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How does the gut microbiome impact rheumatoid arthritis?

Xiyan Xie

Suzhou High School-SIP, Suzhou, China

avaxie2008@hotmail.com

Abstract. This dissertation investigates how the gut microbiota impacts Rheumatoid Arthritis (RA), a project that spans three core disciplines: rheumatology, microbiology, and immunobiology. It first outlines the key changes in the gut microbiome observed in rheumatoid arthritis. It also examines possible mechanisms linking the gut to joint inflammation, such as impaired intestinal barrier function and ongoing inflammatory processes. In addition, the potential use of the gut microbiome as a diagnostic biomarker is considered. The findings demonstrate the effects of gut microbiome dysbiosis on the progression of rheumatoid arthritis, providing a connection to clinical diagnostics and therapeutics. The literature review elaborates on the autoimmune nature of RA, details its inducing factors—genetics and the environment—and explains how serum biomarkers and the mucosal hypothesis link inflammatory responses to microbial dysbiosis, in turn triggering abnormal autoimmune activity and ultimately leading to the onset of the disease. The discussion section conducts a two-sided analysis of existing medical technologies for RA diagnosis and treatment, evaluating their promising prospects. For instance, the detection of several bacterial taxa with significant abundance changes enables the identification of the disease in patients at the early stage or even before its onset, and targeted probiotic supplementation and drug administration can be adopted to ameliorate microbial dysbiosis. At the same time, the limitations of existing studies, such as one-sided research outcomes caused by the failure to account for all confounding variables, are also pointed out. The dissertation concludes that current medical advances have achieved effective improvements in mitigating RA's adverse impact on human health. However, the presence of numerous uncertain variables means that scientists have not yet developed a fully validated and comprehensive diagnostic and therapeutic protocol that can be fully trusted. The compilation of this dissertation is based on the analysis of literature on RA itself and related clinical test reports, together with personal perspectives formed throughout the research process.

Keywords: rheumatoid arthritis, gut microbiome, dysbiosis, biomarker, diagnosis and prediction

1. Introduction

RA is a long-term autoimmune condition that is marked by inflammation of the synovial joints, gradual joint damage, and a range of complications affecting other parts of the body. Millions of people around the world are diagnosed with—and continue to live with—this condition, which is most commonly known for causing irreversible joint damage. In addition to this, it also elevates the risk of comorbidities including cardiovascular diseases, osteoporosis and other infections. In spite of significant advances in disease-modifying antirheumatic drugs and other biological treatments, the precise mechanisms responsible for RA remain poorly understood.

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Therefore, identifying more pathogenic factors is critical to help early diagnosis and develop more effective therapeutic strategies.

The gut microbiome refers to a vast number of microorganisms that live within the digestive tract. It plays an important role in the body's metabolic and immune functions, as well as also maintaining the gut lining. If the balance is disturbed, it leads to a condition known as dysbiosis, that has been associated with several inflammatory and autoimmune diseases. Indeed, there is some evidence to suggest that such alterations in the microbiome may be implicated in the induction and progression of rheumatoid arthritis, potentially via effects on the immune system.

Toward the end of the 20th century, scientists began to propose that the gut microbiome may be implicated in rheumatoid arthritis. At the time, research was limited due to absence of sophisticated technology, and so most studies were based on minimal culture techniques and their conclusions were not imprecise. However, during the last two decades, the development of technologies like 16S rRNA sequencing have enabled more in-depth studies of the microbiome. Consequently, some studies have reported marked differences between the gut microbiota in rheumatoid arthritis patients and healthy control groups. In particular, there appears to be a higher abundance of pro-inflammatory bacteria and a reduced presence of beneficial species in RA patients. The concept of the "gut–joint axis" has thus been proposed to explain this, although there is still some controversy in the field since different studies have reported different microbial markers, while results can also be influenced by external factors.

Consequently, an increasing body of evidence suggests that alterations in the gut microbiota may be involved in the pathogenesis of rheumatoid arthritis. One possible explanation is that an imbalance in gut bacteria influences the intestinal barrier, perhaps increasing its permeability. This may allow microbial products to enter the blood, stimulating immune responses and contributing to systemic inflammation. Moreover, certain bacteria have been found to have been enriched or depleted in RA patients. The genus *Prevotella copri* has been singled out for particular attention, given its repeated association with early-stage RA and its considered role in driving pro-inflammatory immune responses.

Nevertheless, the precise importance of key microbes like *P. copri* is still debated. No conclusions can yet be made on causal relationships between *Collinsella* and *Lactobacillus* and RA. So far, only correlations of abundance have been observed, and there's no direct evidence for a mechanism of pathogenesis. It remains to be determined how host genetic background (e.g. HLA-DRB1) modulates gut microbial profile, and how environmental factors such as smoking and dietary interact with host genome and microbiome. It is also not clear whether dysbiosis is a cause or consequence of RA.

This research is of great importance as RA, a highly disabling chronic disease, places a substantial burden on social and healthcare systems for diagnosis and care. Gut microbiome research may contribute to early screening, diagnosis and treatment of RA, reducing late-stage disability rates and medical resource consumption, while providing synergistic ideas for preventing RA-related comorbidities such as osteoporosis and cardiovascular diseases. In addition, gut microbiome offers novel drug targets (e.g., specific microbes and microbial metabolites) for the biopharmaceutical industry, driving the development of therapeutics like probiotics and engineered bacteria, and boosting the growth of related industries like gut microbial detection and faecal microbiota transplantation. This could help to create new healthcare economic growth and facilitate the innovative upgrading of the biopharmaceutical industry.

This dissertation is divided principally into two main parts: a literature review and a discussion. The literature review summarises current research on RA, with a focus on key gut microbiota that show significant changes in abundance and the mechanisms through which they may contribute to the disease. The discussion then examines recent progress in RA diagnosis and prediction, highlighting the potential of microbial

biomarkers for early detection. It also highlights several current limitations, including the lack of standardised biomarkers and the influence of confounding factors such as diet and medication. Based on the evidence, a more critical perspective is then considered.

2. Literature review

2.1. What is rheumatoid arthritis

RA is a multifactorial condition, strongly influenced by both genetic predisposition and environmental determinants [1]. Among these, the microbiome is increasingly recognised as a key contributing factor. It is a serious autoimmune disease that afflicts 1% of the world population. The term "genetically related" refers to the familial inheritance risk (seropositive) of RA, which is estimated to be around 50%. In particular, first-degree relatives have the highest risk. HLA-DRB1 is the primary genetic contributor, encoding the HLA-DR protein, which also presents autoantigens. The genetic association of RA has been positioned into the specific regions beside the HLA-DR peptide-chain acid 70-74, called "shared susceptibility epitope [2]. In individuals with seropositive conditions, key autoantibodies include Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA). ACPA can recognise a range of citrullinated peptide epitopes, while RF remains a characteristic marker of the disease. The interaction between immunogenetic susceptibility and environmental exposures is thought to drive disease progression. At the same time, environmental factors include exposure to textile dust, periodontal disease, obesity, the use of oral contraceptives, and bronchiectasis, which can affect mucosal surfaces across the respiratory, oral, intestinal and genitourinary systems [3, 4]. Among these risk factors, gut microbiota has become a key factor that has attracted much attention.

2.2. Gut microbiome

The gut microbiome in healthy individuals performs a range of essential functions that support overall health and survival. For instance, it contributes to the production of several vitamins, including cobalamin (B12), biotin (B7), folate, thiamine (B1) and vitamin K [5]. It is also involved in processes such as detoxification, the regulation of lipid metabolic processes and the prevention of colonisation by pathogenic microorganisms. In addition, Short-Chain Fatty Acids (SCFAs), which are produced by gut bacteria, can be used as an energy source and may also affect gene expression [6]. Overall, the gastrointestinal tract contains a large and diverse microbial community, with trillions of microorganisms and around 1,500 different species.

Gut bacteria are usually divided into a few major phyla. Bacteroidetes are Gram-negative anaerobic bacteria and include genera such as *Bacteroides*, Parabacteroides and *Prevotella*. Firmicutes are mostly Gram-positive and include genera like *Roseburia*, *Ruminococcus*, *Streptococcus* and *Faecalibacterium*. Another important group is Proteobacteria, which includes the family Enterobacteriaceae and the genus Escherichia. In addition to bacteria, the gut microbiome also includes other microorganisms such as archaea, fungi, viruses and bacteriophages. Each of these occupies a specific ecological niche in the gut. They interact with each other and with the host. This complex ecosystem helps maintain a balanced internal environment under normal conditions.

2.3. Intestinal microbiome in RA

Rheumatoid arthritis patients suffer from an unbalanced bacterial flora. A great deal of research on the first-degree relatives' faecal microbiota was conducted. Compared with asymptomatic individuals without autoantibodies, RA patients at the preclinical stage (those who are positive for rheumatoid factor or show RA

symptoms) have a significantly changed microbiome. One remarkable feature, identified in a recent peer-reviewed study, is the increased abundance of Prevotellaceae [7]. Meanwhile, another peer-reviewed study likewise reported an expansion of Prevotellaceae in patients from 6 weeks to 6 months after diagnosis. At the same time, a reduction in Bacteroides species and other beneficial microorganisms has also been observed [2].

Further analysis suggested that HLA-DR molecules can present peptide fragments derived from a 27-kDa protein associated with *P. copri*. In the study by Pianta et al. [8], around 42% of patients with rheumatoid arthritis showed a T cell response to these peptides. Both newly diagnosed and established patients were also found to have IgA-related antibody responses, which appeared to correlate with Th17 cytokine production. In addition, some patients showed IgG responses against *Prevotella*. Yet, this pattern does not seem to be common in other rheumatic diseases or in healthy individuals, where antibodies against *Prevotella* are rarely detected [9]. This difference may suggest a more specific link between *P. copri* and rheumatoid arthritis, although the exact mechanism is still not fully understood.

Although this bacterial family is often regarded as a key contributor to microbial imbalance in patients with RA, the expansion of less abundant gut microorganisms may also represent a notable feature of the condition. Research in 2016 showed that compared with normal individuals and the first-degree relatives, the biodiversity of gut microbiome in RA patients has been reduced, and in particular *Collinsella and Eggerthella* [10]. Abundant *Collinsella* also relates to the serum concentrations of metabolites aminoadipic acid and asparagine, as well as the production of IL-17A closely [10]. Even more recently, evidence linking gut microbiota to the presence of ACPAs suggests a potential role for microbial factors in the development of autoimmune responses. A recent clinical study from China found that microbial imbalance appeared to be more pronounced in ACPA-positive rheumatoid arthritis patients, compared to those who were ACPA-negative [11].

2.3.1. Prevotella copri

Among the bacterial groups mentioned above, *Prevotella*, and particularly *Prevotella copri* (*P. Copri*), has received the most attention. Several studies have found that RA is related to gut microbiome imbalance, but the results of relevant research are different. Several peer-reviewed clinical studies have reported that, compared with healthy controls, individuals with early rheumatoid arthritis exhibit an increased abundance of *Prevotella* [2, 7]. Among the RA patients who are given treatment, theoverbreeding of *P. copri* was not found [12, 13]. Moreover, using recent metagenomic shotgun sequencing [14], other species of *Prevotella* also increase, not only for *P. copri*, which takes part in potential mechanisms of pathogenesis, including inducing inflammatory responses and molecular mimicry between microbial and host epitopes [15].

Evidence from controlled animal-model studies using germ-free SKG mice have shown that mono-colonisation with *P. copri* can induce arthritis, along with increased levels of Th17 cells and related cytokines such as IL-17 and IL-23 [15]. Similarly, SKG mice colonised with Prevotella-dominated microbiota from rheumatoid arthritis patients developed more severe disease, with higher levels of Th17 cells and associated cytokines. Overall, these data illustrate that dysbiosis precedes arthritis and *Prevotella*, especially *P. copri*, may prompt the development of arthritis [16].

The pro-inflammatory role of *P. copri* has been supported by test results not only from experimental models. Research by Pianta et al. [8] identified a peptide derived from *P. copri* that is capable of binding to HLA-DR molecules and triggering Th1-mediated inflammatory responses in patients with early rheumatoid arthritis. Further evidence indicates that both IgA and IgG antibodies targeting *P. copri* are present in individuals at early stages of the disease, and these immune responses appear to correlate with levels of Th17-related cytokines and ACPAs. Moreover, *P. copri* 16S rDNA has been detected in the synovial fluid of some patients, suggesting a potential link between gut microbial activity and joint inflammation. However, it is still

unclear whether intestinal *P. copri* is directly responsible, as no clear correlation has been shown with its derived proteins. One possible explanation is that *P. copri* antigens and N-acetylglucosamine-6-sulfatase have almost the same structure, a known autoantigen in rheumatoid arthritis [9]. This could mean that, in genetically susceptible individuals, immune-triggered responses in the gut may later affect the joints. While this idea is plausible, the exact mechanism is still not fully understood [17].

Meanwhile, some other studies have also shown that the role of *Prevotella* is not entirely straightforward. They suggest that certain species, such as *Prevotella histicola*, may reduce disease severity in mouse models [18]. Other studies have shown that *Prevotella* is also commonly found in healthy individuals with beneficial effects [19]. These findings give us a contradictory picture, which suggests that other factors, including host genetics and interactions with different microbes, are likely to be involved. More long-term studies would be useful to clarify its role in rheumatoid arthritis.

2.3.2. Collinsella

Yet *P. Copri* is not the only microbial group that may be involved. Other genera, including *Collinsella*, *Lactobacillus*, *Eggerthella and Actinomyces*, have also been associated with RA in some peer-reviewed microbiome studies [20, 21]. This points to a more complex interaction between different microbial species, as well as genetic and environmental factors, in the development of inflammatory arthritis.

For instance, peer-reviewed experimental research has reported that *Collinsella aerofaciens* may enhance intestinal permeability in rheumatoid arthritis mouse models, possibly through reducing the tight junction protein expression. It may help explain how changes in the gut microbiome contribute to disease progression [20]. In addition, several pro-inflammatory mediators, including IL-17A, CXCL1, CXCL5 and NF-κB1, have been reported to increase in response to *Collinsella aerofaciens*, together with an increased incidence and greater severity of arthritis. All these findings suggest another possible mechanism by which gut dysbiosis may contribute to rheumatoid arthritis, especially through increased intestinal permeability [15]. It has also been proposed that the expansion of *C. aerofaciens* may promote intestinal inflammation and compromise epithelial barrier integrity. Consequently, bacterial antigens may translocate into the circulation, potentially initiating immune responses at distant sites such as the joints.

In contrast, some studies have found reduced levels of beneficial bacteria such as *Roseburia* and *Faecalibacterium* in certain rheumatoid arthritis patients [20]. These bacteria are known to produce butyrate, which has anti-inflammatory effects and helps maintain the integrity of the intestinal barrier.

All the collected evidence supports the idea that the disruption of the gut barrier may be a relevant factor concerning the development of rheumatoid arthritis. The evidence also indicates that the gut microbiome might become a potential target for future treatments, though this will require research to identify which exact bacteria or metabolites are best suited to protect the intestinal barrier. Butyrate has been shown to reduce arthritis symptoms in Collagen-Induced Arthritis (CIA) mouse models [22], which may be explained by the fact that butyrate affects immune cells in a way that helps to reduce inflammation, although its exact role is not simple. This is because it is also being linked to IL-23 and TH-17 cell differentiation, both of which are also believed to contribute to inflammation. Overall, although maintaining gut barrier integrity may indeed prove to be a promising direction of research, more evidence is needed before it can consider treating it as a reliable target in RA.

2.3.3. Lactobacillus

Lactobacillus provides another example of why RA-related dysbiosis is difficult to interpret. An increased abundance of *Lactobacillus* has been reported in early and established RA patients [23, 24]. Following treatment, the gut and oral microbiome appear to be disrupted, though they may become partially normalised over time. At the same time, some studies have observed a decrease in *Lactobacillus* levels in established

disease [20], which indicates a level of inconsistency in their findings. Moreover, *Lactobacillus* salivarius, which is present in the oral cavity and the gut alike, has also been linked to disease activity, even though the exact nature of this relationship is still somewhat mysterious [24].

Evidence from animal models broadly supports a link between *Lactobacillus* and arthritis. For example, monocolonisation with *Lactobacillus* bifidus has been shown to induce arthritis in mice [25], and increased levels of *Lactobacillus* were detected in CIA mice prior to disease onset [26]. This may suggest a role in early immune activation. Like *Prevotella*, certain *Lactobacillus* species have been proposed to contribute to disease development by promoting Th17 responses and activating Th1 cells [15]

At the same time, there is also evidence in the opposite direction. Some investigations have demonstrated that supplementation with *Lactobacillus* species can actually reduce inflammation and even improve arthritis outcomes, at least in animal models [7]. For example, treatment with *Lactobacillus casei* was found to restore gut microbial balance and reduce both disease severity and pro-inflammatory cytokine levels in rat models [27]. Similarly, multiple separate *Lactobacillus* varieties have been reported to decrease Th17 cell levels in CIA mice. This resulted in a milder disease phenotype [20]. Nonetheless, evidence from human studies is less convincing. A peer-reviewed systematic review and meta-analysis found that although *Lactobacillus* supplementation may lower IL-6 levels, it does not appear to result in significant clinical improvement in patients [28].

In conclusion, these mixed findings suggest that the role of *Lactobacillus* in rheumatoid arthritis is complex and not yet fully understood. It may depend on specific species, disease stage, or host factors, and therefore should be interpreted with caution. Further investigation is required to elucidate its precise role.

2.4. Mechanisms linking gut mucosa to RA

2.4.1. Autoantibody production

Having considered several bacterial groups associated with RA, the next question is how changes in the gut microbiome might actually contribute to joint inflammation. Gut inflammation and the reduction of its barrier function (both of which have been detected in RA patients) promote the development of clinical RA. The connections between them may be because both are mediated by non-mutually exclusive pathways. Firstly, the gut with inflammation will produce autoantibodies. Secondly, the pro-inflammatory immune cells triggered by intestinal tissue can be transferred into each part of the body and joints [18].

At this stage, the immune system begins to produce autoantibodies. Evidence from peer-reviewed clinical and review studies shows that, even before the clinical onset of rheumatoid arthritis, levels of self-reactive IgA antibodies are already elevated in the serum [29, 30]. This is consistent with the mucosal hypothesis, which suggests that early immune dysregulation may originate at mucosal surfaces. Since IgA is primarily produced at sites such as the gut, it is possible that RA-associated autoantibodies are initially generated in these regions before becoming detectable systemically [29]. Interestingly, peer-reviewed evidence seems to suggest that, even before the onset of clinical RA, an increase in the concentration of rheumatoid factor in the serum is associated with inflammation of the mucosa and periodontal disease [31, 32]. Moreover, these findings highlight a potential link between inflammation at mucosal sites and the early production of autoantibodies, which may eventually contribute to the development of autoimmunity and the initiation of rheumatoid arthritis [33]. More recent peer-reviewed research has extended this timeline considerably. For instance, a study published in 2020 reported that differences in IgA rheumatoid factor levels could be detected up to 14 years before diagnosis, and several years before conventional markers like rheumatoid factor turned positive. In addition, both IgA and ACPAs have been observed approximately six years prior to the onset of clinical

symptoms. This means that the preclinical mucosal process of the disease promotes the transformation to the clinical RA [34].

Surprisingly, the gut tissue of patients also showed the increasing concentration of IgA and IgM—they can recognise the antigen food [35]. Overall, these data showed that the mucosal surface, especially the gut, is the site that produces antibodies in response to outside stimuli, including the antigens from food sources and self-antigens of susceptible individuals.

2.4.2. Immune cells originating from mucosal tissues

Autoantibody production is one possible gut–joint pathway, but immune cell movement from the gut to the joints may provide another explanation. Alterations in intestinal barrier function, together with increased gut permeability, may facilitate the migration of inflammatory immune cells from the gut to the joints. It is possible that immune responses first triggered in intestinal tissues could later contribute to inflammation elsewhere in the body. Some pieces of research support cell transfer into joints, such as the intestinal activated B cells, which can stick to the gut and Synovial hyperendothelial micro veins efficiently, but do not stick to the high endothelial micro veins in the peripheral lymph nodes. This signifies that the immunity cells from the gut may enter the joints [36].

Among RA patients, several natural immunity cells from the origin of synovial membranes have been activated and expanded, which supports the point of the gut-joint cell axis. Pathogenic microorganisms have been shown to increase the production of zonulin through CXCR3 and MYD88-dependent signalling pathways, which may in turn promote a more inflammatory phenotype in epithelial cells [37]. Based on peer-reviewed mechanistic research, Zonulin has been linked to the disruption of epithelial tight junctions, which may increase the passage of microorganisms and their metabolites, such as ATP, as well as molecules that activate Free Fatty Acid Receptor 2 (FFAR2), into the submucosa [38].

Dendritic cells may respond to these changes by encouraging the differentiation of T cells into IL-17–producing Th17 cells. At the same time, bacterial metabolites, including FFAR2 agonists, can directly activate group 3 Innate Lymphoid Cells (ILC3s), leading to the secretion of IL-22. In addition, microorganisms are able to stimulate innate immune cells such as macrophages and Mucosa-Associated Invariant T (MAIT) cells, further contributing to the overall inflammatory response. This will lead to the amplification cascade reaction and cause T cells of intestinal inflammation, macrophages, and the local activation and differentiation of ILC3s [39]. Th17 cells, ILC3s and MAIT cells may enter the bloodstream, increasing the likelihood that inflammatory signals are carried to the joints. This movement of immune cells could provide a link between local immune activation in the gut and inflammation at distant sites.

3. Discussion

The literature review has demonstrated how changes in gut microbiome are linked to RA through a number of potential pathways, including immune activation, changes to the gut barrier function, and changes in specific bacterial groups. Moving on, the discussion will now consider and evaluate what these findings mean for practical application, and in particular, whether or not gut microbiome research can meaningfully support the diagnosis, prediction, and future treatment of RA.

3.1. Possible clinical applications

3.1.1. Diagnosis: gut microbiome characteristics as the microbial biomarkers of RA

The key diagnostic issue is whether changes in the gut microbiome are associated with RA alone or whether they are clear and consistent enough to be able to help identify and diagnose the disease earlier.

Several clinical studies have reported clear differences in the composition of the gut microbiome between individuals with rheumatoid arthritis and healthy controls. This suggests that changes in the gut microbiota may be a characteristic feature of the disease. Some intestinal bacteria can induce autoimmune responses in genetically susceptible animal models [39]. The imbalances of specific bacterial lineages can alter the immune characteristics of hosts, thereby promoting the development of RA [9]. The mouse model was employed in this study to investigate the distribution and abundance of gut microbiomes, serving as a surrogate to simulate and assess human disease conditions. Researchers reported that the abundance of the *Prevotella*, especially the *P.copri*, was significantly increased.

These are consequential findings. If the same strand of bacteria is repeatedly found in higher levels in RA patients, it offers researchers a signal for how to identify a clear pattern that is linked to this disease. Therefore, as one of the bacteria that shows more obvious and significant change, it would be reasonable for researchers to focus their attention more specifically on *P. copri*.

At the molecular level, these bacteria's antigens are capable of inducing cross-reactive autoantibodies by sharing homologous sequences with human joint tissue-related proteins. It causes the immune system to mistakenly attack joint tissues. Simultaneously, the lipopolysaccharide LPS, which is found within its cell wall, functions as a key inflammatory signal molecule, binding to TLR4 receptors on immune cells and activating the downstream NF-κB inflammatory pathway. This serves to stimulate a release of pro-inflammatory factors, specifically Tumor Necrosis Factor-α (TNF-α) and Interleukin-6 (IL-6), and thereby triggers a systemic inflammatory response. In fact, this indicates that *P. copri*. It is not only useful for diagnosis owing to its higher levels, but also because it is likely involved in the inflammation that is detected in RA patients.

However, it is unlikely to be able to diagnose RA simply by looking at a single bacterium. Instead, researchers should target a wider range of bacterial imbalances. The abundance of certain beneficial bacteria, such as Bacteroides and *Faecalibacterium*, was reduced. In addition, the microbial diversity in mice had already shown a dropping trend before the onset of the disease, which was specifically reflected in "enrichment of pro-inflammatory microbiota and reduction of anti-inflammatory microbiota". This experiment used the CIA mouse model, which was established in 1977.

After nearly 50 years of application and testing, it has become the "gold standard" in scientific research for studying the pathogenesis of RA and corresponding drug treatments, so this model is reliable. Moreover, the "cross-contamination" or synergistic effect between oral and gut microbiomes enhances the diagnostic values, too. For example, the colonisation rate of *Porphyromonas gingivalis* in the oral cavity of RA patients has obviously risen. This bacterium can induce protein citrullination by producing Peptidylarginine Deiminase (PAD) and further triggers autoimmune responses. The antibody level of this enzyme (PPAD) is positively correlated with the abundance of *P. copri* in the gut, and the detection of their combination can improve the sensitivity of RA diagnosis.

Before this onset of disease, the traditional diagnosis of arthritis mainly relied on clinical symptoms, autoantibodies (such as ACPA and RF for RA) and imaging examinations, which can only detect the disease when it has progressed to a clinically significant stage. However, some early-stage patients may lack typical symptoms or show a negative result of autoantibodies, making it impossible to identify RA in the early stages or even before morbidity, resulting in delayed diagnosis.

Fortunately, the examination of gut microbiomes can improve this drawback. Studies have found that around 30% of the early-stage RA patients had an imbalance of gut microbiomes even when ACPA tests are negative, and this can be observed by the increased abundance of *Collinsella* and *Eggerthella* [10, 11]. This microbial change is positively correlated with the degree of joint inflammation. These studies were

presumably conducted after scientists discovered that the emergence or abnormality of relevant biomarkers may precede the clinical onset of RA, which demonstrates the foresight of scientists at that time in understanding disease progression. They considered more possibilities along the disease timeline, thereby gaining valuable time for the treatment and rehabilitation of patients. For patients with Spondyloarthritis (SpA), who are also the typical groups that used to be diagnostic samples. Around 50% have subclinical intestinal inflammation.

An increased presence of *E. coli* 2A in the gut microbiome has been observed prior to detectable imaging changes in the sacroiliac joints, suggesting it may have potential as an early indicator of disease. In addition, functional features of the gut microbiome, such as its capacity to produce Short-Chain Fatty Acids (SCFAs) and levels of Lipopolysaccharide (LPS), may also serve as supplementary markers for diagnosis. For example, the number of SCFA-producing bacteria decreased in the gut of RA patients, leading to damage to intestinal barrier function and an increase in LPS levels. This indicator is obviously correlated with the Disease Activity Score 28 (DAS28) and can be used in evaluating disease severity. Therefore, the gut microbiome's greatest diagnostic-related value is likely to be as an extra piece of evidence that helps to support blood tests, imaging, and other clinical symptoms. Although by itself the evidence is not conclusive, it can play a key supporting role at the stage of diagnosis.

3.1.2. Prediction: microbiota changes as early warning signs for RA risk and disease progression

Diagnosis focuses on identifying RA once it has already started, but prediction tries to determine whether microbiome changes may be able to warn doctors about the future risk of this disease's progression.

Because of the high heritability of RA (40%–60%), if not treated promptly, it can cause complications involving all organs. Experts have discovered that the disorder of gut microbiomes has existed in the preclinical stage of arthritis, which has taken the control and prediction of the disease to a new level. They investigated the faecal microbiomes of First-Degree Relatives (FDRs) of RA patients and found that high-risk individuals who are ACPA-positive or have arthralgia symptoms have significantly higher abundance of *Prevotellaceae* than those who are asymptomatic [1]. This dysbiosis can be detected 5–10 years before the onset of RA symptoms. Besides, when the abundance of *P. copri* is over 5%, the risk of developing into RA in the future increases by more than 3 times [7]. This suggests that *P. copri* can be a useful early warning marker, particularly for individuals who already show higher genetic or immune risks of developing RA.

However, prediction is only convincing if any microbiome changes are not just present before RA takes hold, but also if it can explain their role in triggering the disease process. Indeed, scientists have explored whether there is a "trigger" for the onset of RA. They transplanted the faecal microbiomes from RA patients into germ-free SKG mice, which significantly increased the incidence of arthritis. At the same time, the transplantation into healthy individuals had no such effect, suggesting that gut microbiomes are a "potential trigger" for the disease.

Moreover, prediction is not necessarily limited only to identifying whether RA will or will not appear. But it may also provide an estimate as to how severe the disease may become, as well as how well a patient is likely to respond to treatment. In that sense, the status of gut microbiomes can potentially also evaluate the rate of disease progression and any possible therapeutic effect.

RA patients with a high abundance of *P. copri,* accompanied by reduced *Faecalibacterium* in the gut, get faster joint erosion progression, with a 2.5-fold higher risk of bone destruction within 5 years compared with other patients. The composition and diversity of the gut microbiome also appear to be associated with response to Methotrexate (MTX) treatment. A study recruited 27 untreated NORA patients, 39% were MTX-Responders (MTX-R) and 61% were MTX-Non-Responders (MTX-NR). Through the 16S rRNA gene sequencing and metagenomic sequencing, the abundance of Clostridia had an obviously increased and that of

Bacteroidia had an obviously decreased ($p < 0.05$; $q < 0.2$), which illustrated that dysbacteriosis still existed. This discovery further promoted the production of robust basic predictive models.

If there is a decrease in the abundance of these bacteria after treatment, it suggests that the disease has improved. Conversely, continuously rising may indicate progression to chronic inflammation. In addition, probiotic intervention trials have shown that supplementation with Bifidobacterium can improve the gut microbiome's structure in some RA patients, and its efficacy is associated with the baseline abundance of beneficial bacteria in the patients' gut.

The evidence, therefore, suggests that microbiome changes may be useful for building a much more personalised individual prediction system for RA. At the same time, they are most likely to be effective when combined with other risk factors, including the patient's family history, other symptoms and treatment response, rather than being used alone.

3.2. Limitations

After considering the potential value of gut microbiome research for RA diagnosis, prediction and treatment, it is important to balance this with several limitations. Although the evidence is promising, microbiome-based approaches are still affected by inconsistent findings, confounding factors and uncertainty over causation, meaning they are not yet reliable enough to be used independently in routine clinical practice.

3.2.1. Diagnosis

The first point is that the characteristics of dysbacteriosis are a lack of unity. Gut microbiome alterations in patients with arthritis have a wide range, and a unified diagnostic microbial signature has not yet been formed. For instance, some studies reported a rising abundance of *Lactobacillus salivarius* in RA patients, whereas another study targeted at Asians found a decreased abundance of *Lactobacillus* in RA patients. Such results may depend on the genetic background, dietary structure, geographical environment, and others. Consequently, people cannot give a definite impact of RA on the gut microbiomes, which reduces the precision of targeted therapy.

Yet the literature has failed to account for these factors, which necessitates a controlled variable group survey. This affects the accuracy of current studies, and readers will gain one-sided resources. Furthermore, the gut microbiomes' composition of RA patients does not differ distinctly from that of healthy individuals. Healthy people may also illustrate a rising abundance of *P. copri*, but do not develop into arthritis. This means insufficient specificity of single microbial markers and further limits diagnostic specificity. These research results lack uniformity; meanwhile, the duration, dosage and efficacy of the intervention are still unclear, which restricts the widespread use of microbial targeted therapy in clinical practice.

Another limitation is that the results of microbiome testing may be shaped and influenced by many factors other than RA. This makes it difficult to define the relationship with arthritis. As for diet, a high-fiber diet can increase the abundance of Short-Chain Fatty Acid (SCFA)-producing bacteria, while a fat diet may promote the growth of pathogenic bacteria. About 40% of patients with RA had changes in dietary preferences, so the alteration of microbiomes may not be caused by the disease itself at all but by the diet. And the pharmacological factors also cannot be ignored—Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), Disease-Modifying Antirheumatic Drugs (DMARDs), and other medications that are commonly used by RA patients can directly alter gut microbiomes' composition. For example, methotrexate reduces the abundance of *Enterobacteriales*, and sulfasalazine decreases Clostridium perfringens. These alterations of the drug-induced microbiomes may cover up the microbial characteristics of the disease itself. Furthermore, environmental factors such as smoking, obesity and periodontal disease will not only affect the gut microbiomes but also are risk factors for arthritis, further confounding the direct association between microbiomes and disease, which

also becomes a challenge to distinguish whether the disease is caused by dysbiosis or causes dysbiosis. That's the obstacle to treating accurately.

The final diagnosis-related limitation concerns the fact that these diagnostic issues will inevitably affect treatment decisions when doctors are trying to predict which patients will respond well to a particular drug. For instance, although MTX is a foundational and core therapeutic drug worldwide, its bioavailability has significant individual differences. More than 50% of patients with moderate to severe RA show no response or inadequate response to MTX for symptom improvement. The reasons for the distinct treatment response still remain unclear. Studies in mice have demonstrated that the biotransformation of MTX is altered in germ-free or microbiome-depleted mice, showing that this drug cannot deal with large individual variations in the gut microbiomes.

Indeed, current gut microbiome detection mainly relies on 16S rRNA sequencing and metagenomic sequencing, yet different studies use different methods, sequencing platforms and bioinformatic analysis pipelines that lead to poor comparability of results. For example, 16S rRNA sequencing can only identify taxa at the genus level and cannot distinguish different species within the same genus (e.g. *P. copri* and other *Prevotella* species). Although metagenomic sequencing enables reaching a precise species identification, its high cost limits widespread clinical application. In addition, sampling sites (feces, colonic mucosa) and sampling time (fasting, postprandial) also influence the result. The consistency of microbiome abundance between faecal and colonic mucosal samples is only around 60%. But the change in RA patients' gut microbiome differs significantly between active and remission stages. The lack of standardised sampling protocols and reference thresholds reduces the reliability of diagnostic results.

This leads us to conclude that currently, microbiome-based diagnosis still needs to secure a higher level of standardisation and reliability before it can be reliably used in clinical medical practice. Despite this, it may still be realistic to view microbiome testing as a secondary supporting tool, though it will not replace established diagnostic methods.

3.2.2. Prediction

Prediction is even more challenging than diagnosis. Because it demands a forecast for the future risk of RA or the later disease progression well in advance of these outcomes becoming certain, there are many factors and variables that can limit accuracy.

The first limitation is that prediction models do not work equally effectively across different populations. Most existing microbiota-based prediction models are based on a single cohort or specific populations, lacking interregional and interracial interactions. For example, an RA microbial prediction model based on European populations (using *P. copri* and the genus *Collinsella* as core markers) showed a drop in predictive accuracy from 75% to 52% when applied to Asian populations. One possible reason here is that the diets of Asian tend to have a higher proportion of dietary fibre. Moreover, the abundance of bacteroides in the gut is higher than that in Europeans, which eliminates the model's applicability.

In addition, genetic background has a great influence on predictive performance. Individuals at high risk of RA who carry the HLA-DRB1*04 genotype show a stronger predictive effect of gut microbiomes on disease development, whereas no significant association between microbiome markers and disease risk is observed in individuals without this genotype. This makes prediction models difficult to cover all high-risk individuals and also reduces the cure rates of the disease.

The second limitation is that RA is not caused solely by changes in microbiome, and the gut microbiomes cannot act as a single core predictor. The development of arthritis results from the combined effects of genetics, environment and microbiomes. The gut microbiome is only one of the components, so just depending on microbiome markers alone is insufficient for precise prediction. For example, among risk factors, genetic

factor (mainly the HLA-DRB1 gene) accounts for approximately 50% of RA risk, environmental factors like smoking and silica exposure account for 30%, and microbial factors for only 20%. Therefore, even high-risk individuals with gut dysbiosis may not develop disease without exposure to environmental triggers.

Another complicating factor is that microbiomes at other mucosal sites (notably the oral cavity and respiratory tract) also participate in the occurrence of the disease. For example, oral microbiomes in patients with periodontal disease can disseminate via the bloodstream and affect the balance of gut microbiomes [3, 4]. The predictive value for RA is comparable to that of gut microbiomes. Therefore, relying on gut microbiota markers alone will miss this information and cause insufficient predictive sensitivity.

The association between gut microbiome alterations and arthritis progression also lacks consistency. Dysbiosis of some patients may resolve with disease remission, but still exists in others, making it difficult to determine prognosis through microbiomes' characteristics alone.

For example, some RA patients have symptom relief after treatment with TNF inhibitors, but the abundance of *P. copri* is still maintained at a high level in the gut, with no clear conclusion regarding their future risk of relapse. The predictive value of the microbiomes for treatment response remains controversial: one study suggested that RA patients with a high abundance of *Faecalibacterium* have a better response to methotrexate, whereas another study did not find such an association. This may have a relationship to many mixed factors, including concurrent medications and dietary interventions, resulting in insufficient stability of prediction models.

As in the case of diagnosis, it should therefore view microbiome testing-based prediction as a potentially useful but nonetheless incomplete tool. It will be most effective when combined with other clinical information, but should likely not be used as a standalone predictor.

3.3. Future directions

Based on all the evidence above, the authors can conclude that gut microbiome research currently has the greatest value when combined with existing clinical markers and diagnostic tools rather than being viewed as a comprehensive replacement for them.

This paper has considered the clinical relevance of the gut microbiome as a potential diagnostic biomarker, explored a range of microbiota-targeted treatment approaches for rheumatoid arthritis and related conditions, including faecal microbiota transplantation, probiotics, engineered bacteria, prebiotics and postbiotics, microbial-derived metabolites, antimicrobial therapies and phage therapy. Therefore, the core value of the gut microbiome lies in complementing deficiencies of traditional markers, rather than replacing them wholesale.

In clinical use, personalised combined detection methods should be designed for different types of arthritis. In fact, this is particularly relevant for early-stage RA because patients may not yet show any evidence of symptoms or autoantibody results. Therefore, for detecting early-stage RA, a panel integrating oral microbiota (Porphyromonas gingivalis antibody) + gut microbiota (*P. copri* abundance, genus *Collinsella* abundance) + autoantibodies (ACPA, RF) is recommended.

Among them, microbiome markers can improve the diagnostic sensitivity of early-stage RA, especially in ACPA-negative patients, while autoantibodies ensure diagnostic specificity. The accuracy of combined detection can reach more than 85%. Meanwhile, standardised detection techniques are required. It is recommended to adopt metagenomic sequencing combined with standardised faecal sample collection (empty stomach, avoiding periods of drug influence), establish microbiomes reference databases for different populations (ethnicity, region), define the abnormal thresholds of disease-associated microbiomes, and reduce interference from inter-individual variations in detection results.

3.3.1. Recommendations for future research: building combined and functional microbiome models

Future research should move beyond trying to measure the abundance of individual bacterial species. Rather than focusing on the abundance of individual bacterial species, it may be more useful to consider the functional characteristics of the gut microbiome. Features such as Short-Chain Fatty Acid (SCFA) production and citrullination-related enzyme activity could provide a better indication of its potential role in arthritis and may serve as more reliable predictive markers. For example, intestinal barrier function can be assessed by looking at the abundance of SCFA-producing bacteria in the gut, such as *Faecalibacterium* and *Roseburia*, as well as SCFA levels in the blood. When combined with factors like HLA genotype, smoking history and periodontal disease, this may help to build a model for predicting the risk of developing RA and identifying high-risk individuals. Therefore, future investigations need to test how accurate these combined models may be, and especially whether their accuracy surpasses models that are based on bacteria alone.

A second recommendation is that, for disease progression, it is important to consider how the microbiota interacts with immune cells. For instance, higher levels of Th17-inducing bacteria in the gut, such as SFB and *P. copri*, have been linked to increased Th17 activity in the joints, which could act as an early indicator of disease progression. Changes in the microbiome during treatment should also be monitored. If treatment with DMARDs is linked to an increase in beneficial bacteria and a reduction in those associated with Th17 responses, this may suggest a better treatment outcome and possibly a lower risk of relapse. More large-scale studies are still needed, especially involving people from different age groups and ethnic backgrounds. This would help to test how reliable these prediction models are and improve understanding of how microbiome-related factors vary between populations, which could support their use in clinical practice.

Thirdly, when discussing the effects of different bacteria on RA, especially *P. copri*, there has been quite a lot of debate. Some researchers, based on mouse studies using faecal microbiota transplantation, have suggested that *P. copri* could act as a pathobiont and contribute to joint inflammation, possibly by promoting Th17-related responses. However, later studies have not fully supported this idea. It has been suggested that the effects of *P. copri* may depend on the specific strain, meaning that not all strains are harmful and some might even have neutral or beneficial roles. Earlier research has also been criticised for not clearly distinguishing between strains, which may have affected the results.

Overall, these disagreements may partly be due to the limitations of current research, and therefore, it is clear that much more research in this area is still necessary. Many studies do not fully consider factors such as diet, genetic background (including HLA type), or differences between populations. This makes it harder to draw clear conclusions and could explain why findings are sometimes inconsistent. Overall, future research needs to control for these variables much more carefully so that findings can be more easily and reliably compared across different studies.

4. Conclusion

In researching all the available literature, this study has found that the gut microbiome appears to impact rheumatoid arthritis through multiple interconnected pathways. In particular, these are related to immune regulation, intestinal barrier function, and changes in specific bacterial groups, especially *P. copri*, *Collinsella* and *Lactobacillus.*

It was found that dysbiosis may be responsible for weakening the intestinal barrier, which thereby allows microbial products or immune signals to move beyond the gut. The effect of this is a contribution to inflammation, auto-antibody production, and the movement of immune cells towards the joints. This is the major biological mechanism at play.

However, microbiome changes show some potential in terms of identifying early signs of RA, particularly in cases where traditional diagnosis methods, such as clinical symptoms and other imaging, are inconclusive. However, this concludes that microbiome testing should only be viewed realistically as a support tool and not an entire replacement for diagnosis. Both prediction and progression may also be assisted by microbiome testing. In the case of high-risk individuals in particular, predicting RA risk, disease progression, and even treatment response may be possible, although this is complicated because RA is also affected by factors as diverse as genetics, environment, diet, and other medications.

Nonetheless, while the evidence is somewhat promising, it remains inconsistent. Different populations and studies have shown varied microbial patterns, and it is as yet undetermined whether dysbiosis is the main cause of our RA, simply worsens it, or partly results from the disease and its treatment.

Therefore, overall, the gut microbiome should be viewed as an important component within RA's development, but not necessarily the single cause. Its greatest value seems to be in providing an added layer of evidence that can assist medical practitioners in their diagnosis and predictive work.

Future studies should therefore seek to involve larger and more diverse patient groups. It is also important to standardise sampling methods and ensure stronger controls for the key compounding factors such as diet, medication and genetic background. Moreover, a greater focus on microbiome function over bacterial abundance would be wise.

Overall, the gut microbiome provides a highly promising but still developing way to understand, detect, and potentially even manage rheumatoid arthritis. Its greatest value can be unlocked when combined with accurate information on the patient's genetics and other clinical information.

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