One year in review 2023: pathogenesis of rheumatoid arthritis. Clin Exp Rheumatol. 2023;41(2):225–33.

87. Matei DE, Menon M, Alber DG, Smith AM, Nedjat-Shokouhi B, Fasano A, et al. Large-scale anti-inflammatory and gut microbiota-modulating effects of short-chain fatty acids in human rheumatoid arthritis. Sci Adv. 2022;8(19):eabj8956.
88. Rakieh C, Gilbert K, Pratt A, Subesinghe S, Waters D, Hensor EMA, et al. APTITUDE: anti-inflammatory diet in rheumatoid arthritis (a randomized trial). Arthritis Rheumatol. 2023;75(Suppl 9):abstract 0907.
89. Haßelbarth J, Schmidt C, Geillinger KE, Daniel H, Germer CT, Lehrke M. Propionic acid modulates immune cell migration in rheumatoid arthritis. Pharmaceutics. 2021;13(12):2118.
90. Reichardt N, Duncan SH, Young P, Belenguer A, McWilliam Leitch EC, Scott KP, et al. Microbial metabolites: supporting immunity and immunity-supporting metabolites. Clin Transl Immunol. 2022;11(6):e1395.
91. Salli K, Lehtoranta L, Tiihonen K, Ouwehand AC. The effect of 3-month probiotic supplementation on inflammatory markers and disease activity in rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. Rheumatol Int. 2019;39(12):2193–9.
92. Hayashi H, Sekizuka T, Okuda K, Sasaki K, Tokimatsu I, Ohkusa T, et al. Periodontal pathogen Aggregatibacter actinomycetemcomitans in gut microbiota induces bone loss. iScience. 2023;26(3):106125.
93. Hansildaar R, Vedder D, Baniaamam M, Tausche AK, Gerritsen M, Nurmohamed MT. Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout. Lancet Rheumatol. 2021;3(1):e58–70.
94. Hanssen NMJ, Penders J, Hollander DA, Zaiss MM, Reichardt N, Ståhlman M. Gut microbiome and metabolic health: mechanism and translational potential. Gut. 2023;72(10):2035–48.
95. Bressan V, Tonon M, Gallo N, Pinton P, Vettor R, Lunardi C, et al. Effects of a synbiotic on intestinal microbiota in rheumatoid arthritis. J Transl Autoimmun. 2022;5:100150.
96. Pianta A, Arvikar SL, Strle K, Drouin EE, Wang Q, Costello CE, et al. Evidence of the immune relevance of Prevotella copri, a gut microbe, in patients with new-onset rheumatoid arthritis. Arthritis Rheumatol. 2017;69(S10):abstract 06L.
97. Rodríguez-Carrio J, Horta D, Suárez A, Fasano A, Mieli-Vergani G, Vergani D, et al. Prevotella and Porphyromonas genomic transcripts are increased in the gut of early rheumatoid arthritis patients and correlate with autoimmunity markers. Genes (Basel). 2022;13(9):1555.
98. Horta D, Quintana FJ, Ferreira RB, Rosário LM. The translational potential of targeting IL-6 and IL-17 in atherosclerosis with a focus on rheumatoid arthritis. Int J Mol Sci. 2020;21(18):6512.
99. Guo X, Wang T, Yu M, Li X, Zhang Y, Lin X, et al. Multi-omics analyses of gut microbiota and plasma metabolites in rheumatoid arthritis: a case–control study. Front Immunol. 2023;14:1110867.
100. Sparks JA, Aletaha D, Wolfe F, Michaud K, Karlson EW. Periodontitis and circulating anti-PPAD antibody in the development of rheumatoid arthritis. Arthritis Rheumatol. 2020;72(1):57–65.