Rosacea: Microbiome and therapy associated with microbiome

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Abstract

Flush, transitory erythema, persistent erythema, telangiectasia, papules, pustules, and stinging or burning discomfort on the facial skin are all symptoms of rosacea, a chronic inflammatory skin disease. Although its exact cause is unknown, rosacea has been linked to the autonomic nervous system, immunological system, and blood vessels. Bacillus oleronius, Demodex folliculorum, Cutibacterium acnes, Staphylococcus epidermidis, and Even the microbes that live in your gut have a role in the emergence of rosacea. The existence of alteration in microbiome of the skin and gut can be a consideration for giving probiotics as adjuvant therapy to maintain the balance of microbiome in rosacea

Keywords: Rosacea; Microbiome; Skin Microbiome; Gut Microbiome

1. Introduction

Flush, persistent erythema, transient erythema, papules, telangiectasia, papules, pustules, discomfort, and burning are all symptoms of rosacea, a chronic inflammatory condition of the skin that primarily affects the face. Although its exact cause is uncertain, rosacea has been linked to changes in the immune system, neurological system, and blood that boost microbial and Demodex mite populations. Life quality is diminished and psychological effects are felt more strongly when lesions are located in the central face.

Bacillus oleronius, Demodex folliculorum, Cutibacterium acne and Staphylococcus epidermidis have all been implicated in the pathophysiology of rosacea. Demodex folliculorum is a member of the skin microbiome that lives in the sebaceous glands of healthy skin, but it is increasing in rosacea patients. Demodex folliculorum is thought to coexist with Bacillus oleronius which is a proinflammatory and gram-negative bacterium. Staphylococcus epidermidis is a bacterium, that can be found in rosacea pustules. Cutibacterium acnes is dominant on healthy facial skin, but it decrease in rosacea patient.

Rosacea is linked to the gram-negative bacteria in the gut microbiome, such as Helicobacter pylori. Although the precise connection between rosacea and Helicobacter pylori has yet to be established, the bacterium has been shown to play a part in the condition and its severity can be ameliorated by being eliminated. It's also common for people with rosacea to suffer from inflammatory bowel disease and small intestine bacterial overgrowth.

Rosacea therapy is often given with antibiotics and antiparasitic which can improve the clinical appearances of rosacea. Alteration of skin and gut microbiome were found in rosacea patient. Giving additional therapy is expected to repatriate the balance of microbiome.

Regarding the many roles of microbiome in rosacea as mentioned above, it is important to make a literature review aimed at discussing theories and scientific evidence that can be used as adjuvant therapy for rosacea, which will be discussed in this review.

2. Rosacea

Flushing, telangiectasia, persistent erythema, pain, papules, pustules, burning or stinging sensation, and itching (very rarely) are all symptoms of rosacea, a chronic inflammatory skin condition that typically affects the skin of the central face and can lead to phymatous alterations (hypertrophy of the sebaceous glands and fibrosis), including rhinophyma (round nose) and eye involvement.[1,2]

The National Rosacea Society (NRS) (2002) distinguishes between four distinct forms of rosacea: papulopustular rosacea (PPR), erythematotelangiectatic rosacea (ETR), ocular rosacea and phymatous rosacea (2002).[1,2,3] Latest classification in 2016-2017 was divided based on the pathophysiology of the disease.[1,2]

Table 1. Classification of rosasea from 2002[1]

Subtipes	Clinical Characteristics
Subtype 1: erythematotelangiectatic	Persistent central facial erythema, frequent flushing; may be telangiectatic vessels
Subtype 2: papulopustular	Dome-shaped, erythematous papules, some with ascending postulation, distributed centrally on the face, superimposed on a prolonged erythematous background
Subtype 3: phymatous	Varieties of persistent face swelling due to tissue hypertrophy (rhinophyma) are discussed
Subtype 4: OR	Ocular inflammation (eg blepharitis, conjungtivitis)

Table 2. Classification of rosasea from 2016[1]

Diagnostic Features	Major Features	Secondary Features
Facial redness in the center that lasts and flares up occasionally due to unknown causes.	Flushing or transient erythema	Feeling like the skin is on fire
Phymatous changes	Inflammatory papules and pustules	Prickling pain on the skin
	Telangiectasia	Edema
	Ocular manifestations Eyelid margin telangiectasis Blepharitis Keratitis, conjungtivitis, or sclerokeratitis	Feeling of skin dryness

There are reports of rosacea cases as high as 10% in nations with racially diverse populations, including those in Africa, Asia, and South America. Nearly 12% of 291 rosacea patients in a Colombian epidemiological study had Fitzpatrick skin phototype IV or V. Forty percent of 168 rosacea sufferers in a Korean study were classified as having Fitzpatrick skin phototypes IV or V. Five-and-a-half percent of rosacea patients in Estonia belonged to Fitzpatrick skin phototypes I and II, 38 percent to Fitzpatrick skin phototype III, and 7 percent to Fitzpatrick skin phototype IV, according to a recent study[4]. This shows that rosacea can affect people of all skin tones all over the world.

There has been no definitive discovery of what causes rosacea. Multiple studies have implicated immune system dysfunction, nervous system abnormalities, face blood vessel abnormalities, bacteria, and Demodex mites in the pathophysiology of rosacea. The symptoms can be made worse by exposure to things like heat, UV light, stress, hot drinks, spicy meals, alcohol and smoking.[1]

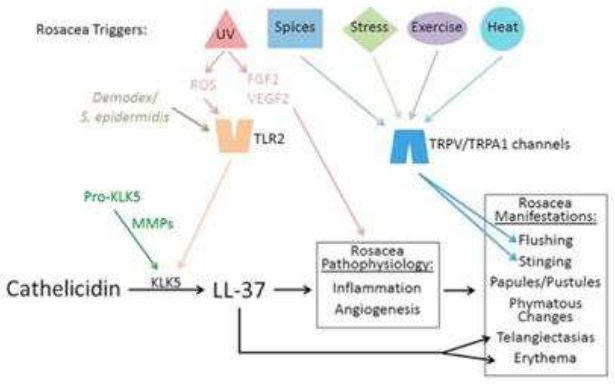

Fig 1. Pathophisiology and manifestation of rosacea[5]

3. Microbiome

The microbiome is all the microbes that live in the human body, animals, plants, and so on. Microbiome not only refers to the microorganisms involved but also includes the genes and genomes of these microorganisms to form a specific ecological formation.[6]

The microbiome have main contribution maintaining normal bodily functions. The microbiome has an impact on both health and disease, contributing to increased or impaired metabolic and immune functions.[7] The presence of immune system dysfunction and misregulation of inflammation are causes of non-communicable diseases and conditions (NCDs). Furthermore, microbiota disturbance may increase vulnerability to infection.[7]

The microbiome associated with humans is called the microbiota, but often both of them are used together. Microbiota is a collection of microorganisms (eg bacteria, archaea, eukaryotes, viruses) present in a particular environment.[2] Most of the human body consists of microbes. Bacteria in the microbiome play a role in immunity, nutrition, and human development.

4. The Role of Microbiome in Rosacea

4.1. Skin Microbiome

The skin's immune system is influenced by the microbiome. Bacillus oleronius, Demodex folliculorum, Cutibacterium acnes and Staphylococcus epidermidis are only some of the bacteria that hav main contribution in the development of rosacea. The innate immune system is activated by TLR-2 and other receptors when these microorganisms undergo aberrant activation. Cathelicidin, an AMP expressed by both leukocytes and epithelial cells, was likewise significantly increased in rosacea-affected skin compared to normal skin. Alterations such as leukocyte chemotaxis, vasodilation, angiogenesis, and the deposition of extracellular matrix may occur. This effect may be helpful in treating a skin problem caused by dysbiotic bacteria. As a corollary, the increased heat of rosacea sufferers' skin may cause a shift in the normal microbial balance.[7]

4.2. Demodex folliculorum

The cause of increasing Demodex is unknown, but it is related to increase activity of the immune system, altered in environmental factors due to increased blood vessel flow, and altered in connective tissue in rosacea.

Demodex folliculorum was found more frequently in rosacea patients compared to age-matched controls, as noted by Casas et al. Demodex folliculorum was found at a density that was 5.9 times greater in rosacea

patients than in controls.[8] Murillo, et al., also found that Demodex were increased in rosacea patients.[9] Demodex folliculorum contributes to the pathophysiology of rosacea by secreting TLR-2 that activate chitin.[5]

The increasing of vascularity leads to the increasing of Demodex folliculorum, which induce the inflammatory reaction, aggravate the mechanism and continuous circulation of the cycle.[8]

4.3. Bacillus oleronius

The gram-negative, nonmotile bacteria Bacillus oleronius, a close relative of Demodex, is involved in rosacea because of the endospore it produces. Bacillus oleronius enhanced MMP-9, tumor necrosis factor (TNF), and interleukin 8 production in rosacea patients (IL8). Bacillus oleronius triggers a proliferative response of large numbers of mononuclear cells in the blood, which triggers the symptoms of rosacea.[2]

4.4. Cutibacterium acnes

By converting the triglycerides in sebum into free fatty acids, which in turn acidify and moisturize the skin, Cutibacterium acnes has a protective impact on normal skin. Colonization of the skin by other bacteria is prevented by C. acnes. As C. acnes levels drop in rosacea patients, we can infer that this bacterium contributes to the development of this skin condition.[2]

Healthy skin is protected by Cutibacterium acnes. By converting sebum into free fatty acids, C. acnes keeps the skin free from infection from other microorganisms.[11]

4.5. Staphylococcus epidermidis

Staphylococcus epidermidis is normally found on healthy human skin and aids in the body's immune response to foreign invaders. Unlike the non-hemolytic S. epidermidis prevalent in healthy skin, the S. epidermidis isolated from PPR patients exhibited beta-hemolytic variations associated with higher virulence.[10]

S. epidermidis contributes to the pathophysiology of rosacea by stimulating TLR-2. The innate immune system is activated by the virulence factors that are secreted by these bacteria, which in turn exacerbates rosacea symptoms.[2]

5. Intestinal Microbiome

5.1. The Gut-skin axis

There is evidence to suggest that the gut microbiome influences skin homeostasis and allostasis through influencing both innate and adaptive immunity. One way in which the gut microbiota may affect the host immune system is by increasing immunological tolerance to food and environmental antigens, and another is by protecting against the invasion of exogenous pathogens through direct competitive binding to endothelial cells and inducing an immunoprotective response. The formation of proinflammatory Th1 and Th17 cells, as well as the modification of T cell regulatory responses, are under the control of non-cultivable species of the genus Clostridia, also known as segmented filamentous bacteria.[7]

Short chain fatty acids (SCFAs) are created by the gut microbiome by fermentation of dietary fiber. SCFAs include , acetate, propionateand and butyrate. It has been found that short-chain fatty acids (SCFAs) regulate activation and apoptosis of immune cells and dampen the immune response by preventing inflammatory cell proliferation, adhesion and migration, inhibiting histone deacetylase, decreasing cytokine production, and inactivating the nuclear factor kappa light-chain-enhancer of activated B cell (NFkB) signaling pathway. There is evidence that SCFAs can prevent the onset of inflammatory diseases. Emerging

evidence, however, suggests that gut microbiota should influence skin microbiota. It has been suggested that SCFAs play a significant role in modulating the preponderance of skin microbiota, and thus the skin's immunological response. In addition, it has been discovered that when the gut barrier is compromised, the microbiota and its metabolites can travel via the bloodstream to the skin, where they can aggregate and wreak havoc on skin homeostasis.[7]

5.2. Helicobacter pylori

Helicobacter pylori is a spiral-shaped, gram-negative bacterium that secretes urease into the stomach lining. H. pylori's potential significance in rosacea development is still up for debate. Several studies have demonstrated that people with rosacea have antibodies against H. pylori strains that lack the cytotoxin-associated gene A (CagA) protein. CagA, an infectious component in Helicobacter pylori. The prevalence of CagA positivity is high (67% in H pylori-related rosacea patients) and so is the prevalence of CagA antibodies (75% in all rosacea patients).[5] CagA penetrates cells and causes a prolonged inflammatory response by releasing proinflammatory cytokines like TNF and IL-8.[7]

Patients with rosacea have higher levels of ROS (reactive oxygen species) in their plasma than controls, and H. pylori is a known producer of ROS, particularly NO (nitric oxide). Vasodilation, inflammation, and immunological regulation are only some of the skin's physiological activities that NO is involved in. This may play a pathogenic role in the inflammation that characterizes rosacea, causing the characteristic flushing and erythema of the condition.[6]

The prevalence of H. pylori infection was higher in rosacea patients compared to the general population, but there was no statistically significant link between the two conditions.[12]

5.3 Small Intestinal Bacterial Overgrowth

Over 10^5 CFU/ml of colony-forming units in the small bowel aspirate is considered to be indicative of small intestinal bacterial overgrowth (SIBO). A prospective study found that nearly half of individuals with rosacea also had SIBO, a significantly greater incidence than in healthy controls. The rosacea patients who tested positive for SIBO tended to have papulopustular forms of the disease.[7]

Exactly how SIBO can cause rosacea is still a mystery. Skin inflammation may be triggered by systemic circulation of bacterial components and proinflammatory cytokines, which may occur as a result of increased intestinal permeability caused by SIBO. The bacteria in the gut have been found to be capable of imitating immune system triggers. Upregulation of TNF and other cytokines, downregulation of IL-17, and upregulation of the T helper 1-mediated immunological response have all been associated to the start of rosacea in the presence of SIBO. The results of this study have important implications for the treatment of rosacea since they imply that dysbiosis may play a substantial role in its development.[7]

5.4 Small Inflammatory Bowel Disease

IBD, or inflammatory bowel disease, is a disorder of the digestive system characterized by persistent inflammation and abnormal immune response. Genetic predisposition to disease and environmental factors that compromise immune function both contribute to the development of chronic intertinal inflammation.[13]

Crohn's disease (CD) and ulcerative colitis (UC) are the two kinds of inflammatory bowel disease (which affects mainly the colon and rectum). Related conditions include eczema, psoriasis, and rosacea, all of which are inflammatory skin illnesses.[13]

Activation of macrophages and Toll-like receptor 2 as well as dysregulation of mast cells and fibroblasts

as well as the production of reactive oxygen species, matrix metalloproteinase, TNF, and IL-1 have all been associated to innate immune system malfunction and inflammation in both rosacea and IBD.[7]

B cells and Thelper type 1 and 17 cells secrete interferon-gamma (IFNc), tumor necrosis factor (TNF), interleukin-17 (IL-17), and a range of immunoglobulins, which all contribute to the pathogenesis of both rosacea and IBD.[7]

Patients with rosacea had a higher incidence of inflammatory bowel illness. Rosacea and UC were connected. It has been proposed that these connections between the two disorders may be explained by shared genetic and environmental risk factors, as well as expression of cathelicidin LL-37 in both rosacea and IBD. Patients with inflammatory bowel illness had significantly higher levels of the cathelicidin LL-37, pointing to a role for this protein in the rosacea pathogenesis.[13]

6. Therapy

Rosacea treatment is aimed at alleviating both the condition's outward manifestations and its underlying triggers. Sun exposure, temperature fluctuations, spicy meals, and alcohol intake are just some of the potential triggers that must be avoided as part of the initial treatment process.[1]

Metronidazole (1% cream and 0.75% gel) and azelaic acid (20% cream) are two common topical treatments for papulopustular rosacea. A recent study stated that 1% Ivermectin lotion can be utilized in rosacea patients, and Demodex mites are known to play a role in the etiology of rosacea.[14]

5% Permethrin cream reduced the amount of Demodex significantly but it was not better than topical antibiotic 0.75% Metronidazole cream in rosacea. This indicates the possible involvement of pathogenic bacteria in rosacea patients.[14]

Systemic antibiotics are administered to patients who have a significant number of papules and pustules. Lower doses of this antibiotic have an anti-inflammatory action, whereas greater doses have a bactericidal effect.

In rosacea, antibiotics are used to reduce redness, swelling, and pustules.[14] Administration of antibiotics for therapeutic purposes affects the microbiome both quantitatively and qualitatively by reducing or eliminating microbes. This microbial imbalance affects health and disease. Research into antibiotics' impact on the microbiome's make-up and variety is extensive.[14]

A study stated that antibiotics play a role in reducing or modifying the microbiome and other physiological aspects of the gastrointestinal tract.[15] According to certain scientific data, using antibiotics can disrupt the composition and function of the gut microbiota and result in dysbiosis.

Woo et al. compared the pre- and post-oral antibiotic composition and diversity of cutaneous microbiome in rosacea. Six weeks of therapy with doxycycline resulted in a 3.43-fold rise in the number of Weissella confuse.[16]

The alpha-hemolytic bacteria of the genus Weissella are Gram-positive, catalase-negative, short rods or coco-bacilli that are found in pairs or chains. It may be Lactobacillus spp. or Streptococcus viridans, according to the Gram stain morphology. Weissella is a typical gut bacterium but a rare skin germ. Weissella confusa is linked to sepsis and infection in humans, albeit its precise function is still unknown.[11]

The microbial makeup of the skin was not altered by topical metronidazole (1% cream twice a day for one month).[17] In another study of rosacea patients, patients were given a combination therapy of oral doxycycline 40 mg daily for 8 weeks and oral probiotics twice daily (Bifidobacterium breve BR03, Lactobacillus paracasei LS01 1x109 UFC/dose). The patient came after 8 weeks of treatment that showed significant improvement in skin lesions. Antibiotic therapy was discontinued but probiotics were still given. The patient did not relapse after 6 months of control.[18]

Intestinal epithelial cells' innate immune response is boosted by probiotics, leading to reduced inflammation. These probiotic mechanisms include upregulation of epithelial barrier function, upregulation of epithelial TNF-alpha production, and NF-kappaB pathway activation.[18]

Probiotics manipulate intestinal flora and maintain a balanced microbiota in the host. Probiotics produce SCFA, which will improve intestinal function and integrity, stimulate the immune system and inflammatory response, and influence fat and sugar metabolism. Probiotics containing skin commensal microbes, including Lactobacillus, Bifidobacterium, or Streptococcus show cutaneous immunoregulatory effects by inhibiting biofilm formation, reduces systemic inflammatory cytokines and direct competitive inhibition at binding sites. Lactobacilli have antimicrobial activity against skin pathogens, such as Escherichia coli, Pseudomonas aeruginosa, and pathobionts (Cutibacterium acnes).[19]

7. Conclusion

Microbiome imbalances including Demodex folliculorum, Staphylococcus epidermidis, Bacillus oleronius, Cutibacterium acnes, Helicobacter pylori, and microbiome imbalances due to gastrointestinal diseases, that contribute to the rosacea pathogenesis. It is still unclear for certain whether changes of microbiome in rosacea are the cause of inflammation or whether inflammation is a response to changes of microbiome.

Rosacea therapy currently used is anti-Demodex and antibiotics. Although appropriate of using this drug, it can cause alteration of microbiome. Alteration of microbiome can affect the cure rate of rosacea. Probiotics can be considered as adjuvant therapy in rosacea, that is a dysbiosis of microbiome in rosacea patients. Further research is needed to support the newest therapy in rosacea.

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