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The Effect of Proton Pump Inhibitors on Normal Gastrointestinal Flora Leading to Weight Change

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by

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Table of Contents

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Abstract

The goal of this literature review was to determine what effects proton pump inhibitors (PPIs) have on the normal gastrointestinal (GI) flora and how that may lead to weight loss or weight gain. A literature search was performed using the database PubMed. Only articles from the last ten years (2009-2019) were included in this review. Keywords used in the search are listed below. After exclusion criteria was applied, 30 articles were relevant and used in this review. Five themes were identified in the literature review. An investigation of normal GI flora associated with weight loss and weight gain identified a common conclusion that the ratio of *Firmicutes* to *Bacteroidetes* was higher in obesity. The investigation of PPIs effects on the normal GI flora was less conclusive; however, a common finding was an increase in *Streptococcaceae* (phylum *Firmicutes),* which can commonly be found in the oral cavity. This finding suggests that oral flora may have a greater survival rate in lower parts of the GI system with treatment of PPIs due to the decreased gastric acidity. The final investigation, which looked into the association between PPI use and weight change revealed a greater likelihood that PPIs will cause weight gain with four studies supporting weight gain and two studies supporting weight loss. Alternative treatments such as H2 receptor antagonists, laparoscopic Roux-en-Y gastric bypass, probiotics, and lifestyle management were also explored. Although further research needs to be completed, it appears that PPIs are associated with an increase in *Streptococcaceae* of the phylum *Firmicutes,* which has been linked to weight gain.

Keywords: proton pump inhibitor, PPI, weight, weight gain, weight loss, bacteria, microbiome, gastrointestinal flora, normal flora, intestinal flora, gut bacteria

Introduction

Obtaining a patient's BMI, or body mass index, is a routine part of any clinic or hospital visit. Obesity is a rising crisis in the United States. According to the Centers for Disease Control (CDC), 39.8% of the US adult population suffers from obesity. That percent does not even include individuals who are overweight. There is also epidemiological data that shows obesity and gastroesophageal reflux disease (GERD) are linked. GERD occurs when the lower esophageal sphincter becomes relaxed and allows gastric acid pass into the esophagus to irritate the mucosal lining.

One of the first line treatments for those suffering from gastric acid related symptoms are proton pump inhibitors (PPIs). Proton pump inhibitors decrease gastric acid and therefore relieve the irritation caused by it. Although lowering gastric acid may increase healing of ulcers and reduce symptoms of GERD, the stomach's low pH is an important factor in controlling bacteria within the gastrointestinal system (Ambizas, 2017). Without that control system, bacteria are free to grow as other factors allow. There have been recent studies showing that different normal flora are related to an increased ability to lose or gain weight.

The purpose of this study is to explore the effects of PPI use on normal gastrointestinal flora and how that relates to weight change. This study will also mention alternative treatments such as H2 antagonists, lifestyle modifications, and surgical intervention.

Statement of the Problem

Weight gain is a significant side effect of some medications and is a strong factor that influences whether a patient chooses to take a drug or not. This is not only due to aesthetic reasons, but also risk factors for other diseases. According to the National Institutes of Health

(NIH), excess weight is linked to greater risk for cardiovascular disease, diabetes, stroke, renal disease, liver disease, cancer, and many others.

PPIs come with an array of gastrointestinal related side effects. According to U.S. Pharmacist, PPIs commonly cause nausea, vomiting, diarrhea, and an increased risk of *Clostridium difficile* infection. If PPIs have been shown to affect pathogenic bacteria of the gastrointestinal system like *C. difficile*, they most certainly influence normal flora as well.

Weight determination is a complex interaction between diet, genetics, physical activity, medical conditions, and stress. Certain bacteria of the GI system have been found in higher concentration in overweight individuals compared to those of thin individuals, showing a clear link between the normal flora of the GI system and weight, making it another factor to consider.

If PPIs do affect the normal flora of the GI system in a way that leads to weight gain, it will be important to find an alternative treatment of gastric acid related symptoms for those individuals who are overweight or obese.

Research Question

In patients using PPIs, do the PPI's effects on normal GI flora lead to weight gain or weight loss?

Methods

A literature search was performed on PubMed using the following search terms in various combinations: "proton pump inhibitor," PPI, weight, "weight gain," "weight loss," bacteria, microbiome, "gastrointestinal flora," "normal flora," "intestinal flora," and "gut bacteria." Only articles from the last 10 years were included (2009-2019). Out of 281 total search results, 38 articles were relevant. Seven were later removed as they were reviews. One study was also later removed due to the subjects of study being insects, not mammals. All others not

included in this review lacked relevance because they discussed the effect of PPIs in the treatment of H. pylori only, or the main topic of the article was not directed at PPIs or weight.

Literature Review

A review of the literature shows that PPIs' effects on GI flora have been heavily studied; however, PPIs' effects on weight has not. The current literature that is available demonstrates many conflicting results on whether PPIs cause weight gain, weight loss, or no change in weight. Although there are conflicting results regarding PPIs and weight, there is solid evidence regarding PPIs' effects on GI flora and which flora are associated with weight gain and weight loss.

Normal GI Flora Associated with Weight Gain

The ratio of *Firmicutes* to *Bacteroidetes* was higher in obesity (Hou et al., 2017). *Enterococcus, Blautia, Sutterella, Klebsiella,* and *Collinsella* were also increased in obesity. Hou and colleagues obtained these results through investigating the differences in gut microbiota in obese and healthy children. 87 obese children and 56 healthy children age 3-18 had fecal DNA samples analyzed. None of these children had antibiotics in the three months prior to the study. The researchers looked at the 16S rRNA gene, the enterotypes, and quantity of the gut microbiota. They also analyzed the fecal samples of the obese children during weight reduction. Unfortunately, this study lacked information about the time frame of fecal collection and demographics of the children, as well as their health history. Although the study failed to record some information, results showed significant differences between gut microbiota in obese children and healthy children (principal coordinate analysis, $P < 0.01$). It also showed that the amount of *Bifidobacterium* and *Lactobacillus* increased during weight reduction (Wilcoxon's rank sum test, $P < 0.01$). There was also a higher ratio of *Firmicutes* to *Bacteroidetes* in obese

children, as well as an enrichment of *Enterococcus, Blautia, Sutterella, Klebsiella, and Collinsella*. According to another study referenced in the Hou study, *Collinsella* has been found to positively correlate with insulin and is enriched in type 2 diabetes suggesting a relationship with insulin resistance in obese individuals. In healthy children, *Bacteroides, Parabacteroides*, *Anaerotruncus*, and *Coprobacillus* were enriched.

Menni et al. (2017) showed conflicting results to that of Hou et al. (2017). Menni showed that *Bacteroides* is associated with increased risk of weight gain and that *Firmicutes* (part of *Ruminococcaceae*) is associated with lower long-term weight gain. *Ruminococcaceae* and *Lachnospiraceae* were associated with lower long-term weight gain (OR=0.89 (0.05), *P*=0.038) via logistic regressions. Although *Bacteroides* was associated with increased risk of weight gain, the correlation seemed to be driven by the lower levels of diversity. A low gut microbiome diversity appears to be associated with greater weight gain over time. Gut microbiota diversity was negatively associated with long-term weight gain via random intercept logistic regressions (P <0.05). The gut microbiota diversity was also positively correlated with fiber intake (Shannon: beta (s.e.)= 0.01 (0.004), *P*=0.002) and negatively associated with risk of being in the high weight gain group (OR (s.e.)= 0.977 (0.96-0.99), P= 0.017) via linear regressions. It is unclear if the low bacterial diversity is a cause or consequence of weight gain. The goal of this study was to determine if there was a correlation between change in body weight over time and gut microbiome composition. Not only did this study accomplish its goal, it also determined that weight gain relies more heavily on environmental factors than heritability. Less than half of the variation in long-term weight change was found to be heritable (h^2=0.41 (CI: 0.31, 0.47)). To obtain the results discussed above, 1632 Caucasian, female twins from the TwinsUK registry had fecal samples collected. 16S ribosomal RNA gene sequence data (composition of gut

microbiome) was analyzed as well as BMI (average 9.09 years apart with SD 3.45), calorie intake (via food frequency questionnaires), and physical activity (using a Likert scale). The strength of this study is the number of factors considered: age, sex, smoking, calorie intake, physical activity, family relatedness, and BMI. The limitations of this study were that diet and physical activity information was drawn from questionnaires and not an observed program. The study also only analyzed women, therefore failing to consider sex differences. Finally, the study lacked measures of microbiome composition at baseline.

The study performed by Muniz Pedrogo et al. agreed with Hou's results, *Dialister* (phylum Firmicutes) was increased in those with reduced weight loss (Muniz Pedrogo et al., 2018). *Dialister* is associated with oral infections. If *Dialister* is able to make it to the intestinal tract, possibly via gastric acid suppression with PPIs, it could explain an association between PPIs and weight gain. The goal of this study was to determine if compositional and functional characteristics of the gut microbiota in adults predicted responses to a comprehensive lifestyle intervention program in overweight and obese adults. To investigate their goal, 26 adults age 18-65 with a BMI of 27-39.9 from the Mayo Clinic Obesity Treatment Research Program were recruited between August to September 2013 to participate in a lifestyle intervention program for weight loss. The mean age of all participants was 53.5 years (95% CI: 50.3 – 56.8) with 81% of participants being female. None of the participants had health problems that prevented them from physical activity or a history of previous surgeries for weight loss. They also were not currently in another weight loss program and had not taken weight loss medications or antibiotics in the previous 30 days. The participants were also not allowed to take probiotics. The participants were required to get 10,000 steps per day (monitored by a 7-day pedometer) and increase the amount of fruits, vegetables, and low energy density food intake while lower foods with greater

nutrient density. They met weekly for the first 3 months and used the outline of the Look AHEAD protocol to guide their meetings. At baseline and at 3 months, data was collected: age, sex, race, weight, height, BMI, smoking status, hypertension, pre-diabetes, type 2 diabetes, fasting blood glucose, HDL levels, LDL levels, triglycerides, and stool samples. Success was defined as 5% or greater weight loss. Stool samples were analyzed based on 16S rRNA. Two-sided Wilcoxon rank-sum tests were used to compare baseline differences in bacterial composition and alpha diversity. It was also used for interval changes in bacterial composition and diversity between baseline and three months. Permanova was used for beta diversity. The results showed *Phascolarctobacterium* was significantly increased at baseline in subjects that lost at least a 5% weight loss after 3 months (LDA 2.09, *P*=.008) and *Dialister* was significantly increased in those with less than 5% weight loss (LDA −2.07, *P*=.03). There was no change in the gut microbial composition and diversity after 3 months. The strengths of this study were the close observation of the participants and the many metabolic factors they take into account at baseline and at 3 months. However, the study was limited by its small sample size and the short time frame.

A study performed by Stark, Susi, Emerick, and Nylund notes that *Actinobacter* (higher in obese), *Bacteroidetes* (lower in obese), and *Firmicutes* (increased in obese) have been found to be increased in PPI users (Stark, Susi, Emerick, & Nylund, 2019). They also found that PPIs have a greater influence on weight than either H2RAs or antibiotics. This information was discovered while investigating the association of antibiotic, histamine-2 receptor antagonist, and proton pump inhibitor prescriptions in children diagnosed with obesity. To study this association, a retrospective cohort study of 333,353 children born into the US Military Health System between October 2006 and September 2013 was performed. To be included in the study, they

had to have a set of vital signs with height and weight recorded between October 2008 and September 2015 and be eligible for TRICARE. They excluded infants who were low birth weight, premature, or had an initial hospital stay greater than seven days. An exposure was considered a prescription for an antibiotic, H2RA, or PPI in the first two years of life. Obesity was defined by the US CDC as a BMI greater than or equal to the 95^{th} percentile for age and sex. A single event analysis of obesity was performed using Cox proportional hazards regression starting at age two because the CDC growth charts are recommended starting at age two. An ordinal variable was created for acid suppressing medications representing 30-day intervals. Antibiotics were divided into subgroups of one, two, three, or greater than three antibiotic class exposures. A similar subgrouping was made for those exposed to one, two, three, or none of the medications groups in the study. The results showed that of the 333,353 children, 11.8% were prescribed H2Ras, 3.3% were prescribed PPIs, and 72.4% were prescribed antibiotics. 14.1% developed obesity with the median age (P25-P75) for the first reading being 3.03 (2.27-4.07). 11% of the children who developed obesity were not exposed to any of the medications. For PPI prescriptions, the percent of obesity was greater than either H2RAs or antibiotics (16.6% compared to 15.1% and 15.3% respectively). For PPI prescriptions, the incidence density of obesity was 3.85, the unadjusted HR (95% CI) was 1.04 (1.03-1.05), and the adjusted HR (95% CI) was 1.02 (1.01-1.03). The strengths of this study are the large and diverse population, and the standardized measurements such as the CDC growth chart. The limitations of this study include the lack of information regarding if the patient actually took the medication prescribed, as this study only took into account prescriptions that were filled. Medications could have also been purchased or obtained outside of TRICARE such as in the ER or urgent care setting. It is also unknown what the mother's health habits were and how well the children were fed.

A study by Ward et al. agrees with three of the four studies above. PPI use before and after the surgery was correlated with an increase in *Firmicutes* and a decrease in *Bacteroidetes* (Ward et al., 2014). PPI use also was associated with decreased weight loss. This information supports other articles in that low *Bacteroidetes* and high *Firmicutes* is considered an obese profile and that PPIs may be responsible for the shift in microbiota. The goal of this study was to assess the association between PPI use and the gut microbiota prior to laparoscopic Roux-en-Y gastric bypass (LRYGB) and at six months post-LRYGB and the relationship of post-LYRGB PPI use with weight loss. Eight severely obese adult patients (BMI >40) at the Ohio State Wexner Medical Center who were candidates for LRYGB were recruited for this study between December 2010 and December 2011. Their weight had to be stable one month before surgery, and they could not be taking antibiotics, probiotics, steroids, or other immunosuppressant medications 30 days before providing a stool sample. Data collected were weight, height, and PPI use as defined by the use of a PPI for four or more per week for the prior month. Nonusers must not have taken a single dose of a PPI or H2 blocker in the two weeks before stool collection and they must not have been a regular PPI or H2 blocker user at any time during the previous three months. Fecal samples provided were self-collected and stored at -80^{o}C until analysis. Only 5/8 patients provided the six-month sample. The fecal samples were analyzed using 16S rRNA genes. Mean percent relative abundances (PRA) were compared between PPI users and PPI nonusers using an unpaired Student's *t* test. Weight loss was defined by percent weight loss (PWL) and percent excess weight loss (PEWL), which were both calculated. The results showed the mean PRA of *Firmicutes* was higher in PPI users (71.6%, 48.6%) than in non-PPI users (52.1%, 35.6%) (before and after LRYGB respectively). The mean PRA of *Bacteroidetes* was lower in PPI users (5.4%, 5.9%) than in non-PPI users (15.8%, 22.6%) (before and after

LRYGB respectively). The PRA of *Proteobacteria* was lower in PPI users (6.8%) than non-PPI users (19.5%) before LRYGB; however, after the results were similar (13.8% compared to 12.4%). *Escherichia* of *Proteobacteria* was higher in PPI users both before (4.5% vs. 0.4%) and after (10.8% vs. 3.7%). The PRA of *Akkermansia* of *Verrucomicrobia* was higher in PPI users (12.8%) than non-PPI users (7.2%) before LRYGB; however, after *Akkermansia* increased in both groups (28% and 26.3% respectively). Patients using PPIs had poorer weight loss than non-PPI users (PWL of 27.4 ± 4.6 % compared to 31.1 ± 8.0 %, and PEWL of 49.3 ± 9.0 % compared to 61.4 ± 2.0 %). The major limitation of this study was its small sample size.

Normal GI Flora Associated with Weight Loss

Akkermansia muciniphila is associated with a better metabolic profile or weight loss (Dao et al., 2016). The goal of this study was to evaluate the association between *Akkermansia muciniphila* abundance, fecal microbiome gene richness, diet, host characteristics, and their changes after calorie restriction. *A. muciniphila* is a bacterial species inversely associated with body fat mass and glucose intolerance in mice. This human study involved 49 overweight and obese adults in Paris, France that were enrolled in a 6-week calorie restriction followed by 6 weeks of a weight stabilization diet. Anthropometric measurements, subcutaneous white adipose tissue samples, 7-day dietary records, fecal samples, and blood samples were taken at baseline, week 6, and week 12. The results showed that individuals with higher abundance of *Akkermansia* had a lower waist-to-hip ratio (0.96 (0.01) for low and 0.92 (0.02) for high, p value 0.04), lower leptin (44.1 ng/ml (3.6) for low and 30.9 ng/ml (3.9) for high, p value 0.005), lower fasting blood glucose (5.4 mmol/L (0.1) for low and 5.2 mmol/L (0.1) for high, p value 0.02), and lower insulin (11.3 ulU/ml (0.9) for low and 8.9 ulU/ml (0.9) for high, p value 0.03). These results suggest a better metabolic profile for those with higher abundance of *Akkermansia.* The strength

of this study was the many metabolic parameters being measured. The limitation of this study was that they did not a have a control (healthy) population. Also, of the 49 participants 41 were female, which does not provide a good sample size for gender differences.

As discussed in Normal GI Flora Associated with Weight Gain, Hou's goal was to investigate the differences in gut microbiota in obese and healthy children to develop further understanding of the mechanism of obesity development (Hou et al., 2017). The study found that *Bacteroides, Parabacteroides, Anaerotruncus,* and *Coprobacillus* were enriched in healthy children, suggesting these bacteria may be correlated with weight loss. It also showed that the amount of *Bifidobacterium* and *Lactobacillus* increased during weight reduction (Wilcoxon's rank sum test, $P < 0.01$). There was also a higher ratio of *Firmicutes* to *Bacteroidetes* in obese children compared to healthy children. Therefore, the bacteria associated with a lower weight are*: Bacteroides, Parabacteroides, Anaerotruncus, Coprobacillus, Bifidobacterium, and Lactobacillus.*

Another study, like Ward et al. (2014), investigated the association of bariatric surgeries and changes to the GI microbiome. According to Ilhan et al. (2017), *Gammaproteobacteria, Prevotellaceae,* and *Bacilli* may be associated with greater weight loss. The goal of the study was to determine differences in the microbiota after Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding surgeries and reveal links between microbiome and weight loss associated products after bariatric surgeries. The study notes that the higher gastric pH in RYGB patients allows for greater microbial diversity because it increases the chance of survival of acid-sensitive microorganisms. Between 2011 and 2014, researchers recruited four different groups of people from Mayo Clinic, AZ: patients who had RYGB (24) or LAGB (14) surgeries, healthy normal weight (10), and morbidly obese controls who were scheduled to undergo bariatric

surgery (15). Patients were to not use prebiotics/probiotics and preferably no PPIs two weeks before fecal collection. They were also not allowed to be on antibiotics within two months of fecal collection. The surgical group had to have had their surgery at least 9 months before testing. Participants also provided a 4-day food diary and food frequency questionnaire 2 weeks before stool sampling. DNA analysis was performed on the stool using 16S rRNA gene data. The results showed that percent excess weight loss was significantly higher for the RYGB group than the LAGB group ($P<0.05$). When analyzing the microbiomes, they did not cluster based on BMI, diet composition, sex, or age (permutational analysis of variance $P>0.05$). This meant that RYGB surgery was the main factor for the change in the gut microbiota. *Gammaproteobacteria* and *Prevotellaceae* were found more in RYGB than in nonsurgical patients. *Gammaproteobacteria* and *Bacilli* were elevated in RYGB compared to LAGB. They also found that RYGB had higher microbial diversity than LAGB or pre-surgical patients ($P<0.05$). Low diversity has been associated with obesity. This study's strength was its focus on long term changes to the gastrointestinal microbiome, however, many of the results were statistically insignificant.

Mailhe et al. showed that the change in gastrointestinal pH due to PPI use changes the microbiota diversity (Mailhe et al., 2018). Patients using PPIs had greater bacterial diversity ($p<0.001$). In other studies, the higher diversity is associated with weight loss. The goal of this study was to analyze the human microbiota from the upper to the lower GI tract using culturomics and metagenomics. One strength of this study is the sampling from multiple areas of the GI system. Unlike most studies that have just taken stool samples, this study also obtained samples from the upper GI system. There were six patients who underwent a colonoscopy and endoscopy simultaneously with gastrointestinal content sampled in five different locations along

the GI tract. These samples were analyzed via MALDI-TOF and 16S rRNA gene amplification and sequencing. This was another strength of this study- using two different methods to analyze the bacteria. A comparison of the human microbiota of patients treated with PPIs to those who were not revealed that PPI use raised stomach and duodenal pH (untreated stomach and duodenum vs treated: 1.8 and 2.5 vs. 7.0 and 7.1 [$p<0.001$]). In untreated individuals, they isolated 754 species with 377 being aerotolerant. In treated individuals, they isolated 960 species with 462 being aerotolerant. The limitations of this study were its small sample size, the lack of information regarding how long the patients were on PPIs, and the lack of information on other parameters of the patients they sampled from such as: BMI, diet, exercise, gender, and age.

Muniz Pedrogo et al. (2018), as discussed in the theme Normal GI Flora Associated with Weight Gain, not only found that *Dialister* was associated with increased weight, the study also found that *Phascolarctobacterium* was increased in those with increased weight loss. *Phascolarctobacterium* was significantly increased at baseline in subjects that lost at least a 5% weight loss after three months (LDA 2.09, P=.008).

A study by Nadal et al. (2009), showed an increase in *Bacteroides* is related to weight loss, which supports other articles' results. It also showed that reductions in *C. histolyticum* and proportions of *E. rectale* to *C. coccoides* correlated with decreased weight. The group that didn't experience significant weight loss also didn't experience any significant change to their microbiota, which suggests microbial change is directly related to weight change. The goal of this study was to evaluate the effects of a weight loss program on the fecal microbiome of overweight and obese adolescents and how that relates to weight loss. This was a longitudinal intervention study in Spain on 39 teenagers (ages 13-16) who had BMIs that ranged from 23.7-50.4. There were 20 females and 19 males. They were placed on calorie restriction (10-40%) and

increased their physical activity (determined by accelerometry) for 10 weeks. They were also provided counseling to educate them on diet, give them techniques to help change behaviors, and provide general support. They kept food diaries for 72 hours before the study and 72 hours at the end of the study to determine average intake of energy. Blood work was taken to determine their lipids, glucose, and fasting plasma insulin levels. Fecal samples were also taken at baseline and at 10 weeks. Fluorescent in situ hybridization followed by flow cytometry was used to determine the bacterial groups present in the feces. Feces were also dried into duplicate 1.5 g samples and their energy content was determined by the Automatic Adiabatic Bomb Calorimeter. The results showed that 26 of the 39 had significant weight loss with a mean of 7.6 kg (P= 0.050). Thirteen of the 39 did not have significant weight loss with a mean decrease of 1.1 kg (P=0.798). Both groups had a significant decrease in caloric intake (P<0.050). They found reductions in *Clostridium histolyticum* correlated with weight loss (r=0.43; P=0.009) and BMI z-scores (r=0.41; P=0.012). Reductions in proportions of *E. rectale* to *C. coccoides* also correlated with weight loss (r=0.50; P=0.001) and BMI z-scores (r=0.39; P=0.014).They also found a significant increase in *Bacteroides* (P=0.047) which almost reached correlation with weight loss (r=-0.28; P=0.083). Although there were other shifts in bacterial groups, they were not significantly correlated with weight loss or with BMI z-scores. In the group that didn't experience significant weight loss, there was no significant shift in bacterial groups or correlations with bacteria to body weight or BMI z-scores. There were no conflicts of interest. The limitations of this study are the small sample size and the lack of control over the type of food eaten and the type of exercise performed.

The study by Sanmiguel et al. (2017) not only suggests various bacteria that may be responsible for weight loss, but also the way they contribute to weight loss. For example,

Enterococcus is associated with lower appetite and *Akkermansia* is associated with reduced hedonic eating. This study also agreed with many others regarding a decrease in the *Firmicutes* to *Bacteroides* ratio being related to weight loss. The goal of this study was to determine if laparoscopic sleeve gastrectomy causes changes to the gastrointestinal microbiota and whether those changes are related to weight loss. Eight obese adult women (BMI= 44.1 [5.6]) at the UCLA Ronald Reagan Medical Center who were to undergo laparoscopic sleeve gastrectomy (LSG) were recruited between June 2014 and June 2015. They measured height, weight, BMI, waist circumference, percent body fat, lean body mass, dietary intake, hunger and satiety ratings, and Yale Food Addiction Scale scores at baseline and at one month post-surgery. Stool samples were also analyzed at baseline and at one month post-surgery using 16S rRNA gene sequencing. Diversity analysis was performed on the stool samples for alpha diversity (within a sample) and beta diversity (across samples). Differences in taxonomic abundance of the gastrointestinal microbiome pre- and post LSG were also evaluated. The results showed that LSG was associated with a significant increase in *Fusobacteria* (log2FC= 4.0, q=4.1E-07) and a significant decrease in *Firmicutes/Bacteroidetes* ratio (p=0.008) due to a decrease in *Firmicutes* (log2FC= -0.71, q=0.0055). After surgery *Bifidobacteriacceae* decreased (log2FC= -8.4, q=0.0003), and *Fusobacterium* (log2FC= 4.3, q= 0.0005), *Atopobium* (log2FC= 4.1, q=0.01), and *Bulleidia* (log2FC= 3.8, q= 0.04) increased. “Several bacterial genera were significantly associated with weight loss (*Bilophila*, q = 3E-05; *Faecalibacterium* q = 4E-05), lower appetite (*Enterococcus*, q = 3E-05), and reduced hedonic eating (*Akkermansia*, q = .037) after surgery” (Sanmiguel et al., 2017). The strength of this study lies in its statistical analysis. The limitation of this study is the small sample size in a short timeframe. This study also involved a questionnaire, in which it is possible that the women did not truthfully report their hedonic eating.

Shin et al. (2016) found that PPI use is associated with weight loss. It also disagreed with other studies, showing *Firmicutes* was the predominant bacterial phylum associated with weight loss/PPI use. The goal of this study was to assess changes in gastrointestinal microbiota of rats treated long-term with a proton pump inhibitor, lansoprazole. There were eleven 24-week-old male Fischer rats used in this study. For 50 weeks, five rats were fed Purina rat chow and six rats were fed the same feed with lansoprazole (5 mg/kg/day). To make the medicated chow, one gram of lansoprazole was mixed with 20 kg of rat chow. The average rat body weight was presumed to be 400 g and daily chow intake was presumed to be 40 g. After the 50 weeks, the rats were anesthetized, killed, and stripped of a 1-cm length of their terminal ileum. The lumen of the terminal ileum was flushed with phosphate buffered saline and the flushed material was formed into pellets via centrifugation. Barcoded pyrosequencing of the 16S rRNA gene was performed on the microbial DNA extracted from the pellets. The results showed that "rats treated with lansoprazole showed significantly reduced body weight compared to controls (322.3±15.3 g vs 403.2±5.2 g, $p<0.001$)." The microbiota of the control rats showed 93.9% *Proteobacteria* (increased *Escherichia* and *Pasteurella*). The microbiota of the PPI treated rats showed 66.9% *Firmicutes* (*Clostridium* or *Lactobacillus*). There was no statistical significance in the diversity of the microbiota within the control and treated groups. The strength of this study was its length. The limitations of this study were the small sample size, the lack of control of food intake, and that they only examined the microbiota of the terminal ileum. Because the rats were fed ad libitum, the daily dose of PPI could not be determined and therefore the change in weight may be due to differences in food intake. This study was also performed on rats, meaning that their results may not translate to human studies.

Proton Pump Inhibitors' Effects on Normal GI Flora

Streptococcaceae increases in the gut after PPI therapy (Bajaj et al., 2014). *Streptococcaceae* is abundant in the oral cavity, but it is usually destroyed by gastric acid. PPIs increase of gastric pH may be contributing to the survival of *Streptococcaceae* in the intestinal tract. The goal of this study was to assess the changes in gut microbiota composition and function in patients with cirrhosis and without after a two week course of omeprazole. Fifteen patients with cirrhosis without decompensation and 15 healthy age-matched controls who had not been on PPIs were recruited for the study. At baseline and at two weeks, patients had blood gastrin levels drawn, a 24 hour food recall was done, their MELD score determined, and fecal and urine samples collected. For two weeks, patients were given 40 mg of omeprazole at breakfast while maintaining their dietary pattern. Microbial DNA was analyzed using Length Heterogeneity PCR fingerprinting of 16S rRNA, Multitag Pyrosequencing, and the Bayesian analysis tool in RDP10. The results showed >95% adherence to omeprazole as demonstrated by pill bottle return. There was no significant change in MELD score (P=0.5), the controls' caloric intake (P=0.4), or the cirrhosis patients' caloric intake (P=0.6). There was a significant increase in *Streptococcaceae* after omeprazole therapy in both cirrhosis patients (baseline 0.0 vs. 8.9%, P = 0.0008, FDR = 0.008) and controls (baseline 0.2 vs. 5.7%, P = 0.0009, FDR = 0.007). The strengths of this study are there are no conflicts of interest in this study and they also age-matched their controls. The limitations of this study are its small sample size and short study period.

Another study found a relationship between PPI use and *Streptococcaceae*. *Haemophilus* and *Streptococcus* increase with PPI therapy, and *Lactobacillus* and *Stenotrophomonas* decrease with PPI therapy (Castellani et al., 2017). The goal of this study was to determine how PPIs

affect the microbiome of infants with gastroesophageal reflux disease. This was a prospective longitudinal interventional study. Twelve infants (8 males, 4 females) with proven GERD under the age of one were enrolled in this study between November 2014 and August 2016. Stool samples were collected before initiation of esomeprazole therapy (1 mg/kg body weight oral), after four weeks of therapy, and at four weeks post PPI therapy. Patients received the PPI for a variable amount of time (8-44 weeks) depending on their symptoms. They didn't receive any antibiotics or other acid suppressant, and their diets were recorded. Microbial DNA was extracted from the stool samples and analyzed using 16S rRNA gene data. The results showed that alpha (Chao1 index, p=0.729) and beta (unweighted UniFrac, p=0.913) diversity of the microbial populations did not change after treatment with PPIs. However, after the PPI was discontinued, the third sample showed increased alpha (p=0.003) and beta (p=0.003) diversity. PPI therapy caused a significant increase in *Haemophilus*, and a significant decrease in *Lactobacillus* and *Stenotrophomonas*. *Streptococcus* was also increased, although not significantly. The strengths of this study were that GERD was proven in the infants by 24-hour pH impedance monitoring. All of the patients' GERD resolved, suggesting appropriate acid suppression. There were also no conflicts of interest. The limitations of this study were the small sample size and the variable lengths of time patients were exposed to esomeprazole. This study also lacked a control group (one that was not exposed to PPI therapy).

PPI use decreases the abundance of *Bacteroidetes* and increases the abundance of *Firmicutes* (Clooney et al., 2016). This is an important finding because the other studies have found that increased Firmicutes was associated with an obese profile. In this study, the bacteria that increased within *Firmicutes* were *Holdemania, Streptococcus,* and *Blautia*. The goal of this study was "to compare the fecal microbiomes of long-term PPI users to those with no history of

PPI use" (Clooney et al., 2016). Sixty-one participants were enrolled in this cross-sectional study, 32 PPI users and 29 controls. All participants were found using the Manitoba Health Population Health Registry. The PPIs users had to be age 50 or over and been dispensed over 180 PPI tablets in five years prior to the study. The controls had to be age 50 or older and not been dispensed any PPIs in the five years prior to the study. All participants gave data regarding current or prior PPI use, the type of PPI, the dose, the indication for PPI use, gastrointestinal symptoms, and other medications used. All participants also completed a Food Frequency Questionnaire. The participants then collected a stool sample at home and were told to store it in a refrigerator until shipment to the study center in Manitoba. The stool samples were then frozen and shipped to Ireland for microbial DNA analysis using 16S rRNA gene data. The results showed that "the abundance of *Bacteroidetes* was lower in PPI users relative to the non-PPI control group ($P < 0.007$), while the abundance of *Firmicutes* was higher ($P < 0.008$)." Within *Firmicutes*, three genera were significantly increased: *Holdemania* ($P<0.0003$), *Streptococcus* ($P<0.036$), and *Blautia* ($P <0.077$). The two most commonly used PPIs were omeprazole and rabeprazole. The strengths of this study were the larger sample size and the long term use of PPIs. The limitations of this study were that they did not survey participants on their antibiotic usage, they could not determine if there was a change from the baseline gut microbiome in PPI users as this was a cross-sectional study, and they could not determine if the effects would be the same with short-term PPI use.

Freedberg et al. agreed with Castellani et al. and Bajaj et al., PPI use increases *Enterococcaceae* and *Streptococcaceae* (Freedberg et al., 2015).The goal of this study was to determine if PPIs alter the gut microbiome to increase the risk of *Clostridium difficile* infection. The study was an open-label, randomized crossover trial that involved 12 healthy participants

age 18 or older who had not used antibiotics, PPIs, or H2 antagonists within one year, had not used new medications within one month, did not have chronic GI mucosal disease or abnormal bowel frequency, did not use medications that interact with PPIs, were not pregnant, and did not have travel plans outside the US during the study period. Fecal samples were taken at week zero and week four of which they were not on any PPIs. The participants were then randomized into groups of four weeks vs eight weeks of PPI treatment with 40 mg of omeprazole twice daily. After four weeks of treatment, they all donated another fecal sample. After eight weeks of treatment, the final fecal samples were collected. Fecal microbiomes were determined using 16S rRNA gene sequencing. The results showed that microbial diversity did not change after four weeks or 8 weeks of PPI treatment. After four weeks of PPI therapy, *Enterococcaceae* and *Streptococcaceae* increased. *Enterococcaceae* has been associated with *C. diff* infections in other studies, and *Streptococcaceae* is predominantly an upper GI microbe that has been associated with small intestinal bacterial overgrowth in other studies. They also found a 44% median decrease in *Clostridiaceae* (P= 0.03). No further changes were seen in participants on the eight week trial of PPIs. The strengths of this study were in its exclusion criteria of participants and the randomization of four vs eight week PPI groups. The limitations of this study were its focus on bacteria that have already been associated with *C. difficile* infection, as well as its small sample size.

In the study by Gommers et al. (2019), PPIs induce a change in the gastrointestinal microbiome including: a decrease in diversity, an increase in *Lactobacillus*, and an increase in *Bifidobacterium.* The goal of this study was to examine how PPIs and magnesium intake affect the gut microbiome. Forty-eight male mice were randomly placed into four experimental groups. Two groups were fed low magnesium (0.05%) diets and two groups were fed normal magnesium

(0.22%) diets. Omeprazole 20 mg/kg body weight was then given for four weeks to a group from each diet and the other two groups were given a placebo. The mice were weighed daily. At baseline, two weeks, and after four weeks of treatment, urine and feces were collected and their food and water intake was determined. After the treatment was completed, the mice were anesthetized and killed. Their stomach pH was measured using diagnostic test strips. The fecal microbiome was determined via extraction of DNA followed by 16S rRNA gene analysis. The results showed that omeprazole decreased the microbial diversity compared with the controls (P=0.027) independent of magnesium intake. In omeprazole treated mice, *Lactobacillus* increased 3-fold compared to the placebo treated mice, and *Bifidobacterium* increased 2-fold compared to the placebo treated mice. These genera rose independently of magnesium differences. The strength of this study was that the mice were placed in a controlled environment. The limitation of this study was that the test subjects were mice and therefore these results may not transfer to human studies.

According to Hojo et al. (2018), PPIs increase the abundance of facultative anaerobes in the GI tract: *Lactobacillus, Streptococcus, Enterobacteriaceae,* and *Staphylococcus.* The goal of this study was to examine the fecal microbiota composition after PPI use. This observational study examined 20 patients (13 males, 7 females) who were at least 20 years old and had confirmed grade A or greater reflux esophagitis. They were recruited between October 2014 and September 2016 from Juntendo University Hospital Department of Gastroenterology. Exclusions included: PPI use or antibiotic use within one month of the study, living probiotic or yogurt within one month of the study, a history of GI resection, and patients with upper GI ulcers or malignancies. Eight weeks of either esomeprazole (20 mg), rabeprazole (10 mg), or lansoprazole (30 mg) were given once daily. Fecal samples were collected for DNA analysis by 16S and 23S

rRNA targeted quantitative RT-PCR at baseline, at four weeks of treatment, and at eight weeks of treatment with PPIs. They also measured fecal pH with an IQ 150 pH Thermometer. The results showed *Lactobacillus,* a facultative anaerobe, significantly increased between baseline and four weeks (P= 0.011), as well as baseline and eight weeks (P= 0.002). *Streptococcus*, another facultative anaerobe genus, significantly increased between baseline and four weeks (P= 0.005) and baseline and eight weeks (P < 0.0001). *Enterobacteriaceae* and *Staphylococcus*, two more facultative anaerobes, significantly increased between baseline and eight weeks (P= 0.003 and P= 0.002, respectively). The strength of this study is its use of two methods of DNA detection (16S and 23S rRNA). The limitations of this study are its small sample size and the short duration of the study. They were not able to determine if gastrointestinal microbiome changes with PPI use stayed following discontinuation of the PPIs. They also did not use the same PPI or dose between patients.

Imhann et al. (2016) found that PPI use is correlated with an increase in facultative anaerobes such as Enterococcus and Streptococcus, which was in agreement with Hojo et al. *Enterococcus*, *Streptococcus* and *Veillonella* can all be found in the oral cavity. Some of the bacterial changes were increases in oral bacteria in the gut, supporting the idea that PPI use decreases stomach acid, therefore allowing oral bacteria to survive into the gut. The study also found PPI use correlated with increased BMI. The goal of this study was to determine how PPIs affect the gut microbiome. A total of 1815 adults from the Netherlands were recruited from three different cohorts: 1174 individuals from a general population study LifeLines-DEEP (Cohort 1), 300 inflammatory bowel disease patients from the University Medical Center Groningen (Cohort 2), and 189 irritable bowel syndrome patients and 152 matched controls from Maastricht University Medical Center (Cohort 3). The patients' medications and PPI use was recorded for

all three cohorts with Cohort 1 and 3 self-reporting via a standardized questionnaire, and Cohort 2 information coming from electronic medical records. Age, gender, and BMI of all patients was recorded. Cohorts 1 and 2 collected stool samples at home and immediately froze their samples in their home freezer to be collected by a research nurse at a later date. Cohort 3 provided a stool sample within 24 hours of production to the research facility where it was then frozen. One hundred sixteen healthy volunteers also gave oral cavity mucus samples via buccal swab. Bacterial DNA analysis was performed using sequencing of the 16S rRNA gene. The results showed that 211 of the 1815 individuals used PPIs and generally had higher BMIs compared to non-users: 26.9 (SD 5.0) and 24.9 (SD 4.2), ($p=1.89*^{10}$-8, WMW test). *Firmicutes* was the most abundant phylum in all cohorts. PPI use in all three cohorts resulted in a moderate decrease in alpha diversity (Shannon index p=0.01, species richness p=0.02). 92 of 460 bacterial taxa significantly increased or decreased in PPI users compared to non-users (FDR<0.05). Some increases include *Bacilli* (*Lactobacillales, Staphylococcaceae, Bacillales), Gammaproteobacteria (Pasteurellaceae, Enterobacteriaceae), Actinomycetales (Streptococcoceae, Micrococcoceae),* and *Veillonella*. Some decreases include *Bifidobacteriaceae, Ruminococcaceae, and Tenericutes*. In PPI users, the gut microbiome shifted towards bacteria found in the oral samples compared with non-users ($p= 1.39*10^{-20}$, Wilcoxon test). Stool frequency and consistency was not related to PPI use in Cohort 1. The strengths of this study are its large sample size and comparison of gut bacteria to oral bacteria. It also used meta-analysis to compare the three cohorts. The limitations of this study are inconsistent stool sampling methods between the cohorts and the many factors needing to be accounted for such as bowel disease, other medication use, differing diets and exercise, and different duration and dose of PPI treatment- of which many of these factors were not studied.

Jackson et al. (2016) is in agreement with the previous two studies regarding the increase in oral flora within the GI tract after PPI use. This study showed an increase in oral/mouth/nose/skin bacteria in the gut with PPI use, which supports the survival of these bacteria past the decreased stomach acidity. *Bacteroidales, Rothia,* and *Streptococcus* increased while *Firmicutes* decreased with PPI use. There was also lower diversity with PPI use. The goal of this study was to evaluate the relationship between PPI use and the gut microbiome. One thousand eight hundred twenty-seven healthy, elderly twins (90% female) from TwinsUK had PPI data, fecal samples, food frequency questionnaire data, and height and weight measurements taken. Fecal samples were analyzed using 16S rRNA profiling. Forty-nine percent had self-reported a GI indication for PPIs, 12% had been prescribed PPIs, and 39% had no PPI prescriptions or GI indications. The results showed PPI users had higher BMIs ($p=0.002$) and had significantly lower microbial diversity ($p<0.05$) compared to non-users. *Firmicutes* phylum was significantly lower in PPI users. *Bacteroidales* family, *Rothia* genus ($q<10^{-5}$, $B=0.51$), and *Streptococcus* genus ($q<^{10-}6$, $B=0.47$) were significantly increased in PPI users. Using data from the human microbiome project, the researchers were able to assign bacterial families to their body site preference. It was found that six of the 10 families positively associated with PPI use showed site preference for the mouth or throat, a significant positive correlation ($p=0.38$, $p=0.0019$). One of the 10 families showed site preference for the skin or nose, a significant positive correlation ($p=0.36$, $p=0.003$). Along with most increased families associated with PPI use showing site preference outside of the gut, gut site preference bacteria were decreased with PPI use. The strengths of this study are the large sample size and the use of twins. The limitations of this study are that 90% of the population is female and PPI use was not controlled (timing, dose, brand).

Bacilli, Lactobacillus, Streptococcaceae, and *Veillonella* increased with PPI use, as *Enterobacteriaceae* was negatively associated with PPI use (Koo et al., 2018). Although PPI use changed the gut microbiome, this study also showed that the gut does have the ability to reverse the changes with cessation of treatment if treatment is short term. The goal of this study was to determine how PPI use, ethnicity, and gender impact the gut microbiome. Thirty-four healthy individuals of Asian ethnicity of the age range 21-37 years old were enrolled in this study in Singapore. The three Asian ethnicities were Chinese (n=12, 50% male), Malay (n=12, 50% male), and Indian (n=10, 40% male). They all provided a baseline stool sample, then took omeprazole 20 mg daily for seven days, provided a second stool sample at day seven, and then provided the final stool sample seven days after cessation of treatment at day 14. Throughout the study, they were required to keep a log of any side effects or diarrhea. After stool collection, the samples were frozen and sent to the laboratory within four hours. Microbial DNA analysis was performed using the 16S rRNA gene. The results showed that after seven days of treatment, species richness (p=0.018) and alpha diversity (p=0.14) increased but then reverted to baseline by day 14. There was no diversity difference between ethnicities or gender. There was also no difference in beta diversity. At seven days of treatment, there was a significant increase in *Bacilli* class (p=0.0001), *Lactobacillus* order (p=0.0001), *Streptococcaceae* family (0=0.0001), and genera *Streptococcus* (p=0.0001) and *Viellonella* (p=0.0041). These results all returned to baseline by day 14. *Enterobacteriaceae* family decreased with PPI use. The strengths of this study are the consistent use of PPIs and the balance of gender distribution. The limitations of this study are small sample size and the short timeframe.

Streptococcus increased as a result of PPI use according to Mishiro et al. (2018). This study also found that PPI use affects not only the gut, but also the oral cavity. The goal of this

study was to determine the effects of PPIs on oral and gut microbiota. Ten healthy adults (eight male, two female) had fecal, saliva, and periodontal pocket fluid samples taken at baseline and after four weeks of treatment with esomeprazole 20 mg daily. The participants were 100% compliant with treatment and reported no gastrointestinal symptoms before or after treatment with the PPI. The microbiome DNA of each sample was analyzed using 16S rRNA sequences. The results showed alpha diversity was significantly different between the three sampling locations, but not between PPI use and no PPI use. There were no changes seen in the phyla before and after PPI usage, but changes were seen at the genus level. *Streptococcus* significantly increased in fecal samples with PPI use ($P=0.044$, $q<0.05$). All other fecal microbiota remained stable before and after PPI usage, but *Fusobacterium* and *Leptotrichia* increased in periodontal pocket fluid ($P= 0.030$, $q=$ NS; $P=0.002$, $q<0.05$), and *Neisseria* and *Veillonella* decreased in saliva ($P=0.034$, $q<0.05$; $P=0.008$, $q<0.05$). The strengths of this study are there are no conflicts of interest and that they analyzed samples from mouth to colon. The limitation of this study was the small sample size.

Streptococcaceae is increased compared to *Prevotellaceae* in PPI users, which were results opposite that of the controls (Parsons et al., 2017). It also showed that the ratio of *Firmicutes* to *Bacteroidetes* increased in PPI users. *Actinobacillus* and *Tannerella* decreased with PPI use. The goal of this study was to determine the gastric mucosal microbiota profiles in patients with hypochlorhydria induced by *H. pylori* induced atrophic gastritis, autoimmune atrophic gastritis, and PPI use. Twenty normal adults and 19 PPI treated adults were included in this study involving a total of 95 participants. All study individuals underwent gastric corpus biopsies. From these samples, microbial DNA was analyzed via 16S rRNA sequencing. The results showed PPI treated patients had slightly more *Firmicutes* and fewer *Bacteroidetes* than

normal stomachs. Normal stomachs had significantly more alpha diversity than any other group. The most abundant bacterial family in PPI users was *Streptococcaceae* (17%) followed by *Prevotellaceae* (11%), as normal stomachs had opposite results with *Prevotellaceae* (23%) being the most abundant followed by *Streptococcaceae* (10%). Genera *Actinobacillus* and *Tannerella* were decreased in PPI users. The strength of this study was the sampling method, taking biopsies. The limitations of this study were the small sample size and lack of data regarding PPI use and diets.

PPI use reduces microbial diversity (Seto, Jeraldo, Orenstein, Chia, & DiBaise, 2014). The goal of this study was to examine how PPI use (short- and long-term) affects the fecal microbiome and how the changes compare with newly diagnosed *C. Difficile* infections. Ten healthy adults from Mayo Clinic in Arizona were split into two groups: five received 20 mg of omeprazole once daily for 28 days, and five received 20 mg of omeprazole twice daily for 28 days. Their BMIs were recorded and stool samples were collected at baseline, seven days of treatment, 28 days of treatment, and at one month after treatment cessation. Fecal microbiota DNA analysis was performed using 16S rRNA gene data. The data collected was then compared to fecal DNA data from five PPI treatment-naïve *C. Difficile* infection patients. The results showed decreased bacterial species count from baseline to one month of PPI use (50,000 to 25,000 reads/sample). There was no difference in operational taxonomic unit counts between high and low dose PPI use at each stool sampling time points ($p= 0.2778$, $p=0.2063$, $p=0.5556$, $p=0.2778$). The strengths of this study were the length of the study and the controlled use of PPIs. The limitations of this study were its small sample size and its lack of investigation into the upper gastrointestinal tract.

Shi et al. (2019) showed that PPI use altered both the gastric mucosal microbiota and the

fecal microbiota. *Planococcaceae, Oxalobacteraceae,* and *Sphingomondaceae* were elevated in gastric mucosal samples, and fecal samples of PPI users showed significantly higher abundances of *Streptococcaceae, Veillonellaceae, Acidaminococcaceae, Micrococcaceae,* and *Flavobacteriaceae.* The goal of this study was to investigate the association between changes in gastric mucosal and fecal microbiota and PPI use. From June 2013 to July 2014, 40 Chinese gastroesophageal reflux (GERD) patients and 15 healthy controls were enrolled in this study. Healthy controls had a normal clinical exam as well as no use of PPIs at least 30 days before the study. GERD patients were confirmed to have esophagitis via endoscopy. PPI use was broken into two categories: short-term (at least two months but less than one year) and long-term (at least one year), All patients provided fecal samples, and five healthy controls, 10 non-PPI-users, and 20 PPI users provided gastric mucosal samples. Microbial DNA analysis was performed using 16S rRNA gene data. The results showed no significant alpha diversity differences in the gastric mucosal samples between healthy controls and PPI-users. Alpha diversity differences between fecal samples in PPI use compared to non-PPI use was not significantly different. PPI users had higher abundances of *Planococcaceae, Oxalobacteraceae,* and *Sphingomondaceae* in gastric mucosal samples. Fecal samples of PPI users showed significantly higher abundances of *Streptococcaceae, Veillonellaceae, Acidaminococcaceae, Micrococcaceae,* and *Flavobacteriaceae. Ruminococcus* was lower in the short-term PPI use group compared to non-users and long-term users, as *Streptococcus* was higher in short-term users compared to non-users. The strengths of this study were no conflicts of interest and sampling from the upper and lower gastrointestinal system. The limitations of this study were the small sample size and the possible contamination of gastric mucosal samples with gastric fluid.

Shin et al. (2016) found that *Firmicutes* was the predominant bacterial phylum associated

with weight loss/PPI use, as discussed in Normal GI Flora Associated with Weight Loss. The microbiota of the PPI treated rats showed 66.9% *Firmicutes* (*Clostridium* or *Lactobacillus*) as compared to the control rats, which showed 93.9% *Proteobacteria* (increased *Escherichia* and *Pasteurella*). There was no statistical significance in the diversity of the microbiota within the control and treated groups. Lansoprazole was the PPI used in this study on rats.

Sterbini et al. (2016) showed that PPI use increased gastric *Firmicutes,* specifically *Streptococcaceae*. Genera that decreased with PPI use were *Tannerella*, *Enhydrobacter,* and *Mogibacterium*. The goal of this study was to determine the effect PPIs have on gastric mucosal associated microbiota in patients with dyspepsia. This study was unlike the other because it demonstrated the bacterial changes occurring in the gastric mucosa as opposed to stool samples. Twenty-four adults who underwent upper gastrointestinal endoscopy for dyspepsia in Rome, Italy at the Agostino Gemelli Hospital were included in this study. Twelve patients were currently on 40 mg daily of omeprazole and twelve patients were either PPI naïve or had stopped PPI treatment at least six months before the study. Exclusion criteria were: PPI users less than 12 months, antibiotics sooner than three months before the study, history of peptic ulcer disease, history of gastric surgery, chronic NSAID use, or use of any other acid reducing drugs (H2 antagonists, antacids). After a 12-hour fast, patients underwent upper GI endoscopy to have biopsies taken from the stomach antrum. Bacterial DNA was analyzed using 16S rRNA gene pyrosequencing. The results showed that PPI use and *H. pylori* status did not influence species richness (Chao1, ANOVA, $P>0.05$). The relative abundance of *Firmicutes* was higher in PPI users than non-users (FDR-adjusted $Q=0.047$). *Streptococcaceae* (phylum *Firmicutes*) were significantly more abundant in PPI users (FDR-adjusted $Q=0.0001$). The genera that decreased with PPI use were *Tannerella* (*Bacteroidetes,* $P=0.009$), *Enhydrobacter* (*Proteobacteria,*

P=0.043), and *Mogibacterium* (*Firmicutes*, P=0.040). The strengths of this study were the use of a consistent dose and brand of PPI and the technique for which samples were collected. The limitations of this study were the lack of information regarding microbiota changes lower in the gastrointestinal system and the small sample size.

Takagi et al. (2018) showed there was change in beta diversity but not alpha diversity in PPI users. It also showed that *Firmicutes* and *Bacteroidetes* phyla did not change with PPI use which is in disagreement with many of the other articles. Interestingly, it revealed a significant increase mostly in *Streptococcus* and a significant decrease mostly in *Faecalibacterium*. The goal of this study was to determine how long-term PPI use affects the microbiome of Japanese individuals. From November 2016 to November 2017, 72 Japanese patients from an outpatient clinic were recruited to participate in this study. Half were PPI users consisting of PPI treatment at least one year prior to the study. The PPIs used were esomeprazole, lansoprazole, rabeprazole, and omeprazole. The other half of study individuals were age and sex-matched controls that had not used PPIs at least five years prior to the study. Fecal samples were collected and stored for seven days at a temperature no greater than room temperature. DNA sequencing was performed using the 16S rRNA gene, followed by microbiome analysis. The results showed significant beta diversity between PPI users and non-users (unweighted $p<0.02$, weighted $p<0.01$), but no significant difference in alpha diversity. The abundance of *Firmicutes* and *Bacteroidetes* in PPI users compared to non-users showed no significant difference. The abundance of *Proteobacteria* and *Actinobacteria* was higher in PPI users than non-users but the results were not statistically significant. Eight genera were significantly decreased in PPI users: *Faecalibacterium*, SMB53, and *Clostridium* ($p<0.01$); *Turicibacter, Slackia, Defluviitalea, Dehalobacteriaceae, and Oribacterium* ($p<0.05$). Five genera were significantly increased in PPI users: *Streptococcus*

($p<0.01$); *Ruminococcus, Megasphaera, Actinomyces,* and *Granulicatella* ($p<0.05$). The strength of this study was the age and sex-matched controls. The limitations of this study were the small sample size, the various PPIs used for varying durations, and the fecal samples not being chilled. Two of the authors also received funding from pharmaceutical companies, which represents a conflict of interest.

Ward et al. (2014) found that PPI use before and after laparoscopic Roux-en-Y gastric bypass (LRYGB) was correlated with an increase in *Firmicutes* and a decrease in *Bacteroidetes.* It also found that PPI use was associated with decreased weight loss. This information supports other articles in that low *Bacteroidetes* and high *Firmicutes* is considered an obese profile and that PPIs may be responsible for the shift in microbiota. Other bacteria that were affected by PPI use were *Escherichia* and *Akkermansia*. Both *Escherichia* and *Akkermansia* were increased with PPI use, however, *Akkermansia* increased in non-PPI users after LRYGB as well. Refer back to Ward under Normal GI Flora Associated with Weight Gain for the complete data.

Yamamoto et al. (2019) found that the abundance of *Firmicutes* was less in PPI users than non-users, and the abundance of *Bacteroidetes* was greater in PPI users than non-users. This study also listed various genera affected by PPIs: *Lactobacillus, Streptococcus, Selenomonas, Veillonella, Campylobacter,* and *Haemophilus* were all abundant in the PPI group. The goal of this study was to investigate the changes PPIs cause to gut microbiota in Japanese patients with chronic liver disease. They were also interested in the relationship between PPI use and hepatic encephalopathy and spontaneous bacterial peritonitis. Sixty-two age, sex, and Child-Turcotte-Pugh score-matched Japanese patients from the NAGOYA gut microbiota database were included in the study. 31 were PPI users for at least one year before stool collection and 31 had not used PPIs at least one year prior to stool collection. PPIs used included: esomeprazole (20

mg daily), rabeprazole (10 mg daily), lansoprazole (15 mg daily), and vonoprazan (20 mg daily). Stool samples were collected at the beginning of the study, and every 3-6 months after stool collection, liver function tests were obtained. Stool samples were collected either in the hospital or in their homes, and then analyzed via 16S rRNA gene sequencing. The results showed *Firmicutes* was higher in the non-PPI group (36.7% vs. 31.9%) and *Bacteroidetes* was higher in the PPI group (58.4% vs. 50.7%). The strength of this study was groups are age, sex, and Child-Turcotte-Pugh score-matched. The limitations of this study were the small sample size and its use of only fecal samples, which may not account for small intestine bacteria or mucosal bacteria.

Proton Pump Inhibitors' Effects on Weight

PPI use was associated with obesity and an increased weight gain in the study by Czwornog and Austin (2015). There is still some question as to if the weight gain is due to a slightly higher fat intake or due to decreased muscle strengthening exercise. The goal of this study was to examine if there are differences in energy intake, diet composition, and physical activity between PPI users and nonusers. They also investigated whether PPI use was associated with change in body weight. This was a cross-sectional study using information from the National Health and Nutrition Examination Survey. They examined 3073 adults age 20-74 between 2005 and 2006. Exclusion criteria were BMI < 18.5, pregnant, individuals who answered that they were on a diet. Surveys were conducted in person, online, and via questionnaires. They collected data on medication use, two 24-h dietary recalls, physical activity and sedentary behaviors in the previous 30 days, self-reported weight change over the past year, and basic demographics. Multivariable regression analyses (adjusted for covariates) were performed to determine the relationship between PPI use and the other survey data. The results

showed “PPI users had a higher BMI ($p < 0.001$) and were more likely to be obese (45.4% vs. 30.6%; $p = 0.008$).” People who took PPIs consumed a similar number of calories compared to non-PPI users ($p= 0.95$). PPI users did consume a higher proportion of fat in their diet (34.5% vs. 33.2%; $p=0.02$). Their intake of carbohydrates, protein, and alcohol was similar to non-PPI users. PPI users reported similar frequencies of walking, biking, moderate/vigorous activity, computer use, and TV use. The only activity that PPI users engaged in less was muscle-strengthening activities (OR: 0.53; 95% CI: 0.30-0.95). Women self-reported more weight gain in one year compared to men. Men who were PPI users gained 1.52 ± 0.6 kg more than non-PPI users ($p= 0.021$). Women who used PPIs gained 0.39 ± 1.0 kg compared to women who did not use PPIs ($p=0.71$). The strength of this study was the large sample size. The limitation of this study was its subjective nature. All data in the study is self-reported meaning that people could be falsifying information or underreporting.

Hsien-Hao, Harn-Shen, and Chih-Yen (2015) present an alternative answer to most of the studies included in this literature review. It states that PPIs do not have an effect on weight. The goal of this study was to evaluate whether PPI use is related to weight gain in adults older than 40 years of age. 25 patients who had a normal BMI and *H. pylori* gastric ulcer proven by upper endoscopy were recruited for this study. All patients were treated for H. pylori with rabeprazole 20 mg twice daily, as well as clarithromycin 500 mg twice daily and amoxicillin 1000 mg twice daily for seven days. After antibiotic treatment was complete, patients continued rabeprazole 20 mg once daily for four months. After four months, BMI and body weight were obtained as well as upper endoscopy to confirm *H. pylori* eradication. The results showed there was no significant change in body weight or BMI associated with PPI use or *H. pylori* eradication. Nineteen of the 25 patients had eradicated *H. pylori*. The strength of this study was the consistent treatment

between all study individuals. The limitation of this study was its small sample size and lack of information regarding diet. Antibiotics were also used in this study which are known to affect gastrointestinal flora, and therefore may impact weight.

As discussed in Normal GI Flora Associated with Weight Loss, Mailhe et al. (2018) shows that the change in gastrointestinal pH due to PPIs changes the microbiota diversity. Patients using PPIs had greater bacterial diversity ($p<0.001$). In other studies, the higher diversity is associated with weight loss.

PPI use is associated with weight loss in the study by Shin et al. (2016). The results showed that "rats treated with lansoprazole showed significantly reduced body weight compared to controls (322.3±15.3 g vs 403.2±5.2 g, $p<0.001$)." It also showed *Firmicutes* was the predominant bacterial phylum associated with weight loss/PPI use as discussed under Normal GI Flora Associated with Weight Loss. This study disagreed with many other studies which found that increased *Bacteroides*, not *Firmicutes*, was associated with weight loss. However, this study was performed on rats and therefore may not translate to human studies.

As discussed in Normal GI Flora Associated with Weight Gain, Stark et al. (2019) found that PPIs have a greater influence on weight than either H2RAs or antibiotics. The goal of this study was to investigate the association of antibiotic, histamine-2 receptor antagonist, and proton pump inhibitor prescriptions during early childhood with a diagnosis of obesity. An exposure was considered a prescription for an antibiotic, H2RA, or PPI in the first 2 years of life. Obesity was defined by the US CDC as a BMI greater than or equal to the 95th percentile for age and sex. Of the 333,353 children, 11.8% were prescribed H2Ras, 3.3% were prescribed PPIs, and 72.4% were prescribed antibiotics. Fourteen point one percent developed obesity with the median age (P25-P75) for the first reading being 3.03 (2.27-4.07). Eleven percent of the children

who developed obesity were not exposed to any of the medications. For PPI prescriptions, the percent of obesity was greater than either H2RAs or antibiotics (16.6% compared to 15.1% and 15.3% respectively). For PPI prescriptions, the incidence density of obesity was 3.85, the unadjusted HR (95% CI) was 1.04 (1.03-1.05), and the adjusted HR (95% CI) was 1.02 (1.01-1.03). We must also remember that this study lacked information regarding if the patient actually took the medication prescribed, as this study only considered prescriptions that were filled. Medications could have also been purchased or obtained outside of TRICARE such as in the ER or urgent care setting.

PPI use was associated with decreased weight loss according to Ward et al. (2014). Patients using PPIs had poorer weight loss than non-PPI users (percent weight loss of 27.4 ± 4.6 % compared to 31.1 ± 8.0 %, and percent excess weight loss of 49.3 ± 9.0 % compared to 61.4 ± 2.0 %). This could be due to the finding of increased *Firmicutes* and a decrease in *Bacteroidetes,* which is associated with an obese profile in other studies. Refer back to Ward under Normal GI Flora Associated with Weight Gain for the complete data.

PPI use was correlated with weight gain in the study by Yoshikawa, Nagato, Yamasaki, Kume, and Otsuki (2009). The goal of this study was to examine how PPI use affects weight and BMI in patients being treated for GERD. 52 patients with GERD and 58 age- and sex- matched controls in Japan were selected between June and November of 2005. The patients with GERD were treated with PPIs between 0.8 and 5.7 years and were also advised on lifestyle modifications such as avoiding overeating, decrease fat intake, elevate the head of their bed, stop smoking, avoid laying down after eating for at least three hours, and body weight control. The controls did not have reflux symptoms, were not using PPIs or H2 antagonists, and had annual follow up visits. The controls did not receive lifestyle modification advice. The PPIs used were

omeprazole (20 mg), rabeprazole (20 mg), or lansoprazole (30 mg) once daily for eight weeks followed by a daily half-dose maintenance therapy. Every four weeks the GERD patients were monitored for their symptoms and either taken off of the PPI or placed back on it. At baseline (four weeks before the start of the study) and at the end of treatment, GERD patients and the controls had weight, height, blood pressure, fasting total protein, total cholesterol, and triglycerides measured. The results showed a significant weight gain ($P < 0.0001$) and increased BMI ($P < 0.0005$) between baseline and their last visit in patients who were treated with PPIs. There was no significant change in weight or BMI in the control group. Ninety-one percent of the control groups weight remained stable compared to only 60% of the PPI group. Thirty-six percent of the PPI treated group gained greater than 5% of their baseline weight as compared to only 4% of the control group ($P < 0.0001$). The strengths of this study were the large sample size and the similarities between the treatment group and the control group in regard to demographics. The limitations of this study were the lack of control of time of PPI treatment, the type and dose of PPI, and the lack of information regarding adherence to lifestyle modifications.

Alternative Treatments and the Effects on GI Flora or Weight

The study by Hou et al. (2017), discussed in previous sections, not only showed various bacteria associated with obesity and with healthy weight in children, it also shows that dietary change as a method of weight reduction can influence the gastrointestinal microbiota. It showed that the amount of *Bifidobacterium* and *Lactobacillus* increased during weight reduction (Wilcoxon's rank sum test, $P <0.01$). Both of these bacteria are commonly found in probiotics.

Ilhan et al. (2017) shows that RYGB is the best surgical method for weight loss. The results showed that percent excess weight loss was significantly higher for the RYGB group than the LAGB group ($P<0.05$). This can be explained by the higher gastric pH in RYGB patients,

which allows for greater microbial diversity because it increases the chance of survival of acid-sensitive microorganisms. Greater microbial diversity in other studies has been associated with a decreased risk of obesity. This study found that RYGB had higher microbial diversity than LAGB or pre-surgical patients ($P<0.05$).

H2RAs may be an alternative solution to decreasing gastric acid that have less of an effect on weight than PPIs. This is supported by the results found in Stark et al. (2019). Stark et al. found that PPIs have a greater influence on weight than either H2RAs or antibiotics. For PPI prescriptions, the percent of obesity was greater than either H2RAs or antibiotics (16.6% compared to 15.1% and 15.3% respectively). As discussed in previous sections, the goal of this study was to investigate the association of antibiotic, histamine-2 receptor antagonist, and proton pump inhibitor prescriptions during early childhood with a diagnosis of obesity.

As discussed in the prior theme, PPI use was correlated with weight gain in the study by Yoshikawa et al. (2009). This study also offered alternative solutions to treating GERD. Lifestyle management may be not only an addition to PPI therapy, but also an alternative to PPI therapy. Lifestyle modifications include dietary changes, sleep position modifications, smoking cessation, and weight control. Patients with GERD in this study were advised on lifestyle modifications such as avoiding overeating, decreasing fat intake, elevating the head of their bed, stop smoking, avoid laying down after eating for at least three hours, and body weight control.

Discussion

Proton pump inhibitors (PPIs) are a first line treatment for patients who have conditions related to over production of gastric acid such as gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD). According to Mayo Clinic, obesity puts patients at a greater risk for

developing GERD; therefore, it is important that the medications a patient takes to treat GERD will not cause further weight gain.

PPIs work by irreversibly binding to the hydrogen potassium adenosine triphosphatase enzyme (proton pump) in the parietal cells of the stomach (Ambizas & Etzel, 2017). This binding suppresses acid production, which raises the pH of the stomach. Stomach acid is known to be a protective mechanism against pathogens trying to colonize lower parts of the gastrointestinal tract (Ambizas & Etzel, 2017). If the acidity is suppressed, microorganisms from the oral cavity and from the food we eat are able to survive into the lower parts of the GI tract. One of the microorganisms found to be increased in the lower parts of the GI tract after PPI use is *Streptococcaceae*. Of the studies investigating PPIs effects on normal GI flora, 14 of 18 found that *Streptococcaceae* was increased with PPI use. *Streptococcaceae* is abundant in the oral cavity, but it is usually destroyed by gastric acid (Bajaj et al., 2014). The suppression of gastric acid by PPIs appears to allow *Streptococcaceae* to survive past the stomach.

Streptococcaceae belongs to the phylum *Firmicutes*. *Firmicutes* is found to be associated with an obese profile according to four of the five studies investigating normal GI flora associated with weight gain. Combining these results, we see that the use of PPIs increases *Streptococcaceae* of *Firmicutes,* which is associated with an obese profile or weight gain, and therefore it appears that PPI use may lead to weight gain. This result is supported by four of the seven studies investigating PPIs effect on weight. Of the three studies that did not support weight gain with PPI use, one found PPIs had no effect on weight and two found PPI use was correlated with weight loss. Mailhe et al. found that the weight loss was due to the greater microbial diversity with PPI use. Shin et al. found PPI use was associated with weight loss in a study conducted on rats. The four studies correlating with weight gain were performed on humans.

By combining the results found in this literature review, it appears that PPI use is more likely to lead to weight gain than weight loss. Alternative treatment options may be preferred for people who are struggling with obesity. Some of those treatment options may include H2 antagonists, lifestyle modifications, or surgical intervention. Another option may be utilizing probiotics with PPIs to balance the effects on GI flora. Although further research needs to be performed on probiotic use, some bacteria that may be useful in weight loss are *Akkermansia* and *Bacteroides. Lactobacillus* is a common bacterium used in current probiotics, but it is unclear if *Lactobacillus* is associated with weight loss or weight gain as there are conflicting results in the studies included in this literature review.

In conclusion, PPI use appears to increase *Streptococcaceae* of *Firmicutes,* leading to weight gain. People who are overweight should consider alternative or combined treatments.

Applicability to Clinical Practice

With the information provided in this literature review, providers will be able to choose whether PPIs are right for their patients suffering from conditions related to elevated gastric acid. They will be able to accurately disclose to their patients how weight is affected with PPI use. By knowing how PPIs affect weight, patients will be able to make lifestyle modifications should they choose to continue using PPIs. Patients may also choose alternative treatments such as H2 receptor antagonists. With further research, probiotics may prove beneficial in conjunction with PPIs.

References

Adult Obesity Facts | Overweight & Obesity | CDC. (2019, January 31). https://www.cdc.gov/obesity/data/adult.html

Ambizas, E., Etzel, J. (2017). Proton Pump Inhibitors: Considerations With Long-Term Use. US Pharm: 42(7), 4-7. https://www.uspharmacist.com/article/proton-pump-inhibitors-considerations-with-longterm-use

Bajaj, J., Cox, I., Betrapally, N., Heuman, D., Schubert, M., Ratneswaran, M., … Gillevet, P. (2014). Systems biology analysis of omeprazole therapy in cirrhosis demonstrates significant shifts in gut microbiota composition and function. American Journal of Physiology. Gastrointestinal and Liver Physiology, 307(10), G951-957. https://doi.org/10.1152/ajpgi.00268.2014

Castellani, C., Singer, G., Kashofer, K., Huber-Zeyringer, A., Flucher, C., Kaiser, M., & Till, H. (2017). The Influence of Proton Pump Inhibitors on the Fecal Microbiome of Infants with Gastroesophageal Reflux-A Prospective Longitudinal Interventional Study. Frontiers in Cellular and Infection Microbiology, 7, 444. https://doi.org/10.3389/fcimb.2017.00444

Clooney, A., Bernstein, C., Leslie, W., Vagianos, K., Sargent, M., Laserna-Mendieta, E., … Targownik, L. (2016). A comparison of the gut microbiome between long-term users and non-users of proton pump inhibitors. Alimentary Pharmacology & Therapeutics, 43(9), 974–984. https://doi.org/10.1111/apt.13568

Czwornog, J., & Austin, G. (2015). Association of Proton Pump Inhibitor (PPI) Use with Energy Intake, Physical Activity, and Weight Gain. Nutrients, 7(10), 8592–8601. https://doi.org/10.3390/nu7105416

Dao, M., Everard, A., Aron-Wisnewsky, J., Sokolovska, N., Prifti, E., Verger, E., … Clément, K. (2016). Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: Relationship with gut microbiome richness and ecology. Gut, 65(3), 426–436. https://doi.org/10.1136/gutjnl-2014-308778

Factors Affecting Weight & Health | National Institute of Diabetes and Digestive and Kidney Diseases. (n.d.). U.S. Department of Health and Human Services. NIH website: https://www.niddk.nih.gov/health-information/weight-management/adult-overweight-obesity/factors-affecting-weight-health

Freedberg, D., Toussaint, N., Chen, S., Ratner, A., Whittier, S., Wang, T., Wang, H., Abrams, J. (2015). Proton Pump Inhibitors Alter Specific Taxa in the Human Gastrointestinal Microbiome: A Crossover Trial. Gastroenterology.149(4):883-5.e9. https://doi.org/10.1053/j.gastro.2015.06.043.

Gommers, L., Ederveen, T., van der Wijst, J., Overmars-Bos, C., Kortman, G., Boekhorst, J., … Hoenderop, J. (2019). Low gut microbiota diversity and dietary magnesium intake are associated with the development of PPI-induced hypomagnesemia. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 33(10), 11235–11246. https://doi.org/10.1096/fj.201900839R

Hojo, M., Asahara, T., Nagahara, A., Takeda, T., Matsumoto, K., Ueyama, H., … Watanabe, S. (2018). Gut Microbiota Composition Before and After Use of Proton Pump Inhibitors. Digestive Diseases and Sciences, 63(11), 2940–2949. https://doi.org/10.1007/s10620-018-5122-4

Hou, Y., He, Q., Ouyang, H., Peng, H., Wang, Q., Li, J., … Yin, A. (2017). Human Gut Microbiota Associated with Obesity in Chinese Children and Adolescents. BioMed

Research International, 2017, 7585989. https://doi.org/10.1155/2017/7585989

Hsien-Hao, H., Harn-Shen, C., Chih-Yen, C. (2015). Association of short-term proton pump inhibitor therapy with weight gain in patients older than 40 years with gastric ulcer. Surgery for Obesity and Related Diseases. 11(5), 1187-1189. https://www-clinicalkey-com.ezproxylr.med.und.edu/#!/content/journal/1-s2.0-S1550728915001562

Ilhan, Z., DiBaise, J., Isern, N., Hoyt, D., Marcus, A., Kang, D., … Krajmalnik-Brown, R. (2017). Distinctive microbiomes and metabolites linked with weight loss after gastric bypass, but not gastric banding. The ISME Journal, 11(9), 2047–2058. https://doi.org/10.1038/ismej.2017.71

Imhann, F., Bonder, M., Vich Vila, A., Fu, J., Mujagic, Z., Vork, L., … Zhernakova, A. (2016). Proton pump inhibitors affect the gut microbiome. Gut, 65(5), 740–748. https://doi.org/10.1136/gutjnl-2015-310376

Jackson, M., Goodrich, J., Maxan, M., Freedberg, D., Abrams, J., Poole, A., Sutter, J., Welter, D., Ley, R., Bell, J., Spector, T., Steves, C. (2016) Proton pump inhibitors alter the composition of the gut microbiota. Gut. 65(5):749-56. https://doi.org/10.1136/gutjnl-2015-310861

Koo, S., Deng, J., Ang, D., Hsiang, J., Lee, L., Aazmi, S., … Ang, T. (2018). Effects of proton pump inhibitor on the human gut microbiome profile in multi-ethnic groups in Singapore. Singapore Medical Journal. https://doi.org/10.11622/smedj.2018152

Mailhe, M., Ricaboni, D., Vitton, V., Gonzalez, J., Bachar, D., Dubourg, G., … Raoult, D. (2018). Repertoire of the gut microbiota from stomach to colon using culturomics and next-generation sequencing. BMC Microbiology, 18(1), 157. https://doi.org/10.1186/s12866-018-1304-7

Menni, C., Jackson, M., Pallister, T., Steves, C., Spector, T., & Valdes, A. (2017). Gut microbiome diversity and high-fibre intake are related to lower long-term weight gain. International Journal of Obesity (2005), 41(7), 1099–1105. https://doi.org/10.1038/ijo.2017.66

Mishiro, T., Oka, K., Kuroki, Y., Takahashi, M., Tatsumi, K., Saitoh, T., … Kinoshita, Y. (2018). Oral microbiome alterations of healthy volunteers with proton pump inhibitor. Journal of Gastroenterology and Hepatology, 33(5), 1059–1066. https://doi.org/10.1111/jgh.14040

Muñiz Pedrogo, D., Jensen, M., Van Dyke, C., Murray, J., Woods, J., Chen, J., … Nehra, V. (2018). Gut Microbial Carbohydrate Metabolism Hinders Weight Loss in Overweight Adults Undergoing Lifestyle Intervention with a Volumetric Diet. Mayo Clinic Proceedings, 93(8), 1104–1110. https://doi.org/10.1016/j.mayocp.2018.02.019

Nadal, I., Santacruz, A., Marcos, A., Warnberg, J., Garagorri, J. M., Garagorri, M., … Sanz, Y. (2009). Shifts in clostridia, bacteroides and immunoglobulin-coating fecal bacteria associated with weight loss in obese adolescents. International Journal of Obesity (2005), 33(7), 758–767. https://doi.org/10.1038/ijo.2008.260

Parsons, B., Ijaz, U., D'Amore, R., Burkitt, M., Eccles, R., Lenzi, L., … Pritchard, D. (2017). Comparison of the human gastric microbiota in hypochlorhydric states arising as a result of Helicobacter pylori-induced atrophic gastritis, autoimmune atrophic gastritis and proton pump inhibitor use. PLoS Pathogens, 13(11). https://doi.org/10.1371/journal.ppat.1006653

Sanmiguel, C., Jacobs, J., Gupta, A., Ju, T., Stains, J., Coveleskie, K., … Labus, J. S. (2017). Surgically Induced Changes in Gut Microbiome and Hedonic Eating as Related to

Weight Loss: Preliminary Findings in Obese Women Undergoing Bariatric Surgery. Psychosomatic Medicine, 79(8), 880–887. https://doi.org/10.1097/PSY.0000000000000494

Seto, C., Jeraldo, P., Orenstein, R., Chia, N., DiBaise, J. (2014). Prolonged use of a proton pump inhibitor reduces microbial diversity: Implications for Clostridium difficile susceptibility. Microbiome. 25;2:42. https://doi.org/10.1186/2049-2618-2-42

Shi, Y., Cai, S., Tian, Y., Zhao, H., Zhang, Y., Chen, J., … Yang, Y. (2019). Effects of Proton Pump Inhibitors on the Gastrointestinal Microbiota in Gastroesophageal Reflux Disease. Genomics, Proteomics & Bioinformatics, 17(1), 52–63. https://doi.org/10.1016/j.gpb.2018.12.004

Shin, C., Kim, N., Kim, Y., Nam, R., Park, J., Lee, D., … Jung, H. (2016). Impact of Long-Term Proton Pump Inhibitor Therapy on Gut Microbiota in F344 Rats: Pilot Study. Gut and Liver, 10(6), 896–901. https://doi.org/10.5009/gnl15529

Stark, C., Susi, A., Emerick, J., & Nylund, C. (2019). Antibiotic and acid-suppression medications during early childhood are associated with obesity. Gut, 68(1), 62–69. https://doi.org/10.1136/gutjnl-2017-314971

Sterbini, F., Palladini, A., Masucci, L., Cannistraci, C., Pastorino, R., Ianiro, G., Bugli, F., Martini, C., et. al. (2016). Effects of Proton Pump Inhibitors on the Gastric Mucosa-Associated Microbiota in Dyspeptic Patients. Applied and Environmental Microbiology. https://doi.org/10.1128/AEM.01437-16

Takagi, T., Naito, Y., Inoue, R., Kashiwagi, S., Uchiyama, K., Mizushima, K., … Itoh, Y. (2018). The influence of long-term use of proton pump inhibitors on the gut microbiota: An age-sex-matched case-control study. Journal of Clinical Biochemistry and Nutrition,

62(1), 100–105. https://doi.org/10.3164/jcbn.17-78

Ward, E., Schuster, D., Stowers, K., Royse, A., Ir, D., Robertson, C., … Austin, G. (2014). The Effect of PPI Use on Human Gut Microbiota and Weight Loss in Patients Undergoing Laparoscopic Roux-en-Y Gastric Bypass. Obesity Surgery, 24(9), 1567–1571. https://doi.org/10.1007/s11695-014-1275-1

Yamamoto, K., Ishigami, M., Honda, T., Takeyama, T., Ito, T., Ishizu, Y., … Hirooka, Y. (2019). Influence of proton pump inhibitors on microbiota in chronic liver disease patients. Hepatology International, 13(2), 234–244. https://doi.org/10.1007/s12072-019-09932-9

Yoshikawa, I., Nagato, M., Yamasaki, M., Kume, K., & Otsuki, M. (2009). Long-term treatment with proton pump inhibitor is associated with undesired weight gain. World Journal of Gastroenterology : WJG, 15(38), 4794–4798. https://doi.org/10.3748/wjg.15.4794