

Behcet's disease and Microbiome

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Abstract

Behçet's disease (BD) is a chronic, relapsing vasculitis that affects multiple organ systems, with its underlying causes still not fully understood. Emerging research points to the potential role of the human microbiome in shaping immune responses involved in BD. This systematic review summarizes findings from 15 studies that investigated alterations in gut and oral microbiota among BD patients. The included studies - mostly cross-sectional and case-control - encompassed diverse populations from countries such as Italy, the UK, Turkey, Japan, China, Mongolia, South Korea, and the Netherlands. A recurring pattern across these studies was a decline in microbial diversity and a consistent reduction in beneficial, short-chain fatty acid-producing bacteria, including *Faecalibacterium prausnitzii*, *Roseburia*, and *Akkermansia*. At the same time, there was a considerable increase in potentially pro-inflammatory genera, such as *Eggerthella*, *Prevotella*, and *Streptococcus sanguinis*. The dysbiosis of gut and oral microbiome might be a key driver of BD pathogenesis, leading to the dysfunction of intestinal barrier and sustained inflammation. Understanding the mechanisms of microbiome-driven inflammation can contribute to developing new therapeutic methods.

Introduction

1.1 Background

Behcet's disease (BD) represents a chronic, multisystem, relapsing disorder of unknown etiology. Recurrent mucocutaneous ulcers, variable vasculitis and systemic involvement of multiple organs are typical for BD. One of the main features of BD is its geographical distribution, since it predominantly affects populations along the ancient Silk Road, including regions from the Mediterranean countries to East Asia (Sulu et al., 2025). The epidemiology of BD can be described with its global prevalence of approximately 10.3 per 100,000 individuals; Turkey has the highest rates at 420 cases and Iran with 80 cases per 100,000, whereas the disease is relatively uncommon in Western Europe and North America (Davatchi et al., 2017). Behcet's disease commonly occurs in individuals with the age from twenty to forty with the male-to-female ratio being different according to geographical location (Oguz et al., 2017). It is a very fatal disease because of systemic involvement, an unpredictable course, and severe forms with multiple complications like loss of vision, vascular thrombosis, or perforation of the gastrointestinal tract (Evereklioglu, 2005). BD pathogenesis is unknown, but it is suggested by recent studies that a genetic predisposition in close association with HLA-B51 and environmental triggers, such as microbial stimuli, may trigger abnormal immune responses and induce Behcet's disease (Joubert et al., 2023). Microbial dysbiosis was suggested as a second key factor involved in immune dysregulation and BD chronic inflammation, i.e., modulation of disease activity and course by gut and oral microbiota (Leccese & Alpsoy, 2019). Therefore, microbiome change in BD should be studied to understand the pathogenesis and develop effective treatment techniques.

Although the exact cause of BD remains unclear, current evidence suggests a multifactorial etiology including genetic, environmental, and immunological factors. Among genetic risk factors, the highest association with the HLA-B51 allele has been most strongly associated with BD susceptibility (Joubert et al., 2023). However, the presence of HLA-B51 alone is not enough to cause disease. The environmental factors, including infections and microbial exposures, may act as triggers in genetically predisposed people. In recent years, the role of the microbiome in BD, particularly alterations in gut and oral microbial communities received increasing attention. Microbial dysbiosis may disrupt immune homeostasis, contribute to chronic inflammation, and influence disease activity and progression (Leccese & Alpsoy, 2019). Therefore, exploring microbiota alterations in BD is relevant for understanding disease mechanisms and identifying potential therapeutic targets.

1.2 Clinical manifestations

Behcet's disease presents with a wide range of clinical features due to its systemic inflammatory nature and capacity to involve multiple organ systems. Patients often show a combination of mucocutaneous, ocular, vascular, neurological, and gastrointestinal symptoms, which may vary in severity and prevalence depending on the individual's age, sex, and geographic origin (Seyahi, 2019). The most consistent and early manifestations are mucocutaneous lesions—specifically recurrent oral and genital ulcers. Oral aphthous ulcers occur in nearly all patients (approximately 95%), while genital ulcers are reported in 80–90% of cases. These ulcers are

typically painful, recurrent, and can precede systemic involvement by months or even years (Bettioli et al., 2020).

For the diagnosis of BD, recurrent oral ulcers and at least two out of the following four features are needed according to international criteria: genital ulcers, eye lesions, classical skin lesions, or a positive pathergy test (Davatchi, 2012). The more recent International Criteria for Behçet's Disease (ICBD) adds vascular and neurological manifestations to the classification criteria, acknowledging the full range of the disease's systemic forms (Davatchi et al., 2014).

Neurological presentation, or neuro-Behçet's disease (NBD), occurs less often and is observed in approximately 5–10% of patients but with severe morbidity. NBD appears in two general forms: parenchymal presentation, including meningoencephalitis, brainstem syndromes, and inflammation of the spinal cord; and non-parenchymal presentation, with dural sinus thrombosis and intracranial hypertension (Saip et al., 2014; Haghighi et al., 2005).

Ocular involvement affects up to 70% of BD patients and is one of the most severe complications. It often follows the appearance of oral ulcers. The most common presentation is uveitis, which may affect the anterior chamber, posterior segment, or both (panuveitis). If left untreated, ocular BD can progress to irreversible complications such as retinal vasculitis, optic atrophy, and blindness (Verity et al., 2003; Zierhut et al., 2013).

Gastrointestinal involvement is termed intestinal BD, primarily affects the ileocecal region and presents with abdominal pain, nausea, vomiting, diarrhea, gastrointestinal bleeding, and intestinal ulceration, sometimes mimicking Crohn's disease (CD) (Nguyen et al., 2021).

Musculoskeletal manifestations include non-erosive, oligoarticular arthritis and arthralgia with 40 and 70% prevalence, commonly affecting large joints: knees, wrists, ankles and elbows (Bicer, 2012). Additionally, BD has clinical similarities with spondyloarthropathy (SpA) due to the presence of sacroiliitis (Chang et al., 2002). The disease follows a relapsing-remitting course, and the severity of organ involvement varies among individuals.

1.3 Etiology

The etiology of BD is multifactorial, involving a complex combination of genetic predisposition, immune system dysregulation, environmental triggers, and more recently, microbiome alterations (Mattioli et al., 2021). The geographical distribution of BD suggests a strong genetic risk factor in association with HLA-B51, a major histocompatibility complex (MHC) class I allele, that plays a role in antigen presentation and immune response regulation, but HLA-B51 alone is not sufficient for disease development (Akkoç, 2018). Genome-wide association studies (GWAS) confirmed the strong association of HLA-B51 with BD and have identified several non-HLA genetic loci that emerge as risk factors for BD, including genes involved in cytokine signaling such as IL10 and IL12, and genes involved in inflammation as endoplasmic reticulum aminopeptidase 1 (ERAP1) (Gao et al., 2022). Genetic predispositions can contribute to onset of BD coupled with environmental triggers as infectious pathogens (Lavalle et al., 2024). Different bacterial and viral agents such as streptococcal species, mycobacteria, *Staphylococcus aureus*, *Helicobacter pylori*, Herpes simplex virus-1 (HSV), and Epstein-Barr virus (EBV) have been suggested in pathogenesis of BD (Di Cianni et al., 2024). The interaction between infections and the host's immune system can lead to an abnormal immune response of both innate and adaptive immunity (Cheng et al., 2023).

Immunologically, BD has characteristics of both autoimmune and autoinflammatory diseases due to overlapping pathological mechanisms. From the autoinflammatory side of BD, neutrophils initiate and maintain increased innate immune response without the presence of pathogenic autoimmune T and B cells (Gül, 2015). Tissue damage and chronic inflammation are mediated by hyperactive neutrophils due to increased levels of pro-inflammatory cytokines such as IL-1, IL-8, TNF- α and IFN- γ (Le Joncour, 2023). Neutrophil hyperresponsiveness leads to perivascular infiltration in the initial phase of inflammation in BD ulcers (Tong et al., 2019). During inflammation, neutrophils undergo oxidative burst leading to excessive production of reactive oxygen species (ROS), which promote chemotaxis, modulate expression of adhesive molecules, adhesion of neutrophils to the endothelial surface, and extravasation into tissues (Emmi et al., 2019). ROS released by activated neutrophils can oxidize fibrinogen, disrupting its structure and function, thereby increasing thrombus formation (Becatti et al., 2016). Moreover, the production of ROS drives a key molecular mechanism of neutrophil death called NETosis (Batu et al., 2020). During this apoptosis, neutrophils release decondensed chromatin structures embedded with antimicrobial proteins and citrullinated histones to form neutrophil extracellular traps (NETs) (Vural et al., 2021). NETs can trap pathogens and also contribute to vascular damage and thrombosis (Sørensen & Borregaard, 2016). In addition to autoinflammatory characteristics, neutrophils activate adaptive immune response in BD by antigen presentation, and therefore sharing features of autoimmunity. Posttranslationally modified histones of NETs with bacterial antigens can be uptaken by phagocytes during acute inflammation and presented to immune system as a threat and break the tolerance of immune system, leading to production of pathogenic autoantibodies (Dwivedi & Radic, 2013). Elevated NET autoantigens were detected in several autoimmune diseases as rheumatoid arthritis (RA), multiple sclerosis (MS), and systemic lupus erythematosus (SLE) (Fousert et al., 2020). Similarly, samples of BD patients in an active disease state revealed higher NETs production compared to inactive BD and control groups (Le Joncour et al., 2019).

Another autoimmune feature of BD is immune dysregulation, which is seen via imbalance of T helper cell subsets when T helper 1 (Th1) and T helper 17 (Th17) cell levels are increased in blood, cerebrospinal fluid (CSF), skin, and the number of regulatory T cells (Tregs) are reduced in BD patients (Emmi et al., 2016). Th1 and Th17 cells produce pro-inflammatory cytokines IFN- γ , IL-17, and IL-23, while Tregs inhibit the activity of these autoreactive T cells to sustain immune tolerance (Mehana et al., 2022). Th17/Treg ratio ($p=0.0008$) and IL-17 ($p=0.0003$), IL-23 ($p=0.0023$) levels were found to be elevated in BD patients, indicating that Th17/Treg imbalance leads to aberrant secretion of inflammatory and immunosuppressive cells and cytokines (Ahmadi et al., 2018). The exact mechanisms of BD pathogenesis is unclear; while innate and adaptive immune pathways overlap, other environmental triggers such as infectious agents and mucosal microbiota influence the disease course.

1.4 Immunopathogenesis and the Role of the Microbiome

Recent research is discovering the role of mucosal microbiota in the immunopathogenesis of Behçet's disease (BD), highlighting a potential link between environmental exposures and immune system dysfunction. Imbalance in the composition, diversity, or function of the microbiota is called dysbiosis and has been implicated in the development of several autoimmune and autoinflammatory diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis (RA), multiple sclerosis (MS), and systemic lupus erythematosus (SLE) (Zhou et al., 2025). A common finding across these

conditions includes reduced microbial diversity, a loss of short-chain fatty acid (SCFA)-producing bacteria, and an enrichment of pro-inflammatory or pathogenic species (Wang et al., 2021).

1.5 Microbiota-targeted therapeutic strategies in BD

Therapies aimed at restoring a healthy microbiome are gaining interest as complementary approaches for managing Behçet's disease (BD). Preliminary studies suggest that supplementing with butyrate, a short-chain fatty acid with known anti-inflammatory properties, can help reduce disease activity. For instance, adherence to a Mediterranean diet supplemented with butyrate was associated with symptom improvement and lower systemic inflammation in BD patients (Emmi et al., 2021; Ersoy et al., 2024). Another promising approach is fecal microbiota transplantation (FMT), which has shown potential in alleviating chronic inflammatory symptoms by rebalancing the microbial community. However, FMT remains experimental in BD and carries risks such as infection and adverse immune reactions (M. Wu et al., 2024). While these early findings are encouraging, robust clinical trials are still needed to establish the safety, efficacy, and long-term benefits of microbiota-targeted interventions in BD.

1.6 Rationale

Gut and oral microbiome play a significant role in regulating immune responses in autoinflammatory and autoimmune diseases. Multiple studies suggested that dysbiosis of microbiota may initiate and worsen BD (Joubert et al., 2023). Despite these insights, a clear signature of microbiome alterations associated with BD is lacking and this study aims to conduct a systematic review to comprehensively evaluate the microbiota dysbiosis in BD and its role in immune dysregulation.

Specific aim(s):

1. Analyze gut and oral microbiota composition in BD patients compared to healthy individuals, identifying microbial signatures associated with disease presence and activity.
2. Assess the association between microbiota composition and immune dysregulation, particularly regarding cytokine imbalances, NETosis, and gut barrier integrity.

Hypothesis:

This review hypothesizes that BD is associated with gut and oral microbiota dysbiosis, characterized by a reduction in butyrate-producing bacteria and an increase in pro-inflammatory microbial species. Furthermore, microbial alterations are expected to correlate with disease subtypes and immune dysfunction, particularly Th1/Th17-driven inflammation and neutrophil hyperactivity. Identifying these microbial signatures could provide insights into BD pathogenesis and pave the way for microbiome-targeted interventions as adjunctive therapies.

Materials and Methods

2.1 Search strategy and selection process

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological quality. A comprehensive literature search was conducted across PubMed, Scopus, and Cochrane library databases, using the MeSH terms “Behcet Syndrome”[MeSH Terms] AND “microbiome” OR “microbiota” OR “dysbiosis” to identify relevant peer-reviewed studies published up to March 31 2025. For the synthesis, the selected studies were imported into Rayyan for deduplication and screening. Duplicates were removed using the automatic screening function of Rayyan. Two reviewers independently screened titles/abstracts and full texts according to inclusion/exclusion criteria; disagreements were resolved by a third reviewer or by discussion among the two primary reviewers.

2.2 Eligibility Criteria

Inclusion criteria for study selection were: original research articles with the gut and/or oral microbiome data of BD patients using sequencing techniques (16s rRNA), comparing BD patients with healthy controls, and only studies available in English. There was no restriction on sample size and patient demographics, including age, sex, or health status. Exclusion criteria were as follows: studies focusing on diseases other than BD, studies without microbiome composition data, animal or in vitro studies. Out of 99 articles, 79 were excluded due to duplication, irrelevance to the disease of interest, classification as case reports or review articles. Ultimately, 15 studies met the eligibility criteria and were incorporated into the final systematic review (Fig. 1).

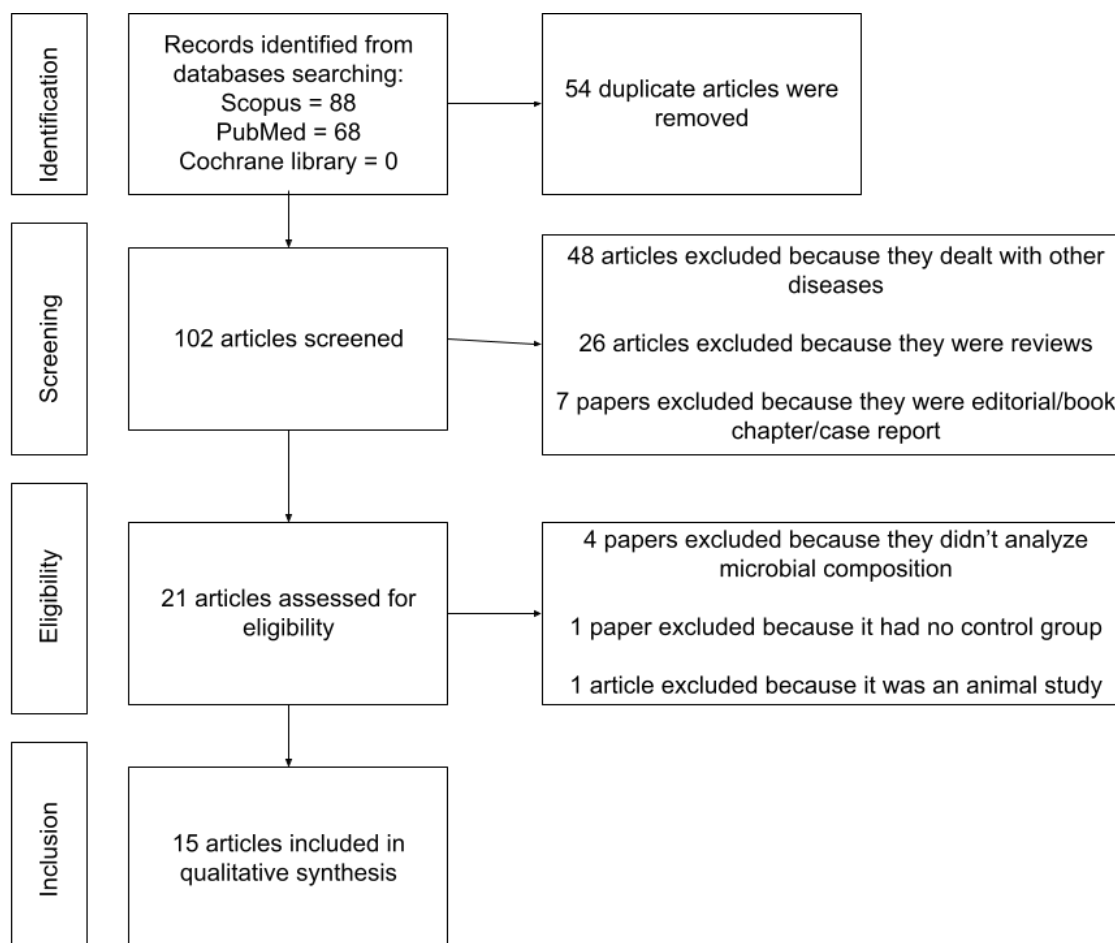
2.3 Data Extraction

Data were extracted from each included study using a standardized form. The extracted items for table 1 included: study design (cross-sectional, case-control, cohort), country, patient demographics (sample size, age, sex, BD phenotype), microbiome sample type (feces and oral cavity), V regions sequenced on 16S rRNA; for tables 2 and 3: key microbiome outcomes, including taxa-level differences of bacterial abundance, changes in alpha and beta diversity, presence of the *HLA-B51* gene and inflammatory markers and blood cell composition where available.

2.4 Synthesis methods

A qualitative synthesis was conducted without a meta-analysis due to the low number of studies and the heterogeneity in study designs, microbiome sampling sites and reported outcomes. The papers were categorized based on several key parameters to facilitate a structured analysis of microbiota alterations in BD. Studies were first grouped according to the type of microbiome analyzed (gut, oral, or both). Further classification was made based on study design including cohort studies, cross-sectional studies, and case-control studies. Additionally, studies were stratified by clinical subtypes of BD, such as mucocutaneous, uveitis, and vascular involvement, to assess potential differences in microbial composition across disease phenotypes. Methodological approaches, including 16S rRNA sequencing, metagenomic shotgun sequencing, were also considered in subgroup analyses. Lastly, studies were categorized by geographical region to explore potential variations in microbial dysbiosis across different BD-prevalent populations. Key findings were compiled in summary tables for comparative analysis. Given the limited number of studies (n=15) and the methodological variability, meta-analysis was not performed.

Figure 1. PRISMA flow diagram through the successive phases of a systematic review



2.5 Assessment of Publication Bias

Due to the qualitative nature of this synthesis and the small number of included studies, formal assessment of publication bias was not conducted. Similarly, GRADE assessment of the certainty of evidence was not performed, since most studies were observational and lacked standardized outcome measures.

Results

3.1 Study characteristics

15 studies (10 case-control studies, 3 cross-sectional studies, 2 cohort studies) met inclusion criteria, comprising a total of 362 BD patients, 116 patients with other diseases as comparison and 376 healthy controls (Table 1). Sample sizes ranged from 24 to 141, and patients were from diverse regions including Italy, the UK, Turkey, Japan, China, Mongolia, South Korea, and the Netherlands. Nine studies examined the gut microbiome, three the oral microbiome, and four both (Table 1). All of the studies used 16s rRNA sequencing of V1-V9 regions, and one study used the 16s rRNA sequencing in combination with metagenomics.

Table 1. Study characteristics

Authors	Study design	Country	Patient number	Sex (M/F)	Mean age	Control group	Sex	Mean age	Sample type	V regions sequenced
Consolandi et al., 2015	Case-control study	Italy	BD=22	12 M, 10 F	41.1	HC=16	6 M, 10 F	43.4	Feces	V3-V4 regions
Seoudi et al., 2015	Cross-sectional study	UK	BD=54 RAS=8	35 M, 19 F 5 M, 3 F	41.7 43.5	HC=25	15 M, 10 F	38	Oral Cavity	V4 region
Coit et al., 2016	Case-control study	Turkey	BD=31	15M, 16 F	36.5	HC=15	7 M, 8 F	37.8	Oral Cavity	V4 region
Shimizu et al., 2016	Observational case-control study	Japan	BD=12	5 M, 7 F	48.8	HC=12	6 M, 6 F	48.6	Feces	V1-V2 regions
Ye et al., 2018	Metagenomic case-control	China	BD=32	-	-	HC=74	Matched BD group	Matched BD group	Feces / Oral Cavity	V3-V4 regions
Oezguen et al., 2019	Observational case-control study	Turkey	neuro-BD=13	8 M, 5 F	42.1	HC=14	10 M, 4 F	37.8	Feces	V3-V5 regions
Shimizu et al., 2019	Case-control study	Japan	BD=13	5 M, 8 F	49.2	HC=27	12 M, 15 F	52.8	Feces	V1-V2 regions
Balt et al., 2020	Case-control study	Mongolia	BD=47	16 M, 31 F	44.2	HC=48	17 M, 31 F	38.4	Oral cavity	V3-V4 regions
Bilge et al., 2020	Prospective cohort study	Turkey	BD=27	17 M, 10 F	40.8	HC=10	6 M, 4 F	38.9	Feces	V3-V4 regions

Tecer et al., 2020	Case-control study	Turkey	BD with uveitis=7 CD=9 FMF=12	5 M, 2 F 3 M, 6 F 6 M, 6 F	35.6 35 32.2	HC=16	6 M, 10 F	39.4	Feces	V2-V4-V8, V3-V6, V7-V9 regions
Van der Houwen et al., 2020	Cross-sectional study	Netherlands	BD=19	9 M, 10 F	50	HC=17	9 M, 8 F	47	Feces / Oral Cavity	V3-V4 regions
		Italy	BD=13	6 M, 7 F	54	HC=15	7 M, 8 F	44	Feces / Oral Cavity	
Kim et al., 2021	Observational cohort study	South Korea	BD=9 RAU=7	1 M, 8 F 2 M, 5 F	33 47	BD-matched HC=9 RAU-matched HC=7	4 M, 5 F 3 M, 4 F	53 44	Feces / Oral cavity	V3-V4 regions
Liu et al., 2024	Case-control study	China	BD=11	8 M, 3 F	42.64	Fuchs=15 HC=18	9 M, 6 F 10 M, 8 F	40.07 39.11	Feces	V3-V4 regions
Park et al., 2024	Case-control study	South Korea	BD=35 UC=35 CD=30	-	-	HC=41	-	-	Colon tissue, stool, blood samples	V1-V3, V3-V4 regions
Shang et al., 2025	Cross-sectional study	China	BD=17	8 M, 9 F	35.25	HC=12	5 M 7 F	35.91	Feces	V4 region

BD: Behcet's disease, HC: healthy control, F: female, FMF: familial Mediterranean fever, CD: Crohn's disease, UC: ulcerative colitis, RAU: recurrent aphthous ulceration, RAS: recurrent aphthous stomatitis, M: male, MMP (Mucous membrane pemphigoid), SR: Shire group, non-SR: non-Shire group

3.2 Gut microbiota dysbiosis in BD

The human microbiome consists of bacteria, viruses, archaea, and eukaryotic microbes inhabiting various body sites, and the microbiome plays a critical role in regulation of metabolism, immune function, and defense against pathogens (Shreiner et al., 2014). According to the Human Microbiome Project, the microbiome tends to be more alike between different people than across body sites within the same person (Kennedy & Chang, 2020). The gut microbiota, which comprises

trillions of microorganisms, is predominantly composed of *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia*, with *Firmicutes* and *Bacteroidetes* being the most dominant phyla in most individuals (Ye et al., 2018). Under normal conditions, commensal bacteria help protect the organism from infections. Moreover, they regulate the immune system through maintaining mucosal homeostasis and epithelial barrier integrity, promoting the differentiation of Tregs, and modulating cytokine and metabolite production (Coccia et al., 2024). Dysbiosis, defined by alterations in bacterial diversity or abundance, is typically assessed through 16S rRNA analysis, which involves DNA extraction, PCR amplification of the 16S ribosomal RNA gene using specific primers, and sequencing of its hypervariable regions (V1-V9) (Seoudi et al., 2015). Several studies investigating the gut microbial dysbiosis in BD patients are summarized in Table 2. The authors have identified variations in bacterial abundance, with either increased or decreased levels, with considerable heterogeneity across studies regarding specific microbial changes. The studies reported bacterial taxa at different taxonomic levels, and a recurring pattern emerges at the genus and species level. Two studies reported reduced alpha diversity in BD patients' microbiota compared to healthy controls, six studies found significant beta diversity differences between BD and comparison group microbiome composition (Table 2). Three papers did not find significant diversity changes, and four studies did not report any diversity data.

The results in Table 2 highlighted reduction in class *Clostridia*, consisting of beneficial SCFAs-producing bacterial genera in four out of six studies. *Roseburia* and *Subdoligranulum* genera in this class showed decreased abundance in BD patients in two studies. The relative abundance of *Roseburia* was $10.45 \pm 6.01\%$ in healthy controls and $4.97 \pm 5.09\%$ in BD group; similarly, the relative abundance of *Subdoligranulum* was $3.28 \pm 2.20\%$ in control group and twice as low $1.93 \pm 1.75\%$ in Behcet's patients with reduced alpha diversity ($p < 0.01$) in comparison to healthy controls (Consolandi et al., 2015). Notably, butyrate levels demonstrated a significant reduction ($p = 0.0033$), and were positively associated with *Roseburia* showing Kendall correlation = 0.207 in the same study, but no correlation with *Subdoligranulum* (Consolandi et al., 2015). Park et al. (2024) reported similar reduction of butyrate-producing bacteria *Subdoligranulum variabile* and *Roseburia cecicola* on a species level. It should be noted that the study of Kim et al. (2024) found lower abundance of *Clostridium g24* only in comparison of BD patients with uveitis versus without uveitis, and not compared to healthy individuals, but reported reduced alpha diversity ($p = 0.03$) when the disease goes from active to inactive state. Another two out of six studies which mentioned alterations of *Clostridia* found its increased abundance in BD patients (Liu et al., 2024 and Shang et al., 2025). *Faecalibacterium* is another butyrate-producing bacteria of class *Clostridia*, but mixed results were given in three studies, Liu et al. (2024) mentioning its reduced abundance, while Ye et al. (2018) and Kim et al. (2021) indicated elevated levels of *Faecalibacterium prausnitzii* species. Three studies each revealed decrease in abundance of commensal genera *Lachnospira* (Oezguen et al., 2019, Bilge et al., 2020, and van der Houwen et al., 2020) and *Bacteroides* (Bilge et al., 2020, Liu et al., 2024, and Park et al., 2024). However, both of these bacteria *Lachnospira* and *Bacteroides uniformis* showed elevated abundance by Park et al. (2024) and Kim et al. (2021) respectively. Further reductions were noted for genera such as *Acinetobacter*, *Fusicatenibacter*, *Barnesiellaceae*, *Akkermansia* and *Filifactor* in single studies (Shimizu et al., 2019, Bilge et al., 2020, Van der Houwen et al., 2020, Liu et al., 2024 and Park et al., 2024). Geography appeared to influence microbiota: for example, BD patients in an Italian cohort had reduced abundance of *Barnesiellaceae*

and *Lachnospira* genera compared to a Dutch cohort, which didn't have statistically significant alterations, and it might reflect dietary differences (van der Houwen et al., 2020).

In contrast, several studies reported elevated abundance of bacterial taxa with pro-inflammatory characteristics in the gut microbiota of BD patients, such as *Parabacteroides*, *Stenotrophomonas*, *Actinomyces*, *Eggerthella*, and *Prevotella* (Table 2). Both Ye et al. (2018) and Oezguen et al. (2019) demonstrated increased abundance of *Parabacteroides*. Some inconsistencies were observed in the evaluation of *Prevotella* abundance in faecal samples of BD patients: three papers observed increase of *Prevotella* and closely related *Alloprevotella* and *Paraprevotella* (Ye et al., 2018, Tecer et al., 2020 and Liu et al., 2024), meanwhile other two papers reported decreased abundance (Shimizu et al., 2016 and Oezguen et al., 2019). It is worth noting that *Stenotrophomonas* was found to be increased in the gut of BD patients, but it is a genus often associated with environmental or respiratory sources and was not mentioned in oral microbiota changes (Ye et al., 2018). Furthermore, multiple single studies reported an increase in the abundance of opportunistic bacteria *Bilophila*, *Moraxella*, *Succinivibrio* and *Atopobium* (Shimizu et al., 2016, Tecer et al., 2020, Liu et al., 2024 and Ye et al., 2018) (see Table 1 for a summary of the key microbiome findings of each study).

Table 2. Characterization of gut microbiota dysbiosis in Behcet's disease patients compared to healthy or disease controls

Authors	↑ bacterial abundance in BD patients (species)	↑ bacterial abundance in BD patients (genus)	↓ bacterial abundance in BD patients (species)	↓ bacterial abundance in BD patients (genus)	Diversity	HLA -B51	Markers in BD patients
Consolandi et al., 2015	-	-	-	<i>Roseburia</i> <i>Subdoligranulum</i>	↓ alpha diversity (p<0.01) in BD compared to HC	50%	
Shimizu et al., 2016		<i>Bifidobacterium</i> <i>Eggerthella</i> <i>Atopobium</i>		<i>Megamonas</i> <i>Prevotella</i>	beta diversity: significant differences between BD and HC	-	↑ Fecal sIgA concentrations (p<0.05)
Ye et al., 2018	<i>Parabacteroides</i> spp. <i>Stenotrophomonas</i> spp. <i>Actinomyces</i> spp.	<i>Bilophila</i> <i>Alistipes</i> <i>Paraprevotella</i>	<i>Clostridium</i> spp. <i>Methanoculleus</i> spp. <i>Methanomethylophilus</i> spp.		NA	-	

	<i>Corynebacterium</i> <i>spp.</i> <i>Fusobacterium</i> <i>spp.</i> <i>Faecalibacterium</i> <i>prausnitzii</i>						
Oezguen et al., 2019		<i>Parabacteroides</i> <i>Clostridium</i> <i>Geminger</i> <i>Butyricimonas</i> <i>Erysipelotrichaceae</i> <i>incertae sedis</i>		<i>Vampirovibrio</i> <i>Unclassified</i> <i>Lachnospiraceae</i> <i>Prevotella</i>	beta diversity: significant differences between BD and HC	-	
Shimizu et al., 2019	<i>Eggerthella lenta</i> <i>Acidaminococcus</i> <i>species</i> <i>Lactobacillus</i> <i>mucosae</i> <i>Bifidobacterium</i> <i>bifidum</i> <i>Lactobacillus iners</i> <i>Streptococcus</i> <i>species</i> <i>Lactobacillus</i> <i>salivarius</i>		<i>Megamonas</i> <i>hypermegale</i> <i>Streptococcus</i> <i>infantis</i>	<i>Butyrivibrio</i> <i>Filifactor</i>	beta diversity: significant differences between BD and HC	-	↑ IL-17, TNF-α
Bilge et al., 2020	-	<i>Actinomyces</i> <i>Libanicoccus</i> <i>Collinsella</i> <i>Eggerthella</i> <i>Enetrohabdus</i> <i>Catenibacterium</i> <i>Enterobacter</i>		<i>Bacteroides</i> <i>Cricetibacter</i> <i>Alistipes</i> <i>Lachnospira</i> <i>Akkermansia</i> <i>Sutterella</i> <i>Anaerofilum</i> <i>Dielma</i> <i>Acetanaerobacterium</i> <i>Coprophaacter</i>	NS (beta diversity differed between BD subgroups)	-	

Tecer et al., 2020	<i>Prevotella copri</i>	<i>Succinivibrio</i> <i>Mitsuokella</i> <i>Prevotella</i>		<i>Bacteroidaceae</i>	Significant differences among BD, CD, FMF, HC	55%	
Van der Houwen et al., 2020	<i>Bifidobacterium spp.</i> <i>Dorea spp.</i> <i>Ruminococcus bromii</i>			<i>Barnesiellaceae</i> <i>Lachnospira</i>	NS (significant clustering by country)	47% of Dutch, 54% of Italian cohort	
Kim et al., 2021	<i>Bacteroides uniformis</i> <i>Faecalibacterium prausnitzii</i> group <i>Bifidobacterium adolescentis</i> group			<i>Clostridium_g24</i> (BD with uveitis vs. BD without uveitis)	↓ alpha diversity in inactive BD vs. active BD	100% ↑ ESR and CRP	
Liu et al., 2024		<i>Prevotella</i> <i>Moraxella</i> <i>Clostridia_UCG-014_unclassified</i> <i>Alloprevotella</i>		<i>Fusicatenibacter</i> <i>Bacteroides</i> <i>Faecalibacterium</i> <i>Escherichia-Shigella</i>	NS	-	↑ zonulin, IL-6, IL-17, TNF-α
Park et al., 2024	-	<i>Lachnospira</i>	<i>Dorea formicigenerans</i> <i>Subdoligranulum variabile</i> <i>Roseburia cecicola</i> <i>Coprococcus comes</i> <i>Caproiciproducens</i>	<i>Bacteroides</i> <i>Acinetobacter</i> <i>Subdoligranulum</i>	beta diversity: significant differences between BD and CD,UC	-	
Shang et al., 2025			<i>Rhodobacter sphaeroides</i> <i>Rose Bengal</i>		NA	-	

			<i>Clostridium difficile</i>				
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BD: Behcet's disease, HC: healthy control, NS: non-significant; NA: not available, RAS: recurrent aphthous stomatitis, CD: Crohn's disease, UC: ulcerative colitis, WBC: white blood cells, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

3.3 Oral microbiota dysbiosis in BD

Table 3 provides the main oral microbiome dysbiosis in BD patients compared to healthy controls. The oral microbiome in BD exhibits distinct alterations, potentially contributing to disease pathogenesis. Studies have shown significant differences in bacterial composition between BD patients and healthy controls, with increased abundance of *Haemophilus parainfluenzae* and *Streptococcus* species and a decrease in *Leptotrichia* and *Veillonella* in BD patients (Table 3). Given that *H. parainfluenzae* is associated with systemic infections and inflammation, its overrepresentation in oral swabs may indicate a role in immune activation (Coit et al., 2016). Additionally, BD patients with active oral disease show elevated levels of *Streptococcus salivarius* and *Streptococcus sanguinis* in the sites of lesions, while *Rothia dentocariosa* is more prevalent in the non-lesion sites of BD patients (Seoudi et al., 2015). Comparative studies have also found *Rothia mucilaginosa* enriched in BD patients in comparison with recurrent aphthous ulceration (RAU) group, streptococcal and *Neisseria sicca* species also showed increased relative abundance in BD patients with uveitis versus without uveitis (Kim et al., 2021). However, bacterial genus *Neisseria* was found to be depleted in BD patients by the study of Seoudi et al. (2015), which also indicated reduction in *Veillonella* genus. Similarly, *Veillonella* was reduced in BD patients with uveitis compared to BD patients without uveitis, suggesting this bacteria's ocular involvement in BD (Kim et al., 2021). A separate study on Mongolian BD patients further identified a significant reduction in *Akkermansia*, a genus known for its role in maintaining mucosal integrity, and reported significant differences in beta diversities between BD and control groups (Balt et al., 2020).

Table 3. Characterization of oral microbiota dysbiosis in Behcet's disease patients compared to healthy or disease controls

Authors	Increased bacterial abundance in BD patients (species)	Increased bacterial abundance in BD patients (genus)	Reduced bacterial abundance in BD patients (species)	Reduced bacterial abundance in BD patients (genus)	Diversity	HLA-B*51	Markers in BD patients
Seoudi et al., 2015	non-ulcer sites: <i>Rothia dentocariosa</i> ulcer sites: <i>Streptococcus salivarius</i> <i>Streptococcus sanguinis</i>			<i>Neisseria</i> <i>Veillonella</i>	NA	-	

Coit et al., 2016	<i>Haemophilus parainfluenzae</i>			<i>Leptotrichia</i> <i>Alloprevotella</i>	NA	-	
Ye et al., 2018		<i>Bifidobacterium</i> <i>Prevotella</i> <i>Scardovia</i>	-	-	NA	-	
Balt et al., 2020	-		<i>Akkermansia</i> species S24-7 family species		beta diversity: significant differences between BD and HC	-	
Van der Houwen et al., 2020		<i>Treponema</i> <i>TG5</i>			NS (significant clustering by country)	47% of Dutch, 54% of Italian cohort	
Kim et al., 2021	<i>Streptococcus pneumoniae</i> group <i>Streptococcus peroris</i> group <i>Neisseria sicca</i> group (BD with uveitis vs. BD without uveitis) <i>Rothia mucilaginosa</i> (BD vs. RAU)	<i>Lachnoanaerobaculum</i>		<i>Veillonella</i> (BD with uveitis vs. without uveitis)	↓ alpha diversity in inactive BD vs. active BD	100%	↑ ESR and CRP

BD: Behcet's disease, HC: healthy control, NA: not available, RAS: recurrent aphthous stomatitis, RAU: recurrent aphthous ulceration, CD: Crohn's disease, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

3.4 Immune correlations

Some included studies measured inflammatory markers in BD patients, four studies also correlated microbiome changes with clinical or laboratory measures. For instance, patients with higher IL-6 or IL-17 levels had lower abundance of butyrate producers (Table 2). Zonulin (a gut

permeability marker) was significantly elevated in BD and positively associated with *Moraxella*, *Clostridia* and *Alloprevotella*, and inversely correlated to *Fusicatenibacter* (Liu et al., 2024). Secretory IgA (sIgA) levels were significantly increased ($p < 0.05$) in feces of BD patients, but no correlation was found with bacterial abundance of BD and control groups (Shimizu et al., 2016).

3.5 Microbiome and Organ Involvement in Behçet's Disease

Several studies have explored how microbiome alterations may relate to clinical features of BD, including neuro-Behçet disease (neuro-BD), recurrent oral ulcers and uveitis, by comparing microbiome profiles between patients, healthy controls, and individuals with other diseases. One study analyzed the fecal microbiota community compositions in healthy controls ($n=14$), neuro-BD ($n=13$), and multiple sclerosis ($n=13$) patients using 16S rRNA gene sequencing and standard bioinformatics pipelines (Oezguen et al., 2019). Despite the limited sample size, the study revealed that patients with neuro-BD showed increased levels of *Prevotella*, *Parabacteroides*, and *Geminger*, while *Vampirovibrio* and members of *Lachnospiraceae* were less abundant. Also, the study found that *Prevotella* and *Bacteroides*-dominated subsample clusters were present across all three cohorts, suggesting shared dysbiotic patterns between the two neurological conditions. The differences did not demonstrate statistical significance, and future research is important to clarify if the differences arise from the disease itself or from treatment regimens, since neuro-BD patients received azathioprine (sometimes combined with colchicine), while MS patients were on unspecified immunomodulatory drugs.

Oral ulcers are a hallmark manifestation of BD and have been linked to disruptions in the oral microbiome. Several studies suggest that microbial imbalances, combined with immune dysregulation, may contribute to mucosal inflammation in BD (Seoudi et al., 2015). Chinese study analyzing paired genital and oral samples from 106 patients, microbial communities were compared between active disease state and healthy controls. The most common genera identified in the oral cavity were *Bifidobacterium*, *Prevotella* and *Scardovia*. Genital samples showed different profiles, featuring *Parabacteroides* spp., *Stenotrophomonas* spp., *Actinomyces* spp., *Corynebacterium* spp., *Fusobacterium* spp., and *Faecalibacterium prausnitzii* species (Ye et al., 2018). The results indicated substantial increase in *Bilophila* and substantial reduction in *Clostridia* in gut, and it was feasible to utilize it as a new marker of disease activity.

In addition, an additional research study compared the gut microbiota composition of Behçet's disease and uveitis patients with the microbial composition of subjects with Familial Mediterranean Fever (FMF), Crohn's Disease (CD), and healthy controls and represented a total of 44 subjects ($n=7$ BD uveitis, $n=12$ FMF, $n=9$ CD, and $n=16$ healthy controls) (Tecer et al., 2020). The fecal microbiota of BD patients was also characterized by dominance by *Firmicutes* and *Proteobacteria*, such as *Enterobacteriaceae* and *Prevotellaceae*. In healthy controls, microbiota was found to be enriched by *Bacteroidetes*, especially the *Bacteroides* and *Prevotella* genera. *Bacteroidaceae* were low in CD and FMF groups but were entirely absent among BD patients. In CD patients, *Enterobacteriaceae* seemed to overgrow the normal flora, and then *Veillonellaceae*, whereas that of FMF patients was dominated by *Prevotellaceae*, followed by *Ruminococcaceae*, *Lachnospiraceae*, *Enterobacteriaceae*, and *Veillonellaceae*. In the present study, they investigated fecal microbial composition in seven BD patients with uveitis and determined the dominant

microbial communities at the phylum, class, order, family, genus, and species levels. In BD patients, fecal microbiota at the phylum level were dominated by *Firmicutes*, at the class level by *Clostridia*, at the order level by *Clostridiales*, and at the species level by *Prevotella copri*. The implications of these findings in uveitis are unknown.

3.6 Comparative Microbiome Analysis of Behçet's Disease and Other Immune-Mediated Disorders

Multiple metagenomic studies have explored the relationship between gut microbiome composition and immune-mediated disorders, such as ulcerative colitis (UC), Crohn's disease (CD), and Vogt-Koyanagi-Harada (VKH) disease. Notably, intestinal Behçet's disease (BD) shares clinical similarities with inflammatory bowel disease (IBD), including chronic inflammation of the GI tract and systemic involvement. Park et al. (2024) conducted a comparative analysis to characterize microbial and metabolic features across intestinal BD, CD, and UC, and healthy controls. The study enrolled 141 subjects, comprising 35 intestinal BD, 35 with UC, and 30 with CD, and 41 healthy individuals, and analyzed 192 stool and plasma samples using metagenomic and metabolomic profiling. At the phylum level, patients with UC, CD, and intestinal BD showed an increase in *Proteobacteria* and *Fusobacteria*, alongside a reduction in *Bacteroidetes* when compared to healthy controls. UC samples demonstrated a higher abundance of *Fusobacteriales*, *Fusobacteriaceae*, *Burkholderiaceae*, and the genera *Fusobacterium* and *Ralstonia*, while *Roseburia* was reduced. CD samples were enriched in *Enterobacteriaceae* and *Escherichia*, and depleted in *Ruminococcaceae*, *Coriobacteriaceae*, *Blautia*, *Anaerostipes*, *Faecalibacterium*, and *Roseburia*. In intestinal BD, significant reductions were found in *Bacteroidaceae*, and in the genera *Bacteroides*, *Acinetobacter*, and *Subdoligranulum*—though these differences reached significance primarily in comparison with healthy controls rather than with other IBD groups.

Across all three disease groups, a common trend was observed in the loss of short-chain fatty acid (SCFA)-producing bacteria, including species such as *Fusicatenibacter saccharivorans*, *Coprococcus comes*, *Blautia obeum*, *Dorea formicigenerans*, and *Roseburia cecicola*. In intestinal BD specifically, additional depletion of *Subdoligranulum*, *Roseburia*, and *Bacteroides fragilis* was reported, indicating potential disease-specific dysbiosis within this group.

Discussion

4.1 Summary and Interpretation of Findings

This systematic review aimed to explore alterations in the gut and oral microbiota of patients with Behçet's disease (BD) and to understand their potential role in disease pathogenesis. The 15 included studies highlight significant microbiome alterations in BD patients, supporting the hypothesis that BD is associated with a distinct microbiota profile. This profile involves a decrease in beneficial SCFA-producing bacteria within the class of *Clostridia* (e.g., *Faecalibacterium*, *Roseburia*), crucial for maintaining immune homeostasis, and enrichment of potential proinflammatory species (e.g., *Parabacteroides*, *Haemophilus*), and reduced alpha diversity in some cohorts. These microbial signatures were observed in both mucocutaneous and intestinal BD subtypes, and both at ulcerated and non-ulcerated mucosal sites, suggesting a systemic pattern of dysbiosis. Some studies report significant differences in beta diversity between BD patients and controls, though the precise bacterial taxa varied by study due to regional, methodological, and population differences.

4.2 Immunological Implications of Microbiome Alterations

Dysbiosis within the gut and oral microbiota is an important contributor to immunopathology of BD. The reduction of butyrate-producing bacteria such as *Faecalibacterium*, *Roseburia*, and *Subdoligranulum* lead to decreased levels of SCFAs, especially butyrate (Consolandi et al., 2015). Butyrate is crucial for maintaining gut barrier integrity by nourishing colonocytes and enhancing tight junctions, thus preventing intestinal permeability (Hamer et al., 2007). Its depletion contributes to gut barrier dysfunction, allowing microbial products to translocate and trigger systemic inflammation (Berzack & Galor, 2024). Butyrate also plays a vital role in immune regulation by promoting the induction and function of regulatory T cells (Tregs), which suppress excessive immune responses and maintain tolerance (Shimizu et al., 2022). Reduced butyrate levels in BD impair Treg differentiation, tipping the balance toward pro-inflammatory Th17 cells. This shift results in elevated Th17 responses, which produce IL-17, a potent pro-inflammatory cytokine involved in neutrophil recruitment and tissue inflammation. Treg differentiation happens through a mechanism of histone deacetylase (HDAC) inhibition by butyrate, a process that influences expression of proinflammatory genes and further epigenetic modifications (C. Liu et al., 2024). Most studies in Tables 2 and 3 showed a reduction in SCFA-producing bacteria and lower levels of butyrate in BD groups that impair Treg function and promote Th-17-mediated inflammation. Consistent with this, BD patients exhibit increased circulating levels of pro-inflammatory cytokines including IL-17, IL-6, and tumor necrosis factor-alpha (TNF- α), reflecting the heightened Th17-mediated inflammation and systemic immune activation characteristic of the disease.

Furthermore, several pathogenic bacteria such as *Actinomyces* and *Parabacteroides* were found to be increased, which are known to activate Toll-like receptors (TLRs) (Nara et al., 2008), elevating Th1 immune responses by stimulating dendritic cells and macrophages to produce cytokines like interferon-gamma (IFN- γ) and IL-12, which promote Th1 differentiation (Van der Houwen et al., 2020).

The oral microbiome has also been found to show significant alterations, studies using 16S rRNA sequencing have reported an increased abundance of pro-inflammatory species, such as *Haemophilus parainfluenzae* and *Streptococcus sanguinis*, while beneficial bacteria are depleted,

including *Alloprevotella rava* and *Leptotrichia* (Coit et al., 2016). The oral cavity serves as a major immune interface, and disruptions in microbial homeostasis may contribute to mucosal inflammation and worsen BD-related symptoms such as recurrent aphthous ulcers (Mumcu & Fortune, 2021). One proposed mechanism suggesting microbial-driven inflammation is molecular mimicry, in which bacterial antigens resemble host proteins, leading to cross-reactive immune responses that sustain chronic inflammation (Lehner, 1997). For example, *Streptococcus sanguinis* have been shown to resemble host peptides, triggering autoreactive T cells with false signaling, and the abnormal immune response might persist even in the absence of the original microbial trigger (Galeone et al., 2012). In addition, bacterial antigens could initiate NETosis, since presentation of streptococcal antigens has been reported to aggravate BD (Hügler et al., 2011), contributing to mucosal and vascular lesions.

4.3 Neutrophils, NETosis, and Mucosal Inflammation

Increased abundance of oral bacteria such as *Streptococcus sanguinis*, *Haemophilus parainfluenzae*, and *Streptococcus salivarius* in BD patients suggests these microbes may drive neutrophil activation at ulcerated mucosal sites (Perazzio et al., 2020). BD is known for neutrophil hyperactivity and excessive formation of neutrophil extracellular traps (NETs). NETosis is markedly stimulated by soluble CD40 ligands, especially in active BD patients, correlating with disease severity (Li et al., 2024). Certain oral bacteria are potent NET inducers; in BD, their abundance at ulcerated sites may perpetuate tissue damage via NET-mediated inflammation. This connection is supported by the presence of NETs in mucosal and vascular BD lesions (Kawakami et al., 2022). NETs promote local tissue damage by sustaining inflammation through recruitment and activation of immune cells, including macrophages that produce pro-inflammatory cytokines like IL-8 and TNF- α (Li et al., 2024). The presence of NETs at ulcer sites may perpetuate mucosal injury and delay healing, contributing to the chronicity of BD ulcers, and clinical evidence shows that antiseptic mouthwash reduces oral ulcer frequency in BD (Min et al., 2023). Further research is needed to clarify whether NETosis is a secondary consequence of dysbiosis or a primary pathogenic mechanism.

4.4 Barrier Integrity and Systemic Inflammation

One other main feature of BD dysbiosis is its influence on gut epithelial barrier integrity. Some of the studies comprising this review had high concentrations of zonulin, a determinant of elevated intestinal permeability, and this correlated with taxa such as *Moraxella* and *Clostridia*. Zonulin is a physiologic regulator of intercellular tight junctions in intestinal epithelium, controlling intestinal barrier permeability (Fasano, 2011). It regulates the macromolecule flow between the gut lumen and the host and the balance of immune tolerance and immune response against non-self antigens (Heidt et al., 2023). Dysregulation of the zonulin system results in enhanced intestinal permeability or "leaky gut" and facilitates macromolecules and microbial products to move across the intestinal wall abnormally (Said et al., 2022). This disruption is involved in the pathogenesis of several autoimmune, inflammatory, and neoplastic conditions, such as BD, through induction of systemic immune activation. Leaky gut barrier can permit microbial antigens such as lipopolysaccharide (LPS) or peptidoglycans to translocate into systemic circulation, inducing generalized inflammation (Clarke et al., 2010) and potentially accounting for BD's multi-organ involvement. Specific bacterial taxa implicated in intestinal barrier damage and inflammation have been found in BD patients. Sulfate-reducing bacteria (SRB) like *Bilophila* species are elevated in the

gut microbiota of BD patients. They are H₂S-producing bacteria that can induce damage to the intestinal epithelium and, at the same time, induce inflammatory reaction (Figliuolo et al., 2017). Decrease of *Akkermansia*, a mucin-degrading genus that serves to maintain the integrity of the gut barrier, also indicates the involvement of this mechanism. Other opportunistic pathogen *Moraxella* and associated bacteria are involved in BD. These bacteria may cause dysbiosis, disruption of epithelial barrier function, and activation of systemic immunity (Ye et al., 2018).

4.5 Organ-specific Findings and Clinical Correlations

Oezguen et al. contrasted gut microbiota of patients with Neuro-Behçet's Disease (NBD) and healthy controls and with multiple sclerosis (MS) patients. They have concluded that the NBD and MS patients can be stratified into *Prevotella*- or *Bacteroides*-dominated groups. Dysbiosis in NBD was characterized by the occurrence of higher *Clostridiales* genera and *Oscillibacter* and *Bacteroides* enrichment within the *Prevotella*-stratified group. The study validated reduced *Prevotella* in MS but highlighted complex alterations in NBD microbiota. *Prevotella* is suggested to have a protective role in inflammatory diseases, as certain species like *Prevotella histicola* suppress experimental autoimmune encephalomyelitis (EAE) in mouse models, implying anti-inflammatory potential (Oezguen et al., 2019). *Parabacteroides* were also increased in IL-17A-deficient mouse models (a cytokine of interest in BD and MS), with disease-related increased Treg induction and reduced disease phenotypes (Shahi et al., 2022). This suggests that *Prevotella* and *Parabacteroides* may have a role in immune regulation and disease modulation in neuroinflammatory BD.

Investigation of Behçet's uveitis (BU) has found depletion of *Veillonella* species in patients when compared to healthy controls (Seoudi et al., 2015). *Veillonella* is normal oral and gut commensal microbiota and has been implicated in immune homeostasis. Its depletion in BU can indicate loss of protective microbial communities that are involved in the regulation of immune responses and mucosal barrier integrity (Kim et al., 2021). *Veillonella* reduction is associated with innate and adaptive immunity dysregulation in BU, such as overactive neutrophils and skewed T cell subsets (Th1, Th17) that are responsible for ocular inflammation (Guan et al., 2024). *Veillonella* reduction could therefore eliminate a microbial influence that would otherwise inhibit excessive immune activation, which can worsen uveitis.

A Korean study found a significant association between oral ulcers and BD. with an altered oral microbiome characterized by increased abundance of *Streptococcus* species, particularly *Streptococcus sanguinis* and *Streptococcus pneumoniae* (Kim et al., 2021). These bacteria are implicated in triggering immune responses and maintaining chronic inflammation in the oral mucosa. At the same time, there is a reduction in beneficial commensals such as *Veillonella* and *Leptotrichia*, which are normally abundant in healthy oral mucosa and contribute to microbial balance and mucosal health (Coit et al., 2016). The loss of these commensals alongside *Streptococcus* overgrowth may disrupt local immune homeostasis, facilitating recurrent aphthous ulcers and mucosal barrier dysfunction.

Comparison with Other Diseases

When comparing BD and IBD, studies found a decrease in the level of *Bacteroides fragilis*, and it usually regulates the immune system, and has been noted in BD but is less consistently reported in IBD (Tecer et al., 2020). This loss may reduce anti-inflammatory signaling in BD patients. Van der Houwen et al. (2020) revealed even more considerable reduction in another

important butyrate producer *Subdoligranulum* in BD, which appears more pronounced than in some IBD cohorts, suggesting a unique pattern of SCFA depletion. BD patients also show increased abundance of *Bifidobacterium*, *Eggerthella*, *Lactobacillus*, and *Streptococcus* species, which contrasts with some IBD profiles where these taxa may be reduced or unchanged.

BD and FMF are both autoinflammatory diseases, more common in Mediterranean populations, and share overlapping microbiome features. Both of these diseases show dominance of *Firmicutes* phylum and a relative reduction in *Bacteroidetes* compared to healthy individuals (Tecer et al., 2020). It reflects a shift toward pro-inflammatory bacterial communities. FMF and BD patients share enrichment in *Prevotellaceae*, *Ruminococcaceae*, and *Lachnospiraceae* families, though the exact species and abundance vary (Tecer et al., 2020).

4.6 Functional and Multi-Omic Insights

While taxonomic shifts provide valuable insight, functional microbiome changes may be even more critical in understanding BD. One study using combined metagenomic and metabolomic profiling demonstrated that BD patients exhibit substantial shifts in plasma metabolite profiles, including lower levels of tryptophan and butyrate-derived metabolites (Ye et al., 2018). These functional disruptions may have systemic consequences beyond the gut. For instance, tryptophan metabolites regulate IL-22 production, a cytokine relevant for mucosal healing and barrier integrity. Despite more subtle taxonomic alterations in BD than UC or CD, BD patients showed broader metabolic disturbances, suggesting functional microbiome contributions to systemic immune activation (Park et al., 2024). Future studies using transcriptomics and metagenomics are needed to further elucidate these effects.

4.7 Causality vs. Association

Whether dysbiosis in BD is a driver or consequence of disease remains unresolved. Most included studies were cross-sectional and could not establish temporal relationships. Still, correlations between microbiome profiles and inflammatory markers (e.g., IL-6, IL-17, zonulin) suggest a potential role in shaping the disease course. Preliminary experimental data (BD patient microbiota transferred to germ-free mice) support a pathogenic role for dysbiosis. However, confounding factors such as immunosuppressive treatments may alter microbial communities independently of disease. Longitudinal and interventional studies will be essential to address causality.

4.8 Limitations of Current Evidence

Despite these promising insights, the existing literature presents several limitations. Most studies employed 16S rRNA gene sequencing, which restricts taxonomic resolution and lacks functional information. Moreover, sample sizes were generally small, and many studies lacked longitudinal design or control for confounding factors such as diet, medications (e.g., colchicine, immunosuppressants), and disease activity status. Geographical variation is another important factor, as BD prevalence and microbiota composition vary significantly across populations.

Another limitation is the cross-sectional nature of most studies, which prevents determination of causality. It remains unclear whether dysbiosis is a cause or consequence of the disease. Longitudinal studies and mechanistic experiments are needed to clarify temporal

relationships and identify potential microbial biomarkers for diagnosis, disease monitoring, or treatment response.

4.9 Clinical Implications and Future Directions

Understanding the role of the microbiome in BD may open new avenues for therapeutic intervention. Strategies such as probiotics, prebiotics, dietary modulation, or fecal microbiota transplantation (FMT) could be explored to restore microbial balance and improve clinical outcomes. Probiotics containing *Bifidobacterium* and *Lactobacillus* strains have shown some benefits in related conditions such as irritable bowel syndrome (Y. Wu et al., 2024), and shifts in these bacterial populations have been observed in BD patients (Mehmood et al., 2021). FMT involves transferring fecal material from a healthy donor to a patient to restore gut microbiota diversity and can achieve long-term engraftment of donor strains and increase microbial diversity without causing dysbiosis associated with antibiotics (Cooke et al., 2021). Preclinical studies have demonstrated that fecal transplants from BD patients to mice exacerbate autoimmune symptoms, while administration of beneficial bacteria like *Eubacterium rectale* (a butyrate producer) improves BD symptoms in animal models (Joubert et al., 2023). However, such approaches require careful validation in randomized controlled trials.

Future research should focus on integrating multi-omics technologies (e.g., metagenomics, metabolomics, transcriptomics) to obtain a more comprehensive view of host-microbe interactions. In vitro and in vivo studies are also crucial to investigate the immunological effects of specific taxa and microbial metabolites implicated in BD pathogenesis.

Conclusion

In conclusion, this review highlights a consistent pattern of gut and oral microbiota dysbiosis in BD, characterized by loss of beneficial commensals and enrichment of pro-inflammatory taxa. These changes may contribute to immune dysregulation and chronic inflammation via multiple mechanisms. While current evidence supports a link between microbiota alterations and BD pathogenesis, further mechanistic and longitudinal studies are necessary to establish causality and evaluate microbiota-targeted therapies. The integration of microbiome research into the broader context of BD may provide novel insights into disease mechanisms and personalized treatment approaches.

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