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Rifaximin in the Treatment of Gastroesophageal Reflux Disease: A New Idea Based on the Relationship between Intestinal Microecology and Gastroesophageal Reflux Disease

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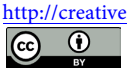

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Abstract

Gastroesophageal Reflux Disease (GERD) is a common clinical disorder, the most common symptom of which is a burning sensation behind the breastbone (heartburn) or reflux of stomach contents into the upper pharynx (acid reflux). The prevalence in China is increasing year by year, which can affect the quality of life of patients and also increase the economic burden on families and society. The pathogenesis of GERD is still unclear, and some studies suggest that intestinal microecology may be closely related to the development of GERD. Rifaximin is not readily absorbed orally and acts locally in the intestine, so it has mild adverse effects and good safety, and can be used to treat gastrointestinal diseases such as irritable bowel syndrome, traveler's diarrhea, small intestinal bacterial overgrowth, diverticulosis, inflammatory bowel disease and hepatic encephalopathy. Therefore, this paper focuses on intestinal microecology as a possible pathogenesis of GERD and further explores the feasibility of rifaximin for the treatment of GERD.

Keywords

Gastroesophageal Reflux Disease, Intestinal Microecology, Rifaximin

1. Introduction

Gastroesophageal reflux is a common clinical condition, and it is estimated that about 20% of the adult population in the Western world suffers from GERD [1],

and the prevalence in China is increasing year by year, and population-based epidemiological surveys in China have shown that the prevalence of at least one episode of heartburn symptoms per week is 1.9% to 7.0% [2] [3]. The most common symptom of GERD is a burning sensation behind the sternum (heartburn) or reflux of gastric contents into the upper throat (acid reflux), and recurrent episodes of GERD can affect the quality of life of patients and also increase the economic burden on families and society. The mechanism of GERD is still unclear and its pathogenesis is multifactorial, such as: anti-reflux barriers, esophageal clearance and weakened esophageal mucosal resistance [4], and several recent studies have shown that small intestinal bacterial overgrowth is significantly higher in populations where GERD occurs than in normal populations, and Jordan J. Haworth *et al.* [5] showed for the first time that refractory GERD symptoms may be the result of altered gut microbiota result. Currently proton pump inhibitors (PPIs: proton pump inhibitors) are still the drug of choice for the treatment of GERD to induce remission and maintenance therapy; however, some articles have reported that long-term PPI intake is likely to cause several complications such as: osteoporosis, fractures, micronutrient deficiencies, chronic kidney disease, and can even increase the risk of novel coronavirus pneumonia infection, etc. [6] [7] [8] [9], where long-term PPI use may also lead to changes in the structure of the intestinal flora. Therefore, it seems to be contradictory that the alteration of intestinal microecology caused by PPIs in the treatment of GERD may also cause the occurrence of GERD. In this paper, we focus on the feasibility of rifaximin treatment for GERD, starting from the fact that intestinal microecology may be the pathogenesis of GERD.

2. Definition and Diagnosis of GERD

GERD is a multifaceted disease that includes a series of syndromes caused by or exacerbated by gastroesophageal reflux. These syndromes mainly cause morbidity through troublesome symptoms, of which heartburn and reflux are typical symptoms of GERD, and some of them only show atypical symptoms and extra-esophageal symptoms. According to the Montreal definition, "GERD is a disease with uncomfortable symptoms and/or complications caused by the reflux of gastric contents." The strength of this definition lies in its simplicity, combining a number of symptoms with potential complications. While the Lyon consensus remains positive about diagnosing GERD by typical symptoms and by empirical PPI treatment, the Lyon consensus focuses more on making a diagnosis of GERD in physiological morphology, by evaluating various diagnostic tests including upper gastrointestinal endoscopy, 24-hour dynamic pH or pH-impedance monitoring, esophageal high-resolution manometry, and by providing various definitive diagnostic and exclusionary parameters to give specific definitions [10].

3. Pathogenesis of GERD

Although GERD is a common clinical disease, its pathogenesis is quite complex,

involving the interaction of chemical, mechanical, psychological and neurological mechanisms. Under normal conditions, intra-abdominal pressure is positive while intrathoracic pressure is negative, a physical principle that should promote reflux of gastric contents into the esophagus. Not surprisingly, small amounts of reflux occur in everyone throughout the day, but pathological GERD is prevented by the normal anatomy and physiology of the esophagus, the lower esophageal sphincter (LES), the transverse septum at the foramen ovale, and the stomach. In general, the LES is the most important physiological structure of the normal reflux barrier [11] [12], but it may also be due to increased pressure gradients between the abdomen and the chest (e.g. morbid obesity and pregnancy) or impaired motility of the esophagus, the muscles of the foramen ovale and/or the stomach. Some recent studies suggest that alterations in intestinal microecology likewise play an important role in the development of GERD.

4. Relationship between GERD and Intestinal Microecology

4.1. Small Intestinal Bacterial Overgrowth and GERD

Based on the gross endoscopic presentation of the esophageal mucosa, GERD is divided into three types, namely Barrett's esophagus (Barrett's esophagus), reflux esophagitis (RE), and non-erosive gastroesophageal reflux disease (non -In 2012, a pilot study was conducted by Kim *et al.* [13] who hypothesized a possible relationship between RE and small intestinal bacterial overgrowth (SIBO) may have a relationship with each other. Since bacteria are the only source of intestinal hydrogen and methane, hydrogen and methane gas in the exhaled breath were used as markers of colonic fermentation, and they compared the prevalence of SIBO in healthy subjects and RE subjects separately by the lactulose hydrogen breath testing (LHBT). The results showed that 19 of 28 RE patients had abnormal LHBT (67%) compared to 11 of 29 controls (37%) and that the prevalence of SIBO was higher in RE subjects than in controls, an association that was statistically significant. Their preliminary data support this new hypothesis that SIBO may be an important prevalence factor in some GERD patients.

4.2. Colonic Fermentation and GERD

In 2021 Tanisa Patcharatrakul *et al.* [14] conducted a randomized crossover study of 21 patients with GERD to assess the effect of the level of low short-chain carbohydrates (FODMAPs) in food on typical GERD symptoms and the correlation between GERD symptoms and intestinal gas production. The results showed that after ingestion of wheat flour with high FODMAPs, patients experienced increased bloating, satiety and chest discomfort, maximum reflux symptoms after 15 minutes compared to rice with low FODMAPs, and reflux severity scores were significantly and positively correlated with the area under the curve of exhaled hydrogen concentration and the area under the curve of methane concentration. This study showed that wheat flour with high levels of FODMAPs was more likely to produce typical GERD symptom scores after a meal, especially 15

minutes after lunch, and that the effect of wheat pasta on GERD symptoms was associated with increased gut gas production after lunch, confirming a link between GERD symptoms and colonic fermentation.

Most carbohydrates are metabolized by colonic bacterial flora to short-chain fatty acids (SCFA) and hydrogen gas, and A Ropert *et al.* [15] found that gastric tone was also reduced by intracolonic infusion of lactose and short-chain fatty acids, with the most pronounced effect after the highest dose of SCFA; similarly, Suppawatsa Plaidum *et al.* [16] assessed immediately after lunch for 2 hours after TLESR and monitored for 2 hours, during the first 30 minutes of recording (1.38 ± 0.32 versus 0.50 ± 0.19 beats/30 minutes, $p < 0.05$), 30 - 60 minutes (1.38 ± 0.32 versus 0.75 ± 0.16 beats/30 minutes, $p < 0.05$) and 60 - 90 minutes after the meal (1.63 ± 0.38 versus 0.63 ± 0.18 beats/30min, $p < 0.05$), it was found that the intake of wheat flour significantly produced more TLESR events than the intake of rice flour in the 2 hours after lunch. It was also found that wheat ingestion was significantly associated with higher hydrogen and methane levels after lunch compared to rice ingestion, and that the area under the hydrogen and methane concentration curve was significantly associated with the number of TLESR events. Their findings suggest that FODMAPs meals may regulate TLESR through colonic fermentation or intestinal H_2 production.

Thus, disturbances in intestinal microecology may contribute to the development of GERD: 1) small intestinal bacterial overgrowth can lead to fermentation of food in the intestine, and excessive gas production can increase the pressure gradient between the abdomen and the chest, contributing to the development of reflux; 2) fermentation in the intestine decreases the LES pressure, causing a significant increase in the occurrence of postprandial TLESR; 3) excessive fermentation products can reduce gastric tone, leading to prolonged gastric emptying time and an increased chance of reflux occurrence.

5. Treatment of GERD—PPI Use and Disturbance of Intestinal Microecology

Four different modalities are currently available for the treatment of GERD: 1) lifestyle modification, 2) pharmacological treatment, 3) endoscopic intervention, and 4) surgery.

In terms of lifestyle, patients can be asked to elevate the head of the bed and avoid late night meals, advised to avoid alcohol, smoking, and foods such as chocolate, coffee, and carbonated beverages, and, most importantly, to lose weight [17]. Currently, the American Gastroenterological Association states in its recent guidelines that current endoscopic treatment should not be considered as an alternative to pharmacological or surgical treatment [18] and that treatment options remain between PPI and surgery. However, for the choice between medical medication and surgical treatment, patients tend to prefer endoscopic treatment first and opt for surgical treatment only after ineffective medical treatment and rigorous evaluation.

In terms of medical treatment, histamine receptor antagonists and PPIs have been the main agents of treatment, and studies of the new acid-suppressing drug potassium channel acid blocker (P-CAB) in the treatment of RE patients have shown a mucosal healing rate of about 90% at 4 weeks after treatment, and its representative drug, vornoprazine, also has a slightly higher healing rate than the lansoprazole group [19]. Therefore, PPI or P-CAB is the drug of choice for the treatment of GERD, this is because it is more effective than histamine receptor antagonists in relieving symptoms and curing esophagitis, and the recommended course of treatment for GERD with PPI or P-CAB is 4 - 8 weeks.

5.1. PPI and Intestinal Flora

PPIs are widely used and readily available in clinical settings, and are commonly used by clinicians to prevent the development of stress ulcers or to reduce gastrointestinal toxicity associated with certain medications, and proton pump inhibitors are often overused in outpatient care settings without a documented effective indication [20]. However, it is worth noting that long-term use of PPIs is by no means risk-free, and possible associations have been reported for osteoporosis, fractures, and micronutrient deficiencies [6] [7] [8] [9], and numerous studies have shown that PPI use is closely associated with C. difficile infection and recurrence, and recent meta-analyses have confirmed this view [21].

Human intestinal bacteria have a large population with genes about 100 times larger than the genome [22], and thanks to the remarkable development of gene sequencing, we can now determine bacterial species and their numbers faster and more economically compared to the past, and it has been confirmed that the long-term use of PPIs can lead to significant changes in the diversity and composition of the intestinal microbiota. In 2015, Matthew A Jackson *et al.* [23] investigated the association between PPI use and gut microbiota by 16S ribosomal RNA amplification from stool samples of 1827 healthy twins, and PPI users had significantly lower abundance of gut commensal bacteria, lower microbial diversity, and associated significantly increased abundance of oral and upper gastrointestinal commensal bacteria. Gastric acid is important in the digestion and absorption of food and medications and in maintaining a relatively sterile gastric environment, and many pathogens cannot survive in a highly acidic environment, so a decrease in gastric acid production may increase the risk of infection transmission through fecal-oral contact. What we can assume is that under normal conditions, gastric acid is a barrier to the downward movement of pharyngeal commensal and environmental bacteria along the gastrointestinal tract and that these bacteria do not adapt well to low pH. Treatment with PPI removes this barrier and allows further colonization of these bacteria along the gastrointestinal tract, and these bacteria can reach more distal parts of the gastrointestinal tract, with the resulting changes in the gut microbiota, as shown in a meta-analysis by Wai-Kit Lo *et al.* [24] in 2013, in a study using duodenal or jejunal aspirate cultures for the diagnosis of SIBO, where SIBO was associated with PPI use, but no relationship was found between SIBO and PPI use in studies using

glucose hydrogen breath tests, which explains the different previous findings that may be associated with poor diagnostic accuracy.

5.2. Regulation of Intestinal Flora Improves GERD

Moreover, PPI treatment for GERD still leaves some patients with insignificant symptom relief or rapid re-emergence of symptoms after discontinuation of the drug. 2020 Chinese GERD Guidelines and Consensus consider that those with no significant improvement in symptoms such as reflux and heartburn after double standard dose and 8-week course of acid suppressant treatment are defined as refractory GERD, and those with symptoms that are not controlled after adequate acid suppressant treatment and the presence of Anti-reflux surgery may be considered if symptoms are associated with reflux [25]. 2020 Jordan J. Haworth *et al.* [5] retrospectively evaluated data from patients referred to specialized reflux centers (n = 104) and found a high prevalence of gut flora dysbiosis in GERD patients and a seemingly increased likelihood of positive reflux symptoms, a common indication for anti-reflux surgery. These patients were more likely to report gas-related symptoms prior to anti-reflux surgery, and therefore endogenous bacterial fermentation in the small intestine is presumed to be a contributing factor to refractory reflux symptoms.

In 2021, Zheng, Y. M. *et al.* [26] suggested that recurrence of symptoms and long-term PPI use in patients with GERD (including NERD) may be related to changes induced by gut microbiota and SIBO after previous PPI use, and they investigated whether washed microbiota transplantation (WMT: washed microbiota transplantation) to see if it improves the symptoms of proton pump inhibitor-dependent non-celiac reflux disease. The total remission rate in the WMT and PPI groups was 93.3% vs 41.7%. Compared with the PPI group, the WMT group showed better results in the GERDQ scores (7 vs 11, $p = 0.004$) and RDQ scores (8 vs 20.5, $p = 0.003$), as well as in the remission months [8 (3, 17) vs 2 (0, 4), $p = 0.002$]. Compared with the PPI group, the WMT group showed better results in terms of GERDQ score and RDQ score as well as months of remission, which were statistically significant. WMT significantly relieved the symptoms of NERD patients, reduced PPI dependence, prolonged symptom remission, reduced relapse, and also increased the diversity and balance of the bacterial community.

During treatment with proton pump inhibitors, changes in the intestinal microbiota, such as reduced microbial diversity or small intestinal bacterial overgrowth, can result from the alteration of the acid-base environment in the intestine where bacteria live, yet the altered intestinal microecology may also contribute to the development of GERD, and therefore there are conflicting aspects of treatment with PPIs.

6. Rifaximin—A Broad-Spectrum Antibiotic for the Intestine

Rifaximin, a semi-synthetic derivative of rifamycin SV, is a broad-spectrum intestinal antibiotic. The in vitro antibacterial activity of rifaximin shows that it

has high antibacterial activity against Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus and Clostridium difficile among the Gram-positive aerobic bacteria, and rifaximin is almost not absorbed after oral administration (absorption < 1%), and only acts locally in the gastrointestinal tract, so it has a very high concentration in the intestinal tract and is rarely distributed in other organs, and it has a wide antibacterial spectrum, so it is a kind of drug used for local intestinal infections and is mostly used for the treatment of travelers' diarrhea, hepatic encephalopathy and irritable bowel syndrome [27].

Animal studies suggest that the use of antibiotics such as vancomycin, imipenem and ciprofloxacin can greatly reduce the diversity in the intestinal microbiota and increase antibiotic resistance [28]. However, rifaximin maintains and functionally regulates the overall composition and diversity of the intestinal microbiota and may reduce the abundance of harmful bacteria (e.g., Klebsiella, Streptococcus, and Clostridium) and increase the abundance of probiotic bacteria (e.g., Bifidobacterium and Synechococcus) [29]. Hiccups and bloating are common symptoms in patients with GERD, and in a randomized, double-blind, placebo-controlled trial, patients with bloating responded positively to rifaximin and symptom improvement was associated with a reduction in H_2 expiratory excretion [30], and Tan *et al.* [31] found that rifaximin relieved hiccups and postprandial bloating in patients with functional dyspepsia without IBS. Given the properties of rifaximin, which may reset the microbial diversity in the environment and reduce bacterial fermentation, thus reducing the occurrence of GERD, and presumably reducing the occurrence of intestinal microecological disorders due to long-term PPI use and reducing the recurrence of GERD after PPI discontinuation.

7. Conclusion and Outlook

The intestinal microecology is a huge microbiota in the human body, and its composition is also complex. Changes in the intestinal microecology can lead to a series of pathologies in the body, and is far from being limited to the digestive tract. Thanks to a number of studies at home and abroad, we initially found that the intestinal flora and the occurrence of GERD may be inextricably linked, as long-term PPI treatment of GERD often leads to the dysbiosis of the intestinal flora, which may contribute to the occurrence of GERD in the process of treatment. However, the mechanism of intestinal microecological disorders causing reflux is still unclear and needs to be discovered and verified by deeper studies, and there is also a lack of prospective studies pointing to the effectiveness of rifaximin in the treatment of GERD. Therefore, it is expected that more studies will be conducted in the near future to reveal the relationship between intestinal microecology and GERD and to enrich the therapeutic diversity.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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