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The potential role of *Helicobacter pylori* and other gut dysbiosis factors in the development of rosacea

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ABSTRACT

Rosacea is a chronic inflammatory disease that presents with erythema, telangiectasia, papules, or pustules. Its mechanism of onset still needs to be fully understood. There has been an increasing number of studies and reports confirming the beneficial influence of eradication of *Helicobacter pylori* on the course of the disease. It has been recognized that the bacterium leads to the activation of the inflammatory immune response, resulting in the induction of symptoms similar to rosacea. Another thesis suggests a close connection between the gut–brain–skin axis, which relates to the influence of normal microbiota and gut health, and dermatological diseases. Correlations have been noted between the increased incidence of Crohn's disease, ulcerative colitis, and irritable bowel syndrome in patients with rosacea.

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Keywords: rosacea, *Helicobacter pylori*, eradication, microbiota

INTRODUCTION

Rosacea is a chronic skin disease characterized by papules and pustules on an erythematous base with the presence of telangiectasias and periodic paroxysmal erythema. Rosacea is divided into four subtypes: erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea and ocular rosacea [1]. Abnormal blood supply to the facial skin plays a major role in the development of rosacea. Enlarged sebaceous glands, dilated vessels, and features of sun damage to the skin are present in patients. Genetic predisposition, hormonal disorders and diseases of internal organs, including the gastrointestinal tract, also influence the course of the disease. Rosacea is not rare, as it affects 5% of the world's population [2]. Some authors in the literature indicate that the prevalence of the disease is similar in both sexes, while others indicate that the disease affects women more often [2]. Rosacea is usually diagnosed in adults between 30 and 50 years of age. It is most common in fair-skinned, northwestern residents with skin phototype I or II, or their relatives. However, it should be noted that in about 10% of cases, it affects dark-skinned individuals with IV, V or VI phototype (according to Fitzpatrick) [3]. In these cases, the clinical presentation is different, which can delay the diagnosis [2]. This is particularly true for erythematous lesions and telangiectasias. The pathogenesis of the disease is not yet sufficiently understood, or at least remains very unclear. There is an increasing number of studies suggesting an association of rosacea with various gastrointestinal diseases, including *Helicobacter pylori* infection [4], inflammatory bowel disease, celiac disease, irritable bowel syndrome, gastroesophageal reflux disease and small bowel bacterial overgrowth [5, 6].

A dysbiotic microbiome, dysregulation of the innate immune system and genetic factors, along with the aforementioned chronic diseases, contribute to the pathophysiology of rosacea [5]. To date, studies have reported an increased incidence of rosacea in individuals who are carriers of the gastric bacterium *Helicobacter pylori* (*H. pylori*) [5]. Based on this, a new concept of the pathogenesis of many inflammatory diseases — including rosacea — the gut–skin axis — has emerged [5].

As with many dermatological diseases, in addition to pharmacotherapy, proper skincare procedures and lifestyle changes should be followed. It is recommended to use gentle skincare cosmetics that will not further irritate the skin and cause erythema, and use high photoprotection [6, 7]. Triggers that aggravate skin symptoms such as alcohol, stress, use of saunas and pools with chlorinated water

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should be avoided [8]. There are three types of therapeutic methods for rosacea: topical, general (oral) and selection of appropriate dermocosmetics. The choice of treatment depends on the subtype of the disease. In addition to curing skin symptoms, an additional therapeutic goal is to alleviate associated symptoms such as burning and burning sensation of the skin through excessive congestion and to reduce the visibility of erythema, which significantly affects the patient's self-esteem and comfort [9, 10].

HELICOBACTER PYLORI

H. pylori is a gram-negative bacterium found by Marshall and Warren in the early 1980^{s} [11]. The microbe may be identified in biological samples as old as several tens of thousands of years [12]. Medically, around 70% of patients diagnosed with gastric mucosa *H. pylori* colonisation are asymptomatic [13]. However, it is proven to cause various gastro and duodenal-related diseases, from which the most common ones remain peptic ulcers [14]. The bacterium is graded as a class 1 carcinogen by the World Health Organization (WHO) [15]; therefore, other reported cases of the pathogen in question infections include gastric adenocarcinoma, mucosa-associated lymphoid tissue lymphoma of the stomach (MALT lymphoma) [14].

Generally, any *H. pylori* infection is typically related to a significant number of medical conditions (Fig. 1), among which several dermatological ones may be observed. Although the direct link between *H. pylori* infection and rosacea remains the subject of controversy, many research papers suggest some influence of the microbe in triggering skin changes via two distinct mechanisms. Not only is the bacterium assumed to produce specific cytotoxins leading to the release of histamine, prostaglandins, leukotrienes and cytokines and to an inflammatory immunological reaction with the increase in nitrous oxide-related vasodilatation but it also plays a significant role in the expression of cytotoxin-associated gene A, TNF-α and IL-8. Subsequently, the entire chain of reactions is induced which may result in a symptom representation that is similar to rosacea [16]. Although antibodies against gene *CagA* (*H. pylori* virulent factor) are found in most patients with rosacea [17], as of this moment, the exact mechanism behind *H. pylori* infection and rosacea relationship remains unclear.

THE EFFECT OF *H. PYLORI* STANDARD ERADICATION PROTOCOL ON THE ROSACEA CLINICAL COURSE

While the conventional rosacea treatment protocols may be associated with frequent relapses and limited effectiveness, the use of *H. pylori* eradication may constitute an important approach. Various drug-combined therapies may be applied for *H. pylori* eradication; the latest recommended regimen, which is bismuth-based quadruple therapy, includes proton pump inhibitors (PPI), bismuth, metronidazole and tetracycline [18].

Significant research concerning the matter was conducted producing controversial and conflicting outcomes. The thesis suggesting the advantage of eradication methods in controlling symptoms of rosacea over conventional treatment, which once emerged in the 1900^{s} [19], has been widely tested in many clinical trials — both confirming its positive effect [4] on managing the course of the dermatosis and finding no relationship between the pathogen and rosacea [20]. Intriguingly, some research showed that the rosacea patients' improvement after the eradication protocol implementation was equally observed in the control group, which may suggest its placebo effect [21]. The study may be complicated by the similarity of the infection and the dermatosis antibiotic therapy; thus some cases of rosacea recoveries may only be associated with the alleviation of the inflammation process that is the key to the development of both conditions [18]. Accordingly, the link between the *H. pylori* eradication and rosacea still needs to be clarified. Indications for *H. pylori* eradication [25]:

- peptic ulcer disease,
- gastric MALT lymphoma,
- functional dyspepsia after esophagogastroduodenoscopy,
- idiopathic thrombocytopenic purpura (ITP),
- iron deficiency of unexplained cause (after adequate diagnostic investigation),
- in a patient with a history of peptic ulcer disease before the initiation of long-term treatment with acetylsalicylic acid (ASA) or a nonsteroidal anti-inflammatory drug (NSAID),
- upper gastrointestinal haemorrhage under treatment with ASA or NSAID,
- prophylaxis against gastric carcinoma in a patient at high-risk.

COMPOSITION OF GUT MICROBIOTA IN ROSACEA

Only two studies have been conducted regarding significant differences between the structure of the gut microbiota of healthy, in terms of dermatosis and rosacea patients. However, the presented data proved the limited compliance in terms of the results of both papers, in some cases making them even contradictory. Although both studies suggest some conflicting outcomes, they agree on several alterations being present in rosacea patients [26].

Nam et al. [27] found a decrease of *Methanobrevibacter*, *Slackia*, *Coprobacillus*, *Citrobacter*, *Desulfovibrio*, and *Peptococcaceae* family unknown genus and an increase of *Megasphaera, Acidaminococcus* and *Lactobacillales* order unknown family unknown genus in rosacea patients.

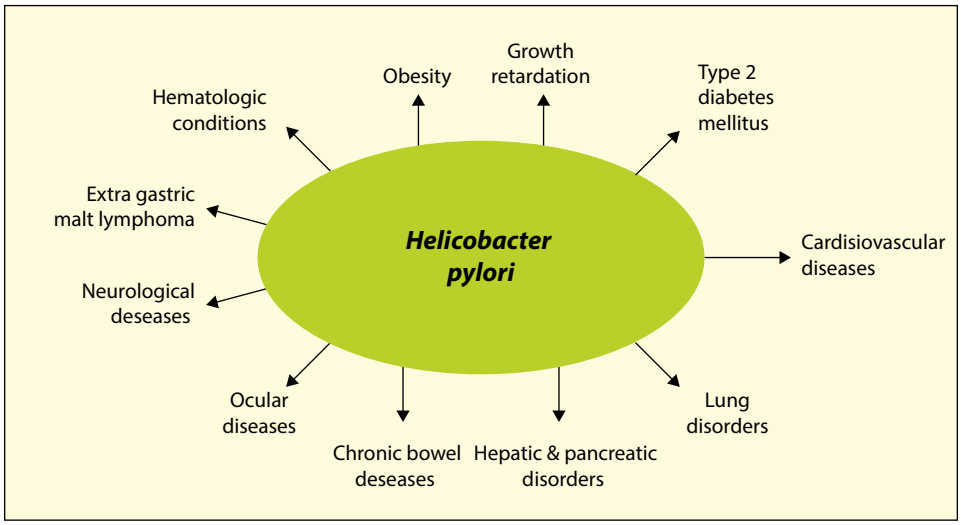

Figure 1. *Helicobacter pylori's* contribution to development of different diseases

Chen et al. found elevated presence of *Rhabdochlamydia, CF231, Bifidobacterium, Sarcina and Ruminococcus,* and reduced presence of *Lactobacillus, Megasphaera, Acidaminococcus, Hemophilus, Roseburi,* and *Clostridium* [28].

There is still a need for further research to be done on the composition of gut microbiota in Caucasian rosacea patients as these two papers cover mainly Asians as the research group and cannot pose as reliable sources of alterations that would be true for every rosacea patient [26].

GUT–BRAIN–SKIN AXIS

The GBS axis is represented by the relationship between the microbiota, neuroendocrine pathways, that the skin and gut both have, and the skin microbiome [23]. Thus several dermatological conditions may be associated with gastrointestinal health [24] and a higher risk of gastrointestinal (GI) disorders was observed in rosacea patients [25].

INFLAMMATORY BOWEL DISEASES

The term inflammatory bowel diseases (IBD) is mainly used to refer to Leśniowski–Crohn's disease (CD) and ulcerative colitis (UC). They are chronic inflammatory diseases of the GI tract which are characterized by periods of activity and remission [29]. IBD arises as a result of dysregulation of the balance between commensal microbiota and mucosal-associated immune system. The symptoms may be mild to severe, and they may appear suddenly or come on gradually. It is worth emphasizing that one in four patients with IBD has clinical manifestations of the disease which are not related to the GI system [30].

Taking into consideration that IBD and rosacea occur at the surface of skin or mucosa and involve abnormal innate immune response, it may be suggested that both of these diseases are pathogenetically similar [31]. Patients with rosacea are more likely to suffer from CD or UC than the general population [32]. That is why all patients with rosacea who suffer from GI symptoms should be investigated for IBD [33].

SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

The gut is inhabited by a huge number of microorganisms (bacteria, archaea, fungi, viruses) composing a vast and complex ecosystem with high intra- and inter-individual variability. In normal conditions, the cross-talk between the gut microbiota and the host is highly beneficial for both of them [34]. Gut dysbiosis is a condition caused by alterations of balance between the quantity and quality of microorganisms in the intestinal microbiota.

The small intestinal bacterial overgrowth (SIBO) is caused by excessive colonization of the small intestine by large intestine bacteria. There is no standard definition of SIBO. It is commonly used that bacterial count of at least 105 colony-forming units (CFU) per mL of small intestine fluid as the cut-off for diagnosis of this condition [35]. The altered microbiota produces a variety of inflammatory mediators and metabolites. This may lead to an immune response being triggered and may increase the risk of pathogenic invasion [36]. It is estimated that SIBO occurs 2–20 times more often in rosacea patients than in the healthy population [37]. In a randomized trial conducted by Parodi et al. [38], patients with rosacea and SIBO were randomized to receive rifaximin (1200 mg/day for 10 days) or placebo. In this study, successful treatment of SIBO resulted in almost complete regression of rosacea's cutaneous lesions [38].

According to the nationwide cohort study with 4 312 213 patients including 49 475 with rosacea, the

prevalence of SIBO was higher in patients with rosacea [32]. Some other studies point out the prevalence of SIBO in 51% of 63 patients with rosacea (based on a positive lactulose breath test) [32].

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a functional bowel disorder defined by recurrent abdominal pain for at least 1 day per week in the last 3 months that is associated either with a change in stool form or frequency [39]. Typically, symptoms occur at least 6 months prior to the diagnosis of IBS.

The pathogenesis of irritable bowel syndrome still remains uncertain [40]. The intestinal immune activation has been postulated to participate in brain-gut dysfunction which can lead to the development of IBS symptoms [41].

In 2017 new data showed a link IBS and rosacea. In a British nationwide cohort study, Egeberg et al. noticed an increased risk of new-onset IBS in subjects with rosacea. His findings may be a result of misdiagnosed IBS or they may reflect yet another comorbidity of rosacea [32].

CONCLUSIONS

Rosacea is a chronic, inflammatory, multifactorial condition whose pathogenesis still remains unknown. As the conventional rosacea treatment protocols are hardly effective, *H. pylori* eradication regimens may pose as a temporary solution producing moderately positive outcomes, until there is enough research to identify the relation between the pathogen and this dermatosis. This review found some strong associations between the course of the disease and the influence of the gut-skin axis, thus higher risk of GI diseases may be observed among rosacea patients. New influence factors that may concern the development of rosacea are found all the time, however, to be assured that they are indeed the key to inhibiting this dermatosis and not just a random correlation, we need more reliable research evidence.

Although all of the studies showed significant alterations in the composition of the skin, blood, or gut microbiome in rosacea, the results were highly inconsistent, or even, in some cases, contradictory. Major limitations included the low number of participants, and different study populations (mainly Asians). Further studies are needed in order to reliably analyse the composition of microbiota in rosacea, and the potential application of microbiome modifications for the treatment of this dermatosis.

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All authors worked together on the final result and approved the final manuscript.

Conflict of interest

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