Review

Discovery Medicine 2026; 38(208): 1371–1391
https://doi.org/10.24976/Discov.Med.202638208.108

Neuroimmune and Metabolic Dimensions of Rheumatoid Arthritis: The Gut-Brain Axis as a Therapeutic Frontier

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Submitted: 2 February 2026 Revised: 11 April 2026 Accepted: 23 April 2026 Published: 20 May 2026

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that significantly impairs mobility and is one of the most prevalent autoimmune diseases worldwide. Extensive research has been conducted to elucidate its pathogenesis, genetic susceptibility, and neurological implications. This review provides a concise overview of RA, with particular emphasis on the gut-brain axis, dietary patterns, and interactions with brain-associated biomolecules, including neurotransmitters, sphingolipids, and glycerophospholipids. A deeper understanding of dynamic host-microbiome interactions may enable the development of personalized therapeutic strategies for RA and facilitate the identification of novel drug targets. In addition, metabolomics approaches are increasingly employed to uncover disease-specific biomarkers and metabolic alterations, contributing to a more precise understanding of RA pathogenesis and improving diagnostic accuracy. Collectively, these insights offer promising directions for future immunological research, with the potential to clarify underlying mechanisms of RA and enhance the quality of life for individuals affected by the disease.

Keywords: autoimmune diseases; rheumatoid arthritis; gut microbiota; biomarkers

Introduction

Autoimmune diseases arise due to impairments in the immune system. Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease, mostly characterized by its symmetric occurrence in the peripheral joints [1–3]. Numerous studies have been conducted to understand the pathogenesis of rheumatoid arthritis, its relationship with genetic predisposition, the effects of diet type, and its influence on the brain. The global prevalence of rheumatoid arthritis is approximately 1% [4], with a higher incidence observed in females compared with males [5]. The exact etiology of the disease is not fully understood; however, genetic susceptibility and environmental factors play a significant role in disease progression [4]. Among the 100 identified genes, human leukocyte antigen (HLA) genes were most prominent in terms of genetic susceptibility [6]. In addition, smoking and aging are the main environmental variables that impact the citrullination and carbamylation of proteins, which lead to inflammation and joint damage.

Various cytokines and chemokines are secreted in the synovial fluid and cause inflammation during the preclinical period of RA [7]. These secreted components increase Reactive Oxygen Species (ROS) levels, leading to pannus formation and cartilage destruction [8]. For the diagnosis of RA, levels of rheumatoid factor (RF) in the serum samples and anti-citrullinated protein/peptide antibodies (ACPA) are analyzed. Since only 70–80% of patients display RF in their serum, additional tests are required to confirm the presence of RA [9].

Recent research suggests that the pathophysiology of RA is influenced by certain gut bacteria, which play a role in the immune system and inflammation. Specific gut bacteria have been associated with either an increased risk of developing RA or the exacerbation of disease activity. For example, *Streptococcus*, *Prevotella*, and *Eggerthella* have been associated with either an increased risk of RA onset or exacerbation of disease activity [10]. These bacteria are also linked to the production of autoantibodies or the activation of Th17 cells in immune-related diseases [10]. Furthermore, RA is associated with central nervous system effects, including fatigue and mood disorders. This highlights the potential involvement of the gut-brain axis in RA. The gut-brain axis refers to the complex communication between the gastrointestinal system, immune system, and central nervous system. This interaction is regulated through neural, endocrine, and immune pathways.

In the present review, the gut-brain axis in RA patients is elaborated, including the effects of diet, and newly identified putative biomarkers are reported (Fig. 1), aiming to propose new intervention strategies to improve the quality of life of individuals suffering from RA.

Biomarkers for Rheumatoid Arthritis

Rheumatoid arthritis (RA) can be systematically characterized by organizing the disease around its core

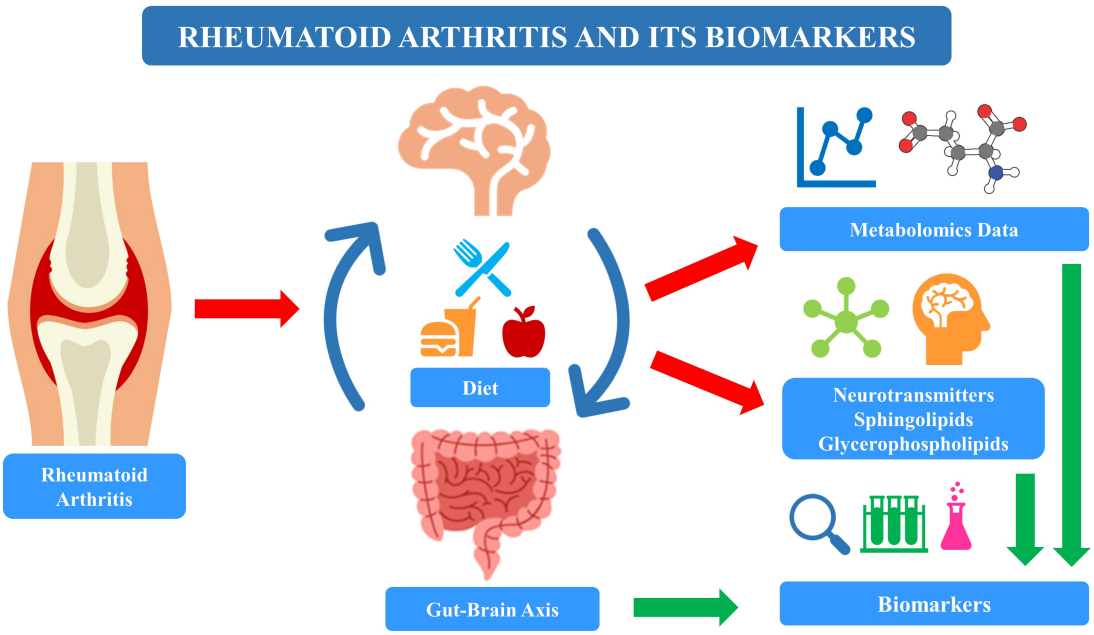

Fig. 1. Overview of the study.

pathogenic mechanisms. The main biological processes include autoimmunity, systemic inflammation, joint destruction, and immune-microbiome interactions. These mechanisms provide a framework for linking measurable biomarkers to specific stages of disease progression (Table 1).

Blood Biomarkers

Blood biomarkers are typically grouped into three categories. First, autoantibodies, such as rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), and Anti-carbamylated protein (Anti-CarP) antibodies, indicate a breakdown of immune tolerance [11]. In the early stages of RA, it is recommended to conduct RF tests and ACPA assays, since ACPA can identify approximately 20–30% of patients with negative RF [11]. ACPA is strongly associated with RA, and in most patients diagnosed with RA, certain autoantibodies, especially ACPA, can be detected months or years before the onset of clinical symptoms [12]. Second, inflammatory markers, including C-reactive protein (CRP) [13], erythrocyte sedimentation rate (ESR) [13], and cytokines such as IL-6, IL-1β and TNF-α [14], reflect systemic immune activation and correlate with disease activity. High erythrocyte sedimentation rate (ESR) values might indicate inflammation, injury, and infection. Similarly, an elevated concentration of C-reactive protein (CRP) is considered an indicator of RA [11], but the reference level for CRP may vary across different laboratories. There are studies where ESR and CRP levels did not alter for slightly above 50% of the patients [15]. Compared to CRP, changes in the level of ESR tend to be more sensitive in RA [16]. Therefore, to determine RA, combined assays must be performed to confirm its presence. Third, tissue damage markers, such as matrix metalloproteinase-3 (MMP-3) [17], cartilage oligomeric matrix protein (COMP) involved in cartilage degradation [18], and C-terminal telopeptide of type II collagen (CTX-II) involved in collagen breakdown [19], indicate ongoing joint destruction and structural damage.

Novel biomarkers in RA research are rapidly reshaping how the disease is detected, monitored, and predicted across its clinical course. At the mechanistic level, recent studies have identified several promising candidates beyond the classical anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) markers. Anti-carbamylated protein antibodies (anti-CarP) have demonstrated positivity in up to 45% of seronegative RA patients, offering diagnostic reach into a population previously undetectable by standard serology [20]. Likewise, the 14-3-3η protein, a synovial damage mediator, has shown a sensitivity of ~40–50% and a specificity of ~90% in early RA, and its serum levels correlate with radiographic joint damage progression, making it valuable for both diagnosis and structural prognosis [21].

The serum metabolic profiles of RA patients have been examined through metabolomics approaches in order to investigate altered metabolite profiles in the disease and identify unique metabolic signatures [22]. Serum samples from RA patients, primary Sjogren's syndrome (pSS) patients, and healthy controls (HC) were analyzed by ultra-high-performance liquid chromatography coupled with high-resolution mass spectrometry (UPLC-HRMS) [22]. Elevated serum levels of 4-methoxyphenylacetic acid, glutamic acid, L-leucine, L-phenylalanine, L-tryptophan,

Table 1. Biomarkers related to rheumatoid arthritis (RA) according to disease mechanisms, blood biomarkers, gut biomarkers, and gut-joint axis.

Category/Mechanism	Biomarker	Sample source	Biological role
Autoimmunity	Rheumatoid Factor (RF)	Blood	Autoantibody against IgG; common diagnostic marker of RA
	Anti-citrullinated protein antibodies (ACPA/Anti-CCP)	Blood	Highly specific RA marker; often appears before symptoms
	Anti-CarP antibodies	Blood	Associated with severe disease and joint damage
Systemic Inflammation	C-reactive protein (CRP)	Blood	Acute phase protein reflecting systemic inflammation
	Erythrocyte sedimentation rate (ESR)	Blood	General marker of inflammatory activity
	Interleukin-6 (IL-6)	Blood	Key cytokine driving RA inflammation
	Tumor necrosis factor-α (TNF-α)	Blood	Central inflammatory mediator in RA pathogenesis
	Interleukin-1β (IL-1β)	Blood	Promotes inflammatory signaling and cartilage degradation
Joint/Tissue Damage	Matrix metalloproteinase-3 (MMP-3)	Blood/Synovial fluid	Reflects synovial inflammation and tissue remodeling
	Cartilage oligomeric matrix protein (COMP)	Blood	Indicator of cartilage breakdown
	C-terminal telopeptide of type II collagen (CTX-II)	Blood/Urine	Marker of collagen degradation in cartilage
Gut Microbiome Composition	*Prevotella copri*	Gut microbiota	Increased abundance linked to early RA
	Collinsella aerofaciens	Gut microbiota	Associated with increased intestinal permeability
	Bacteroides fragilis	Gut microbiota	Involved in immune regulation
	Lactobacillus spp.	Gut microbiota	Altered abundance in RA; immune modulation
Gut Barrier Function	Zonulin	Blood/Gut	Marker of intestinal permeability (“leaky gut”)
	Lipopolysaccharide (LPS)	Blood	Bacterial endotoxin indicating microbial translocation
	LPS-binding protein (LBP)	Blood	Host response to circulating endotoxins
Microbial Metabolites	Short-chain fatty acids (SCFAs)	Gut/Blood	Anti-inflammatory metabolites regulating immune responses
	Trimethylamine-N-oxide (TMAO)	Blood	Microbiome-derived metabolite linked to inflammation
	Secondary bile acids	Gut/Blood	Modulate immune signaling and host metabolism

L-proline, glyceraldehyde, fumaric acid, and cholesterol, and decreased serum levels of capric acid, argininosuccinic acid, and bilirubin were observed in RA patients when compared with pSS and HC groups [22]. Furthermore, three metabolites—4-methoxyphenylacetic acid, L-phenylalanine, and L-leucine—were detected as biomarkers of RA [22].

In another study, a gas chromatography-mass spectrometry (GC-MS) method was carried out to analyze serum samples from RA patients and healthy controls to investigate distinctive metabolic profiles in RA patients [23]. Data analysis revealed that distinct metabolic profiles between RA patients and controls, such that reduced levels of Serums from RA patients were featured by decreased levels of amino acids and glucose, and increased levels of fatty acids and cholesterol, which were mainly linked to the glycolytic pathway, fatty acid and amino acid metabolism, as well as other pathways such as the TCA cycle and urea cycle [23]. In another study, some metabolites such as succinate, glutamine, citrulline, octadecanol, glycerol, and isopalmitic acid were demonstrated as potential biomarkers of RA, which were linked to the urea and TCA cycles as well as fatty acid and amino acid metabolism [24].

Tryptophan and kynurenine concentrations were determined using high-performance liquid chromatography in samples from RA patients at different disease stages and healthy controls [25]. Tryptophan concentrations were lower in RA patients and the serum level of tryptophan was inversely proportional to the stage of the disease [25]. The concentration of neopterin, which is a macrophage activation marker, was elevated in most of the RA patients [25]. Another study that has used metabolomics approaches to investigate relevant biomarkers of RA via ^{1}H NMR spectroscopy; results showed that the relative concentrations of valine, isoleucine, lactate, alanine, creatinine, GPC + APC and histidine were lower, whereas the levels of 3-hydroxyisobutyrate, acetate, NAC, acetoacetate, and acetone were higher in RA compared to healthy controls [26]. In a study in which NMR-based serum metabolomics analysis has been carried out, the circulatory metabolites 3-hydroxybutyrate (3-HB), glucose, isoleucine, leucine, glutamate, glycine, and histidine were increased in RA patients compared to the control group [27]. Also, in RA patients, the concentrations of lipoproteins (LDL and VLDL), PUFA, choline, lactate, creatinine, and various amino acids (such as valine, glutamine, and phenylalanine) were decreased compared to the control group [27]. The metabolic profiles of patients with RA have been compared with the control group using serum metabolites via two different chromatography-mass spectrometry platforms, and the metabolic biomarkers were measured [28]. A study showed that glyceric acid, D-ribofuranose and hypoxanthine levels were increased, whereas histidine, threonic acid, methionine, cholesterol, asparagine and threonine levels were decreased in RA patients compared with the control group [28]. Homocysteine (Hcy) levels were found to be increased in RA patients compared to control groups; the determination of Hcy levels and related biomarkers may be valuable for the detection of cardiovascular risk in RA patients [29]. These metabolomics studies reveal that this method may be a useful tool for investigating the pathogenesis of RA and could support more precise diagnosis of RA.

The practical value of the novel biomarkers converges along three axes at the clinical implementation level. For early diagnosis, combining anti-CarP, 14-3-3η, and miRNA panels into multi-marker algorithms could capture seronegative and pre-clinical RA far earlier than current criteria allow, enabling intervention before irreversible joint damage occurs [30]. For disease assessment, dynamic monitoring of CXCL13 and synovial cfDNA offers a more sensitive and real-time index of disease activity than composite clinical scores like DAS28, which remain vulnerable to subjective inputs [31]. For prognosis, integrating radiographic biomarkers, synovial pathotype classification, and machine-learning-derived multi-omic risk scores could stratify patients at diagnosis into erosive versus non-erosive trajectories, guiding aggressive early intervention where it is most needed and avoiding overtreatment where the disease course is likely to be mild [32,33]. Together, these biomarker advances represent a shift from reactive, symptom-driven diagnosis toward a proactive, biology-anchored model of RA management with measurable clinical impact at every stage of the disease continuum.

Gut Microbiota Biomarkers

Gut-related biomarkers are increasingly recognized as important in RA, given the gut microbiome's role in immune regulation [34]. Alterations in microbial composition, such as the increased abundance of *Prevotella copri*, are frequently observed in early RA, and changes in taxa across studies are summarized in Table 2 (Ref. [6,34–46]). Biomarkers related to gut/intestinal barrier integrity, including zonulin, lipopolysaccharide (LPS) and lipopolysaccharide-binding protein (LBP), can indicate increased gut permeability that allows microbial translocation into the systemic circulation. Zonulin, a biomarker of intestinal permeability, has been demonstrated with high levels in both the serum and feces of patients with rheumatoid arthritis, suggesting the presence of elevated gut permeability in RA [47]. Gut microbial dysbiosis has been associated with the development of autoimmune diseases, and elevated serum zonulin levels are linked to inflammation, dysbiosis and a leaky intestinal barrier [48]. LPS bioactivity correlates with the inflammation and disease activity in patients with rheumatoid arthritis, underscoring its prognostic relevance [49]. LBP, a sensitive serum biomarker, is significantly elevated in RA compared to osteoarthritis (OA), systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS), and healthy controls [50], correlates with

Table 2. Alterations in taxa in RA patients.

Sample source	Elevated Taxa in RA	Reduced Taxa in RA
Gut Microbiome		
Fecal/Gut Samples	*Prevotella copri* [34,38], *Escherichia coli* [42], *Ruminococcus gnavus* [42], *Eggerthella lenta* [39], *Clostridium asparagiforme* [39], *Gordonibacter pamelaeae* [39], *Lachnospiraceae bacterium* [39], *Lactobacillus salivarius* [39], *Staphylococci* [34], *Enterobacteria* [34]	*Faecalibacterium prausnitzii* [42], *Roseburia intestinalis* [42], *Eubacterium rectale* [42], *Alistipes putredinis* [42], *Bifidobacterium* [6], *Bacteroides* [6,34], *Haemophilus spp.* [39], *Lactopositive colibacteria* [34], *Bifidobacteria* [34], *Klebsiella pneumoniae* [39], *Bifidobacterium bifidum* [39], *Sutterella wadsworthensis* [39], *Megamonas hypermegale* [39]
Fecal/Gut Samples (early RA)	*Blautia gnavus* [43], *Lactobacillus ruminis* [40], *Lactobacillus salivarius* [40], *Lactobacillus iners* [40]	*Acetanaerobacterium elongatum* [43], *Cristiansella massiliensis* [43], *Gracilibacter thermotolerans* [43]
Fecal/Gut Samples (moderate or high disease activity)	*Collinsella* [45], *Bifidobacterium* [45], *Alistipes* [45], *Verrucomicrobiae* [41], *Akkermansia* [41], *Escherichia* [35], *Klebsiella* [35], *Eisenbergiella* [35], *Flavobacterium* [35], *Prevotella denticola* [36], *Prevotella copri* [37], *Porphyromonas gingivalis* [44], *Aggregatibacter segnis* [44], *Streptococcus spp.* [44], *Neisseria spp.* [44], *Haemophilus spp.* [44], *Veillonella* [44], *Campylobacter* [44]	*Veillonella* [45], *Dorea* [45], *Coprococcus* [45], *Fusicatenibacter* [35], *Megamonas* [35], *Enterococcus* [35], *Fusobacterium varium* [44], *Clostridium celatum* [44], *Enterococcus faecalis* [44]
Oral Microbiome		
Oral/Saliva Samples	*Porphyromonas gingivalis* [6], *Prevotella intermedia* [6], *Bifidobacterium dentium* [39], *Lactobacillus salivarius* [39], *Atopobium spp.* [39], *Cryptobacterium curtum* [39]	*Veillonella* [39], *Haemophilus spp.* [39]
Blood-Associated Microbial Signatures		
Blood/Systemic Samples	*Halomonas* [46], *Shewanella* [46]	*Achromobacter* [46], *Shigella* [46], *Serratia* [46], *Corynebacterium* [46], *Granulicatella* [46], *Staphylococcus* [46], *Gemella* [46]

Table 3. Modifications in the metabolisms of RA patients.

Metabolic pathway	Sub-Pathway/Process	Predominant change	Reference
Amino Acid Metabolism	Arginine metabolism; L-arginine biosynthesis	Decrease	[35]
	Arginine metabolism; arginase II expression, L-ornithine biosynthesis	Increase	[51]
	Arginine metabolism; L-ornithine biosynthesis	Decrease	[35]
	Asymmetric dimethyl arginine (ADMA) & Mono methyl arginine (MMA)	Increase	[52]
	Aromatic amino acid biosynthesis	Decrease	[35]
	Branched-chain amino acid biosynthesis	Decrease	[35]
	L-lysine fermentation to acetate and butanoate	Decrease	[44]
	Methionine cycle	Decrease	[42]
	L-alanine biosynthesis	Decrease	[45]
	Reverse transsulfuration	Increase	[53]
Lipid Metabolism	Geranylgeranyl diphosphate biosynthesis	Increase	[44]
	Mevalonate pathway	Increase	[44]
Nucleotide Metabolism	Biosynthesis of purine	Increase	[45]
	Purine nucleobases degradation	Increase	[44]
	Allantoin degradation	Decrease	[44]
Vitamin & Cofactor Metabolism	Cobalamin biosynthesis	Increase	[45]
	1,4-dihydroxy-2-naphthoate biosynthesis	Increase	[44]
	Menaquinol biosynthesis	Increase	[44]
	Seleno-amino acid metabolism	Decrease	[44]
	Vitamin K2 biosynthesis	Increase	[44]
	Folate metabolism	Increase	[42]
Other Metabolic Processes	Biosynthesis of heme	Decrease	[45]
	Fermentation of short-chain fatty acids (SCFA)	Increase	[45]

ESR, CRP, and DAS28, and remains positive in approximately half of patients with active disease whose tests were negative for CRP or ESR, making it a clinically useful complement to standard markers [50]. Microbial metabolites, particularly short-chain fatty acids (SCFAs), can modulate immune signaling and inflammatory responses. The modifications in metabolism and the associated changes in metabolites of RA patients are presented in Table 3 (Ref. [35,42,44,45,51–53]) and Table 4 (Ref. [22–29,35,52–55]), respectively.

Multiple 16S rRNA gene sequencing and metagenomic studies have characterized gut dysbiosis in RA. Variations in bacterial abundances and metabolite profiles across studies may reflect differences in study design, methodologies, or population characteristics [35]. A metagenomic analysis using phylogenetic investigation of communities by reconstruction of unobserved states 2 (PICRUSt2) revealed an enrichment of *Klebsiella*, *Escherichia*, *Eisenbergiella*, and *Flavobacterium* in RA and a depletion of *Fusicatenibacter*, *Megamonas*, and *Enterococcus* in healthy controls (Table 2) [35]. KEGG pathway analysis linked RA to disrupted tryptophan, riboflavin, unsaturated fatty acid, and glycerophospholipid metabolism [35]. Biosynthesis of amino acids, including L-arginine, is decreased in RA patients (Table 3) [35]. A 16S rRNA study comparing 29 RA patients and 30 healthy controls identified reduced *Bacteroidetes* as well as elevated *Verrucomicrobia* and *Proteobacteria* in RA patients compared with the healthy controls, with associated changes in purine and histidine metabolism; 9,12-octadecadiynoic acid and 10Z-nonadecenoic acid emerged as potential RA biomarkers [54]. A metagenome-wide association study in a Japanese population using an unsupervised ML-based clustering approach identified *Prevotella denticola* enrichment alongside alterations in fatty acid biosynthesis and glycosaminoglycan degradation in RA patients compared with the healthy controls [36]. Notably, *Prevotella copri* is strongly associated with early RA [37], whereas *Prevotella histicola* suppresses disease progression in RA [38], highlighting opposing immunomodulatory roles within the same genus.

Metagenomic shotgun sequencing and a metagenome-wide association analysis of fecal, dental, and salivary samples revealed pan-mucosal dysbiosis in RA, marked by depletion of *Haemophilus spp.* and enrichment of *Lactobacillus salivarius*, correlating with disease activity and autoantibody levels and partially normalizing with treatment [39]. Functional disruptions in microbial redox balance, amino acid metabolism, and metal transport, along with detectable molecular mimicry of RA-related human antigens, suggest that microbiome profiles could be helpful in prognosis, diagnosis, and treatment [39]. Elevated fecal *Lactobacilli*,

Table 4. Changes in the metabolites of RA patients.

Increased metabolites	Decreased metabolites	Reference
4-Methoxyphenylacetic acid, Cholesterol, Fumaric acid, Glutamic acid, Glyceraldehyde, L-Leucine, L-Phenylalanine, L-Proline, L-Tryptophan	Argininosuccinic acid, Bilirubin, Capric acid	[22]
Arginine, Citrulline	-	[52]
Cholesterol, Fatty acids	Amino acids, Glucose	[23]
Ophthalmic acid, Urinary hypotaurine	Guanidoacetic acid, Homoarginine	[53]
Neopterin	Tryptophan (precursor of serotonin)	[25]
3-Hydroxyisobutyrate, Acetate, Acetoacetate, Acetone, NAC	Alanine, Creatinine, GPC/APC, Histidine, Isoleucine, Lactate, Valine	[26]
Homocysteine	-	[29]
D-Ribofuranose, Glyceric acid, Hypoxanthine	Asparagine, Cholesterol, Histidine, Methionine, Threonic acid, Threonine	[28]
Sphingosine, Monohexosylceramide, Ceramide	-	[55]
Asparagine, Citrulline, Glutamine, Lysine, Octadecanol, Ribitol, Ribose, Salicylaldehyde, Succinate, Terephthalate, Tryptophan, Tyrosine, Uracil, Xylose	Ethanolamine, Glycerol, Hydroxylamine, Isopalmitic acid, Myristic acid, Palmitoleic acid	[24]
Glucose, 3-Hydroxybutyrate, Isoleucine, Leucine, Glutamate, Histidine, Glycine	Lipoproteins (LDL, VLDL), PUFA, Choline, Lactate, Creatinine, Valine, Glutamine, Phenylalanine	[27]
Peptides (Val Thr Ile, Ile Gly Gly Ile, Val Asn Ile, etc.), amino acids (lysine, methionine) and nucleotides (thymidine, deoxyuridine, deoxyinosine, deoxyguanosine)	Lipids (LPA(0:0/16:0), 16,16-dimethyl-PGA, 1,5-HETE, 12(R)-HEPE)	[54]
Glycerophospholipids (PC(18:3(9Z,12Z,15Z)/16:1(9Z)), lysoPE 19:1, lysoPE 18:0, lysoPC(18:0/0:0)), benzene and substituted derivatives (O-toluidine, benzaldehyde), cholesterol, phytosphingosine, His-Pro, glycerol 3-phosphate, dodecanoylcarnitine	Indoles and derivatives (N-methylserotonin, 5-hydroxyindole-3-acetic acid (5-HIAA), 3-formyl-6-hydroxyindole), Sphingolipids (Cer(d18:0/16:0), Cer(d18:0/12:0), Cer(d18:0/14:0)), fatty acyls (traumatic acid, 9,10-epoxyoctadecenoic acid, ricinoleic acid, acylcarnitine 12:3, acylcarnitine 21:4, acylcarnitine 20:6, 2-linoleoylglycerol), kynurenic acid, xanthurenic acid, 3-hydroxyanthranilic acid (3-HAA), (-)-riboflavin and N-alpha-acetyl-L-lysine	[35]

particularly *L. salivarius*, *L. iners*, *L. ruminis*, and *L. mucosae*, in early RA patients suggest that community-level shifts in this genus may contribute to disease development and serve as progression indicators [40].

Several studies have examined how RA treatment modifies the gut microbiome. In drug-naive and treated RA patients with methotrexate (MTX) and/or etanercept (ETN), the archaeal phylum Euryarchaeota was directly related to the disease activity score 28 (DAS-28) and appeared as an independent risk factor [56]. ETN treatment partially provided a beneficial microbiota, highlighting the mutual impact of microbiota composition and immunosuppressive drugs in the treatment of RA [56]. Early RA patients show lower abundances of *Bifidobacteria*, *Bacteroides-Porphyromonas-Prevotella* (including the *Bacteroides fragilis* subgroup), and *Eubacterium rectale-Clostridium coccoides* compared with fibromyalgia patients, implicating these taxa in RA etiopathogenesis [57].

Chiang *et al*. (2019) [41] suggested that RA patients exhibited significantly reduced gut microbiota diversity, specifically among anti-citrullinated peptide antibodies (ACPA)-positive individuals with enrichment of the phylum *Verrucomicrobiae*, the genus *Akkermansia*, *Enterobacteriaceae* (including *Klebsiella*) and a reduction in *Bifidobacterium*, associated with elevated levels of TNF-α and IL-17A. Additionally, ACPA-positive RA showed higher proportions of *Blautia*, *Akkermansia*, and *Clostridiales*, demonstrating a clear correlation between gut dysbiosis, inflammatory markers, autoantibody status, and RA pathogenesis [41]. Reduced gut microbial diversity in RA patients is also associated with disease duration and autoantibody levels more broadly; increased *Collinsella aerofaciens* and *Eggerthella lenta* and decreased *Faecalibacterium* promote a pro-inflammatory gut environment [58]. Pre-clinical RA stages similarly show *Prevotella spp.* enrichment, suggesting the involvement of intestinal dysbiosis in the pathogenesis of RA [59].

A large-scale study of 244 RA patients and 69 healthy controls identified 63 significantly altered metabolites, including L-arginine, creatine, D-proline, ornithine, choline, betaine, L-threonine, LysoPC (18:0), phosphorylcholine and glycerophosphocholine metabolites mapping to arginine and proline metabolism, glycine, serine, and threonine metabolism, and glycerophospholipid metabolism (Tables 3,4) [60]. At the taxonomic level, *Eubacterium hallii*, *Escherichia-Shigella*, and *Streptococcus* were enriched in RA compared to the control group, while *Lactobacillus*, *Alloprevotella*, *Enterobacter*, and *Odoribacter* were depleted [61]. The bacterial genera *Bacteroides* and *Escherichia-Shigella* were present at higher amounts in RA patients compared with the control group [61]. The convergence of microbial and metabolomic shifts in amino acid and lipid metabolism reinforces the gut-immune axis as a driver of systemic inflammation in RA.

In RA, various metabolic changes contribute to disease progression and affect vascular health. Arginase II is upregulated in RA, potentially promoting cell proliferation by supplying L-ornithine, which serves as the substrate of polyamine biosynthesis [51]. Furthermore, patients with RA show elevated levels of asymmetric dimethyl arginine (ADMA) and mono methyl arginine (MMA), which are inhibitors of endothelial nitric oxide synthase (e-NOS), the enzyme that participates in the conversion of L-arginine to citrulline and releases nitric oxide [52]. Elevated levels of ADMA and MMA in RA may contribute to endothelial dysfunction, which can be improved by chronic prednisolone treatment [52].

Metagenomic shotgun analyses have identified additional functionally relevant taxa. *Clostridium* enrichment in RA and in inflammatory bowel disease-associated arthropathy correlates with elevated tyrosine degradation [62]. The alterations in the gut microbiota of RA patients also indicated an increase in the abundance of *Epsilonproteobacteria* and *Campylobacterales* [62]. A large metagenome analysis (221 RA, ankylosing spondylitis, and psoriatic arthritis patients versus 219 controls) suggested disruption of the vitamin B salvage and biosynthesis pathways, increase in folate metabolism pathway and enrichment in iron sequestration, along with marked enrichment of *E. coli* and *R. gnavus* in a small portion of the group and depletion of *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, *Eubacterium rectale*, and *Alistipes putredinis* [42]. Changes in *E. rectale*, which plays a role in SCFA production, were linked to hemoglobin levels and vitamin B12-mediated folate-methionine cycle disruption, suggesting systemic metabolic consequences of gut dysbiosis (Table 3) [42]. A plasma and urine metabolomics study further identified histidine and guanidoacetic acid in plasma and hypotaurine in urine as high-AUC biomarkers [53]. Additionally, several metabolites and intermediates were significantly associated with DAS28-ESR, suggesting increased activation of the reverse transsulfuration pathway as RA disease activity rises [53].

Treatment-associated microbiome recovery has been documented in early RA. After three months of methotrexate and glucocorticoid therapy, gut microbial diversity profiles were normalized toward fibromyalgia patients as the control group; *Blautia gnavus* emerged as a candidate biomarker linked to reduced propionic acid levels in early RA patients [43]. The changes in the gut taxa of RA patients, assessed after treatment with drugs including Huayu-Qiangshen-Tongbi formula (traditional Chinese medicine), methotrexate, and leflunomide, indicated specific bacterial alterations [44]. As shown in Table 2, *Clostridium celatum*, *Enterococcus faecalis*, and *Fusobacterium varium* showed a decrease in their abundances, whereas *Neisseria*, *Haemophilus*, *Veillonella* and *Campylobacter* were enriched in RA patients [44]. After treatment with the Huayu-Qiangshen-Tongbi formula, *Clostridium celatum* was re-

stored in RA patients. The study group also linked the existing KEGG pathways, such as Vitamin K2 biosynthesis, to RA [44].

The causal relationship between RA and gut microbiota is increasingly understood through the gut-immune-joint axis, wherein dysbiosis initiates or amplifies systemic autoimmune responses. Expansion of *Prevotella copri* and certain *Collinsella* species can disrupt immune homeostasis by promoting pro-inflammatory T helper 17 (Th17) responses and reducing regulatory T cell (Treg) activity [10,63]. Dysbiosis may also impair the intestinal epithelial barrier, increasing permeability (leaky gut) and allowing microbial components such as lipopolysaccharide (LPS), peptidoglycans, and microbial metabolites to enter the circulation [64]. These molecules activate innate immune receptors, including Toll-like receptors (TLRs) and NOD-like receptors, leading to systemic production of inflammatory cytokines such as TNF-α, IL-6, and IL-1β, which are central mediators of RA pathogenesis [41,65,66]. In parallel, microbial enzymes and inflammatory conditions in mucosal tissues can promote post-translational protein modifications, particularly citrullination, generating neoantigens that stimulate the production of ACPA, a hallmark of RA [41,68,69]. These autoimmune responses may initially develop at mucosal sites (gut, lung, or oral cavity) before becoming systemic and targeting synovial tissues [70].

Evidence supporting causality comes from multiple lines of research: germ-free animal models show a reduced arthritis incidence until colonized with RA-associated microbes [6], microbiome transfer experiments can induce inflammatory phenotypes [71], and patients with early RA often exhibit reproducible microbial signatures that partially normalize after effective therapy [72]. Thus, gut microbiota alterations are not merely a consequence of inflammation but can function as drivers that initiate or amplify immune dysregulation, linking intestinal microbial ecology with systemic autoimmunity and joint destruction in RA.

Diet Influence on the Gut Microbiota of RA Patients

The changes in gut microbiota according to diet in general and for RA patients are summarized in Table 5 (Ref. [73–79]). A plant-based diet has been shown to be associated with improved human health by supporting the development of a more diverse and stable microbial system [73]. A vegetarian diet excludes animal-based proteins but contains fiber and carbohydrates [80]. Lacto-ovovegetarian diet is similar to a vegetarian diet but includes dairy products [81]. The vegan diet excludes the consumption of animal meat and any animal-derived by-products [82]. Vegans and vegetarians have been found to have a substantially increased abundance of particular Bacteroidetes-related operational taxonomic units relative to omnivores [73]. Dietary fibers consistently enhance the abundance of lactic acid bacteria, such as *Ruminococcus*, *Eubacterium rectale*, and *Roseburia*, and decrease the abundance of *Clostridium* and *Enterococcus* species [73]. Polyphenols, which are found prevalent in plant-based foods, increase the abundance of beneficial lactic acid bacteria such as *Bifidobacterium*, *Lactobacillus*, and *Eubacterium rectale*, which contribute to anti-inflammatory and anti-pathogenic effects, and cardiovascular protection [73]. A study conducted to investigate the effect of a vegetarian diet during pregnancy on maternal gut microbiota has shown that the relative abundances of *Collinsella* and *Holdemania* were decreased, whereas that of *Roseburia and Lachnospiraceae* was increased [74]. A study has demonstrated that a shift to a low-fat vegan diet resulted in an elevated relative abundance of *Faecalibacterium prausnitzii*, and comparatively smaller decrease in the relative abundance of *Bacteroides fragilis* [75]. The abundance of *Enterobacteriaceae* was higher in the vegan group compared to the omnivore group [76]. A vegan diet, through its influence on the gut microbiota, may slow the progression of RA. For example, one study reported that a vegan diet improved the disease activity, inflammatory markers, and quality of life in patients with RA [83], while another found that a low-fat vegan diet reduced symptoms in patients with moderate-to-severe RA [84].

The Mediterranean diet is considered a healthy diet characterized by the consumption of carbohydrates, polyunsaturated fatty acids, and bioactive compounds like flavonoids, phytosterols, terpenes, and polyphenols [85]. RA patients adhering to a strict Mediterranean diet displayed lower *Lactobacillaceae* and *Prevotella copri* in their gut microbiota [77]. Lower *Escherichia coli* and a higher abundance of *Candida albicans* were also reported, along with increased SCFA levels [86]. The relative abundance of *Bacteriodetes* decreased and *Eubacteria* increased on the Mediterranean and Vegan diets [78]. The relative abundance of *Lachnospiraceae* increased on the Mediterranean diet [78].

The Western diet includes high-fat and cholesterol, high protein, high sugar and salt intake. This type of diet leads to obesity and may contribute to the development of various autoimmune diseases [87]. Since red meat and high sugar are consumed in large amounts, the abundance of the *Bacteroides phylum*, which helps in the digestion of polysaccharides and oligosaccharides, is increased in the gut [88]. *Ruminococcus*, which metabolizes cellulose, was also found to be increased [88]. Consumption of high fat reduces the abundance of *Bifidobacterium spp*, *Eubacterium rectale-Clostridium coccoides* and *Bacteroides* [89]. It has been reported that the Western diet is associated with an elevated risk of RA since this type of diet is defined by high consumption of refined carbohydrates, red meat, trans and saturated fats, and low amounts of omega-3 to omega-6 fatty acids, which may result in increased inflammation [90]. Previous research has demonstrated that a healthy diet is inversely associated with RA, whereas a Western diet is

Table 5. Changes in gut microbiota according to diet.

Diet type	High abundance			Low abundance			Reference
	Phylum	Genus	Species	Phylum	Genus	Species	
Vegan-Vegetarian	*Firmicutes_A*	*Ruminococcus*	-	*Firmicutes_A*	*Clostridium*	-	[73]
	Firmicutes_A	*Agathobacter*	*Eubacterium rectale*	*Firmicutes*	*Enterococcus*	-	
	Firmicutes_A	*Roseburia*	-	-	-	-	
	Actinobacteriota	*Bifidobacterium*	-	-	-	-	
	Firmicutes	*Lactobacillus*	-	-	-	-	
	Firmicutes_A	*Roseburia*	-	*Actinobacteriota*	*Collinsella*	-	[74]
	Firmicutes_A	*Lachnospiraceae**	-	*Firmicutes*	*Holdemania*	-	
	Firmicutes_A	*Faecalibacterium*	*Faecalibacterium prausnitzii*	*Bacteroidota*	*Bacteroides*	*Bacteroides fragilis*	[75]
	Bacteroidota	*Prevotella*	-	*Bacteroidota*	*Bacteroides*	-	[79]
	Firmicutes_A	*Clostridium*	-	*Actinobacteriota*	*Bifidobacterium*	-	
	Firmicutes	*Lactobacillus*	-	-	-	-	
	Firmicutes_A	*Ruminococcus*	-	-	-	-	
	Firmicutes_A	*Agathobacter*	*Eubacterium rectale*	-	-	-	
	Firmicutes_A	*Faecalibacterium*	*Faecalibacterium prausnitzii*	-	-	-	
	Firmicutes_A	*Eubacteria*	-	*Proteobacteria*	-	-	[78]
	Proteobacteria	*Enterobacteriaceae**	-	*Bacteriodetes*	-	-	
	Firmicutes_A	*Ruminococcus*	-	-	-	-	
Vegan-Vegetarian RA	*Proteobacteria*	*Enterobacteriaceae**	-	-	-	-	[76]
Mediterranean	*Firmicutes_A*	*Eubacteria*	-	*Bacteriodetes*	-	-	[78]
	Firmicutes_A	*Lachnospiraceae**	-	-	-	-	
Mediterranean RA	-	-	-	*Firmicutes*	*Lactobacillaceae**	-	[77]
	-	-	-	*Bacteroidota*	*Prevotella*	*Prevotella copri*	

* this is not Genus, it is Family.

positively associated with RA [91]. In a previous study, two dietary patterns, namely the Western diet and healthy diet patterns, in which the first one included high intake of sweet snacks, high-fat meats, refined grains, high-fat dairies and salty snacks and the latter one was abundant in fish, low-fat dairies, fruits, vegetables and olives, were investigated in 100 RA patients and 100 healthy individuals [92]. Logistic regression was used to evaluate the correlation between following certain dietary patterns and RA risk [92]. Results showed significantly higher Western diet scores in RA patients compared to the healthy individuals, whereas no significant differences were observed in healthy diet scores between the RA group and healthy individuals [92]. This study showed a positive relation between a Western diet and RA, both in the crude model and after adjustments were made in terms of different classifications such as age, gender, education level, BMI, marital status, income, dietary intake of vitamin E, physical activity, smoking, saturated fatty acids and polyunsaturated fatty acids [92]. Diet-induced alterations in gut microbiota composition and metabolic activity not only influence intestinal and systemic immune responses in rheumatoid arthritis but may also affect gut-derived metabolites that participate in gut-brain communication. Increasing evidence suggests that microbial and host metabolic changes can modulate neuroactive molecules, including neurotransmitters and sphingolipids, which may contribute to neuroimmune interactions associated with RA.

Relationship of Rheumatoid Arthritis With Neurotransmitters and Sphingolipids in the Brain

Since RA is a systemic autoimmune disorder, it not only affects the joints but also the whole body. RA might be observed as comorbid with mental disorders such as depression [93] and bipolar disorder [94], and neurological disorders like Alzheimer's disease [95]. Therefore, the relationship between RA and the brain should be closely investigated, considering the effects of neurotransmitters, their precursors, reactions occurring in the brain region, and the enzymes involved in these processes.

Neurotransmitters Effective in RA

Neurons secrete specific chemical signals called neurotransmitters to communicate with each other [96]. Neurotransmitters are required to achieve certain actions; such as dopamine, which has a key role in modulating the reward processing, motivation and cognitive functions, whereas norepinephrine is essential for regulating arousal, emotional state, and perception of pain [97]. The precursor amino acids, such as tryptophan and tyrosine, modulate the synthesis and function of monoamine neurotransmitters [98]. For instance, tryptophan, which is an essential amino acid for protein synthesis and the precursor of the neurotransmitter serotonin, is closely linked to cognitive function and brain processes [99]. The pathogenesis of immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis (RA), may be influenced by neural and hormonal factors that connect the nervous and immune systems [100]. The presence of multiple receptors for various neurotransmitters on the surface of immune cells implies that neurotransmitters may have a physiological role in modulating the immune response [100]. Exploring the biological mechanisms linking the nervous and immune systems may suggest targeted neuromodulation as a potential therapeutic strategy for the treatment of inflammatory and autoimmune diseases [100]. Neurotransmitters and their precursors are presented in Table 6 (Ref. [101–106]).

Norepinephrine

Norepinephrine (NE) is a neurotransmitter and a hormone that has a significant role in mediating the sympathetic nervous system's response to stress [107]. The precursor of Norepinephrine (NE) is L-threo-3,4-dihydroxyphenylserine (L-DOPS), which is a synthetic catechol amino acid that is converted into the potent vasoconstrictor, norepinephrine (NE) in the presence of L-aromatic amino acid decarboxylase (LAAAD) and pyridoxal phosphate [101]. Tyrosine hydroxylase-positive (TH-positive) nerves were reported to be negatively related to the inflammation index [108]. TH-positive cells have been demonstrated as the source of NE secretion, and a strong correlation has been found between TH-positive cells, NE release, and the severity of synovial inflammation [109]. It has been suggested that NE produced by these cells may represent an anti-inflammatory response to reduce local inflammation [109]. NE has an anti-inflammatory behavior since it suppresses Th17 cell differentiation [63]. A study has shown that NE inhibits Th17 cell differentiation through β2-adrenergic receptor signaling and exerts anti-inflammatory effects in a mouse model of RA [63].

Acetylcholine

Acetylcholine is a neurotransmitter synthesized from choline and acetyl coenzyme A [110]. Acetylcholine is associated with memory, rapid eye movement (REM) sleep, and attention [111]. The precursor of acetylcholine is choline and diet plays a crucial role in precursor intake [102]. For example, although choline can be produced via endogenous synthesis in the body, this synthesis is generally insufficient to meet physiological requirements; hence, adequate amounts must be obtained through the diet to ensure proper levels [112]. While acetylcholine is mostly associated with memory-related diseases like Alzheimer's disease [113], it is closely associated with RA. Nicotinic acetylcholine receptors play a significant role in RA, since they have anti-inflammatory functions [114]. Specifically, the α7 subunit of nicotinic acetylcholine receptors is involved in RA by decreasing inflammation through inhibiting the release of proinflammatory cytokines [114].

Table 6. Neurotransmitters and their precursors involved in RA.

Neurotransmitter	Neurotransmitter Precursors	Reference
Acetylcholine	Choline	[102]
Dopamine	L-dopa (Levodopa), L-tyrosine, L-phenylalanine	[103]
Serotonin	L-tryptophan,5-hydroxytryptophan	[104]
Histamine	L-histidine	[106]
Norepinephrine	L-threo-3,4-dihydroxyphenylserine (L-DOPS) (synthetic amino acid)	[101]
GABA	Glutamine	[105]
Glutamate	Glutamine	[105]

Dopamine

Dopamine is a type of neurotransmitter under the catecholamine family, responsible for emotions and cognition [115]. Since dopamine cannot pass the blood-brain barrier, it is derived from its precursors, like L-dopa, L-tyrosine and L-phenylalanine [103]. Two types of dopamine receptors, namely D1-like subtypes, dopamine D_1 receptor and dopamine D_5 receptor, were found to be higher in RA patients compared to osteoarthritis patients [115]. Also, some metabolites of dopamine, including homovanillic acid, dihydroxyphenylacetic acid, and 3-methoxytyramine, were detected in the RA serum [115]. The D2-like receptor, a dopamine receptor, was also found to reduce cartilage destruction [116,117] and is positively associated with the TNF-α level in the serum [65]. Collagen type I cross-linked telopeptide and matrix metalloproteinase-3 concentrations were higher in RA patients and osteoprotegerin concentration was lower in RA patients compared to osteoarthritis patients and healthy controls [65]. Dopaminergic receptors could cause a slight decrease in IL-8 secretion [118]. The significance of the D3-like receptor to RA was examined by the CIA mouse model. The results indicated that D3-like receptors suppress excessive inflammation in mast cells and alleviate RA in mouse models via degradation of Toll-like receptor 4 (TLR4) [119]. Sex-specific experiments were also conducted, and females tend to have a higher expression of D1-like receptors in B cells, leading to higher levels of IL-8 and CCL-3 [120].

Serotonin

Serotonin (5-hydroxytryptamine) is best known for its usage in the treatment of mental disorders like depression [121]. L-tryptophan and 5-hydroxytryptophan (5-HTP) are the precursors of serotonin, and there has been increasing evidence investigating the treatment of depression, anxiety, panic, and sleep disorders by 5-hydroxytryptophan (5-HTP) [104]. Its precursor, tryptophan, is hydroxylated and decarboxylated to form serotonin [121]. Approximately 95% of serotonin in the body is produced in the gastrointestinal tract by enterochromaffin cells [122]. Thus, being a part of the immune system, serotonin could be useful in interpreting the gut-brain axis. Serotonin has been linked to inflammation, and increased level of serotonin is correlated with the progression of bone erosions in RA [123]. Serotonin levels were higher in RA patients compared to healthy controls; thus, it could be selected as a potential biomarker while observing the RA progression [124].

Gamma-Aminobutyric Acid (GABA)

Glutamine (Gln) is a highly abundant amino acid present in the central nervous system (CNS), which contributes to various metabolic pathways with a major role of being a precursor of certain neurotransmitter amino acids, namely the excitatory amino acids glutamate (Glu) and aspartate (Asp), as well as the inhibitory amino acid γ-aminobutyric acid (GABA) [105]. Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the CNS [125]. It is present in many foods, including green tea, yogurt, and kimchi [126]. Exogenous GABA has limited ability to cross the blood-brain barrier due to low lipophilicity and poor bioavailability; therefore, it may show its activity without causing side effects on the central nervous system [127]. In RA, GABA is associated with the downregulation of the p38 mitogen-activated protein kinase (p38 MAPK) pathway, which is triggered by stress factors including oxidative stress, UV light, and proinflammatory cytokines [128]. To be more specific, GABA affects reducing the proinflammatory cytokines that are related to the pathogenesis of RA such as IL-1 and IL-6 [128].

Amino Acids (Glutamate, Histamine, Glycine, Citrulline)

Glutamate (Glu), which is a nonessential amino acid, serves as the most abundant excitatory neurotransmitter in the nervous system [129]. Since glutamate receptors reside at the exterior of brain cells, this amino acid is closely related to the term “excitotoxicity”, defined as the death of neurons after intense excitement [130]. Circulating glutamate levels are related to bone erosions during early RA [131]. High glutamate levels might also influence synoviocytes, the cells located in the joint cavity [132]. The neurotransmitter histamine is mostly known for its role in the regulation of immune response and inflammatory processes [133]. The precursor of histamine is L-histidine, and histamine is produced from histidine through a reaction catalyzed by L-histidine decarboxylase [106]. Histamine is associated with various biological processes, including the regulation of energy homeostasis, immune function, sleep and wakefulness, gastrointestinal activity, and learning and

memory [134]. Histamine levels were higher in the serum and synovial fluid of the RA patients compared to healthy controls [135]. Also, a histamine receptor, histamine H4, present in the synovial tissue, might be involved in RA by affecting the MMP3, resulting in joint destruction [136]. Glycine is an inhibitory neurotransmitter in the spinal cord and the brainstem [137]. It helps regulate sensory information between the periphery and the central nervous system, and controls motor functions such as movement and respiration [137]. The precursor of glycine is serine and it can be converted into glycine via enzymatic reactions such as those catalyzed by the enzyme serine hydroxymethyltransferase [138]. A meta-analysis of RA metabolomics study identified that glycine levels were significantly lower in patients with RA compared with healthy controls across multiple clinical studies [139]. Citrulline, found predominantly in watermelon, is an α-amino acid that also plays an active role as an intermediate metabolite in cellular metabolism [140]. Citrulline is crucial for cardiometabolic health, and the minimum required intake amount for citrulline to be effective on the human body is approximately 3 g/day [141]. The process by which arginine is converted to citrulline in the presence of protein arginine deiminase (PAD) enzymes, specifically PAD2 and PAD4 [142], and Ca^{2+} is called citrullination. However, post-translational modifications such as citrullination, carbamylation, and acetylation might affect the immune system, and are associated with the pathogenesis of RA [143]. Autoantibodies against these citrullinated molecules are called anti-citrullinated protein autoantibodies (ACPA) [68]. Even though 20–30% of the RA patients are ACPA-negative, ACPA could still be considered a reliable biomarker for RA [68]. Carbamylation, also called homocitrullination, is a nonenzymatic chemical reaction of the ϵ-amino group of lysine that occurs in the presence of the metabolite cynate [144]. Formation of autoantibodies to carbamylated proteins has been linked to more severe bone erosions and higher morbidity and mortality in patients with rheumatoid arthritis. Also, carbamylated protein-DNA complexes are present at higher concentrations in RA samples [145].

Sphingolipids and Glycerophospholipids

Sphingolipids (SLs), which are lipids built on a sphingoid base backbone, are essential constituents of eukaryotic membranes and key signaling molecules [146]. Acyl chain length and degree of saturation are two important variables that differentiate the functionalities of SLs [147]. SLs are involved in cell growth, cell death, cell differentiation, cell proliferation, and inflammation [148]. Subgroups of SLs include ceramide, sphingosine 1-Phosphate (S1P), sphingosine, ceramide 1-phosphate (C1P), and sphingomyelin [148].

TNF-α and IL-1β, proinflammatory cytokines, play active roles in the SL metabolism. They activate sphingosine kinase, which increases S1P levels, affecting cell signaling [66]. S1P regulates immune cell transport through its interaction with S1P receptors [149]. S1P is essential for both innate and adaptive immune responses, and is strongly linked to inflammation [149]. S1P levels were found to be higher in the synovial fluid of RA patients than in osteoarthritis patients [150]. These increased S1P levels may enhance the proliferation rates of RA synoviocytes. *Lamiophlomis rotata*, a traditional Tibetan medicine, was able to reduce increased S1P levels that would result in retarded RA progression [66]. In addition to S1P, sphingosine, monohexosylceramide and ceramide levels were also higher in RA patients compared to controls [55,147].

Glycerophospholipids (GPLs) are the principal lipid molecules forming cellular membranes and contain glycerol at their backbone [151]. GPL was linked with IL-6 levels for RA patients [152,153]. The high IL-6 levels could be interpreted as an indicator of RA [152]. An inverse relationship has been observed between serum IL-6 levels and GPL levels. Moreover, phosphatidylethanolamine has a significant impact on GPL metabolism [154].

Discussion and Future Aspects

Heterogeneous autoimmune diseases are characterized by the disruption of pathways that mediate immunological tolerance, leading to the activation of autoreactive immune cells. Advances in biomarker discovery have substantially enhanced understanding of RA's autoimmune etiology, and an expanding body of mechanistic research is increasingly converging with clinical translation efforts to reshape how RA is diagnosed, monitored, and treated.

Evidence-Based Developments

Several mechanistic insights have now reached sufficient evidential maturity to inform clinical practice or late-stage translational research. An increasing body of research indicates that gut microbiota dysbiosis can influence immune responses and neuroimmune signaling, thereby promoting rheumatoid arthritis (RA)-associated inflammation through interconnected immune, barrier, and neural mechanisms. Alterations in microbial composition, such as increased abundance of pro-inflammatory species and reduced beneficial commensals, can disrupt intestinal immune homeostasis. This imbalance promotes activation of pro-inflammatory immune pathways, particularly the expansion of Th17 cells and increased production of cytokines such as IL-6, IL-17, and TNF-α, while reducing regulatory T cell (Treg) activity that normally suppresses excessive immune responses. At the same time, dysbiosis can impair intestinal barrier integrity, leading to increased permeability, which allows microbial components such as lipopolysaccharide (LPS) and other microbial-associated molecular patterns to enter the circulation and further stimulate systemic inflammation through innate immune receptors like Toll-like receptors [41,64,155]. These immune

changes are closely linked to neuroimmune signaling pathways. Gut microbes produce or regulate metabolites and signaling molecules, including short-chain fatty acids, tryptophan metabolites, and microbial-derived neurotransmitters, that can influence neural pathways such as the vagus nerve and modulate cytokine signaling between the gut, immune system, and central nervous system [156,157]. Dysbiosis-driven inflammatory mediators may therefore alter neuroimmune communication, amplifying systemic immune activation and contributing to chronic inflammatory processes that ultimately target synovial tissues in RA. Together, these mechanisms support the concept that gut microbiota imbalance can act as an upstream driver of immune dysregulation and neuroimmune signaling changes that promote RA pathogenesis. Thus, in individuals with RA, gut bacteria may be a promising diagnostic/prognostic candidate for predicting therapy outcomes. A better understanding of the changes in the gut microbiota and the brain metabolism of RA patients may facilitate the establishment of tailored and supportive therapeutic strategies, enabling safer and more effective patient care.

Computational modeling has also produced validated tools. A hybrid mathematical approach covering gene regulation, signaling and metabolism has been developed by Aghakhani *et al*. in 2022 [158]. A recent attempt to better understand the gut axis in RA has also been made through the reconstruction of in silico metabolic models of the gut microbiota [159]. Specific taxa like *Clostridium celatum*, *Enterobacter aerogenes*, *Enterobacter faecalis*, *Haemophilus parainfluenzae* and *Fusobacterium varium* at the genus level with high growth rates have been identified and interpreted as potential biomarkers of RA. *Clostridium perfringens* was found to be significantly higher in RA patients than in control groups, suggesting an association with RA disease activity [43]. Diet type is particularly important in regulating acetate and formate exchange metabolism in *Clostridium celatum* [159].

At the clinical implementation level (https://clinicaltrials.gov), several trials categorized under Personalized Lifestyle & Dietary Interventions are examining the effects of specific dietary patterns on RA disease activity and gut microbiota composition. These include studies of the Mediterranean Diet (NCT06758817, NCT05799768), a ketogenic diet (NCT05759585), and related nutritional approaches, collectively aiming to elucidate the triad of nutrition, microbiota, and RA. The trials categorized under Personalized Medicine & Diagnostics (NCT03555240, NCT03214263, and NCT06167226) either perform pharmacogenetic analysis to understand how genetic variations influence drug response in RA, or focus on identifying new biomarkers to promote personalized treatment of patients with Inflammatory Rheumatic Diseases, or investigate the response to personalized Ayurveda treatment protocols for various conditions, including RA, based on traditional diagnostic principles.

Five classes of molecular targeted therapies are currently available, i.e., targeting TNF, IL-6, T-cell activation, B cells, and JAK kinases, and the challenge is identifying reliable biomarkers to match each patient's pathogenesis to the right therapy. The PRE-RA Family Study is a randomized trial testing whether a personalized risk estimator (combining biomarkers, genetics, and lifestyle factors) can motivate RA-risk behavior changes in people with a first-degree relative with RA, before the disease develops.

Emerging and Forward-Looking Research Directions

A number of promising avenues remain at earlier stages of mechanistic inquiry or translational development and require further validation before clinical integration. Emerging evidence highlights the role of gut-derived exosomes, which are nano-sized extracellular vesicles released by intestinal epithelial cells and resident microbiota. These vesicles have been shown to carry microRNAs, lipopolysaccharide fragments, and bioactive proteins capable of traversing the intestinal barrier and entering systemic circulation, where they modulate macrophage polarization, activate NF-κB signaling in synovial fibroblasts, and amplify cytokine cascades central to RA pathogenesis [160]. Microbial outer membrane vesicles (OMVs) from *Prevotella copri* in particular have demonstrated the capacity to prime dendritic cells and promote Th17 cell differentiation and induce joint inflammation through an interleukin-6 (IL-6)-dependent pathway, directly implicating the gut-derived vesicular compartment in autoimmune joint inflammation [161]. Therapeutically, these pathways present compelling targets, i.e., probiotic restoration of neurotransmitter-producing taxa, exosome cargo engineering for targeted synovial drug delivery, and microRNA-based diagnostics derived from circulating gut exosomes, and are collectively positioning the microbial neuro-exosomal axis as a frontier of both mechanistic inquiry and translational innovation in RA.

Several metabolites warrant further mechanistic investigation. TMAO, a microbiota-derived metabolite generated from choline and carnitine, has been linked to inflammation and autoimmunity, including RA; however, the directionality and magnitude of its contribution to disease remain to be fully characterized [162]. SCFAs, neurotransmitters, sphingolipids, and glycerophospholipids are under active study with respect to their flux dynamics in RA, although their functional roles in immune modulation have not yet been fully established.

Future RA research can be structured across three interconnected tiers. At the mechanistic level, priorities lie in decoding the molecular drivers of synovial inflammation, including epigenetic reprogramming, fibroblast biology, and microbiome-immune interactions, using tools like single-cell genomics and spatial transcriptomics to uncover novel therapeutic targets. These findings feed into the translational tier, where next-generation bio-

logics, CAR-T therapies, and multi-omic biomarker platforms are being developed to stratify patients for treatments based on disease endotype rather than trial and error. Finally, at the clinical implementation level, integrating multi-omics biomarkers, microbiome profiling, and personalized therapeutic approaches into routine clinical practice may improve early diagnosis, patient stratification, and treatment response monitoring, ultimately advancing precision medicine strategies for RA management. A cutting-edge trial is Regulate-RA (SBT777101-01), a first-in-human study of a personalized cell therapy. The therapy involves collecting a patient's own immune cells (regulatory T cells), modifying them to carry a surface protein targeting inflammation-related markers, and reinfusing them. It is intended for adult patients who have already failed at least three approved biologic or targeted synthetic therapies.

Looking further ahead, the goal is to embed these advances into routine care through AI-assisted decision support systems and treat-to-target protocols guided by dynamic biomarkers and pragmatic trial designs. It is hoped that these efforts will collectively shift the RA field toward drug-free remission as an achievable standard rather than an aspirational exception.

Conclusion

Rheumatoid arthritis is a complex, heterogeneous autoimmune disease in which no single biomarker captures the full spectrum of its pathogenesis, progression, or treatment response. The most clinically informative advances are emerging from the convergence of multiple biological layers (genomic, proteomic, metabolomic, and microbiomic) rather than from any single modality in isolation. Gut microbial dysbiosis, operating through the gut–immune–joint axis, is now recognized not merely as a correlate of systemic inflammation but as a potential upstream driver that initiates autoimmune responses and modulates neuroimmune signaling. Specific microbial taxa, barrier integrity markers, and disrupted metabolic pathways collectively offer candidate biomarkers for disease classification (severity), prognosis, and treatment monitoring, while computational modeling and clinical trials are beginning to translate these findings into clinical practice.

Despite this progress, several important challenges remain. Inter-study variability in microbiome composition, methodological heterogeneity, and the absence of standardized multi-omic pipelines continue to limit the clinical transferability of current findings, and most candidate biomarkers still require prospective validation in large, well-characterized cohorts. Ultimately, a more integrated understanding of the gut-immune-brain axis, combined with precision medicine approaches that account for individual variation in microbiome composition, genetics, and lifestyle, holds the greatest promise for improving early diagnosis, patient stratification, and long-term remission rates in RA.

Availability of Data and Materials

Not applicable.

Author Contributions

OO: Conceptualization, Formal analysis, Methodology, Writing. DEG: Conceptualization, Formal analysis, Methodology, Writing. KOU: Conceptualization, Supervision, Writing—Review & Editing. All authors gave final approval of the version to be published. All authors are responsible for all aspects of the work and approve the submission in its current form.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research is funded by the Scientific Research Projects (BAP) Coordination Unit (Project No 19988).

Conflict of Interest

The authors declare no conflict of interest.

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