



Rosacea, Germs, and Bowels: A Review on Gastrointestinal Comorbidities and Gut–Skin Axis of Rosacea

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ABSTRACT

Rosacea is a chronic inflammatory disease with complicated pathophysiology that involves genetic and environmental elements and dysregulation of innate and adaptive immunity, neurovascular responses, microbiome colonization or infection, resulting in recurrent inflammation. Rosacea has been reported associated with various gastrointestinal diseases including inflammatory bowel disease, celiac disease, irri-

table bowel syndrome, gastroesophageal reflux disease, *Helicobacter pylori* (HP) infection, and small intestine bacterial overgrowth (SIBO). The link may involve common predisposing genetic, microbiota, and immunological factors, comprising the theory of the gut–skin axis. Although the evidence is still controversial, interestingly, medications for eradicating SIBO and HP provided an effective and prolonged therapeutic response in rosacea, and conventional therapy for which is usually disappointing because of frequent relapses. In this article, we review the current evidence and discuss probable mechanisms of the association between rosacea and gastrointestinal comorbidities.

Keywords: Celiac disease; Gut–skin axis; *Helicobacter pylori*; Inflammatory bowel disease; Irritable bowel syndrome; Rosacea; Small intestine bacterial overgrowth

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Key Summary Points

Rosacea has been reported to be associated with various gastrointestinal diseases including inflammatory bowel disease, celiac disease, irritable bowel syndrome, gastroesophageal reflux disease, *Helicobacter pylori* infection, and small intestine bacterial overgrowth.

Among rosacea-associated gastrointestinal diseases, the evidence for inflammatory bowel disease is the strongest.

The link between rosacea and gastrointestinal comorbidities may involve common predisposing genetic, microbiota, and immunological factors, comprising the theory of the gut–skin axis.

The associations of rosacea with gastrointestinal diseases remind us of these possible comorbidities and provide an innovate direction for treating rosacea, and conventional therapy for which is usually unsatisfactory because of frequent relapses.

DIGITAL FEATURES

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INTRODUCTION

Rosacea is a common chronic inflammatory disease that mainly affects the central face and presents with flushing, persistent erythema, papules and pustules, telangiectasia with or without burning or stinging sensation, dry and rough appearance, facial plaques or edema, phymatous changes, and ocular involvement

[1]. Rosacea is classified into four subtypes: erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea, and ocular rosacea [1].

The pathophysiology of rosacea involves genetic and environmental elements and dysregulation of innate and adaptive immunity, neurovascular responses, and microbiome colonization or infection, with resultant chronic recurrent inflammation [2, 3]. Although the exact mechanisms are unclear, rosacea has been associated with many comorbidities such as gastrointestinal, neurologic, cardiovascular, psychiatric, metabolic, and autoimmune diseases [3–5]. Among these comorbidities, the gastrointestinal conditions were the most frequently reported, including inflammatory bowel disease (IBD) which consists of ulcerative colitis (UC) and Crohn’s disease (CD), celiac disease (CeD), irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), *Helicobacter pylori* (HP) infection, and small intestine bacterial overgrowth (SIBO) [3, 5–7]. The gut–skin axis, a newly emerging concept for pathogenesis of many chronic inflammatory diseases, proposes that gastrointestinal health affects the skin homeostasis and allostasis through complicated interactions between the immune, metabolic, and nervous systems [8, 9]. The gut microbiome is regarded as a major regulator of the gut–skin axis with a bidirectional modulation between the gut microbiome and host immunity [8–10]. Perturbations of the gut microbiota would disrupt balance of the immune system not only in the intestinal mucosa but also systemically. Thus, the “leaky gut” theory, noted by increased gut permeability, intestinal dysbiosis, and changed mucosal immunity, has been considered related to the development of chronic inflammatory diseases [10]. In this article, we review the current evidence and discuss probable mechanism of the association between rosacea and gastrointestinal comorbidities. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

GUT–SKIN AXIS: GUT MICROBIOTA AS A LINK BETWEEN ROSACEA AND GASTROINTESTINAL COMORBIDITIES

Gut microbiota have been reported to affect skin homeostasis and allostasis through their effects on both innate and adaptive immunity [8]. The gut microbiome can affect the host immune system in a complicated and intricate way, which can promote immune tolerance of dietary and environmental antigens and provide protection against invasion of exogenous pathogens directly by competitively binding to endothelial cells and triggering immunoprotective responses [9]. Segmented filamentous bacteria, a nonculturable *Clostridia*-related species, orchestrate the differentiation of both proinflammatory Th1 and Th17 cells and regulatory T cell responses [11]. Certain microbes and their metabolites, such as retinoic acid, and polysaccharide A of *Bacteroides fragilis* and *Faecalibacterium prausnitzii*, were reported to promote regulatory T cells [9, 10]. Short chain fatty acids (SCFAs), such as propionate, acetate, and butyrate, were synthesized from dietary fiber fermentation by the gut microbiome. SCFAs have been found to inhibit inflammatory cells proliferation, migration, adhesion, decrease cytokine production, inhibit histone deacetylase, and inactivate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling pathways, and therefore regulate the activation and apoptosis of immune cells and decrease immune response [9, 12]. Not surprisingly, SCFAs have demonstrated protection against the development of inflammatory disorders such as allergy [13]. On the other hand, emerging evidence shows that gut microbiota are supposed to impact the skin microbiota. SCFAs were reported to play a key role in impacting the predominance of skin microbiota and subsequently affect the cutaneous immune response [9]. Also, intestinal microbiota and their metabolites have been found to metastasize to the skin via the bloodstream in cases with disturbed intestinal barriers, accumulate in the skin, and then disrupt skin homeostasis [8, 9]. Skin microbiota are

crucial for the balance of skin immunity and defensive function, like a skin barrier. Perturbation of skin microbiota may abnormally enhance the Toll-like receptor 2-related pathway, activate innate immunity, and amplify the inflammatory response to external stimuli in patients with rosacea [14]. The evidence suggests direct interactions among gut microbiota, skin microbiota, and skin homeostasis. Rosacea is an immune-mediated inflammatory disease and diseases of this kind have shown certain evidence associated with gut dysbiosis [15]. Several studies have suggested a relationship of rosacea with HP infection and SIBO, although the role is still controversial [8]. SIBO produces toxic metabolites which induce enterocytes injury and increased intestinal permeability, and thus contributes to systemic inflammation [9, 12]. Various gastrointestinal diseases such as IBD, CeD, and IBS have also been related to SIBO [16–19]. Microbiota have been considered a link between rosacea and gastrointestinal comorbidities (Fig. 1).

HELICOBACTER PYLORI INFECTION

Helicobacter pylori is a type of spiral-shaped gram-negative bacteria known to cause gastritis and peptic ulcer. The association between HP infection and rosacea is controversial. A case–control study has shown a significantly higher prevalence of HP infection in patients with rosacea than in age- and sex-matched controls, and rosacea has been associated with gastritis, especially involving antrum mucosa [20]. In contrast, another case–control study revealed that patients with rosacea had similar rates of HP infection as healthy controls [21]. Also, a study found no increased risk of non-immunologic gastrointestinal ulcers in patients with rosacea [22]. A meta-analysis of 14 observational studies found a weak but non-significant association between rosacea and HP infection (OR 1.68, 95% CI 1.00–2.84, $P = 0.052$), but a sensitivity analysis restricted to C-urea breath test showed a significant association (OR 3.12, 95% CI 1.92–5.07, $P < 0.0001$) [23]. The conclusion of that article with the highest level of evidence seems to give us a

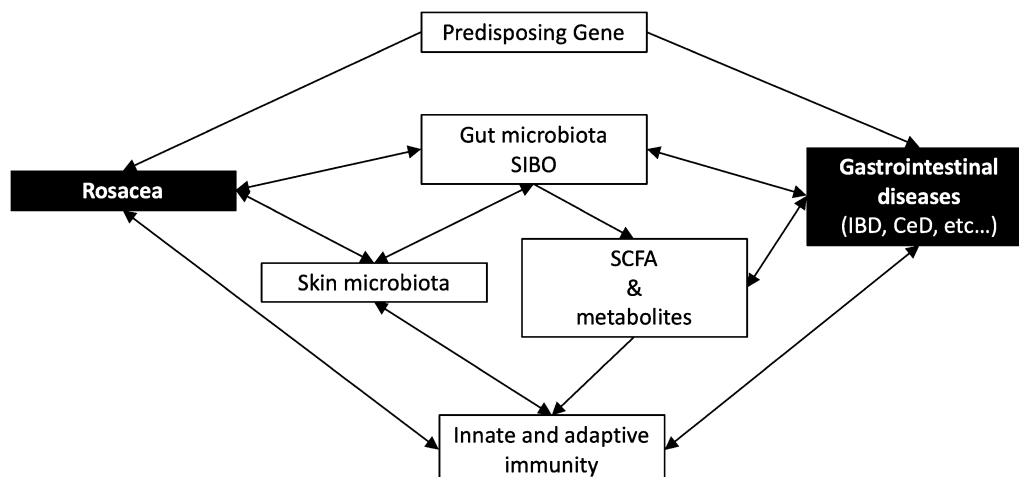


Fig. 1 Probable mechanism for association between rosacea and gastrointestinal comorbidities. CeD celiac disease, IBD inflammatory bowel disease, SCFA short chain fatty acids, SIBO small intestine bacterial overgrowth

temporary answer to the conflicting results. However, the relationship between HP infection and rosacea appears more complicated with many confounding factors. Some studies discovered a higher prevalence of HP infection among patients with moderate to severe rosacea, implying a potential dose–response relationship between the severity of rosacea and concurrent HP infection rates [24, 25]. One case–control study found no significant association between exposure to HP and rosacea, but a strong correlation in those without previous antibiotics use (OR 5.19, $P = 0.005$). The fact is that oral antibiotics are standard treatment options for both diseases, which complicates the interpretation of these findings, and there were two separate studies on patients without previous antibiotic use showing a strong association between rosacea and HP infection [26].

Prolonged use of systemic antibiotics in rosacea may be a confounder in the relationship. Antibiotics could diminish the antigenic effect of HP, and partial treatment of HP can lead to non-reactive serology [27]. Thus, the association between HP infection and rosacea is usually underestimated.

On the other hand, some reports found that eradication of HP successfully treated rosacea, even for patients who failed to improve with prior conventional treatments [28, 29]. However, one meta-analysis of seven studies

revealed a trend but no significant effect of HP eradication on rosacea symptoms (RR 1.28, 95% CI 0.98–1.67, $P = 0.069$) [23]. Actually, reports of improvement in rosacea following antibiotic therapy for HP infection may be attributable to the anti-inflammatory effects of antibiotics used. The association among HP infection, antibiotics effect, and rosacea still needs to be clarified.

Despite the highly conflicting results of current research, there are some reasonable mechanisms to explain the possible association between these two diseases. Rosacea is an immune-mediated inflammatory disease and usually presents with flushing, while HP may induce inflammation and flushing possibly through the release of angiogenic and vasomotor agents. Firstly, HP can increase the in vivo concentrations of nitrous oxide, which induces vasodilation, inflammation, and cytotoxic reaction. HP can also induce delivery of a highly immunogenic protein, cytotoxin-associated gene A, into cells [30] and provoke proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-8, causing a series of inflammatory reactions [27, 30, 31]. On the other hand, gastric HP infection is largely related to hypergastrinemia [32], and gastrin is the endogenous trigger to evoke flushing [30, 33].

SMALL INTESTINAL BACTERIAL OVERGROWTH

SIBO is defined as small bowel aspirate of more than 10^5 colony-forming unit/ml as a gold standard although the diagnosis could be made by various tools [34]. However, a systematic review demonstrated the limited ability to accurately identify SIBO by current detection methods [34]. This may contribute to variable results between SIBO studies as a result of different detection methods.

A nationwide cohort study found no increased incidence of SIBO in patients with rosacea despite the significant higher prevalence, but the study authors stated that SIBO prevalence might have been underestimated [6]. A prospective study demonstrated SIBO in almost half of patients with rosacea, and the prevalence was significantly higher than in healthy controls. Additionally, most of the SIBO-positive patients with rosacea presented with papulopustular-type rosacea [35]. However, another case–control study found that HP infection, rather than SIBO, was significantly more prevalent and may play a pathogenic role in rosacea [29]. In that study, most patients presented with facial flushing and erythema but only 30% with papulopustules [29]. The results of these studies were consistent with a previously proposed hypothesis that HP seems more prevalent in erythematotelangiectatic rosacea, possibly because HP-related angiogenic and vasomotor agents can induce flushing and erythema. Nevertheless, SIBO played a more important role in papulopustular rosacea [35, 36]. The hypothesis was confirmed by the study by Drago, which showed significant higher risk of SIBO in papulopustular rosacea than in erythematotelangiectatic type ($P = 0.018$, OR 12.3, CI 1.4–105.5) [37].

After eradication of SIBO by rifaximin 400 mg three times daily for 10 days, almost all of the patients achieved complete resolution or at least great improvement of rosacea [35]. Skin lesions remained in remission without other treatments in these SIBO-eradicated patients for more than 9 months. By contrast, among those who received placebo, skin lesions remained

stationary or even worsened until they received SIBO eradication afterwards [35]. Another study with 3 years of follow-up also demonstrated persistent therapeutic effects after eradicating SIBO with rifaximin [37]. In addition, there was a report that eradication of SIBO benefitted ocular rosacea greatly [38]. Rifaximin can diminish SIBO but the poor absorbability resulted in less interference with skin microbiota or systemic anti-inflammatory effect; thus SIBO is suggested to be a determinant in persistent inflammation in rosacea [35, 37]. Actually, for those patients without SIBO, rifaximin use did not improve rosacea symptoms [35].

The underlying mechanism linking SIBO to rosacea remains unelucidated. It has been speculated that SIBO increases intestinal permeability, which results in translocation of bacterial components and proinflammatory cytokines into systemic circulation and then triggers inflammation of the skin [7, 15]. Also, gut bacteria have been shown to mimic immunogens. The existence of SIBO may trigger rosacea by increasing TNF or other cytokines, suppressing IL-17, and stimulating the T helper 1-mediated immune reaction [38, 39]. These results provide a new perspective on the pathogenesis and treatment for rosacea in that dysbiosis may play an important role.

INFLAMMATORY BOWEL DISEASE

Among rosacea-associated gastrointestinal diseases, the evidence for IBD is the strongest [3]. A recent meta-analysis indicated an increased prevalence of both CD and UC among patients with rosacea [7]. The association appeared stronger for CD than UC [7, 40]. Another meta-analysis found that the association between rosacea and IBD was bidirectional [41].

Rosacea and IBD are both chronic inflammatory diseases involving the interplay between genetic, immunological, and microbiota elements. As for the genetic aspect, the significant single-nucleotide polymorphisms of butyrophilin-like 2, which likely functions in T cell activation, and polymorphisms of glutathione-S-transferase gene, which encodes enzymes that catalyze toxic oxidative

intermediates, have been related to both rosacea and IBD [7, 42]. Sociobiologically, rosacea and IBD share common risk factors such as obesity and smoking [7, 43].

In the aspect of immunity, both rosacea and IBD are associated with alterations in innate and adaptive immunity [3]. There have been reports that dysfunction of the innate immune system as activation of macrophages and Toll-like receptor 2, dysregulation of mast cells, fibroblasts, and production of reactive oxygen species, matrix metalloproteinases, TNF, and IL-1 β contribute to the development of chronic inflammation and vascular abnormalities, causing inflammation of both rosacea and IBD [3, 7, 44]. For adaptive immunity, T helper type 1 and 17 cells as well as B cells are pathogenic in both rosacea and IBD through production of interferon-gamma (IFN γ), TNF, IL-17, and multiple immunoglobulins [3, 7, 44]. As previously discussed, SIBO is considered linked to rosacea. Similarly, significant higher SIBO has been observed in patients with CD and patients with UC [16], and eradication of SIBO substantially improved clinical symptoms of IBD [7, 45, 46]. Dysbiosis may also play a role in the link between rosacea and IBD. Medication effluence is another possible cause for the association. Patients with rosacea usually received long-term antibiotics, especially tetracycline. A study also demonstrated ever use of tetracycline at baseline was associated with an increased risk for CD and UC [40].

CELIAC DISEASE

Celiac disease is an immune-mediated, gluten-induced small-intestinal mucosal injury and nutrient malabsorption [47]. A Danish population-based cohort study revealed a significant association of rosacea with incident CeD (HR 1.46, 95% CI 1.11–1.93) [6]. In addition, a case–control study demonstrated that patients with rosacea had a twofold odds for prevalent CeD compared with age, sex, and calendar time-matched controls (OR 2.03, 95% CI 1.35–3.07) [4], and stratification by gender revealed a significant association of rosacea with CeD in women, but not in men [4].

Rosacea shares genetic risk loci with CeD. A genome-wide association study (GWAS) found that rosacea was associated with human leukocyte antigen (*HLA*)-*DRB1*03:01*, *HLA-DQB1*02:01*, and *HLA-DQA1*05:01* [42], and both *HLA-DQB1*02:01* and *HLA-DQA1*05:01* were associated with CeD [48]. In CeD, the main immune actions were Th1 and B lymphocyte-related response releasing immunoglobulin E and other immunoglobulins and Th2-related releasing of pro-inflammatory cytokines, such as TNF and IFN γ [49, 50]. On the other hand, a high prevalence of SIBO in patients with CeD was noted, but the evidence was only stronger in those with persistent gastrointestinal symptoms after gluten-free diet [17, 18]. Rosacea and CeD may share common pathogenesis in gene, immune reaction, and SIBO.

IRRITABLE BOWEL SYNDROME

The pathophysiology of IBS remains uncertain. A Danish population-based cohort study found an increased incidence of IBS in patients with rosacea (HR 1.34, 95% CI 1.19–1.50) [6], whereas in the subgroup analysis according to gender, the increased risk for IBS only existed in women (HR 1.35, 95% CI 1.19–1.54), but not in men (HR 1.29, 95% CI 0.98–1.69) [6]. However, the data were based on International Classification of Diseases codes, and the diagnosis of IBS should exclude other identified gastrointestinal diseases which had symptoms overlapping those of IBS. The association of rosacea with IBS still needs further evidence.

Rosacea and IBS also share some common pathogenesis. Peripheral blood mononuclear cells of patients with IBS produce high levels of TNF [51], which plays a role in the pathogenesis of rosacea. SIBO was also reported to be associated with IBS. It has been reported that 78% of patients with IBS had SIBO, and eradication of the overgrowth eliminated IBS in 48% of subjects [19]. However, some studies did not support an association between SIBO and IBS, with only mildly increased amounts of small-bowel bacteria found [52].

Table 1 Reported common mechanisms of rosacea and each associated gastrointestinal comorbidity

Gastrointestinal comorbidities	Possible mechanisms of the association
<i>Helicobacter pylori</i> infection	HP may induce inflammation and flushing possibly through the release of angiogenic and vasomotor agents. HP can increase nitrous oxide concentrations, which induces vasodilation, inflammation, and cytotoxic reaction. HP can also induce delivery of a highly immunogenic protein, cytotoxin-associated gene A, into cells and provoke proinflammatory cytokines such as TNF and IL-8, causing a series of inflammatory reactions. Also, gastric HP infection is largely related to hypergastrinemia, and gastrin is the endogenous trigger to evoke flushing
Small intestinal bacterial overgrowth (SIBO)	SIBO increases intestinal permeability, resulting in translocation of bacterial components and proinflammatory cytokines into systemic circulation and then triggers inflammation of skin. Also, gut bacteria mimic immunogens, so SIBO may trigger rosacea by increasing TNF or other cytokines, suppressing IL-17, and stimulating the T helper 1-mediated immune reaction
Inflammatory bowel disease	Both rosacea and IBD are associated with alterations in innate and adaptive immunity. Dysfunction of the innate immune system as activation of macrophages and Toll-like receptor 2, dysregulation of mast cells, fibroblasts, and production of reactive oxygen species, matrix metalloproteinases, TNF, and IL-1 β contribute to the development of chronic inflammation and vascular abnormalities, causing inflammation of both diseases. For adaptive immunity, T helper type 1 and 17 cells as well as B cells are pathogenic in both rosacea and IBD through production of IFN γ , TNF, IL-17, and multiple immunoglobulins. The common predisposing genes were found, such as the significant polymorphisms of butyrophilin-like 2 and glutathione-S-transferases gene. SIBO is considered linked to both rosacea and IBD. Medication effluence, like ever use of tetracycline in rosacea was associated with an increased risk for CD and UC
Celiac disease	Rosacea shares genetic risk loci with CeD, such as <i>HLA-DQB1*02:01</i> and <i>HLA-DQA1*05:01</i> . In CeD, the main immune actions were Th1 and B lymphocyte-related response releasing immunoglobulin E and other immunoglobulins and Th2-related releasing of pro-inflammatory cytokines, such as TNF and IFN γ . On the other hand, a high prevalence of SIBO seems noted in patients with rosacea and patients with CeD
Irritable bowel syndrome	Peripheral blood mononuclear cells of patients with IBS produce high levels of TNF, which plays a role in the pathogenesis of rosacea. SIBO was also reported associated with IBS and rosacea, and eradication of SIBO benefit in these two diseases in some evidence
Gastroesophageal reflux disease	Some common risk factors, such as smoking and alcohol use, are shared by rosacea and GERD

GASTROESOPHAGEAL REFLUX DISEASE

Only one case–control study reported a significant association between rosacea and GERD (OR

4.2, 95% CI 1.7–10.2) [53]. Some common risk factors, such as smoking and alcohol use, are shared by rosacea and GERD [26, 43, 54, 55]. More studies are awaited to examine the association between the two diseases.

CONCLUSIONS

Rosacea is associated with many gastrointestinal comorbidities although the pathogenesis is not yet fully elucidated, which may involve shared common predisposing factors as genetic, microbiota, and immunological elements. Table 1 summarizes the possible mechanisms of the association of rosacea with the gastrointestinal comorbidities we discussed in this article. As illustrated in Fig. 1, some common genetic loci may predispose subjects to both rosacea and gastrointestinal diseases. Also, microbiota and related changes of immunity play an important role in the association. Dysbiosis and SIBO affect the host immune system in a complicated and intricate way, involving both innate and adaptive immunity through changing SCFA, certain intestinal microbes and their metabolites, and the influence on the skin microbiota, and subsequently affect cutaneous immune response. Interestingly, although the evidence is still equivocal, medication for eradicating SIBO and HP seemed to provide an effective and prolonged therapeutic response for rosacea in some studies. Not only do these associations remind us of these gastrointestinal comorbidities among patients with rosacea but also provide an innovative direction for treating rosacea, conventional therapy for which is usually unsatisfactory because of frequent relapses.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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