Proton pump inhibitor use associated with changes in gut microbiota composition

We read with great interest the recent publications in Gut by Imhann *et al* and Jackson *et al*, which assessed the impact of proton pump inhibitor (PPI) use on gut microbiota diversity and composition in humans.[1 2] PPIs are one of the most commonly used drug classes worldwide. Once initiated, they are often used chronically without clear therapeutic intent.[3] PPIs alter GI pH[4] and delay gastric emptying rate,[5] which could directly affect gut microbiota and survival of enteric pathogens. Using three independent cohorts (211 PPI users and 1604 non-users), Imhann *et al*[1] reported a significant decrease in alpha diversity and changes in 20% of bacterial taxa in PPI users compared with non-users. Among 1827 healthy twins, Jackson *et al*[2] also found a significant decrease in alpha diversity and alteration of bacterial composition in PPI users. Notably, both studies found a higher abundance of oral commensals, including *Streptococcaceae*, among PPI users. These studies controlled for some potential confounders in their analyses; however, intersubject variability could have influenced their results.

We assessed the impact of PPI use on the gut microbiota composition in a prospective study of healthy older adults (age ≥60 years) from San Antonio, Texas, USA. Participants provided a stool sample at baseline, completed a 14-day course of omeprazole 20 mg daily and then provided a follow-up stool sample. Stool 16s rRNA V4 sequences were amplified and sequenced on the Illumina MiSeq platform. Sequences were clustered into operational taxonomic units (OTUs) and classified via mothur's Bayesian classifier referenced against the Greengenes database. Abundance-weighted sample differences were calculated using the Bray-Curtis dissimilarity. PERMANOVA was used to assess the impact of PPI use on beta diversity.

A total of 24 subjects completed the study (mean age 71.4 years and 62.5% women). Mean (±SD) OTU richness was similar between pre-PPI (485±84.3) and post-PPI (496±88.7) samples (p=0.32). Additionally, Shannon diversity was not statistically different between pre-PPI (3.86±0.27) and post-PPI (3.92±0.31)

Table 1 Comparison of taxa relative abundance in pre-PPI and post-PPI samples

Bacteria*	Pre-PPI mean (SD)	Post-PPI mean (SD)	p Value
Phylum			
Firmicutes	70.70 (10.40)	69.00 (10.40)	0.5531
Bacteroidetes	20.60 (12.30)	24.00 (10.70)	0.0914
Actinobacteria	**4.25 (4.76)**	**2.35 (2.44)**	**0.0059**
Proteobacteria	2.51 (2.96)	3.01 (2.55)	0.2296
Verrucomicrobia	1.14 (4.22)	1.10 (2.80)	0.7726
Euryarchaeota	0.65 (1.75)	0.20 (0.54)	0.3242
Tenericutes	0.13 (0.44)	0.22 (0.71)	0.2708
Cyanobacteria	0.02 (0.08)	0.04 (0.11)	0.4591
Family			
Lachnospiraceae	**33.40 (20.50)**	**28.60 (7.70)**	**0.0059**
Ruminococcaceae	20.50 (9.35)	21.30 (7.98)	0.6373
Bacteroidaceae	13.40 (10.70)	14.90 (9.33)	0.1961
Streptococcaceae	**1.49 (1.91)**	**5.93 (5.30)**	**0.0009**
Prevotellaceae	3.21 (8.23)	4.09 (9.87)	0.6814
Erysipelotrichaceae	**4.09 (3.30)**	**2.74 (3.69)**	**0.0132**
Bifidobacteriaceae	**2.83 (4.39)**	**1.39 (2.09)**	**0.0275**
Rikenellaceae	1.61 (1.23)	2.14 (1.90)	0.0914

Bold values indicate statistical significance at p<0.05.
*Table includes only the eight most commonly identified phyla and families.
PPI, proton pump inhibitor.

samples (p=0.28). Pre-PPI samples had significantly higher relative abundance of the phylum Actinobacteria and the families *Lachnospiraceae*, *Erysipelotrichaceae* and *Bifidobacteriaceae* (table 1). Post-PPI samples had significantly higher abundance of *Streptococcaceae*. Beta diversity was significantly associated with PPI use (p<0.0001).

In line with our findings, Jackson *et al*[2] found higher *Streptococcaceae* and lower *Lachnospiraceae* and *Erysipelotrichaceae* abundance in PPI users compared with non-users. Imhann *et al*[1] also noted that PPI users had enrichment for *Streptococcaceae*, but a lower abundance of *Bifidobacteriaceae*. Of note, decreased *Bifidobacterium* is associated with *Clostridium difficile* infection (CDI),[6] whereas supplementation with *Bifidobacterium* is associated with reduced risk of developing CDI in humans.[7] Similarly, the abundance of *Streptococcaceae* is significantly increased in CDI, while *Lachnospiraceae* are reduced compared with healthy controls.[8] While studies have been somewhat inconsistent, a 2012 meta-analysis of 42 studies found that PPI use was associated with an increased risk for initial and recurrent CDI.[9] This led the US Food and Drug Administration to issue a drug safety warning in 2012 regarding this association. Changes in gut microbiota composition could help explain this association. Our findings, in addition to those of Imhann *et al* and Jackson *et al*, highlight the potential for PPIs to affect health through alteration of the gut microbiota and the need to limit inappropriate and unnecessary use of PPIs.

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