

Review

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[Serap Maden](#) *

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Review

An Overview of Small Intestinal Bacterial Overgrowth and Gut Microbiota in Patients with Rosacea

Serap Maden

Near East University, Faculty of Medicine, Department of Dermatology, Cyprus; serap.maden@neu.edu.tr

Abstract

Rosacea is a chronic skin condition, characterized by persistent inflammation, manifesting primarily on the face and causing redness, papules, pustules, and phymatous changes. The etiology of rosacea is multifactorial, with immune system factors playing a crucial role in its pathogenesis. The scientific literature contains an increasing number of studies that suggest a correlation between rosacea and the gut microbiota. Small intestinal bacterial overgrowth (SIBO) is defined as an excessive proliferation of potentially pathogenic bacteria within the small intestine of the gastrointestinal system. Multiple factors have been posited to explain the pathogenesis of rosacea, and the presence of SIBO has been identified as a potential factor in its occurrence. A decrease in the *Lactobacillus* genus, *Prevotella copri*, *Lachnospiraceae*, and *Faecalibacterium* within the gut microbiota may initiate inflammation related to rosacea. These bacterial species are crucial for regulating the intestinal mucosa. The findings indicate that there is an increase of *Bacteriodes*, *Acidaminococcus* and *Megasphaera*, and *Ruminococcus* in the gut microbiome of patients with rosacea. Probiotics can be advantageous for managing the intestinal microbiome, while Rifaximin treatment has shown efficacy in addressing inflammatory rosacea lesions associated related to SIBO. The present review has been undertaken with the objective of enhancing our comprehension of SIBO in rosacea. The emphasis has been placed on the pathogenetic mechanisms and the shift in the gut microbiota that will lead to understanding probiotic benefits and therapy options in rosacea patients.

Keywords: rosacea; gastrointestinal microbiota; pathogenesis; immune response; probiotics

1. Introduction

Rosacea, a prevalent dermatological condition, is estimated to influence between 1% and 20% of the global population [1]. The clinical characteristics of rosacea are typically characterized by recurring flare-ups of flushing, persistent redness, telangiectasia, papulo-pustules, or phymatous changes. Additionally, there is a multiphasic phenotype spectrum of disease, accompanied by burning, pain, or migraine-like symptoms [2]. The clinical classification of rosacea encompasses the following subtypes: erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea, and ocular rosacea. A recent clinical subtype known as neurogenic rosacea has also been documented [3]. Etiology is complex and multifactorial, with potential contributors including microbiological, neurovascular, immune, ultraviolet radiation, genetic, dietary, and psychological stress factors that may collectively contribute to the inflammatory process [4]. Due to the multiple etiological factors; there is considerable heterogeneity in the results of therapeutic interventions for rosacea. The primary approach to managing rosacea involves patient education, the establishment of a skin care routine, treatment with topical and oral medications to control flare-ups, and the use of lasers or light-based therapies. It is imperative that treatment be adapted to the individual's specific needs, and a combination of various therapeutic modalities is frequently necessary to address the diverse manifestations of rosacea [5].

The significance of the skin-gut axis is becoming increasingly evident with the advancement of our understanding of the underlying pathophysiological mechanisms. Although the precise mechanisms of the gut-skin axis have yet to be fully elucidated, mounting evidence indicates that the probiotic intervention may confer benefits in the context of inflammatory cutaneous conditions [6]. Rosacea, as an immune-mediated inflammatory disease, has exhibited notable associations with small intestinal bacterial overgrowth (SIBO), a condition involving an imbalance in the composition of the gut microbiota, suggesting a potential underlying mechanism [7].

This narrative review explores the correlation between rosacea and SIBO, offering a theoretical framework for understanding how SIBO could have a potential effect in the immune mechanism affecting rosacea pathogenesis.

2. Small Intestinal Bacterial Overgrowth

The gut microbiota performs a pivotal and advantageous function in maintaining the normal physiological mechanisms of the human organism. Additionally, the microbiota provides protective benefits against pathogens through several mechanisms, including direct barrier functions, the secretion of antimicrobial peptides, and the stimulation of immune signalling pathways. Dysregulation of the microbiome, whether due to shifts in its location or composition, can have detrimental consequences on overall health [8,9]. Gut commensally bacteria have been shown to function as modulators in the mechanisms that underpin immune toleration [10]. Alterations in the structure of the gut microbiota may result in immunological imbalances in the organ systems external to the gastrointestinal system because almost 70% of lymphocytes are present in the lymphoid tissue of the gut [11].

SIBO is a medical phenomenon defined as the existence of elevated bacterial loads in the small intestine, resulting in gastrointestinal manifestations [12]. While the predominant localization of the gut microbiota is in the large and distal small intestine, there is a possibility of their infiltration into the mid and proximal small intestine, which can result and lead to the development of SIBO. Predominant etiological factor of SIBO is the presence of dysmotility along the gastrointestinal system. The migrating motor complex is a contributing factor to the elimination of fecal matter within the gastrointestinal canal. It has been observed in a range of anatomical intestinal abnormalities or conditions, including intestinal obstructions, diabetic gastroparesis, diverticulosis, and scleroderma [13]. A shift in microbial composition or abundance, referred to as gut dysbiosis, has the potential to disrupt the body's normal homeostasis. The condition known as dysbiosis has been linked to a number of intestinal and extraintestinal pathologies, including SIBO [9]. It is possible for dysbiosis to cause weakening of the mucosa of the intestines, as well as dysfunctions in the intestinal epithels and cellular junctions. This can lead to compromised intestinal barrier integrity and facilitate the migration of bacteria, noxious bacterial metabolites and compounds. In addition, bacterial components capable of trigger the immune response within the gastrointestinal tract to the systemic circulation [14].

The standard diagnostic approach for SIBO involves the administration of a lactulose or glucose breath test, a non-invasive and cost-effective method [8]. The definitive prevalence in the overall demographic remains indeterminate; though, extant researches suggest a range of 2–22%, classifying it as a reasonably prevalent ailment. In addition, there is an observable rise in the prevalence of the condition with increasing age, particularly among populations afflicted with comorbidities [15]. Rifaximin has emerged as a preferred treatment among clinicians for the management of SIBO [8].

3. Pathogenesis of Rosacea and Small Intestinal Bacteria Overgrowth

In rosacea etiology, both innate and adaptive immunity have been demonstrated to exert influence. Toll-like receptor (TLR)-2 is a pattern recognition receptor that can identify molecular patterns present in microbial compounds, thereby activating immune systems as a defense mechanism [16]. Elevated levels of TLR-2, Kallikrein-5 (KLK-5), cathelicidin, and matrix

metalloproteinases (MMPs) expressions have been observed in the patients with rosacea [17]. Stimulation of TLR-2 results in the activation of the nuclear factor-kappa B (NF- κ B) pathway, which leads to the synthesis of chemokines, cytokines and antimicrobial peptides (AMPs) in the proinflammatory cathelicidin pathway [18]. Moreover, activation of TLR-2 leads to the production of active human cathelicidine LL-37 via triggering KLK-5 which is a serine protease that cleaves CAMP into active fragments, including LL-37 [19,20]. KLK5 is expressed in an inactive form that is subsequently converted to an active form through cleavage performed by matrix metalloproteases (MMPs), especially MMP-9 [6].

The increased levels of CAMP and KLK5 can augment the levels of the shorter LL-37 fragment forms in rosacea skin [21,22]. These shorter LL-37 fragments have been demonstrated to induce symptoms consistent with rosacea, including erythema, vasodilatation, flushing, and telangiectasia in mice [21]. Furthermore, the activation of the nucleotide-binding oligomerization domain like receptors family pyrin domain containing 3 (NLRP3) inflammasome, has been determined to play a crucial role in LL-37-induced skin inflammation and rosacea pathogenesis [23]. The inflammasome has been defined as a multiprotein complex that is responsible for the stimulation of caspase-1 and activation of IL-1 β . This leads to the activation of the IL-1 receptor in multiple cells and the infiltration of neutrophils [24].

Increased levels of LL-37 have been shown to induce the release of pro-inflammatory cytokines by neutrophils, including interleukin (IL)-8, IL-1 β , and tumor necrosis factor (TNF)- α . Furthermore, LL-37 has been observed to stimulate the synthesis of vascular endothelial growth factor and activate the epidermal growth factor receptor signaling pathway [19].

In rosacea, T-cell immune responses are initiated through the actions of Th1 and Th17 cells, leading to elevated levels of interferon γ (IFN- γ) and IL-17 [6]. Th17 cells have been observed to produce IL-17, which may play a role in the effects on LL-37 through the expression of atypical forms that are characteristic of rosacea. IL-17 has been shown to induce angiogenesis through the VEGF pathway and to regulate the expression of LL-37 [25,26].

TLR activation is imperative for specific antigen-specific antibody responses in B cells, and TLR agonists have been shown to promote the proliferation of plasma cells from B cells [27]. Cleaved fragments of LL-37 robust B cell immune response accompanied by increased expression of Th17 and Th22 cytokines [6]. All these processes could be explained as contributing factors to the chronic inflammatory process and enhanced angiogenic growth that are characteristic for rosacea.

Pathogen-associated molecular patterns (PAMPs) are defined as biological stimulants that elicit a response in TLRs, including TLR-2 [28]. Short-chain fatty acids (SCFAs) have been demonstrated to facilitate the maintenance of intestinal barrier integrity. These acids are produced by healthy gut microbiota from complex polysaccharides [29]. The significance of SCFAs extends beyond their role in diminishing intestinal permeability, as they also modulate skin barrier integrity by inducing keratinocyte metabolism and differentiation [30]. Butyrate is a short-chain fatty acid and demonstrates a robust anti-inflammatory effect by suppressing immune reactions, via inhibiting cytokine production by inflammatory cells [31]. The presence of elevated PAMPs in the circulation system, along with a decline in butyrate of bacterial origin which is a protective factor for intestinal barrier, might suggest an increased responsiveness of B-cells and impairment in the differentiation of T-cells [32]. Despite the absence of evidence demonstrating the full complement of innate and adaptive pathways in the existing studies, the hypothesis that SIBO may induce analogous pathways is a plausible one. This is due to the fact that dysbiotic bacteria instigate similar pathways in both the gastrointestinal tract and the skin (Figure 1).

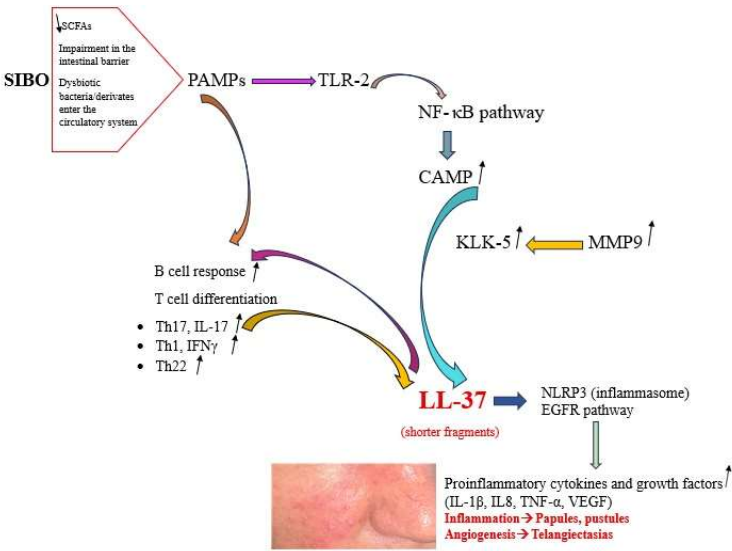


Figure 1. Possible mechanism of small intestinal bacterial overgrowth contributes to the pathogenesis of rosacea. SIBO: small intestinal bacterial overgrowth, SCFAs: short chain fatty acids, PAMP: pathogen-associated molecular patterns, TLR-2: toll-like receptor-2, NF-κB: nuclear factor-kappa B, CAMP: cathelicidin antimicrobial peptide, KLK-5: kallikrein-5, MMP9: matrix metalloproteinase-9, LL-37: human cathelicidin, NLRP3: nucleotide-binding oligomerization domain like receptors family pyrin domain containing 3, EGFR: epidermal growth factor receptor; IL, interleukin, TNF-α: tumour necrosis factor, VEGF: vascular endothelial growth factor, Th: T-helper, IFN-γ: interferon γ.

4. Preventive Effects of Probiotics on Rosacea

In a study employing a mouse model of rosacea, effectiveness of probiotics in addressing rosacea were evaluated by conducting an LL-37-induced model of the skin condition. The mixture of *Lactiseibacillus salivarius* 23-006 and *Lactiseibacillus paracasei* 23-008 exhibited the utmost significance in its effect, thereby alleviating dermatological manifestations, reducing the presence of inflammatory cellular infiltrates, and decreasing the levels of inflammatory mediators in mice. The concomitant administration of these two strains resulted in a reduction in the synthesis of cathelicidin LL-37 and rosacea-associated factors. This effect was achieved by inhibiting the TLR2/MyD88/NF-κB pathway [33], which is responsible for the synthesis of chemokines and AMPs, as well as cytokines, within the proinflammatory cathelicidin cascade [18]. Another study involved 60 patients diagnosed with rosacea, who were randomly divided into three groups: probiotic, placebo, and control. The results demonstrated that the administration of probiotics resulted in improvements to facial skin conditions, a reduction in inflammation, and a decrease in facial skin microbiota diversity, concurrent with an enhancement of gut microbiota heterogeneity [34]. A multitude of studies and reports in the literature demonstrate the efficacy of probiotics in the treatment of rosacea and related skin disorders by virtue of their ability to inhibit inflammation and restore the skin barrier [35–38]. The present findings provide a theoretical base for the treatment of rosacea, thus offering a promising avenue for potential clinical applications.

5. The Intestinal Microbiota in Rosacea Patients

The studies presented herein demonstrate alterations in the intestinal microbiota that may be of particular relevance to patients diagnosed with rosacea (Table 1).

Table 1. Intestinal microbiota of patients with rosacea.

Authors and year	Study design	Increased levels of intestinal microbiota	Decreased levels of intestinal microbiota	Results
Moreno-Arrones et al. [39] 2021	15 PPR patients 12 (80%) females 15 controls 5 (33.3%) females	<i>Syntrophomonadaceae</i> family, <i>Anaerovorax</i> genus, <i>Bacteroidales</i> sp., <i>Tyzzarella</i> sp., <i>Lachnospiraceae</i> family, <i>Akkermansiamuciniphila</i> , <i>Parabacteroides distasonis</i>	<i>Prevotella copri</i>	The study outlines intestinal dysbiosis in rosacea patients.
LEfSe analysis				
Chen et al. [40] 2021	11 patients 4 ETR %36.3 7 PPR %63.7 90.9% female 110 controls 90.9% female	<i>Rhabdochlamydia</i> , CF231, <i>Bifidobacterium</i> , <i>Sarcina</i> , <i>Ruminococcus</i>	<i>Lactobacillus</i> , <i>Megasphaera</i> , <i>Acidaminococcus</i> , <i>Haemophilus</i> , <i>Roseburia</i> , <i>Clostridium</i> , <i>Citrobacter</i>	Faecal microbiota profiles in rosacea patients associated with sulfur metabolism, cobalamin, and carbohydrate transport.
LEfSe analysis				
Nam et al. [41] 2018	12 patients 251 controls MetagenomeSeq	<i>Acidaminococcus</i> , <i>Megasphaera</i> ,	<i>Peptococcaceae</i> , <i>Methanobrevibacter</i> ,	Patients diagnosed with rosacea exhibit a more abundant and distinct profile of enteral microbiota.
Guertler et al. [42] 2024	54 patients 39 females 15 males 50 controls MiSeq 16S rRNA sequencing	<i>Oscillobacter</i> sp., <i>Flavonifractorplauti</i> , <i>Ruminococcaceae</i> UBA1819	<i>Faecalibacteriumprausnitzii</i> <i>Lachnospiraceae</i> group sp, <i>Ruminococcaceae</i>	There is a decline in microbial richness and diversity in rosacea patients.

PPR: papulopustular rosacea, ETR:erythematotelangiectatic rosacea, LEfSe:linear discriminant analysis effect size.

In a study, the gut microbiome of 15 patients diagnosed with PPR was compared with 15 healthy controls. Twelve patients diagnosed with rosacea were female and had a mean age of 36 years; 13 subjects who served as controls were also female and had an average age of 39 years. The results obtained via canonical correspondence analysis were found to be significantly different between the patients and controls. The implementation of a linear discriminant analysis effect size (LEfSe) analysis has led to the identification of an increase in the *Syntrophomonadaceae* family, *Anaerovorax* genus, *Bacteroidales* sp., *Tyzzarella* sp., *Lachnospiraceae*family, *Akkermansiamuciniphila* and *Parabacteroides*

distasonis. It was determined that these bacteria were characterized as compositional elements indicative of PPR patients. The LEfSe analysis indicated a decline in the prevalence of *Prevotella copri*. The study delineates the intestinal microbiological profile of patients afflicted with inflammatory rosacea, thereby substantiating the notion of intestinal dysbiosis [39]. In a research study, the intestinal microbiota of 11 rosacea patients was compared with the microbiota of 110 age- and sex-matched individuals who were considered to be healthy. More than 90% of patients in both groups are female. 90.9% of patients diagnosed with rosacea were female, with a mean age of 49.9 ± 11.3 years. Furthermore, 4 of the patients (36.3%) had ETR and 7 of them (63.7%) had PPR. A decline in abundance, though not in uniqueness of bacteria diversity, was demonstrated in rosacea patients. The incorporation of additional variables, including alcohol consumption, tea or yogurt intake, tobacco use, exercise habits, vegetarian diet, and rosacea subtype revealed no significant impact on the structure of the gut microbiota structure, as indicated by PCoA analysis. A comparative analysis of the gut microbiota revealed that both groups exhibited a predominance of Bacteroidetes, Firmicutes, and Proteobacteria. Nevertheless, a notable distinction was identified in the rosacea subjects, who exhibited an increased prevalence of *Bacteroides* and *Fusobacterium*, and a reduced prevalence of *Prevotella* and *Sutterella*, in contrast to the control group. The LEfSe analysis revealed substantial changes in the composition of the intestinal microbiome in patients with rosacea, characterized by increased abundance of *Rhabdochlamydia*, *Bifidobacterium*, *Sarcina*, and *Ruminococcus*, as well as reduction in levels of *Lactobacillus*, *Megasphaera*, *Acidaminococcus*, *Haemophilus*, *Roseburia*, *Clostridium*, and *Citrobacter*. Rosacea patients exhibit distinctive characteristics in their fecal microbiota, which may be associated with sulphur metabolism, cobalamin, and carbohydrate transport [40]. In a separate study, the relationship between the gut microbiota of 12 female rosacea patients and 251 female healthy controls were evaluated. Rosacea patients exhibited a range of subtypes, including 50% ETR, 17% PPR, and other subtypes. The study revealed no statistically significant disparities in diversity metrics between subjects with rosacea and those without rosacea, suggesting that the presence of this skin condition does not significantly impact biodiversity levels. Additionally, the study indicated that patients with rosacea exhibited distinct compositions of enteral microbiota, yet these compositions were comparable in abundance to control group. Nevertheless, substantial disparities were identified at the level of genera. Using metagenomeSeq for comparison of differentials in the subjects, there was a notable abundance of *Acidaminococcus* and *Megasphaera*, in contrast to the relative paucity of *Peptococcaceae* family, unknown genus, and *Methanobrevibacter* were observed in the patients in comparison with the control group [41]. A recent study examined the disparities in fecal microbial profiles, as analyzed with MiSeq 16S rRNA sequencing, among patients diagnosed with 54 cases of rosacea compared to 50 healthy controls. A decrease in microbial richness and diversity was identified in patients with rosacea in comparison with the control group. In rosacea, a significant decrease was observed in the levels of *Faecalibacteriumprausnitzii*, *Lachnospiraceae* ND 3007 group *sp.*, and *Ruminococcaceae*. Conversely, *Oscillobacter sp.*, *Flavonifractorplautii*, and *Ruminococcaceae* UBA 1819 exhibited a marked increase in their abundance in cases of rosacea when compared to the control group. The present study found no statistically significant associations between the clinical severity levels of rosacea or the existence of gastrointestinal symptoms and intestinal microbiome characteristics [42].

Another study was conducted to ascertain the correlation between the gut microbiome and rosacea. The study did not include a control group, and it did not examine how the levels of intestinal microbiota species changed. In this study, a two-sample Mendelian randomization (MR) design was employed and data derived from the Genome-Wide Association Study focused on gut microbiota and the FinnGen biobank for rosacea. The study identified and analyzed 2078 single nucleotide polymorphisms (SNPs) that are linked to the gut microbiota. The study has indicated that two bacterial genera, *Actinomyces* and *Butyrivibrio*, may play a pivotal role in preventing the development of rosacea. The results of the MR analysis indicated the absence of pleiotropy, with a uniform distribution exhibited across a selected set of SNPs. Tests of directionality indicated a substantial

causative pathway from gut microbiota to rosacea. However, the study's findings did not differentiate among the subtypes of rosacea [43].

6. Discussion

The findings of the studies indicate that there is a substantial change in the gut microbiome in patients with rosacea, which is related to the inflammatory process of the skin. The study conducted by Chen et al. revealed a decline in the prevalence of the *Lactobacillus* genus. This decline may potentially contribute to the development of dysbiosis in patients with rosacea [40], which is compatible with the findings demonstrated the capacity of *Lactobacillus Paracasei* CNCMI-2116 (ST11) to impede substance P-induced skin inflammation. Furthermore, these bacteria were demonstrated to enhance the skin barrier recovery, thereby contributing to a reduction in skin irritability [35]. Moreover, *Lactobacilli* are known to play a vital role in defending against pathogenic microorganisms, modulating inflammation, managing gut flora, and preventing bacterial infections [44].

Morena et al.'s study demonstrated a decline in the levels of *Prevotellacopri* [39], has been shown to have a protective effect on the mucosal barrier and to reduce the likelihood of inflammation by producing SCFAs through the process of fiber metabolism [45]. In addition, Guertler et al.'s study revealed a decline in the abundance of *Lachnospiraceae* and *Faecalibacterium* [42]. These bacteria have been identified as key contributors to the production of butyrate, a short-chain fatty acid with recognized anti-inflammatory properties [46].

The findings indicate that there is an increase of *Bacteriodes* [39], *Acidaminococcus* and *Megasphaera* [41] and *Ruminococcus* [42] in the gut microbiome of patients with rosacea and it is plausible that these results may serve as a rationale for the development of inflammation in these patients. Accordingly, the substantial presence of the genera *Bacteroides*, *Ruminococcus*, *Acidaminococcus*, and *Megasphaera* in the gut microbiome was found to be significantly associated with the disease-related group [46]. These findings may suggest that there is an association between elevated levels of intestinal inflammation and rosacea. Therefore, it would be beneficial to define SIBO as an underlying factor. In addition to analyzing fecal microbiota, the diagnosis of SIBO can be facilitated by a lactulose or glucose breath test. These methods are particularly advantageous in cases of rosacea that exhibit inflammatory characteristics associated with the condition.

The administration of rifaximin could be recommended as a potential therapeutic intervention for the diagnosis of SIBO in rosacea patients, as evidenced by the findings of the conducted studies [8,47,48]. Given the documented increase in the prevalence of SIBO in patients with PPR compared to those with ETR [47], PPR can benefit from anti-inflammatory properties of probiotics, contingent upon the inflammatory etiology of the disease. The potential of probiotics in managing rosacea as the oral use of probiotics, such as *Escherichia coli* Nissle, a mixture of *Bifidobacterium* strains and a mixture of *Bifidobacterium* and *Lactobacillus* in combination with standard therapies of rosacea, resulted in more frequent clinical remission, substantial symptom improvement, and a reduction in relapses lasting up to six months after the initiation of therapy [49].

The present review has limitations due to the restricted number of studies that have been conducted on the microbial flora of patients with rosacea. However, the study's strengths lie in its presentation of the increased potential for alterations in the gut microbiota in individuals diagnosed with rosacea.

7. Conclusion

The identification and management of an underlying SIBO in patients diagnosed with rosacea may offer a therapeutic avenue for reducing the frequency of rosacea flare-ups. Additionally, probiotics play a pivotal role in the regulation of gut flora thus highlighting their significant importance in the management of rosacea symptoms. Consequently, future studies should

encompass large cohort and control studies that delineate the subtypes of bacteria before and after probiotic utilization in rosacea patients.

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