INTRODUCTION

Dyspepsia refers to symptoms originating from the gastroduodenal region and includes etiologies such as gastroesophageal reflux, hiatal hernias, peptic ulcers, *H. pylori* infections, erosive gastritis, and gastroesophageal malignancy. Symptomology often varies, but may include nausea, vomiting, heartburn, dysphagia, and chest pain. Dyspepsia affects about 40% of the general population and etiologies can be diagnosed with the use of esophagogastro-duodenoscopy (EGD). Despite the use of EGDs, 70% of patients diagnosed with dyspepsia are negative for any structural or infectious (i.e., *H. pylori*) etiology. In such patients, the diagnosis of functional dyspepsia (FD) is often made.

FD can be defined as frequent or continuous uncomfortable postprandial fullness, epigastric pain and/or epigastric burning, early satiation in the absence of an organic etiology. The prevalence of these symptoms varies amongst patients with about 90% of patients with FD experiencing epigastric pain, 75 - 88% experiencing postprandial fullness, and 50 - 82% experiencing early satiety. Due to the absence of organic disease, FD can be debilitating to patients as it is difficult to identify and eradicate the inciting factor. Despite this, the use of proton pump inhibitors (PPIs) are used widely as first-line treatment in patients with FD. Although PPIs do not necessarily eradicate FD amongst patients, they moderately may subdue upper gastroduodenal symptoms and subsequently are used widely in outpatient clinics as a treatment modality. For instance, a meta-analysis demonstrated that PPIs were statistically more effective in treating patients with FD than compared to the placebo. However, the effectiveness of PPI therapy in such patients was minimal. For example, the relative risk reduction in the PPI group was only 13% when compared to the placebo group. Additionally, another meta-analysis analyzing various treatment modalities for FD demonstrated that the therapeutic efficacy of PPIs in patients was only 7 - 10%. Consequently, many patients with FD on PPIs are refractory to therapy and continue to experience symptoms.

Given that PPIs are known to increase the pH of the human stomach and that *H. pylori* negative gastritis is relatively common (1.5% - 21% of all gastritis), this review discusses the role of PPIs on the stomach microbiome. More specifically, this review explores the role of non-*H. pylori* bacteria, such as *Streptococcus* genus, as a highly suggestive potential cause for FD in patients, the influence of PPIs on the growth of this type of bacteria, and the implications for treatment of patients with FD.

Microbiome and PPI Use

The human gut microbiome is a diverse community of microorganisms that often can be considered a separate human organ. Weighing up to two kilograms, the gut microbiome plays a critical role in helping maintain homeostasis within the human body. With the stomach’s natural harsher acidic environment, the stomach’s microbial load is much smaller than that of the remaining gastrointestinal tract. In the stomach, the microbial load is often between $10^3$-$10^6$ colony-forming units/mL of bacteria while in the colon, the bacterial load is between $10^{10}$-$10^{12}$ colony-forming units/mL. Despite this substantial decrease in microbial load within the stomach, the existing bacterial diversity of the organ plays a crucial role in its daily function.

While the bacterial community of the stomach is diverse, certain phyla of bacteria dominate the composition in healthy patients at baseline. For instance, a study using 16S rDNA sequencing to classify gastric bacterial phyla found that in *H. pylori* negative patients, five phyla dominated the gastric microbiome. In decreasing order of density, these were non-*H. pylori* Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria, and Fusobacteria. Similarly, another study using barcoded pyrosequencing found that amongst healthy *H. pylori* negative patients, the same five phyla dominated the gastric microbiome. Additionally, a study using 16S rDNA sequencing to compare the gastric microbiome between normal and gastritis patients found similar results with the average composition being Proteobacteria (37%), Firmicutes (22%), Bacteroidetes (28%), Actinobacteria (8%), and Fusobacteria (4%) in healthy patients. The interrelationship that exists between these five phyla and their respective relative compositional ratios between one another seem to maintain gastric homeostasis. Consequently, it is when this gastric microbial compositional ratio is altered favoring Firmicutes growth, specifically the *Streptococcus* genus, that patients become prone to dyspepsia.

A study analyzing gastric microbiota amongst *H. pylori* negative gastritis patients, *H. pylori* positive gastritis patients, and *H. pylori* negative non-gastritis patients (control group) without prior PPI therapy for at least six months found that compared to the healthy control group, *H. pylori* negative gastritis patients had an increased abundance of *Streptococcus* species and *Hemophilus parainfluenza*. *Streptococcus* species and *Hemophilus parainfluenza* were at a significantly increased risk for *H. pylori* negative gastritis with an odds ratio of 18.9 (95% CI 2.1 - 172.8, p < 0.009) and 12.3 (95% CI 1.4 - 109.6, p < 0.025), respectively. Also, in the *H. pylori* positive gastritis group, *H. pylori* was instead the most abundant group. Consequently, *Streptococcus* was indicated as a candidate pathogenic bacterial species for *H. pylori* negative gastritis. Additionally, patients with *H. pylori* negative gastritis without any history of prior non-steroidal anti-inflammatory drug use had a significantly greater abundance of Firmicutes in antral biopsies compared to control patients where proteobacteria was dominant. More specifically, it was *Streptococcus* species within the Firmicutes phyla that was increased significantly amongst gastritis patients. *Streptococcus* species was 72% higher in the antral biopsies and 66% higher in the gastric body biopsies of gastritis patients when compared to control patients.

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Furthermore, similar results were found in a study comparing the bacterial composition of gastric mucosa and gastric juices between patients with and without chronic gastritis. In this study, patients suffering from chronic gastritis, who were not undergoing any PPI or nonsteroidal anti-inflammatory drug therapy, had higher rates of *H. pylori, Streptococcus mitis*, and *Neisseria* species colonizing their gastric mucosa compared to control patients. Finally, another study looking at the mucosa-associated microbiota between FD and healthy patients using 16S rRNA sequencing, found that *Streptococcus* species were increased significantly in the FD patients and the relative abundance of the bacterium was correlated positively with the upper gastrointestinal symptoms in the FD patients. Consequently, there exists a relationship between the bacterial overgrowth of *Streptococcus* species in the stomach and dyspepsia in patients.

This finding is congruent with the limited current literature regarding *Streptococcus* species and the bacteria’s natural acid producing nature. For instance, a study using a pH-sensitive green fluorescent protein as an in vivo, in situ pH meter to monitor *Streptococcus* acid production demonstrated that when introduced to sucrose, the bacteria lowered the environmental pH via acid production. Additionally, Senadhra et al., studying acid production and acid survival in *Streptococcus* mutans, demonstrated that the bacterial species possessed key proteins involved in acid production. While these studies were designed to understand *Streptococcus* species’ role of acid production in the oral cavity better, it is believed that the bacterium retains its acid producing abilities and acts similarly in the stomach.

Finally, a study looking at the differences in bacterial activation of neutrophils demonstrated that streptococcal strains induced significantly higher release of heparin-binding protein (HBP) and the cysteine-rich adipsokytokine, resistin. HBP has been associated with immunostimulatory activity while resistin has been characterized as a potent pro-inflammatory molecule associated with inflammatory conditions. Consequently, through the activation of neutrophils and release of these two proteins, *Streptococcus* species allow for a pro-inflammatory state that could contribute to the symptoms of FD. This notion of a pro-inflammatory response playing a role in FD is similar to the findings by Wauters et al. and Liebregts et al. Wauters et al. demonstrated that amongst *H. pylori* negative FD patients and healthy matched controls, the former group had significantly higher levels of TNF alpha, IL-1B, and IL-10 compared to the latter group. Additionally, amongst the *H. pylori* negative FD patients, an increase in cellular immune activation with increased small bowel homing T cells was seen, indicating an overall pro-inflammatory state involvement in FD patients. Furthermore, IL-1B, IL-10, and small bowel homing T cells also were significantly correlated to the intensity of dyspeptic symptoms including epigastric pain, abdominal cramps, nausea, and vomiting in the *H. pylori* negative FD patient group. While TNF alpha, IL-1B, and the increase in recruitment of T cells were congruent in the overall pro-inflammatory setting of FD, the increase in anti-inflammatory IL-10 was not. One possible explanation for the phenomenon was that IL-10 is produced increasingly to subdue the overly inflammatory state and shift the immune response from a Th1 to a Th2 response. However, studies, such as Kindt et al., demonstrated a decrease in IL-10 amongst FD patients, suggesting that levels of IL-10 depend on the onset of FD (acute vs. chronic) and warranting further research on the topic.

Interestingly, this bacterial overgrowth of *Streptococcus* species has been seen in patients undergoing PPI therapy. For instance, Sterbini et al. analyzed gastric mucosal biopsies of 24 dyspeptic patients, 12 of whom were undergoing PPI therapy for at least the past 12 months and 12 of whom were not on PPI therapy or had not been for at least six months prior to the study. The study demonstrated that the Firmicutes phylum, specifically *Streptococcus* species, was increased significantly in relative abundance in patients on PPI therapy when compared to the untreated group of patients. Additionally, *Streptococcus* species were increased significantly in relation to PPI treatment and independent of *H. pylori* infection.

Another study, analyzing fecal microbiota using 16S and 23S rRNA-target quantitative RT-PCR in patients with reflux esophagitis receiving PPI therapy for eight weeks, demonstrated that *Streptococcus* species was increased significantly in patients at the four and eight weeks of PPI therapy compared to before the start of the treatment. Additionally, Parsons et al. demonstrated using 16S rRNA sequencing on RNA extracted from gastric corpus biopsies on *H. pylori* negative gastritis patients on PPI therapy that *Streptococcus* species were increased significantly in these individuals compared to the control patients whom were without any gastritis nor on PPI therapy.

Finally, a study analyzing the bacterial composition of the gastric juice and gastric mucosa of patients with GERD on acid inhibitory therapy vs. dyspeptic patients with no acid inhibitory therapy demonstrated that the prevalence of non-*H. pylori* bacteria was significantly higher in former group. More specifically, patients on PPI therapy had a higher prevalence of particularly oropharyngeal flora (*Neisseria* species, *Streptococcus* species, and *Corynebacterium* species) in the gastric juice compared to dyspeptic patients not receiving acid inhibitory treatment or histamine 2 blocker therapy.

Furthermore, the effects of PPI therapy extend beyond the gastric microbiome and involve similar changes in the gut microbiome. For instance, Jackson et al. analyzed the relationship between PPI use and the effects on the gut microbiome in 1,827 twins. Using 16S rRNA sequencing on stool samples, PPI users had a significantly higher abundance of pharyngeal commensals in the gut compared to those not on PPI therapy, mainly *Streptococcaceae* and *Micrococcaceae*. In addition, the study showed that amongst monozygotic twins with discordant for PPI use that there was a higher abundance of *Streptococcaceae* in those that were on PPI therapy.

Another study comparing the microbial composition of stool samples of patients with greater than or equal to five years of continuous PPI therapy vs. patients on no PPI therapy demonstrated that Firmicutes was in higher abundance in the stools of the PPI therapy group. More
specifically amongst the Firmicutes phylum, *Streptococcus* along with *Lachnospiraceae* family, *Holdemania* and *Blautia* were found to be in higher abundance. Finally, a meta-analysis analyzing the stool samples of 211 patients on PPI therapy showed that compared to those patients not on PPI therapy, patients on PPI therapy had a significant increase in the following bacteria: *Enterococcus*, *Streptococcus*, *Staphylococcus*, and potentially pathogenic species *Escherichia coli*.29 This change seen in the gut microbiome was more prominent than the changes in the microbiome seen with either antibiotics or other commonly used drugs in the study.

Consequently, a relationship appears to exist between an overgrowth of *Streptococcus* species in the gastric microbiome and dyspepsia in patients. PPI therapy leads to an overgrowth of *Streptococcus* species in the gastric microbiome and subsequently may contribute to dyspepsia in patients. While there is a lack of literature on temporal studies exploring *Streptococcus* species causality in FD, Mishiro et al.29 recently demonstrated that when healthy non-dyspeptic patients with no probiotic use within the past three months or prior medical treatments were treated with esomeprazole 20 mg for four weeks, they had a statistically significant increase in *Streptococcus* species in their fecal microbiome. Additionally, apart from the increase in *Streptococcus* species, the overall fecal microbial composition remained otherwise stable amongst the study population post-PPI treatment. Finally, while patients did not necessarily have an onset of dyspeptic symptoms after the brief study; due to the various strains of *Streptococcus* species that exist, the lack of symptoms could be due to an overgrowth of a particular non-pathological strain of *Streptococcus* in the study patients. Thus, further research is warranted to identify strains of pathologic acid inducing strains of *Streptococcus* species that could multiply with PPI use and lead to FD.29

These findings from the above studies taken together provide a plausible explanation for why patients with dyspepsia often are diagnosed with FD with no known etiology and when put on PPI therapy, have a low rate of therapeutic improvement. With no standard method for streptococcal species detection in gastric biopsies or eradication of the bacteria used in the clinical setting, patients often are undiagnosed after being ruled out for structural causes and *H. pylori* infection of their dyspepsia. With an unknown existing potential overgrowth of streptococcal species, specifically acid producing strains, in patients' gastric microbiome, patients who are prescribed PPIs as part of the standard treatment for FD can exacerbate their pre-existing streptococcal species overgrowth further. Thus, patients enter a vicious cycle in which they can never truly rid themselves of their dyspepsia.

Given the evidence within the literature, especially with studies such as Liu et al.29 demonstrating a statistically significant relationship between the abundance of *Streptococcus* species and FD symptoms in patients, this review proposes the idea that while *Streptococcus* species clearly is correlated to FD in patients, that it may in fact be a pathological cause for FD that is exacerbated by PPI use (Figure 1). Due to the very limited literature on the topic, further studies should be conducted, specifically temporal studies and animal studies with direct inoculation of the microbiome with *Streptococcus* species to explore the very suggestive possible causality of streptococcal species in FD.

**Figure 1.** Diagram shows that *Streptococcus* species is correlated to FD in patients, but it may be a pathological cause for FD that is exacerbated by PPI use.

**Mechanism of Action of PPI Therapy on Streptococcal Overgrowth**

While it is evident that PPI therapy influences the composition of the gastric microbiome, the mechanism by which PPIs alter it is not well known. However, the two main theories that exist are that PPI therapy induces a favorable environment for microbial growth via raising the gastric pH and inducing gastroparesis.8,22,30

The stomach's acidic environment often makes it inhospitable to bacterial overgrowth, killing bacteria within 15 minutes when the pH is less than three.30 However, when placed on PPI therapy, the pH of patients' stomach often is elevated to a pH of four or greater. For instance, Sanduleanu et al.25 found that in their study population, fasting gastric juice pH values above four were measured more frequently in patients on PPI therapy than in those on histamine 2 blockers or patients on no acid suppressive therapy. Consequently, this creation of an achlorhydric environment removes the protective barrier function of the stomach, allowing translocation of oropharyngeal bacteria to the stomach and further colonization of this bacteria in the stomach.26 This overgrowth of bacteria in the stomach offers bacteria the opportunity to later extend into and colonize the gut microbiome, and explains the abundance of *Streptococcus* species found in fecal samples of patients on PPI therapy.

Furthermore, Tsuda et al.26 demonstrated that the saliva microbiota and gastric microbiota were similar in composition in both PPI and non-PPI patients, with a significant increase of *Streptococcus* species in the fecal matter of PPI-users. PPI users had a one thousand times greater bacterial growth in their stomach compared to non-PPI users. Consequently, the study suggested that the suppression of gastric acid secretion in PPI-users allowed the normal oropharyngeal flora that usually passes to the stomach via eating and swallowing to overgrow, subsequently influencing the relative abundance of bacteria as it passed.
to the fecal microbiome. Hojo et al. \textsuperscript{31} theorized that a reason for their findings was that PPI's effects on gastric suppression allowed for potential bacterial translocation from the oral cavity to the upper GI tract.

Regarding the second theory, PPI therapy inducing gastroparesis in patients, it is important to consider the "acid-pepsin maldigestion hypothesis".\textsuperscript{8} Normally, the process of gastric emptying of solids involves peptic hydrolysis. However, with the reduction of gastric acid via PPI use, this hydrolytic process is impaired due to the deactivation of pepsin, subsequently prolonging gastric emptying time.

This hypothesis is supported by several studies in the literature. For instance, Tougas et al.\textsuperscript{32} demonstrated that omeprazole increased the time required for gastric half-emptying by 17 minutes. Benini et al.\textsuperscript{33} showed that with a four-day pretreatment with 40 mg of omeprazole in patients, gastric emptying time significantly increased from 199.6 minutes at baseline to 230.9 minutes. Rasmussen et al.\textsuperscript{34} also demonstrated delayed gastric emptying in patients treated with 40 mg of omeprazole daily for ten days. Lastly, Parkman et al.\textsuperscript{35} showed that omeprazole’s suppression of gastric acid augmented the amplitude of postprandial antral contractions. This increase in antral contractility paradoxically prolongs gastric emptying due to failed harmonization of antral contraction with pyloric opening.\textsuperscript{8,35} These findings compounded with studies demonstrating relationships between delayed gastric emptying times and FD in patients provided a secondary plausible explanation of how PPI therapy can contribute to bacterial overgrowth.\textsuperscript{36,37} With delaying gastric emptying time, PPI therapy allows for increased periods of gastric content stasis, allowing bacteria the opportunity to multiply.

With both theories taken together, PPI use may induce a perfect environment for streptococcal species traveling from the oropharynx to take residence in the stomach and predominate the gastric microbiota leading to FD in patients. However, with the current limited research regarding the matter, further research is warranted to explore other possible theories.

Clinical Implications

While the current literature regarding therapeutic modalities for patients with streptococcal species overgrowth is limited, studies focusing on the use of novel prokinetic agents in patients with FD have showed promising results, offering a potential avenue for therapeutic intervention in patients with \textit{Streptococcus} species overgrowth. For instance, studies have focused on the use of acotiamide, a drug that promotes acetylcholine release and inhibits acetylcholinesterase, to improve gastric emptying time in patients with FD and subsequently diminish symptoms in such patients. One such study was a phase III trial in which patients with FD either received a placebo three times a day for four weeks or 100 mg of acotiamide three times a day for four weeks.\textsuperscript{38} Matsueda et al.\textsuperscript{38} demonstrated that in those patients receiving acotiamide, symptom severity significantly improved, and meal-related symptoms were eliminated. Additionally, they reported that the number needed to treat for a reduction in dyspeptic symptoms was 6, while the number needed to treat for elimination of all dyspeptic symptoms was 16.

Another study analyzing the effectiveness of acotiamide in 34 patients with FD demonstrated that the drug significantly improved gastric accommodation, gastric emptying, and dyspeptic symptoms in patients.\textsuperscript{39} Additionally, a review looking at drug DA-9701 (Motilitone), a botanical drug compound derived from the plants \textit{Pharbitidis Semen} and \textit{Corydalis Tuber} and approved for treatment for FD in South Korea, demonstrated that DA-9701 decreased dyspeptic symptoms and improved GI function in FD patients.\textsuperscript{40} DA-9701 has an affinity for dopamine, serotonin, and adrenergic receptors, thus helps to improve gastric emptying via multiple physiological pathways. However, the side effect profile of the drug is not understood fully. Hence, gastric statins can be reduced with the use of prokinetic agents and consequently reduce bacterial over colonization.

Furthermore, studies looking at directly targeting streptococcal species acid production have created the potential for other treatment modalities. For instance, Senadheera et al.\textsuperscript{41} demonstrated that deletion of the VicK sensor kinase in \textit{Streptococcus} mutans bacterium caused a significant decrease in the bacterium’s acid production, but paradoxically increased the bacterium’s survival in acidic conditions compared to the wild-type strain. Additionally, Sekiya et al.\textsuperscript{42} demonstrated that the compounds piceatannol, curcumin, and demethoxycurcumin strongly reduced the F-ATPase activity of \textit{Streptococcus} mutans, a proton-pump that is important in the bacteria’s acid tolerance abilities. The study showed that these compounds inhibited the growth of \textit{Streptococcus} mutans at a pH of 5.3 and significantly reduced the colony-forming ability at a pH of 4.3. Consequently, with PPI therapy often increasing gastric pH levels to levels greater than 4.0 and allowing overgrowth of \textit{Streptococcus} species, the findings by Sekiya et al.\textsuperscript{42} offer a promising potential therapeutic intervention for \textit{Streptococcus} species eradication in FD patients. Finally, the use of probiotics in resetting the gastric microbiome may be another possibility for treatment of patients with FD but warrants further research.\textsuperscript{31}

CONCLUSIONS

While PPI therapy is the first line treatment in patients with FD, it may worsen patients’ FD through the overgrowth of non-\textit{H. pylori} bacteria in the gastric microbiome, specifically \textit{Streptococcus} species, via gastric acid suppression and delayed gastric emptying. This overgrowth may be translocated to the gut and influence the gut microbiome as well. While the literature is limited, studies have provided promising therapeutic approaches in effectively decreasing symptoms in patients with FD through the inhibition of streptococcal species growth both directly and indirectly. Despite this, further research is warranted to understand the gastric microbiome and its role in FD, explore the highly potential causality of \textit{Streptococcus} species in FD, and develop efficient diagnostic modalities to test patients with FD for different \textit{Streptococcus} species strains in the clinical setting and drug targets against the bacterium.
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