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Dysregulation of gut microbiota composition and function in autoimmune diseases: A meta-analysis

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Abstract
Background and Objectives: Recent research has underscored the crucial function of gut microbiota in regulating immunological homeostasis and the pathogenesis of autoimmune disorders. Nonetheless, discrepancies persist concerning certain microbial modifications across several autoimmune disorders. This meta-analysis sought to assess the dysregulation of gut microbiota composition and functional characteristics in patients with autoimmune disorders relative to healthy controls.
Materials and Methods: A thorough literature review was conducted in the PubMed, Scopus, and Web of Science databases until 2019. Studies detailing gut microbiota makeup in individuals with autoimmune disorders were incorporated. Data were obtained from 60 patients and their comparable healthy controls in eligible trials. A random-effects model was used to look at microbial diversity indices, the relative abundances of important bacterial taxa, and projected functional pathways. The I^2 statistic was used to look at how different studies were, and Egger's test was used to look at publication bias.
Results: The meta-analysis demonstrated a notable decrease in α-diversity indices (Shannon and Simpson) in autoimmune disease patients relative to controls ($p < 0.01$). Analysis of β-diversity revealed distinct clustering of microbial communities, signifying compositional dysbiosis. Relative abundance analysis showed that genera that make short-chain fatty acids (SCFAs), like Faecalibacterium and Roseburia, were much less common, while pro-inflammatory taxa, like Enterobacteriaceae and Prevotella, were much more common. Functional pathway prediction showed that patients had less butyrate metabolism and more lipopolysaccharide biosynthesis pathways. Subgroup analysis pointed to disease-specific microbial signatures, especially in rheumatoid arthritis and systemic lupus erythematosus.
Conclusion: This meta-analysis shows that autoimmune illnesses have a lot of gut microbial dysbiosis, which means that the variety of gut microbes is lower, helpful commensals are less common, and metabolic functions are different. These results highlight the promise of gut microbiota-targeted therapies as supplementary approaches for the prevention and treatment of autoimmune diseases.

Keywords: Gut microbiota, Autoimmune diseases, Dysbiosis, Meta-analysis, Immune modulation, Microbial diversity

Introduction
Autoimmune illnesses are a heterogeneous collection of chronic inflammatory conditions marked by the breakdown of immunological tolerance, leading to the immune system's assault on self-antigens. The causes of autoimmune disorders such rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, and multiple sclerosis are many [1, 2]. They are caused by a combination of genetic predisposition, environmental factors, and problems with the immune system. In recent years, mounting data has underscored the gut microbiota as a pivotal environmental factor affecting immune system development and homeostasis [3, 4].
The human gastrointestinal tract contains trillions of bacteria that are crucial for nutrition metabolism, preservation of epithelial integrity, and regulation of host immunity. A balanced gut microbial community is essential for immunological tolerance; in contrast, microbial imbalance or dysbiosis has been increasingly linked to the etiology of autoimmune disorders [5-7]. Numerous studies have documented changes in the diversity and composition of gut microbiota in individuals with autoimmune diseases, frequently marked by a reduction of beneficial commensals such as Faecalibacterium prausnitzii and Bifidobacterium, alongside an elevation in pro-inflammatory taxa, including Enterobacteriaceae and Prevotella species [8, 9].

Numerous research have examined these correlations, although the findings are inconsistent owing to disparities in study populations, sequencing techniques, and illness characteristics. Moreover, the functional consequences of microbiota modifications especially their impact on metabolic and immunological pathways remain little defined. A rigorous synthesis of existing information using meta-analysis is crucial to elucidate the patterns of gut microbial dysregulation in autoimmune illnesses and to pinpoint shared microbiological and functional signatures that may influence disease [10, 11].

Consequently, the current meta-analysis seeks to thoroughly assess the changes in gut microbiota composition and anticipated functional characteristics in patients with autoimmune disorders relative to healthy controls. The results are anticipated to augment comprehension of the microbiota-immune axis in autoimmunity and may establish a basis for the formulation of microbiota-oriented diagnostic and therapeutic approaches [12, 13].

MaterialS and Methods

This work was executed as a systematic review and meta-analysis to assess changes in gut microbiota composition and functional characteristics in patients with autoimmune disorders relative to healthy controls. This research was executed at the Department of Physiology, Sri Balaji Medical College, Chennai, Tamil Nadu, India, from October 2018 to September 2019. The meta-analysis was conducted following the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Study Selection

All of the records that were found were put into EndNote software to get rid of duplicates. Two reviewers looked over the titles and abstracts separately, and then they looked over the complete text to see if it was eligible. Discrepancies were resolved through consensus or by consulting a third reviewer.

Inclusion Criteria

- Human subjects diagnosed with autoimmune diseases.
- Healthy individuals without autoimmune or chronic inflammatory conditions.
- Studies reporting gut microbiota composition, diversity indices.
- Observational studies.
- Sufficient quantitative data to extract.
- Articles published in English.

Exclusion Criteria

- Reviews, editorials, conference abstracts, case reports, or animal studies.
- Studies involving subjects under antibiotic, probiotic, or immunosuppressive therapy within 3 months prior to sampling.
- Lack of appropriate healthy control group.
- Insufficient or incomplete data on microbiota composition or diversity.
- Non-human or *in vitro* studies.
- Duplicate publications or overlapping datasets.

Data Extraction and Quality Assessment:

Two scientists separately extracted data using a standardized form. The data that was taken out included the author's name, the year the paper was published, the country, the type of autoimmune illness, the sequencing platform, the diversity indices, and the relative abundance of bacterial taxa. The Newcastle-Ottawa Scale (NOS) for observational studies was used to rate the quality of the studies that were included.

Statistical Analysis

We used RevMan (version 5.4) and Comprehensive Meta-Analysis (CMA) software to do meta-analyses. Using a random-effects model, we found pooled estimates of the mean differences for alpha diversity indices and the relative abundances of bacterial taxa. The I^2 statistic was used to measure heterogeneity, and Egger's regression test and funnel plot analysis were used to look for publication bias. A p-value of less than 0.05 was deemed statistically significant.

Results

Initially, electronic database searches found a total of 1,248 documents. After eliminating duplicates and evaluating titles and abstracts, 35 studies underwent comprehensive text evaluation. Finally, the meta-analysis included 12 research that matched the inclusion criteria. These studies included 60 patients with autoimmune disorders and 60 healthy controls.

Table 1: Summary of Studies Included in the Meta-Analysis

Study ID	Country	Disease Type	Sample Size (Patients/Controls)	Sequencing Platform	Major Findings
Zhang *et al*., 2010	China	Rheumatoid Arthritis	10/10	16S rRNA (Illumina MiSeq)	↓ *Faecalibacterium*, ↑ *Prevotella*
Kumar *et al*., 2011	India	Systemic Lupus Erythematosus	6/6	16S rRNA (Ion Torrent)	↓ *Bifidobacterium*, ↑ *Enterobacteriaceae*
Park *et al*., 2019	Korea	Multiple Sclerosis	5/5	16S rRNA (Illumina HiSeq)	↓ *Roseburia*, ↑ *Akkermansia*
Li *et al*., 2012	USA	Type 1 Diabetes	8/8	Whole Metagenome	↓ *Lactobacillus*, ↑ *Desulfovibrio*
Silva *et al*., 2013	Brazil	Inflammatory Bowel Disease	6/6	16S rRNA (Illumina MiSeq)	↓ *F. prausnitzii*, ↑ *Escherichia coli*
Ahmed *et al*., 2014	Egypt	Rheumatoid Arthritis	5/5	16S rRNA	↓ *Clostridium IV*, ↑ *Bacteroides*
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Table 1 provides a summary of the key features of the studies that were part of this meta-analysis. The majority of research utilized 16S rRNA sequencing, concentrating on autoimmune illnesses including rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease. Even though the studies were done in different places and used different methods, the same patterns of microbial dysbiosis were seen.

Table 2: Comparison of α-Diversity Indices between Autoimmune Patients and Controls

Diversity Index	Patients (Mean ± SD)	Controls (Mean ± SD)	Mean Difference	p-Value
Shannon Index	3.42 ± 0.51	4.12 ± 0.47	-0.70	<0.001
Simpson Index	0.75 ± 0.08	0.86 ± 0.06	-0.11	0.002
Chao1 Richness	280 ± 35	340 ± 42	-60	0.004
Observed OTUs	235 ± 28	305 ± 30	-70	<0.001

Patients with autoimmune diseases demonstrated markedly decreased α-diversity across all indices when compared to healthy controls, signifying a decrease in microbial richness and evenness. This indicates that autoimmune disorders correlate with the depletion of beneficial taxa and a reduction in total microbiome complexity.

Table 3: Pooled Relative Abundance of Dominant Bacterial Genera

Bacterial Genus	Patients (%)	Controls (%)	Mean Difference (%)	Direction of Change
Faecalibacterium	5.4	10.2	-4.8	↓ Decreased
Roseburia	3.1	6.5	-3.4	↓ Decreased
Prevotella	8.9	3.7	+5.2	↑ Increased
Enterobacteriaceae	6.8	2.4	+4.4	↑ Increased
Bacteroides	12.3	9.1	+3.2	↑ Increased
Bifidobacterium	4.2	7.5	-3.3	↓ Decreased

Table 3 shows combined data on how common different types of bacteria are. Patients with autoimmune conditions exhibited a significant reduction in SCFA-producing genera (Faecalibacterium, Roseburia, Bifidobacterium) and an increase in pro-inflammatory taxa (Prevotella, Enterobacteriaceae), indicative of an inflammatory gut milieu.

Table 4: Functional Pathway Prediction (PICRUSt/KEGG Analysis)

Functional Pathway	Fold Change (Patients vs. Controls)	Direction	p-Value
Butyrate metabolism	0.56	↓ Decreased	0.001
Lipopolysaccharide (LPS) biosynthesis	1.78	↑ Increased	0.003
Amino acid metabolism	0.74	↓ Decreased	0.021
Bile acid biosynthesis	1.42	↑ Increased	0.012
Vitamin B12 synthesis	0.61	↓ Decreased	0.034

Functional prediction indicated that autoimmune patients demonstrated the inhibition of advantageous metabolic pathways, including butyrate and vitamin B12 synthesis, whereas pro-inflammatory pathways, such as LPS and bile acid production, were elevated. These changes point to possible metabolic pathways that connect dysbiosis to immunological activation.

Table 5: Subgroup Analysis by Disease Type

Disease Type	Significant Changes in Microbiota	Dominant Dysbiotic Features	Effect on α-Diversity
Rheumatoid Arthritis	↓ *Faecalibacterium*, ↑ *Prevotella*	Reduced SCFA producers	↓
Systemic Lupus Erythematosus	↓ *Bifidobacterium*, ↑ *Enterobacteriaceae*	Increased pro-inflammatory taxa	↓
Multiple Sclerosis	↓ *Roseburia*, ↑ *Akkermansia*	Mucus layer thinning	↓
Inflammatory Bowel Disease	↓ *F. prausnitzii*, ↑ *E. coli*	Disrupted mucosal barrier	↓
Type 1 Diabetes	↓ *Lactobacillus*, ↑ *Desulfovibrio*	Enhanced oxidative stress	↓

Subgroup analysis revealed microbial changes specific to the illness. Nonetheless, a prevalent tendency of reduced α-diversity and loss of beneficial commensals was observed across all autoimmune disorders, indicating a common microbial dysregulation pattern in autoimmunity.

Discussion

The results of this meta-analysis offer compelling evidence that the composition and function of gut microbiota are markedly different in individuals with autoimmune disorders compared to healthy controls. The persistent decline in microbial diversity, along with the proliferation of pro-inflammatory taxa and the reduction of short-chain fatty acid (SCFA)-producing bacteria, highlights the pivotal role of intestinal dysbiosis in the etiology of autoimmunity [13-15].

A key finding of this study was the substantial reduction in α-diversity among patients with autoimmune diseases. A decrease in microbial diversity is linked to diminished functional redundancy and resilience in the gut environment, making humans more susceptible to immunological imbalance. This finding aligns with prior meta-analyses and clinical investigations indicating a comparable reduction in variety in rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel illness. The reduction of microbial diversity may compromise mucosal barrier integrity and undermine immunological tolerance, resulting in heightened antigenic exposure and persistent inflammation [16-18].

The aggregated analysis demonstrated a uniform pattern of dysbiosis, marked by the reduction of advantageous commensals, including Faecalibacterium, Roseburia, and Bifidobacterium, alongside the proliferation of pro-inflammatory taxa such as Prevotella and Enterobacteriaceae. Faecalibacterium prausnitzii and Roseburia are well-known for making butyrate, a short-chain fatty acid (SCFA) that keeps the epithelial cells in the colon healthy and has anti-inflammatory effects by helping regulatory T cells differentiate. Consequently, their

depletion in autoimmune disorders may result in compromised epithelial integrity and dysregulated immunological signalling [19-21].

On the other hand, higher levels of Prevotella have been linked to Th17-mediated inflammation, especially in rheumatoid arthritis. This suggests a probable connection between microbial imbalance and autoimmune activation. The increase in Enterobacteriaceae further indicates a pro-inflammatory microbial milieu that can create endotoxins that make immune responses worse [22, 23].

Functional pathway analysis in this meta-analysis revealed the downregulation of butyrate metabolism and vitamin B12 biosynthesis, coupled with the overexpression of lipopolysaccharide (LPS) and bile acid biosynthesis pathways. These alterations show that gut dysbiosis not only modifies the types of microbes in the gut, but also throws off the body's balance of metabolism. Decreased SCFA production compromises intestinal barrier integrity and inhibits anti-inflammatory cytokine synthesis, whereas heightened LPS biosynthesis can activate toll-like receptor 4 (TLR4) pathways, instigating systemic inflammation. Changes in bile acid metabolism may also affect how immune cells develop and how inflammation signals are sent, which could make autoimmune diseases worse [24, 25].

Subgroup analysis identified disease-specific dysbiotic signals. For example, a lot of Prevotella copri was linked to rheumatoid arthritis, while a lot of Akkermansia muciniphila was linked to multiple sclerosis and damage to mucosal layers. Patients with inflammatory bowel illness had higher levels of Escherichia coli and lower levels of Faecalibacterium prausnitzii, which is consistent with earlier findings of gut barrier disruption. Even with these differences, the same traits of decreased diversity and a lack of SCFA producers in autoimmune diseases point to a common microbial dysregulation route that causes distinct illness symptoms [25, 26].

The current results underscore the capability of the gut microbiota to serve as both a biomarker and a therapeutic target in autoimmune disorders. Interventions like probiotics, prebiotics, dietary changes, and fecal microbiota transplantation (FMT) may help bring microbial balance and immunological homeostasis back to normal. New research also backs up the idea that SCFA supplements and metabolites from microbes can be used as immunomodulatory treatments. Subsequent clinical trials are necessary to assess the efficacy and safety of microbiota-targeted strategies in human autoimmune diseases [26, 27].

Conclusion

This meta-analysis offers extensive evidence that individuals with autoimmune disorders demonstrate considerable disruption of gut microbiota composition and function in comparison to healthy persons. The results generally indicate diminished microbial diversity, depletion of advantageous commensal and short-chain fatty acid-producing genera such as Faecalibacterium, Roseburia, and Bifidobacterium, alongside an abundance of pro-inflammatory taxa including Prevotella and Enterobacteriaceae. Functional pathway analysis also indicated the inhibition of butyrate metabolism and the promotion of lipopolysaccharide production, demonstrating a mechanistic connection between microbial dysbiosis and immunological activation. In general, these results show how important gut microbiota are in the development of autoimmune diseases and how microbiota modulation could be a useful addition to treatment. Future longitudinal and multi-omics research are necessary to confirm these findings, elucidate causal linkages, and formulate tailored microbiome-based therapies for immune-mediated diseases.

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Conflict of Interest

None.

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