World Journal of Orthopedics

Submit a Manuscript: https://www.f6publishing.com

World J Orthop 2025 October 18; 16(10): 108374

DOI: 10.5312/wjo.v16.i10.108374

ISSN 2218-5836 (online)

SYSTEMATIC REVIEWS

Metagenomic analysis of gut microbiome and spondyloarthropathy: A systematic review

Madhan Jeyaraman, Easwar Balasubramanian, Naveen Jeyaraman, Arulkumar Nallakumarasamy, Sathish Muthu

Specialty type: Orthopedics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade C

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade A, Grade C

P-Reviewer: Hua QH, MD, Full Professor, Professor, China; Liu J, PhD, Professor, China

Received: April 14, 2025

Revised: May 28, 2025

Accepted: September 10, 2025

Published online: October 18, 2025

Processing time: 187 Days and 14.8 Hours

Madhan Jeyaraman, Naveen Jeyaraman, Department of Orthopaedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, Chennai 600077, Tamil Nadu, India

Madhan Jeyaraman, Naveen Jeyaraman, Arulkumar Nallakumarasamy, Sathish Muthu, Department of Regenerative Medicine, Agathisha Institute of Stemcell and Regenerative Medicine, Chennai 600030, Tamil Nadu, India

Madhan Jeyaraman, Department of Orthopaedics, Brazilian Institute of Regenerative Medicine, Indaiatuba 13334-170, Sao Paulo, Brazil

Madhan Jeyaraman, Naveen Jeyaraman, Sathish Muthu, Department of Orthopaedics, Orthopaedic Research Group, Coimbatore 641045, Tamil Nadu, India

Easwar Balasubramanian, Department of Orthopaedics and Traumatology, Velammal Medical College Hospital and Research Institute, Madurai 625009, Tamil Nadu, India

Arulkumar Nallakumarasamy, Department of Orthopaedics, Jawaharlal Institute of Postgraduate Medical Education and Research, Karaikal 609602, Puducherry, India

Sathish Muthu, Central Research Laboratory, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research, Kanchipuram 631552, Tamil Nadu, India

Corresponding author: Madhan Jeyaraman, MD, PhD, Assistant Professor, Department of Orthopaedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, Velappanchavadi, Chennai 600077, Tamil Nadu, India.
madhanjeyaraman@gmail.com

Abstract

BACKGROUND

Spondyloarthritis (SpA), a prevalent chronic inflammatory disorder, predominantly impacts the axial skeleton, including the spine and sacroiliac joints. Emerging evidence implicates gut dysbiosis in the pathogenesis of SpA.

AIM

To evaluate the association between gut microbiome alterations and SpA through metagenomic sequencing analyses.

METHODS
A systematic review was conducted by querying English-language databases, including PubMed, EMBASE, and Google Scholar, spanning 2000 to 2023. From an initial pool of 150 studies, four articles meeting stringent inclusion and exclusion criteria were selected for analysis.

RESULTS
The reviewed studies identified an enrichment of opportunistic pathogenic bacterial species, such as *Clostridium spp.*, *Prevotella spp.*, and *Bacteroides spp.*, alongside viral families including *Gratiaviridae* and *Quimbyviridae*, in individuals with ankylosing spondylitis compared to healthy controls. Dysregulated metabolic pathways were highlighted as potential mediators of chronic inflammation and arthritic manifestations. Notably, treatment with tumor necrosis factor inhibitors demonstrated efficacy in mitigating SpA symptoms and restoring gut microbial balance.

CONCLUSION
The findings underscore a significant presence of pathogenic gut microbiota in SpA patients, suggesting a pivotal role in disease progression. Future investigations should focus on species-specific microbial targets to develop innovative therapies for preventing and managing SpA and associated gut dysbiosis.

Key Words: Spondyloarthritis; Ankylosing arthritis; Gut microbiome; Metagenomic sequencing

©The Author(s) 2025. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Spondyloarthritis (SpA) is a chronic inflammatory condition impacting the axial skeleton, with emerging links to gut microbiome dysbiosis. A systematic review highlights enrichment of pathogenic bacterial and viral species in SpA patients, suggesting gut microbes contribute to disease progression. Dysregulated metabolic pathways may mediate inflammation, while tumor necrosis factor inhibitors show promise in symptom relief and microbial balance restoration. Targeting specific microbial species may unlock innovative therapies for SpA management and gut dysbiosis prevention.

Citation: Jeyaraman M, Balasubramanian E, Jeyaraman N, Nallakumarasamy A, Muthu S. Metagenomic analysis of gut microbiome and spondyloarthropathy: A systematic review. *World J Orthop* 2025; 16(10): 108374
URL: https://www.wjgnet.com/2218-5836/full/v16/i10/108374.htm
DOI: https://dx.doi.org/10.5312/wjo.v16.i10.108374

INTRODUCTION

The human digestive tract is inhabited by 400 to 600 trillion microorganisms, with anaerobic bacteria outnumbering aerobic bacteria by a ratio of 100 to 1000:1[1]. More than 1000 different bacterial species that can survive in the stomach have been identified by metagenomic sequencing research. These communal bacteria have a significant impact on preserving human health[2]. The human body (host) and microbial communities have evolved interior habitats that support long-term mutual benefit[3]. The enzymes produced by these microbes help in the digestion of dietary foods high in fibre, the release of vitamins and minerals, preventing of the growth of pathogenic microbes, and enhance immunity[4-6]. Furthermore, it has been demonstrated that some microbiomes can thicken the mucus lining of the intestinal tract, which acts as a barrier to the absorption of antigens and compounds that cause inflammation[7]. However, a dysbiosis of the gut is typically caused by an imbalance in the total number of microbial species, which in turn results in the activation of inflammatory cells and poor function of the gut barrier. Gut dysbiosis is associated with numerous disorders such as inflammatory bowel diseases, irritable bowel syndrome, obesity, diabetes cancer, and inflammation at extraintestinal tissue regions[8-12].

Spondyloarthritis (SpA) is a clinically and genetically linked group of back pain-associated inflammatory ailments that includes psoriatic arthritis, ankylosing spondylitis, juvenile SpA, inflammatory bowel disease -related arthritis and reactive arthritis[13]. Depending on the symptoms that predominate, SpA can be further classified as either axial SpA, which includes ankylosing spondylitis and non-radiographical axial SpA (nr-axSpA), or as peripheral SpA[14-16]. Globally, SpA have an estimated incidence of up to 1.2%[17]. Ankylosing spondylitis was found to be comparatively most common SpA with prevalence rate ranging from 9 to 30 individuals per 10000 population[18]. The prevalence rate is higher in males compared to females[19]. Also, prevalence rates are higher in population with higher human leukocytes antigen syndrome or HLA-B27 syndrome[20]. Inflammatory chronic back pain is the major symptom of Spa. In addition, extra-articular symptoms including psoriasis and anterior uveitis as well as musculoskeletal signs like arthritis, enthesitis, dactylitis were observed[21].

Studies shows SpA a significantly correlated or linked to inflammatory bowel disease. Approximately 13% inflammatory bowel disease patients were found to develop ankylosing spondylitis[22]. Gastrointestinal bacterial infections including Yersinia, Shigella, Salmonella and Campylobacter were found to trigger Spa pathogenesis[23]. Considering

over 70 percent of the bacterial population, such as anaerobic bacteria, cannot be cultured *in vitro* conditions, the development of high throughput genome sequencing techniques has provided critical insights into the intestinal metagenome[24]. Metagenomics can identify novel alterations in the human gut microbes function and can assist in understanding the interactions between the host and microbes[25]. Using metagenomic approach, several studies found difference in the microbial concentration of the gut between patients and controls using a metagenomic method[26-28]. The present systematic review aims to evaluate the relationship between gut microbiome (GMB) and SpA identified by metagenomics.

MATERIALS AND METHODS

Literature search

The present study search to evaluate the association of GMB and SpA was conducted in adherence to PRISMA-systematic review and meta-analysis guidelines[29]. The inclusion criteria for screening of the research articles include comparative prospective clinical studies evaluating the association between gut dysbiosis and spondylarthritis using metagenomics published in English. The exclusion criteria include pre-clinical studies, laboratory studies, animal models and case reports. Literature search was done in databases such as PubMed, EMBASE and Google Scholar. Search was confined to time period from 2000 to 2024. For PubMed, the main keywords used are gut microflora, gut dysbiosis, spondylarthritis and metagenomic profiling. The pertinent medical subject headings (MeSH) used include ("ankylosing spondylitis" OR "Undifferentiated spondyloarthropathy" OR "Reactive arthritis" OR "Reiter's syndrome" OR "Enteropathic spondyloarthropathy" OR "Psoriatic arthritis" OR "Spondyloarthropathy" OR "Spondyloarthropath*") AND ("Gastrointestinal Microbiome"[Mesh] OR "gut microbia" OR "gut microbiome") AND ("metagenome" AND "metagenom*"). In order to find other related studies, we thoroughly reviewed the references of the included studies and also looked for publications citing the included studies to identify any relevant publication that was missed in the initial round of screening.

Selection and screening

The screening was performed separately by two researchers. In the first step, research documents were screened based on the title and abstract. Based on the inclusion and exclusion criteria, the selected research documents were thoroughly reviewed and articles not meeting the inclusion criteria were excluded from the study. The research articles were excluded if study was about gut microflora association with diabetics or cancer or bowel diseases. Finally, the researcher independently retrieved pertinent data from the included studies using a pre-designed data-collecting form. Any differences in the data collected were sorted out through discussion. The primary contents of the data collection form include the title of the research article, authors name, year of publication, study design, indication, microbiome data, inclusion and exclusion criteria of the selected article, sample size, study population, methodology, outcomes of the study and significance or conclusion of the study.

Risk of bias analysis

The risk of bias in the included studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates the methodological quality of non-randomized studies[30]. The NOS assigns a maximum of nine stars across three domains: Selection of study groups, comparability of groups, and ascertainment of the outcome of interest. Two independent reviewers assessed each study, with any disagreements resolved through discussion or consultation with a third reviewer. This approach ensured a rigorous and standardized evaluation of study quality, facilitating the interpretation of findings.

RESULTS

Literature search and study characteristics

A summary of the systemic review search strategy with inclusion and exclusion articles was presented in a flowchart (Figure 1). From English databases, 150 studies were retrieved, 17 duplicates were discarded. After the initial article title and abstract screening, 79 were excluded. Further on full-text analysis, 50 non-relevant articles were excluded and 5 research articles were selected for the final study. All the selected articles were cohort based studies[26,31-34]. The total sample size of the present study was 535 ankylosing spondylitis (AS) Chinese patients. Table 1 shows the study characteristics of the selected studies. The risk of bias analysis with NOS is presented in Table 2 and it should the studies does not pose a higher risk of bias to be excluded from analysis. Nevertheless, two studies does not have ascertainment of exposure[32,33]. One of the study did not show a clear follow-up protocol time to assess the outcomes[32].

Gut dysbiosis in ankylosing spondylitis

Bacterial profile of AS patients: A comparative study analyzing the gut microbiota composition among untreated AS patients, those receiving non-steroidal anti-inflammatory drugs (NSAIDs), and individuals treated with Chinese herbal medicine revealed distinct microbial shifts. Untreated AS patients exhibited a significant increase in bacterial taxa such as *Flavonifractor plautii*, *Oscillibacter* species, *Arabacteroides distasonis*, and *Bacteroides nordii*. Conversely, AS patients undergoing NSAID therapy demonstrated an enrichment of opportunistic pathogens, including *Bacillus dorei*, *Clostridium*

Table 1 Study characteristics of the selected studies of Ankylosing Spondylitis

Ref.	Sudy design	Microbia	Method	Cohorts	Results	Conclusion
Zhou *et al* [26], 2020	Cohort study	AS-enriched species including *Parabacteroides distasonis, Acidaminococcus fermentans Bacteroides coprophilus, Eubacterium siraeum*, and *Prevotella copri*	Metagenomic shotgun sequencing of feceal matter. A microbial peptide's molecular mimicry was also proven using the ELISpot assay	85 AS subjects and 62 healthy controls	The study identified several bacterial species including *Parabacteroides distasonis, Acidaminococcus fermentans Bacteroides coprophilus, Eubacterium siraeum*, and *Prevotella copri* in AS patients. Pathway study showed that the gut microbiota of AS had higher levels of oxidative phosphorylation, LPS production, and glycosaminoglycan breakdown. The random forest model's selection of the AS gut's microbial signatures demonstrated great discrimination efficiency. Autoimmune indicators such as *Bacteroides fragilis* and type III secretion system were identified. *In vitro* research showed that a bacterial peptide from an AS-enriched species that mimics type II collagen boosted the number of IFNα production	The results show that untreated AS patients had altered gut microbiota with diagnostic possibility, and few AS-enriched species may act as molecular mimics to cause autoimmunity. Furthermore, several forms of inflammatory arthritis had a few similar microbiological fingerprints
Huang *et al* [33], 2020	Cohort study	*Flavonifractor plautii, Oscillibacter, Parabacteroides distasonis* and *Bacteroides nordii*	Illumina HiSeq 4000	113 patients and 37 controls	AS patients had enriched *Flavonifractor plautii, Oscillibacter, Parabacteroides distasonis* and *Bacteroides nordii. F. plautii* significantly enhanced in AS untreated patients. AS patients had more bacterial species in their faeces that were involved in glycan production and carbohydrate metabolism. Additionally, their bacterial profiles were less capable of degrading xenobiotics or producing and transporting vitamins	The therapy had an impact on the variation in the gut flora between the AS patients and HCs. The results obtained provide knowledge that may help with AS treatment advancements
Yin *et al*[31], 2020	Cohort study		Shotgun metagenomic sequencing of stools. All patients and healthy controls were genotyped using the Illumina CoreExome SNP microarray	127 AS patients and 123 healthy controls	The gut dysbiosis in AS previously reported was validated, and several significant types of bacteria and functional categories were substantially prevalent. The disturbed microbiome seen in untreated AS cases was restored to that of healthy controls after TNFi therapy. In the faeces of patients with AS, there was an enrichment of bacterial peptides that were identical to the epitopes that are presented by HLA-B27, indicating that either HLA-B27 Lacks to clear them or that they are responsible for the immunological responses. TNFi treatment restored the disturbed microbiome identified in untreated AS subjects indicating the efficacy of the treatment	These results highlight the critical function of the gut microbiota in the aetiology of AS and point to possible therapeutic and preventive approaches
Li *et al* [32], 2023	cohort study	*Quimbyviridae, Gratiaviridae, Schitoviridae* and *Drexlerviridae*	Metagenomic analysis of fecal matter	113 patients with AS and 37 healthy controls	The intestinal viral richness and overall viral structure of AS patients were significantly altered and decreased. *Gratiaviridae* and *Quimbyviridae* were more prevalent in AS patients than *Schitoviridae* and *Drexlerviridae*. 1004 viral operational taxonomic units that differed between patients and controls, including *Myoviridae* viruses in AS and *Siphoviridae* viruses in controls were identified. A clear distinction between virus infected host were identified between AS and controls. Furthermore, the frequency of some viral functional orthologs varied noticeably between the AS and controls, pointing to the functional significance of these viruses linked to AS. With an ideal AUC of 0.936, classification models were developed using gut viral profiles to differentiate AS patients from healthy controls, indicating the possible clinical utility of the gut virus in AS diagnosis	On metagenomic analysis, the study identified few virus signatures to differentiate AS patients. Predictive models show virus signatures can play significant role in clinical diagnosis of AS
Wen *et al*[34], 2017	cohort study	Increased abundance of *Prevotella melaninogenica, Prevotella copri, Prevotella sp.* C561, and decreased abundance of *Bacteroides spp.*; enrichment of *Bifidobacterium*, commonly used in probiotics	Metagenomic sequencing of gut microbial DNA from 211 Chinese individuals, with analysis of 23709 genes and 12 metagenomic species differentially abundant in AS patients	73 AS patients and 83 healthy controls in discovery cohort; 24 AS patients and 31 healthy controls in validation cohort	AS patients exhibited pronounced gut microbial dysbiosis compared to inflammatory bowel disease cases. Diagnostic algorithms were developed using gut microbial biomarkers	Gut microbiome alterations are associated with AS development, suggesting potential biomarkers for diagnosis and treatment strategies

AS: Ankylosing spondylitis; HLA: Human leucocyte antigen; SNP: Single nucleotide polymorphism; TNF: Tumor necrosis factor; LPS: Lipopolysaccharide; INF: Interferon.

Table 2 Risk of bias analysis of the selected studies

Ref.	Risk of bias							
	Selection				Comparability	Outcome		
	Is the exposed cohort truly representative of the population?	Was the nonexposed cohort chosen from the same group of people as the exposed cohort?	Did the determination of exposure originate from secure records?	Was the desired outcome missing at the beginning of the study?	Was comparability of cohorts done on the basis of the design or analysis?	Was the evaluation of the outcome based on a record linkage or an independent blind assessment?	Was the follow-up period long enough for results to materialise?	Was the cohort follow-up sufficient (subjects lost to follow-up < 20%)?
Zhou *et al* [26] 2020	+	+	+	-	+	+	+	+
Huang *et al* [33] 2020	+	+	-	+	+	+	+	+
Yin *et al*[31] 2020	+	+	+	-	+	+	+	+
Li *et al* [32], 2023	+	+	-	+	-	+	-	+
Wen *et al*[34], 2017	+	+	+	-	+	+	+	+

"+" indicates studies satisfying the domain item analysed; "-" indicates studies lacking the domain item analysed.

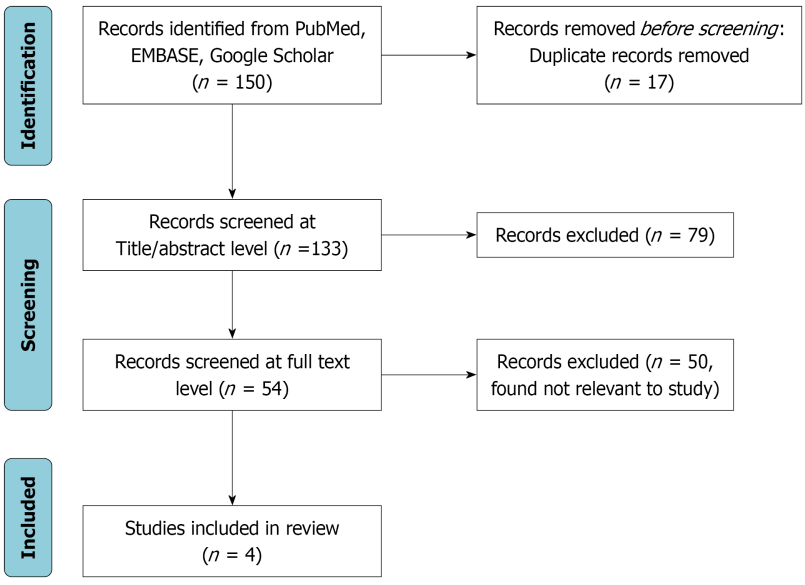


Figure 1 PRISMA flowchart for the systematic database literature research of the articles based on inclusion and exclusion criteria.

asparagiforme, and *Clostridium bolteae*. Notably, patients receiving Chinese herbal medicine did not display a discernible rise in any of these pathogenic bacteria, suggesting a potential therapeutic benefit of Chinese medicine in AS management [33].

Similarly, Yin *et al*[31] reported an altered gut microbial profile in AS patients, characterized by an increased abundance of *Clostridium* species and a depletion of beneficial taxa such as *Bifidobacterium, Coprococcus*, and *Roseburia*. In untreated AS patients, an elevated presence of bacterial peptides homologous to HLA-B27 epitopes was observed, potentially contributing to immune dysregulation. Furthermore, the study highlighted that the disrupted GMB seen in untreated AS cases—encompassing multiple bacterial species previously implicated in AS and related disorders—was largely restored to a healthy profile following TNF-α inhibitors (TNFi) therapy. This therapeutic intervention was also associated with a notable reduction in bacterial peptides capable of triggering arthritic symptoms, distinguishing TNFi treatment from other conventional approaches.

Viridae profile of AS patients: A study conducted by Li *et al*[32], showed a significant decrease in gut viral diversity and the structure of the virus was significantly altered in AS patients. *Gratiaviridae* and *Quimbyviridae* were more prevalent whereas *Drexlerviridae* and *Schitoviridae* were less prevalent in AS patients. The AS-viral operational taxonomic units (vOTUs) were found to infect bacteria like *Achromobacter*, *Flavonifractor* and *Eggerthellaceae* while the control-OTUs infected bacteria like *Ruminococcus*, *Blautia*, *Collinsella*, *Faecalibacterium* and *Prevotella*. Furthermore, the frequency of a few viral functional orthologs varied significantly between the AS-enriched and control-enriched vOTUs, pointing to the functional significance of these AS-associated viruses.

Metagenomic functional analysis

In addition to increase and decrease gut microflora in AS patients, pathway analysis showed that the gut microbiota of AS had higher levels of lipopolysaccharide production, oxidative phosphorylation, and glycosaminoglycan breakdown. There were also several typical autoimmune signatures identified, including Bacteroides fragilis and type III secretion system. A bacterial peptide homologous to type II collagen was shown to cause an increase in IFN-producing cells[26]. Also, Huang *et al*[33], 2020 found increase heparin sulfate degradation and diminished vitamin B12 transportation in AS patients.

DISCUSSION

SpA is a progressive, chronic inflammatory condition and specifically affects spinal cord. Patients frequently develop extra joint symptoms as well as gastrointestinal issues. Previous studies showed gut inflammation and AS are strongly associated, which implies that gut dysbiosis can be the contributing factor in this occurrence as shown in Figure 2[35]. The pathogenesis of AS is mostly influenced by a number of bacteria, including *Klebsiella pneumoniae* and *Bacteroides vulgatus* [36]. Furthermore, numerous mechanisms have been hypothesised to explain the function of the microbiome in the aetiology of AS, including changes in intestinal absorptivity, molecular and immune response stimulation. However, none of these entirely explains the aetiology of AS, therefore experts are still looking for other potential causes.

Microbiology profile in AS cases

The present systematic review revealed seven bacterial species that were frequently differentiating between cases and controls, reaffirming the presence of bacterial gut dysbiosis in AS cases. *Prevotella copri* (*P. copri*), *Bacteroids* and *Clostridium* species were found to significantly prominent in AS patients[26,31,33]. Studies show rheumatoid arthritis patients synovial fluids were also enriched with *P. copri* and *in vivo* studies revealed mouse models infected with *P. copri* developed arthritis[37-39]. It's interesting to note that treatment with TNFi was more effective than treatment with non-steroid antiinflammatory drugs alone in reducing *P. copri*[26,31]. However, Yin *et al*, 2020 noted that *P. copri* increased during the onset of rheumatoid arthritis but diminished in chronic AS. The concentration of *P. copri* varies with the duration in the disease and can be normalized using TNFi treatment. Similarly in case of enteroviridae, the present study found enhanced abundance of *Quimbyviridae* and *Gratiaviridae* in AS patients[32]. *Quimbyviridae* are the new class of viruses, which are widely distributed in the human gut. These are the lytic cycle viruses that frequently infect *Bacteroides*. The enrichment of these viruses in AS raises the possibility that they are crucial to the pathophysiology of the disease[40]. Also, in AS patients most frequent virus host were found to be *Bacteroids*, Flavonifractor, *Clostridium* and other bacterial species[32]. In mice models, the flavonoid-degrading bacterium *Flavonifractor plautii* has been shown to negatively impact the immunological responses caused by antigen-stimulated T2 helper cells and was found to be more prevalent in colorectal cancer young patients. These results show unique virus-host connections in AS patients[41,42].

The observed GMB dysbiosis in SpA patients raises an important question: Are these microbial changes a driving force in disease pathogenesis, or do they merely accompany the inflammatory state? Several studies suggest that specific bacterial taxa may actively contribute to immune dysregulation in SpA[43,44]. For instance, the enrichment of *Prevotella spp*., particularly *P. copri*, has been linked to pro-inflammatory responses, potentially triggering immune activation through molecular mimicry or direct stimulation of Th17 pathways[45-47]. Conversely, the depletion of *Bacteroides spp*. and *Faecalibacterium prausnitzii*, known for their anti-inflammatory properties, may exacerbate disease progression by reducing regulatory immune signals and short-chain fatty acid production[48].

Recent Mendelian randomization analyses have attempted to establish a genetic-level causal link between gut microbiota and SpA, identifying taxa such as *Actinobacteria* and *Rikenellaceae* as potential contributors to disease susceptibility[49]. However, while these findings suggest a mechanistic role for microbial alterations, the directionality remains

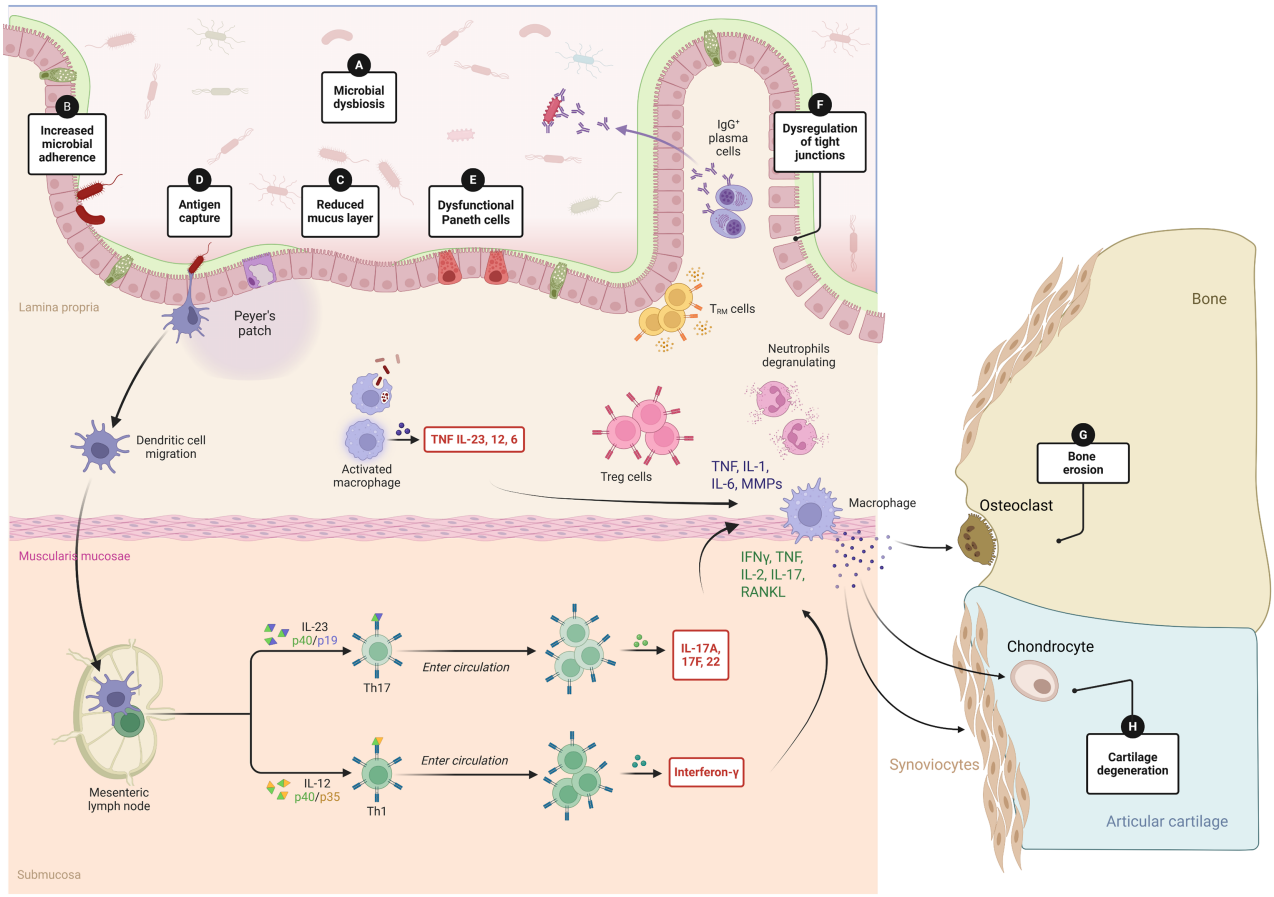


Figure 2 Role of gut dysbiosis and bony erosion and cartilage degeneration noted in spondyloarthritis. Th: T helper; Treg: T regulatory; IL: Interleukin; TNF: Tumor necrosis factor; MMP: Matrix metalloproteases; Ig: Immunoglobulin.

uncertain—whether dysbiosis precedes inflammation or results from immune-mediated changes in gut homeostasis. Additionally, the gut-joint axis hypothesis proposes that microbial translocation and systemic immune activation may bridge intestinal dysbiosis with joint inflammation, further complicating the causality debate[50].

Future research should focus on longitudinal studies and interventional trials to determine whether restoring microbial balance—through probiotics, dietary modifications, or microbiome-targeted therapies—can mitigate SpA progression. Understanding whether microbial shifts are a cause or consequence of SpA will be crucial in developing precision medicine approaches that integrate microbiome modulation into therapeutic strategies.

Metagenomic functional analysis of AS patients

Metagenomic sequencing has revolutionized the study of the GMB, offering functional insights beyond traditional taxonomic profiling. Unlike culture-based methods that are limited to cultivable species, metagenomics enables the identification of unculturable microorganisms, uncovering the vast diversity of microbial communities in the gastrointestinal tract[51,52]. Moreover, metagenomic analysis provides a deeper understanding of microbial metabolic pathways, revealing alterations that may contribute to disease pathogenesis. By characterizing functional gene content, metagenomics allows researchers to assess microbial enzymatic activity, metabolic interactions, and the production of bioactive metabolites that influence immune responses in SpA. This approach enhances our ability to explore host-microbiome relationships and develop targeted interventions based on microbial metabolic signatures. The metagenomic sequences' functional interpretation revealed that AS patients gut microbes had enhanced citrate and oxidative phosphorylation metabolism and lowered glycolysis metabolism. The alteration in energy metabolism can lead to oxidative stress, thereby leading to increase facultative anaerobic microbes compared to normal obligative gut commensals[26]. Disturbance of gut microbes metabolic pathways showed increase in lipopolysaccharide production and transportation. LPS were found induce arthritis and inflammation in mice[53]. Also, decreased concentration of pyroxidal 5-phosphate synthase was observed in AS patients which can lead to low levels to vitamin B6 synthesis[31]. Vitamin B6 was found to play pivotal role in maintaining colon homeostasis. Low levels of vitamin B6 can lead to inflammation and arthritis in mice models[54]. Thus therapeutic treatment with vitamin B6 were found to decrease potential risks of AS.

The GMB plays a pivotal role in immune modulation, and emerging evidence suggests that specific bacterial strains may contribute to SpA pathogenesis through molecular mimicry and immune activation[55]. Molecular mimicry occurs when microbial antigens share structural similarities with host proteins, leading to cross-reactive immune responses[56]. In SpA, certain bacterial peptides—particularly those from *P. copri* and *Klebsiella pneumoniae*—have been found to exhibit homology with HLA-B27 epitopes, potentially triggering autoreactive T-cell responses[57]. This phenomenon may

contribute to chronic inflammation and joint pathology in genetically predisposed individuals.

Beyond molecular mimicry, immune activation pathways driven by gut dysbiosis further exacerbate SpA progression. The enrichment of pro-inflammatory bacteria, such as Clostridium spp. and Bacteroides fragilis, has been linked to excessive interleukin (IL)-23/IL-17 axis activation, a key inflammatory pathway implicated in SpA[55]. These bacteria can stimulate pattern recognition receptors, including Toll-like receptors and NOD-like receptors, leading to heightened production of tumor necrosis factor-α, IL-6, and IL-17, which drive systemic inflammation and enthesitis. Additionally, the depletion of anti-inflammatory taxa like *Faecalibacterium prausnitzii* and *Roseburia spp.* reduces regulatory immune signals, further skewing the immune balance toward a pro-inflammatory state[58].

These findings underscore the complex interplay between gut microbiota and immune mechanisms in SpA. Future research should focus on targeted microbiome interventions, such as probiotic therapies, microbial metabolite modulation, and immune pathway inhibitors, to mitigate disease progression and restore immune homeostasis.

TNFi treatment

While TNFi therapy has demonstrated significant efficacy in managing inflammation and restoring gut microbial balance in AS patients, emerging therapeutic approaches offer alternative or complementary benefits. IL-17 inhibitors, such as secukinumab and ixekizumab, target IL-17—a cytokine strongly implicated in AS pathogenesis—providing symptom relief in patients who may not respond optimally to TNFi therapy[31]. Moreover, Janus kinase (JAK) inhibitors, including tofacitinib and upadacitinib, have shown promise in modulating immune pathways associated with AS, expanding treatment options for refractory cases.

Beyond pharmaceutical interventions, microbiome-targeted therapies are gaining traction as potential modulators of disease progression. Probiotic formulations enriched with beneficial strains like *Bifidobacterium* and *Faecalibacterium* aim to restore gut microbial balance[59,60], while fecal microbiota transplantation (FMT) is being explored for its potential in correcting dysbiosis in immune-mediated diseases[61,62]. Dietary modifications, particularly those emphasizing an anti-inflammatory microbiome-supporting diet, may also play a role in symptom management. These approaches highlight the evolving landscape of AS treatments and underscore the need for personalized strategies based on patient responsiveness and microbiome composition.

The present study also concludes that TNFi therapeutic treatment for AS patients was found to be more effective compared to non-steroid anti-inflammatory drugs. It was able to restore the perturbed gut microflora to normal concentration. TNFi was able to restore diminished gut microbe *Faecalibacterium prausnitzii* in AS patients back to normalcy, thereby indirectly enhancing branched and aromatic aminoacids production[31]. However, our study need to further assess the function genomics of the therapy and is limited due to fewer research articles selection and small sample size.

Therapeutic strategies

The growing evidence linking GMB dysbiosis to AS underscores the need for microbiome-targeted interventions. Beyond observational findings, recent efforts have focused on translating these discoveries into tangible clinical applications. One promising avenue is the development of novel probiotics, specifically strains such as *Bifidobacterium adolescentis* and *Faecalibacterium prausnitzii*, which have demonstrated anti-inflammatory properties and may help restore microbial balance in AS patients[60,63].

Another emerging strategy involves prebiotics, including specific oligosaccharides that selectively promote beneficial microbial populations, potentially enhancing gut barrier function and modulating immune responses. Additionally, microbial metabolite therapies—such as short-chain fatty acids, particularly butyrate—have gained attention for their immunoregulatory effects, with studies showing their ability to suppress pro-inflammatory cytokines and improve intestinal homeostasis[64].

Beyond nutritional approaches, FMT remains an experimental but promising intervention, aiming to reestablish a healthy GMB and mitigate inflammatory disease progression[65]. Future therapeutic strategies should explore personalized interventions based on microbiome profiling, ensuring targeted and optimized treatment outcomes.

Limitations

In the course of our systematic review focused on unraveling the intricate relationship between gut microbiota and SpA, several limitations have emerged, which warrant careful consideration. Foremost among these limitations is the modest sample size, consisting of 438 patients, predominantly of Chinese descent. This constrained sample size raises concerns regarding the generalizability of our findings to a more ethnically diverse and geographically varied population. Furthermore, the heterogeneity in treatment protocols employed across the constituent studies introduces variability that may impede a comprehensive comparative analysis of gut microbiota alterations. It is crucial to acknowledge that our inclusion criteria, which predominantly favored cohort studies, may inadvertently have excluded insights offered by other study designs, such as randomized controlled trials, thereby potentially limiting the robustness of our conclusions. Additionally, while metagenomic sequencing has proven invaluable in assessing microbial diversity, its inherent limitations mean that we may not have captured the full spectrum of functional dynamics within the GMB. This issue becomes particularly salient in our quest to elucidate the precise mechanisms underpinning gut dysbiosis in SpA. A notable omission is our exclusive focus on bacterial and viral profiles, which, while fundamental, omits other essential microbial components such as fungi and protozoa, which may also contribute significantly to the pathogenesis of the disease. Finally, the absence of long-term follow-up data has curtailed our capacity to grasp the chronic dimensions of gut dysbiosis in SpA and its temporal evolution.

Future aspects

To address the aforementioned limitations and further advance our understanding of the intricate interplay between the GMB and SpA, several promising avenues beckon for future exploration. First and foremost, expanding the diversity of the studied population, encompassing various ethnicities and geographical origins, emerges as a priority. By broadening the scope of our investigation, we can enhance the external validity of our findings and offer a more comprehensive picture of the disease's microbiological underpinnings. In tandem, we advocate for the incorporation of a wider array of study designs, including randomized controlled trials and cross-sectional studies, which can furnish a more holistic understanding of the GMB's role in SpA. Moreover, undertaking longitudinal studies represents a critical stride forward, as it will enable us to elucidate the temporal dynamics of gut microbiota and their intricate relationship with disease progression and response to therapeutic interventions. Beyond bacterial and viral profiles, future research should venture into uncharted territories, probing the contributions of fungi and protozoa to the complex landscape of SpA. Embracing advanced metagenomic techniques, which focus on the functional aspects of the microbiome, holds the promise of uncovering specific metabolic pathways that undergo alteration in the context of SpA. Tailoring therapeutic strategies through personalized microbiome profiling is a compelling prospect, offering potential breakthroughs in the efficacy of treatments such as TNFi. Furthermore, the integration of environmental and genetic factors into our analytical framework is an imperative step, recognizing the multifactorial nature of the disease. Finally, conducting clinical trials evaluating microbiome-targeted therapies, including prebiotics, probiotics, and dietary interventions, can chart a novel course in the therapeutic landscape of SpA. These future prospects collectively underscore the necessity for a multifaceted and comprehensive approach to advance our knowledge and therapeutic options in the realm of SpA.

CONCLUSION

The current investigation based on the cohort metagenome sequencing of the selected studies found a small number of bacterial and viral species with significant variations between AS patients and healthy subjects. These species may be potential targets for AS therapy, leading to the development of new preventative and therapy techniques for AS. TNFi treatment was found to be effective in normalization of gut microbes but further studies need to be conducted in development of standard therapeutic procedure.

FOOTNOTES

Author contributions: Jeyaraman M and Balasubramanian E contributed to conceptualization; Balasubramanian E contributed to acquiring clinical data and performing the data analysis; Jeyaraman N and Nallakumarasamy A contributed to manuscript writing; Jeyaraman M and Muthu S helped in manuscript revision; Muthu S contributed for image acquisition; Jeyaraman M contributed to proofreading; Jeyaraman M contributed to administration. All authors have agreed to the final version to be published and agree to be accountable for all aspects of the work.

Conflict-of-interest statement: All authors declare no conflict of interest in publishing the manuscript.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country of origin: India

ORCID number: Madhan Jeyaraman 0000-0002-9045-9493; Naveen Jeyaraman 0000-0002-4362-3326; Arulkumar Nallakumarasamy 0000-0002-2445-2883; Sathish Muthu 0000-0002-7143-4354.

S-Editor: Liu JH
L-Editor: A
P-Editor: Zheng XM

REFERENCES

1 **Sender R**, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS Biol* 2016; **14**: e1002533 [*RCA*] [PMID: 27541692 DOI: 10.1371/journal.pbio.1002533] [FullText] [Full Text(PDF)]

2 **Qin J**, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li J, Xu J, Li S, Li D, Cao J, Wang B, Liang H, Zheng H, Xie Y, Tap J, Lepage P, Bertalan M, Batto JM, Hansen T, Le Paslier D, Linneberg A, Nielsen HB, Pelletier E, Renault P, Sicheritz-Ponten T, Turner K, Zhu H, Yu C, Li S, Jian M, Zhou Y, Li Y, Zhang X, Li S, Qin N, Yang H, Wang J, Brunak S, Doré

J, Guarner F, Kristiansen K, Pedersen O, Parkhill J, Weissenbach J; MetaHIT Consortium, Bork P, Ehrlich SD, Wang J. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 2010; **464**: 59-65 [*RCA*] [PMID: 20203603 DOI: 10.1038/nature08821] [Full Text] [Full Text(PDF)]

3 **David LA**, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 2014; **505**: 559-563 [*RCA*] [PMID: 24336217 DOI: 10.1038/nature12820] [FullText] [Full Text(PDF)]

4 **Lambring CB**, Siraj S, Patel K, Sankpal UT, Mathew S, Basha R. Impact of the Microbiome on the Immune System. *Crit Rev Immunol* 2019; **39**: 313-328 [*RCA*] [PMID: 32422014 DOI: 10.1615/CritRevImmunol.2019033233] [FullText]

5 **Vernocchi P**, Del Chierico F, Putignani L. Gut Microbiota Metabolism and Interaction with Food Components. *Int J Mol Sci* 2020; **21**: 3688 [*RCA*] [PMID: 32456257 DOI: 10.3390/ijms21103688] [FullText] [Full Text(PDF)]

6 **Boulangé CL**, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. *Genome Med* 2016; **8**: 42 [*RCA*] [PMID: 27098727 DOI: 10.1186/s13073-016-0303-2] [FullText] [Full Text(PDF)]

7 **Fernández-Tomé S**, Ortega Moreno L, Chaparro M, Gisbert JP. Gut Microbiota and Dietary Factors as Modulators of the Mucus Layer in Inflammatory Bowel Disease. *Int J Mol Sci* 2021; **22**: 10224 [*RCA*] [PMID: 34638564 DOI: 10.3390/ijms221910224] [FullText] [Full Text (PDF)]

8 **Belizário JE**, Faintuch J. Microbiome and Gut Dysbiosis. *Exp Suppl* 2018; **109**: 459-476 [*RCA*] [PMID: 30535609 DOI: 10.1007/978-3-319-74932-7_13] [FullText]

9 **Kim GH**, Lee K, Shim JO. Gut Bacterial Dysbiosis in Irritable Bowel Syndrome: a Case-Control Study and a Cross-Cohort Analysis Using Publicly Available Data Sets. *Microbiol Spectr* 2023; **11**: e0212522 [*RCA*] [PMID: 36652592 DOI: 10.1128/spectrum.02125-22] [FullText]

10 **Evenepoel P**, Stenvinkel P, Shanahan C, Pacifici R. Inflammation and gut dysbiosis as drivers of CKD-MBD. *Nat Rev Nephrol* 2023; **19**: 646-657 [*RCA*] [PMID: 37488276 DOI: 10.1038/s41581-023-00736-7] [FullText]

11 **Breton J**, Galmiche M, Déchelotte P. Dysbiotic Gut Bacteria in Obesity: An Overview of the Metabolic Mechanisms and Therapeutic Perspectives of Next-Generation Probiotics. *Microorganisms* 2022; **10**: 452 [*RCA*] [PMID: 35208906 DOI: 10.3390/microorganisms10020452] [FullText] [Full Text(PDF)]

12 **Vimal J**, Himal I, Kannan S. Role of microbial dysbiosis in carcinogenesis & cancer therapies. *Indian J Med Res* 2020; **152**: 553-561 [*RCA*] [PMID: 34145094 DOI: 10.4103/ijmr.IJMR_1026_18] [FullText] [Full Text(PDF)]

13 **Akgul O**, Ozgocmen S. Classification criteria for spondyloarthropathies. *World J Orthop* 2011; **2**: 107-115 [*RCA*] [PMID: 22474629 DOI: 10.5312/wjo.v2.i12.07] [FullText]

14 **Carron P**, De Craemer AS, Van den Bosch F. Peripheral spondyloarthritis: a neglected entity-state of the art. *RMD Open* 2020; **6**: e001136 [*RCA*] [PMID: 32385142 DOI: 10.1136/rmdopen-2019-001136] [FullText] [Full Text(PDF)]

15 **Magrey M**, Schwartzman S, de Peyrecave N, Sloan VS, Stark JL. Nonradiographic axial spondyloarthritis: expanding the spectrum of an old disease: A narrative review. *Medicine (Baltimore)* 2022; **101**: e29063 [*RCA*] [PMID: 35475794 DOI: 10.1097/MD.0000000000029063] [Full Text] [Full Text(PDF)]

16 **Poddubnyy D**. Axial spondyloarthritis: is there a treatment of choice? *Ther Adv Musculoskelet Dis* 2013; **5**: 45-54 [*RCA*] [PMID: 23514983 DOI: 10.1177/1759720X12468658] [FullText]

17 **Harper BE**, Reveille JD. Spondyloarthritis: clinical suspicion, diagnosis, and sports. *Curr Sports Med Rep* 2009; **8**: 29-34 [*RCA*] [PMID: 19142077 DOI: 10.1249/JSR.0b013e3181967ac6] [FullText] [Full Text(PDF)]

18 **Wang R**, Ward MM. Epidemiology of axial spondyloarthritis: an update. *Curr Opin Rheumatol* 2018; **30**: 137-143 [*RCA*] [PMID: 29227352 DOI: 10.1097/BOR.0000000000000475] [FullText]

19 **Rusman T**, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender Differences in Axial Spondyloarthritis: Women Are Not So Lucky. *Curr Rheumatol Rep* 2018; **20**: 35 [*RCA*] [PMID: 29754330 DOI: 10.1007/s11926-018-0744-2] [FullText] [Full Text(PDF)]

20 **Kavadichanda CG**, Geng J, Bulusu SN, Negi VS, Raghavan M. Spondyloarthritis and the Human Leukocyte Antigen (HLA)-B(*)27 Connection. *Front Immunol* 2021; **12**: 601518 [*RCA*] [PMID: 33763060 DOI: 10.3389/fimmu.2021.601518] [FullText] [Full Text(PDF)]

21 **Rojas-Vargas M**, Muñoz-Gomariz E, Escudero A, Font P, Zarco P, Almodovar R, Gratacós J, Mulero J, Juanola X, Montilla C, Moreno E, Collantes-Estevez E; Registro Español de Espondiloartritis de la Sociedad Española de Reumatología Working Group. First signs and symptoms of spondyloarthritis--data from an inception cohort with a disease course of two years or less (REGISPONSER-Early). *Rheumatology (Oxford)* 2009; **48**: 404-409 [*RCA*] [PMID: 19208685 DOI: 10.1093/rheumatology/ken506] [FullText] [Full Text(PDF)]

22 **Karreman MC**, Luime JJ, Hazes JMW, Weel AEAM. The Prevalence and Incidence of Axial and Peripheral Spondyloarthritis in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *J Crohns Colitis* 2017; **11**: 631-642 [*RCA*] [PMID: 28453761 DOI: 10.1093/ecco-jcc/jjw199] [FullText]

23 **Cristea D**, Trandafir M, Bojinca VC, Ciontea AS, Andrei MM, Popa A, Lixandru BE, Militaru CM, Nascutiu AM, Predeteanu D, Ionescu R, Popescu C, Cotar AI, Popa MI, Spandidos DA, Codita I. Usefulness of complex bacteriological and serological analysis in patients with spondyloarthritis. *Exp Ther Med* 2019; **17**: 3465-3476 [*RCA*] [PMID: 30988725 DOI: 10.3892/etm.2019.7336] [FullText] [Full Text(PDF)]

24 **Gill T**, Asquith M, Rosenbaum JT, Colbert RA. The intestinal microbiome in spondyloarthritis. *Curr Opin Rheumatol* 2015; **27**: 319-325 [*RCA*] [PMID: 26002022 DOI: 10.1097/BOR.0000000000000187] [FullText]

25 **Wang WL**, Xu SY, Ren ZG, Tao L, Jiang JW, Zheng SS. Application of metagenomics in the human gut microbiome. *World J Gastroenterol* 2015; **21**: 803-814 [*RCA*] [PMID: 25624713 DOI: 10.3748/wjg.v21.i3.803] [FullText] [Full Text(PDF)]

26 **Zhou C**, Zhao H, Xiao XY, Chen BD, Guo RJ, Wang Q, Chen H, Zhao LD, Zhang CC, Jiao YH, Ju YM, Yang HX, Fei YY, Wang L, Shen M, Li H, Wang XH, Lu X, Yang B, Liu JJ, Li J, Peng LY, Zheng WJ, Zhang CY, Zhou JX, Wu QJ, Yang YJ, Su JM, Shi Q, Wu D, Zhang W, Zhang FC, Jia HJ, Liu DP, Jie ZY, Zhang X. Metagenomic profiling of the pro-inflammatory gut microbiota in ankylosing spondylitis. *J Autoimmun* 2020; **107**: 102360 [*RCA*] [PMID: 31806420 DOI: 10.1016/j.jaut.2019.102360] [FullText]

27 **Qin Q**, Yan S, Yang Y, Chen J, Li T, Gao X, Yan H, Wang Y, Wang J, Wang S, Ding S. A Metagenome-Wide Association Study of the Gut Microbiome and Metabolic Syndrome. *Front Microbiol* 2021; **12**: 682721 [*RCA*] [PMID: 34335505 DOI: 10.3389/fmicb.2021.682721] [Full Text] [Full Text(PDF)]

28 **Wei X**, Yan X, Zou D, Yang Z, Wang X, Liu W, Wang S, Li X, Han J, Huang L, Yuan J. Abnormal fecal microbiota community and functions in patients with hepatitis B liver cirrhosis as revealed by a metagenomic approach. *BMC Gastroenterol* 2013; **13**: 175 [*RCA*] [PMID: 24369878 DOI: 10.1186/1471-230X-13-175] [FullText] [Full Text(PDF)]

29 **Page MJ**, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R,

Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71 [*RCA*] [PMID: 33782057 DOI: 10.1136/bmj.n71] [FullText] [Full Text(PDF)]

30 **Deeks JJ**, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003; **7**: iii-iix, 1 [*RCA*] [PMID: 14499048 DOI: 10.3310/hta7270] [FullText]

31 **Yin J**, Sternes PR, Wang M, Song J, Morrison M, Li T, Zhou L, Wu X, He F, Zhu J, Brown MA, Xu H. Shotgun metagenomics reveals an enrichment of potentially cross-reactive bacterial epitopes in ankylosing spondylitis patients, as well as the effects of TNFi therapy upon microbiome composition. *Ann Rheum Dis* 2020; **79**: 132-140 [*RCA*] [PMID: 31662318 DOI: 10.1136/annrheumdis-2019-215763] [FullText]

32 **Li C**, Zhang Y, Yan Q, Guo R, Chen C, Li S, Zhang Y, Meng J, Ma J, You W, Wu Z, Sun W. Alterations in the gut virome in patients with ankylosing spondylitis. *Front Immunol* 2023; **14**: 1154380 [*RCA*] [PMID: 37063855 DOI: 10.3389/fimmu.2023.1154380] [FullText]

33 **Huang R**, Li F, Zhou Y, Zeng Z, He X, Fang L, Pan F, Chen Y, Lin J, Li J, Qiu D, Tian Y, Tan X, Song Y, Xu Y, Lai Y, Yi H, Gao Q, Fang X, Shi M, Zhou C, Huang J, He YT. Metagenome-wide association study of the alterations in the intestinal microbiome composition of ankylosing spondylitis patients and the effect of traditional and herbal treatment. *J Med Microbiol* 2020; **69**: 797-805 [*RCA*] [PMID: 31778109 DOI: 10.1099/jmm.0.001107] [FullText] [Full Text(PDF)]

34 **Wen C**, Zheng Z, Shao T, Liu L, Xie Z, Le Chatelier E, He Z, Zhong W, Fan Y, Zhang L, Li H, Wu C, Hu C, Xu Q, Zhou J, Cai S, Wang D, Huang Y, Breban M, Qin N, Ehrlich SD. Quantitative metagenomics reveals unique gut microbiome biomarkers in ankylosing spondylitis. *Genome Biol* 2017; **18**: 142 [*RCA*] [PMID: 28750650 DOI: 10.1186/s13059-017-1271-6] [FullText] [Full Text(PDF)]

35 **Ciccia F**, Rizzo A, Triolo G. Subclinical gut inflammation in ankylosing spondylitis. *Curr Opin Rheumatol* 2016; **28**: 89-96 [*RCA*] [PMID: 26599385 DOI: 10.1097/BOR.0000000000000239] [FullText]

36 **Rath HC**, Wilson KH, Sartor RB. Differential induction of colitis and gastritis in HLA-B27 transgenic rats selectively colonized with Bacteroides vulgatus or Escherichia coli. *Infect Immun* 1999; **67**: 2969-2974 [*RCA*] [PMID: 10338507 DOI: 10.1128/IAI.67.6.2969-2974.1999] [FullText]

37 **Maeda Y**, Kurakawa T, Umemoto E, Motooka D, Ito Y, Gotoh K, Hirota K, Matsushita M, Furuta Y, Narazaki M, Sakaguchi N, Kayama H, Nakamura S, Iida T, Saeki Y, Kumanogoh A, Sakaguchi S, Takeda K. Dysbiosis Contributes to Arthritis Development *via* Activation of Autoreactive T Cells in the Intestine. *Arthritis Rheumatol* 2016; **68**: 2646-2661 [*RCA*] [PMID: 27333153 DOI: 10.1002/art.39783] [FullText]

38 **Scher JU**, Sczesnak A, Longman RS, Segata N, Ubeda C, Bielski C, Rostron T, Cerundolo V, Pamer EG, Abramson SB, Huttenhower C, Littman DR. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. *Elife* 2013; **2**: e01202 [*RCA*] [PMID: 24192039 DOI: 10.7554/eLife.01202] [FullText] [Full Text(PDF)]

39 **Zhao Y**, Chen B, Li S, Yang L, Zhu D, Wang Y, Wang H, Wang T, Shi B, Gai Z, Yang J, Heng X, Yang J, Zhang L. Detection and characterization of bacterial nucleic acids in culture-negative synovial tissue and fluid samples from rheumatoid arthritis or osteoarthritis patients. *Sci Rep* 2018; **8**: 14305 [*RCA*] [PMID: 30250232 DOI: 10.1038/s41598-018-32675-w] [FullText] [Full Text(PDF)]

40 **Benler S**, Yutin N, Antipov D, Rayko M, Shmakov S, Gussow AB, Pevzner P, Koonin EV. Thousands of previously unknown phages discovered in whole-community human gut metagenomes. *Microbiome* 2021; **9**: 78 [*RCA*] [PMID: 33781338 DOI: 10.1186/s40168-021-01017-w] [FullText] [Full Text(PDF)]

41 **Ogita T**, Yamamoto Y, Mikami A, Shigemori S, Sato T, Shimosato T. Oral Administration of Flavonifractor plautii Strongly Suppresses Th2 Immune Responses in Mice. *Front Immunol* 2020; **11**: 379 [*RCA*] [PMID: 32184789 DOI: 10.3389/fimmu.2020.00379] [FullText] [Full Text (PDF)]

42 **Yang Y**, Du L, Shi D, Kong C, Liu J, Liu G, Li X, Ma Y. Dysbiosis of human gut microbiome in young-onset colorectal cancer. *Nat Commun* 2021; **12**: 6757 [*RCA*] [PMID: 34799562 DOI: 10.1038/s41467-021-27112-y] [FullText] [Full Text(PDF)]

43 **Bhutta NK**, Xu X, Jian C, Wang Y, Liu Y, Sun J, Han B, Wu S, Javeed A. Gut microbiota mediated T cells regulation and autoimmune diseases. *Front Microbiol* 2024; **15**: 1477187 [*RCA*] [PMID: 39749132 DOI: 10.3389/fmicb.2024.1477187] [FullText] [Full Text(PDF)]

44 **Yoo JY**, Groer M, Dutra SVO, Sarkar A, McSkimming DI. Gut Microbiota and Immune System Interactions. *Microorganisms* 2020; **8**: 1587 [*RCA*] [PMID: 33076307 DOI: 10.3390/microorganisms8101587] [FullText] [Full Text(PDF)]

45 **Larsen JM**. The immune response to Prevotella bacteria in chronic inflammatory disease. *Immunology* 2017; **151**: 363-374 [*RCA*] [PMID: 28542929 DOI: 10.1111/imm.12760] [FullText]

46 **Iljazovic A**, Amend L, Galvez EJC, de Oliveira R, Strowig T. Modulation of inflammatory responses by gastrointestinal Prevotella spp. - From associations to functional studies. *Int J Med Microbiol* 2021; **311**: 151472 [*RCA*] [PMID: 33461110 DOI: 10.1016/j.ijmm.2021.151472] [Full Text]

47 **Muruganandam A**, Migliorini F, Jeyaraman N, Vaishya R, Balaji S, Ramasubramanian S, Maffulli N, Jeyaraman M. Molecular Mimicry Between Gut Microbiome and Rheumatoid Arthritis: Current Concepts. *Med Sci (Basel)* 2024; **12**: 72 [*RCA*] [PMID: 39728421 DOI: 10.3390/medsci12040072] [FullText] [Full Text(PDF)]

48 **Mohebali N**, Weigel M, Hain T, Sütel M, Bull J, Kreikemeyer B, Breitrück A. Faecalibacterium prausnitzii, Bacteroides faecis and Roseburia intestinalis attenuate clinical symptoms of experimental colitis by regulating Treg/Th17 cell balance and intestinal barrier integrity. *Biomed Pharmacother* 2023; **167**: 115568 [*RCA*] [PMID: 37793274 DOI: 10.1016/j.biopha.2023.115568] [FullText]

49 **Tang J**, Mo S, Fan L, Fu S, Liu X. Causal association of gut microbiota on spondyloarthritis and its subtypes: a Mendelian randomization analysis. *Front Immunol* 2024; **15**: 1284466 [*RCA*] [PMID: 38390322 DOI: 10.3389/fimmu.2024.1284466] [FullText] [Full Text(PDF)]

50 **Romero-Figueroa MDS**, Ramírez-Durán N, Montiel-Jarquín AJ, Horta-Baas G. Gut-joint axis: Gut dysbiosis can contribute to the onset of rheumatoid arthritis *via* multiple pathways. *Front Cell Infect Microbiol* 2023; **13**: 1092118 [*RCA*] [PMID: 36779190 DOI: 10.3389/fcimb.2023.1092118] [FullText] [Full Text(PDF)]

51 **Zhang L**, Chen F, Zeng Z, Xu M, Sun F, Yang L, Bi X, Lin Y, Gao Y, Hao H, Yi W, Li M, Xie Y. Advances in Metagenomics and Its Application in Environmental Microorganisms. *Front Microbiol* 2021; **12**: 766364 [*RCA*] [PMID: 34975791 DOI: 10.3389/fmicb.2021.766364] [FullText] [Full Text(PDF)]

52 **Yang SY**, Han SM, Lee JY, Kim KS, Lee JE, Lee DW. Advancing Gut Microbiome Research: The Shift from Metagenomics to Multi-Omics and Future Perspectives. *J Microbiol Biotechnol* 2025; **35**: e2412001 [*RCA*] [PMID: 40223273 DOI: 10.4014/jmb.2412.12001] [FullText]

53 **Nakayama M**, Niki Y, Kawasaki T, Takeda Y, Horiuchi K, Sasaki A, Okada Y, Umezawa K, Ikegami H, Toyama Y, Miyamoto T. Enhanced susceptibility to lipopolysaccharide-induced arthritis and endotoxin shock in interleukin-32 alpha transgenic mice through induction of tumor necrosis factor alpha. *Arthritis Res Ther* 2012; **14**: R120 [*RCA*] [PMID: 22613074 DOI: 10.1186/ar3850] [FullText] [Full Text(PDF)]

54 **Magnúsdóttir S**, Ravcheev D, de Crécy-Lagard V, Thiele I. Systematic genome assessment of B-vitamin biosynthesis suggests co-operation among gut microbes. *Front Genet* 2015; **6**: 148 [*RCA*] [PMID: 25941533 DOI: 10.3389/fgene.2015.00148] [FullText] [Full Text(PDF)]

55 **Song ZY**, Yuan D, Zhang SX. Role of the microbiome and its metabolites in ankylosing spondylitis. *Front Immunol* 2022; **13**: 1010572 [*RCA*] [PMID: 36311749 DOI: 10.3389/fimmu.2022.1010572] [FullText] [Full Text(PDF)]

56 **Cusick MF**, Libbey JE, Fujinami RS. Molecular mimicry as a mechanism of autoimmune disease. *Clin Rev Allergy Immunol* 2012; **42**: 102-111 [*RCA*] [PMID: 22095454 DOI: 10.1007/s12016-011-8294-7] [FullText] [Full Text(PDF)]

57 **Zhang L**, Zhang YJ, Chen J, Huang XL, Fang GS, Yang LJ, Duan Y, Wang J. The association of HLA-B27 and Klebsiella pneumoniae in ankylosing spondylitis: A systematic review. *Microb Pathog* 2018; **117**: 49-54 [*RCA*] [PMID: 29438717 DOI: 10.1016/j.micpath.2018.02.020] [FullText]

58 **Maciel-Fiuza MF**, Muller GC, Campos DMS, do Socorro Silva Costa P, Peruzzo J, Bonamigo RR, Veit T, Vianna FSL. Role of gut microbiota in infectious and inflammatory diseases. *Front Microbiol* 2023; **14**: 1098386 [*RCA*] [PMID: 37051522 DOI: 10.3389/fmicb.2023.1098386] [FullText] [Full Text(PDF)]

59 **Plaza-Diaz J**, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of Action of Probiotics. *Adv Nutr* 2019; **10**: S49-S66 [*RCA*] [PMID: 30721959 DOI: 10.1093/advances/nmy063] [FullText]

60 **Abouelela ME**, Helmy YA. Next-Generation Probiotics as Novel Therapeutics for Improving Human Health: Current Trends and Future Perspectives. *Microorganisms* 2024; **12**: 430 [*RCA*] [PMID: 38543481 DOI: 10.3390/microorganisms12030430] [FullText] [Full Text(PDF)]

61 **Belvoncikova P**, Maronek M, Gardlik R. Gut Dysbiosis and Fecal Microbiota Transplantation in Autoimmune Diseases. *Int J Mol Sci* 2022; **23**: 10729 [*RCA*] [PMID: 36142642 DOI: 10.3390/ijms231810729] [FullText] [Full Text(PDF)]

62 **Hou S**, Yu J, Li Y, Zhao D, Zhang Z. Advances in Fecal Microbiota Transplantation for Gut Dysbiosis-Related Diseases. *Adv Sci (Weinh)* 2025; **12**: e2413197 [*RCA*] [PMID: 40013938 DOI: 10.1002/advs.202413197] [FullText] [Full Text(PDF)]

63 **Martín R**, Rios-Covian D, Huillet E, Auger S, Khazaal S, Bermúdez-Humarán LG, Sokol H, Chatel JM, Langella P. Faecalibacterium: a bacterial genus with promising human health applications. *FEMS Microbiol Rev* 2023; **47**: fuad039 [*RCA*] [PMID: 37451743 DOI: 10.1093/femsre/fuad039] [FullText] [Full Text(PDF)]

64 **Liu XF**, Shao JH, Liao YT, Wang LN, Jia Y, Dong PJ, Liu ZZ, He DD, Li C, Zhang X. Regulation of short-chain fatty acids in the immune system. *Front Immunol* 2023; **14**: 1186892 [*RCA*] [PMID: 37215145 DOI: 10.3389/fimmu.2023.1186892] [FullText] [Full Text(PDF)]

65 **Zikou E**, Koliaki C, Makrilakis K. The Role of Fecal Microbiota Transplantation (FMT) in the Management of Metabolic Diseases in Humans: A Narrative Review. *Biomedicines* 2024; **12**: 1871 [*RCA*] [PMID: 39200335 DOI: 10.3390/biomedicines12081871] [FullText] [Full Text (PDF)]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2025 Baishideng Publishing Group Inc. All rights reserved.