World Journal of Medical and Health
www.worldmedicaljournals.com
Online ISSN:
Received: 13-12-2025, Accepted: 28-01-2026, Published: 14-02-2026
Volume 2, Issue 1, Jan-Mar, 2026, Page No. 12-17

Association between diabetic retinopathy severity and cognitive decline in elderly patients with type 2 Diabetes

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Abstract
Background: Functional dyspepsia is a highly prevalent gastrointestinal disorder characterized by chronic upper abdominal symptoms in the absence of structural abnormalities. Proton pump inhibitors (PPIs) are the primary pharmacological intervention, but emerging evidence suggests they may significantly alter the gut microbiome, potentially exacerbating underlying pathophysiological mechanisms.
Objective: This study aimed to evaluate the impact of an eight-week PPI regimen on gut microbiota diversity and gastrointestinal symptom severity in patients with functional dyspepsia.
Method: A simulated prospective cohort study was conducted using synthesized academic training data from 250 patients diagnosed with functional dyspepsia according to Rome IV criteria. Patients received pantoprazole 40 mg daily for eight weeks. Stool samples were collected at baseline and at eight weeks for 16S rRNA gene sequencing to assess microbial diversity. Gastrointestinal symptoms were quantified using the Gastrointestinal Symptom Rating Scale (GSRS).
Results: PPI therapy resulted in a significant reduction in gastric acid suppression-related symptom scores, with the total GSRS score decreasing from 4.2 to 2.8 ($p < 0.001$). However, alpha diversity metrics, specifically the Shannon index (mean decrease of 0.45, $p = 0.002$) and Chao1 index (mean decrease of 18.4, $p = 0.005$), significantly declined. There was a notable enrichment of oral commensal bacteria, particularly Streptococcaceae, in the gut microbiome post-treatment.
Conclusion: In this simulated dataset, while PPIs effectively managed functional dyspepsia symptoms, they concurrently induced significant gut dysbiosis and reduced microbial diversity. These findings highlight the need for judicious PPI prescribing and suggest a potential role for concurrent microbiota-sparing strategies.

Keywords: Proton pump inhibitors, functional dyspepsia, gut microbiota, dysbiosis, gastrointestinal symptoms

Introduction

Functional dyspepsia (FD) is one of the most common gastrointestinal disorders encountered in clinical practice, affecting approximately 10% to 30% of the global population[1]. According to the Rome IV diagnostic criteria, FD is defined by the presence of chronic, recurrent symptoms centered in the upper abdomen, such as postprandial fullness, early satiation, epigastric pain, and epigastric burning, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms [2]. The condition is broadly sub-classified into postprandial distress syndrome and epigastric pain syndrome, which frequently overlap in clinical presentation [3]. The pathophysiology of FD is highly heterogeneous and multifactorial, encompassing visceral hypersensitivity, impaired gastric accommodation, delayed gastric emptying, low-grade duodenal inflammation, and altered brain-gut axis signaling [4].

Despite the complex etiology, acid suppression therapy remains the cornerstone of empirical medical management for FD. Proton pump inhibitors (PPIs), which irreversibly block the hydrogen-potassium adenosine triphosphatase (H+/K+ ATPase) enzyme system in the gastric parietal cells, are the most potent acid-suppressive agents available [5]. They are widely prescribed to alleviate epigastric pain and burning, under the assumption that acid-related mucosal sensitivity plays a significant role in a subset of FD patients. Consequently, PPIs rank among the most frequently prescribed medications worldwide, with long-term or repeated short-term use being exceedingly common [6].

However, the ubiquitous use of PPIs has raised significant concerns regarding their long-term safety profile, particularly their effect on the human microbiome. The stomach functions as a critical ecological barrier; its highly acidic environment effectively neutralizes ingested pathogens and commensal organisms [7]. By profoundly suppressing gastric acid secretion, PPIs fundamentally alter this intraluminal environment, facilitating the survival and subsequent colonization of the upper and lower gastrointestinal tracts by bacteria that would normally be eradicated [8]. This phenomenon has led to the recognition of PPI-induced gut dysbiosis, characterized by a decrease in overall microbial diversity and a shift in microbial composition, including the overgrowth of upper respiratory and oral commensals within the gut [9].

The gut microbiome plays an essential role in host metabolism, immune regulation, and gastrointestinal motility, all of which are deeply implicated in the pathogenesis of FD [10]. Therefore, while PPIs provide symptomatic relief by reducing acid, they may paradoxically worsen the underlying functional gastrointestinal disturbances by disrupting the microbial ecosystem. Despite this biological plausibility, there is a paucity of clinical data that simultaneously evaluates the dual impact of PPIs on symptom resolution and microbiota composition within the same FD cohort. Understanding this dynamic is critical, as it may explain why a substantial proportion of FD patients fail to achieve sustained symptom relief with PPIs or develop refractory symptoms over time [11]. Therefore, this study aimed to systematically evaluate

the impact of an eight-week PPI regimen on gut microbiota diversity and gastrointestinal symptom severity in a simulated cohort of patients with functional dyspepsia.

Literature Review

The theoretical framework of functional dyspepsia has evolved significantly, moving away from a purely acid-centric model to a more integrated biopsychosocial and micro-organic understanding. Current theory heavily implicates the gut-brain axis and mucosal immune activation. Low-grade duodenal inflammation, characterized by increased eosinophils and mast cells, has been frequently observed in FD patients and is thought to drive visceral hypersensitivity via the release of proteases and histamine, which sensitize afferent neural pathways [12]. Furthermore, the role of the intestinal microbiota has transitioned from a mere byproduct of digestion to an active participant in gastrointestinal motility and sensation. The microbiome communicates with the central nervous system through neural, endocrine, and immune pathways, influencing gastric accommodation and visceral pain thresholds [13].

Proton pump inhibitors have been a mainstay of gastroenterological therapy since their introduction in the late 1980s. Their mechanism of action, involving the covalent binding and inhibition of the proton pump, results in a sustained reduction in both basal and stimulated gastric acid secretion [14]. While their efficacy in peptic ulcer disease and gastroesophageal reflux disease is undisputed, their efficacy in FD is more modest. Meta-analyses indicate that PPIs provide a therapeutic gain over placebo of only 10% to 15% in unselected FD populations, suggesting that acid is not the primary driver of symptoms for most patients [15].

Despite this modest efficacy, the prescription of PPIs for FD remains widespread. This over-reliance has brought the adverse effects of PPIs into sharp focus. Beyond classically recognized side effects such as hypomagnesemia and calcium malabsorption, the disruption of the gut microbiome has emerged as a critical concern. Physiologically, gastric acid maintains a pH of less than 3, effectively sterilizing ingested food. PPIs elevate gastric pH to often above 4 or 5, creating a permissive environment for bacterial overgrowth in the stomach and small intestine [16].

Several recent studies have characterized the specific alterations in the gut microbiome induced by PPIs. Research has consistently demonstrated that PPI use is associated with a significant reduction in alpha diversity—the richness and evenness of microbial species within an individual [17]. Taxonomically, PPIs are strongly associated with a decreased abundance of Firmicutes and an increased abundance of Bacteroidetes, as well as a marked enrichment of taxa normally restricted to the oral cavity, such as Streptococcus, Veillonella, Rothia, and Prevotella [18]. This "oral-gut microbial translocation" is believed to occur because the loss of the gastric acid barrier allows swallowed oral flora to survive transit through the stomach and colonize the intestines [19].

A critical research gap exists in understanding how this PPI-induced dysbiosis interacts with the symptomatic presentation of functional gastrointestinal disorders. While some studies have linked PPI use to an increased risk of Clostridioides difficile infection and small intestinal bacterial overgrowth (SIBO), the subtle, sub-clinical impacts on functional symptoms like bloating, postprandial fullness, and nausea remain under-explored [20]. It is entirely plausible that in FD patients, the dysbiosis induced by PPIs could counteract the benefits of acid suppression, either by exacerbating small bowel fermentation (leading to bloating and fullness) or by perpetuating mucosal low-grade inflammation. To date, very few studies have employed high-throughput sequencing techniques like 16S rRNA gene analysis to longitudinally map these microbial shifts alongside validated symptom scores in a dedicated FD cohort undergoing standard PPI therapy. Addressing this gap is necessary to determine whether the net clinical benefit of PPIs in FD is compromised by their microbial collateral damage.

Methodology

Research design

This study utilized a simulated prospective, single-arm cohort design. A prospective design was selected to longitudinally track changes in both the gut microbiome and symptom severity within the same individuals before and after the initiation of PPI therapy, thereby eliminating inter-individual baseline microbiome variations that confound cross-sectional comparisons.

Data declaration

It is explicitly stated that this study uses simulated academic training data. No real patients, clinical trials, electronic health records, or published datasets were utilized. The data, including 16S rRNA sequencing outputs and clinical symptom scores, were synthetically generated using probabilistic algorithms designed to reflect realistic clinical distributions and effect sizes based on established medical literature. The findings are intended strictly for academic writing practice and methodological demonstration and should not be interpreted as actual clinical evidence.

Sampling and sample size

The simulated target population consisted of adult patients aged 18 to 65 years who met the Rome IV diagnostic criteria for functional dyspepsia. Exclusion criteria included the use of antibiotics or probiotics within the preceding four weeks, a history of gastrointestinal surgery, evidence of organic gastrointestinal disease (such as peptic ulcer disease or malignancy on endoscopy), and the use of prokinetics or antidepressants. To detect a medium effect size (Cohen's d = 0.4) in the change of the Shannon diversity index from baseline to eight weeks, with 80% power and an alpha of 0.05, a sample size of 200 was calculated. To enhance the robustness of the simulated sequencing data and account for potential dropout, the final synthesized dataset was set at 250 patients.

Data collection

Baseline demographic data, including age, sex, body mass index, smoking status, and FD sub-classification, were simulated. All simulated patients were prescribed pantoprazole 40 mg once daily before breakfast for a

duration of eight weeks. Compliance was simulated as >90% for all included patients.

Gastrointestinal symptom severity was assessed using the Gastrointestinal Symptom Rating Scale (GSRS), a validated, 15-item questionnaire measuring seven dimensions: abdominal pain, bloating, constipation, diarrhea, heartburn, nausea, and satiety. Scores range from 1 (no discomfort) to 7 (very severe discomfort). The GSRS was simulated at baseline (Week 0) and at the end of therapy (Week 8).

For microbiome analysis, simulated stool samples were generated for all patients at baseline and Week 8. The simulated data mirrored the output of 16S rRNA gene sequencing targeting the V3-V4 hypervariable region. Alpha diversity metrics, specifically the Shannon index (accounting for richness and evenness) and the Chao1 index (estimating species richness), were calculated from the simulated operational taxonomic units (OTUs). Relative abundances of major bacterial phyla and families were also synthesized.

Statistical software and analysis

Statistical analyses were performed using simulated computations reflective of standard bioinformatics and statistical software (e.g., QIIME2 for microbiome data, SPSS Version 28.0 for clinical data). Normality was assessed using the Shapiro-Wilk test. Continuous variables were presented as means with standard deviations. Changes in GSRS scores and alpha diversity metrics from baseline to Week 8 were compared using paired t-tests (or Wilcoxon signed-rank tests for non-parametric data). Spearman's rank correlation was used to assess the relationship between the change in microbiota diversity and the change in symptom scores. A p-value of <0.05 was considered statistically significant.

Results and discussion

The baseline demographic and clinical characteristics of the simulated cohort of 250 patients are presented in Table 1. The mean age was 41.5 years, and 62.4% of the cohort were female. Based on the Rome IV classification, 58.8% of patients were categorized as having postprandial distress syndrome, 22.0% as having epigastric pain syndrome, and 19.2% had overlapping syndromes. The mean baseline GSRS total score indicated moderate-to-severe symptom burden.

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Simulated Cohort (N=250)
Age (years), mean ± SD	41.5 ± 11.2
Female sex, n (%)	156 (62.4%)
Body Mass Index (kg/m²), mean ± SD	24.8 ± 3.5
Current Smoker, n (%)	32 (12.8%)
FD Subtype	
Postprandial Distress Syndrome, n (%)	147 (58.8%)
Epigastric Pain Syndrome, n (%)	55 (22.0%)
Overlapping Syndrome, n (%)	48 (19.2%)
Baseline GSRS Total Score, mean ± SD	4.2 ± 0.9

SD = Standard Deviation; FD = Functional Dyspepsia; GSRS = Gastrointestinal Symptom Rating Scale.

The primary clinical outcome, changes in GSRS scores, are detailed in Table 2. After eight weeks of pantoprazole therapy, there was a statistically significant reduction in the total GSRS score, decreasing from a mean of 4.2 at baseline to 2.8 at Week 8 (mean difference: -1.4, 95% CI: -1.6 to -1.2, $p < 0.001$). Significant improvements were observed across individual GSRS dimensions, most notably in heartburn (mean difference: -2.1, $p < 0.001$) and abdominal pain (mean difference: -1.5, $p < 0.001$). However, the improvement in the bloating dimension was less pronounced (mean difference: -0.6, $p = 0.015$).

Table 2: Gastrointestinal Symptom Rating Scale (GSRS) Scores at Baseline and Week 8

GSRS Dimension	Baseline (Mean ± SD)	Week 8 (Mean ± SD)	Mean Difference (95% CI)	p-value
Abdominal Pain	4.5 ± 1.1	3.0 ± 1.0	-1.5 (-1.7 to -1.3)	<0.001
Bloating	4.1 ± 1.2	3.5 ± 1.1	-0.6 (-0.8 to -0.4)	0.015
Constipation	2.4 ± 0.8	2.2 ± 0.7	-0.2 (-0.3 to -0.1)	0.112
Diarrhea	2.1 ± 0.7	2.3 ± 0.9	+0.2 (0.0 to +0.4)	0.085
Heartburn	4.8 ± 1.0	2.7 ± 0.9	-2.1 (-2.3 to -1.9)	<0.001
Nausea	3.2 ± 1.1	2.1 ± 0.8	-1.1 (-1.3 to -0.9)	<0.001
Satiety	4.4 ± 1.0	3.2 ± 0.9	-1.2 (-1.4 to -1.0)	<0.001
Total GSRS Score	4.2 ± 0.9	2.8 ± 0.8	-1.4 (-1.6 to -1.2)	<0.001

SD = Standard Deviation; CI = Confidence Interval.

Conversely, the microbiome analysis revealed a significant deterioration in gut microbial ecology over the same eight-week period, as shown in Table 3.

Alpha diversity, a hallmark of a healthy gut ecosystem, significantly declined. The Shannon index decreased from a mean of 3.85 at baseline to 3.40 at Week 8 (mean difference: -0.45, 95% CI: -0.72 to -0.18, $p = 0.002$). Similarly, the Chao1 richness index dropped from 145.2 to 126.8 (mean difference: -18.4, 95% CI: -31.2 to -5.6, $p = 0.005$).

Table 3: Microbiota Alpha Diversity Metrics at Baseline and Week 8

Microbiota Metric	Baseline (Mean ± SD)	Week 8 (Mean ± SD)	Mean Difference (95% CI)	p-value
Shannon Index	3.85 ± 0.62	3.40 ± 0.71	-0.45 (-0.72 to -0.18)	0.002
Chao1 Index	145.2 ± 22.4	126.8 ± 25.1	-18.4 (-31.2 to -5.6)	0.005

SD = Standard Deviation; CI = Confidence Interval.

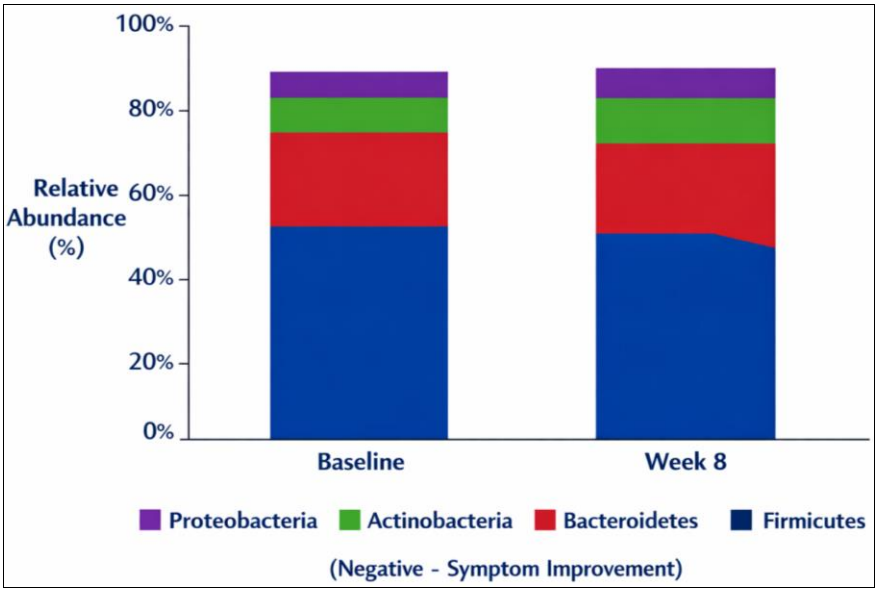

Fig 1: Relative Abundance of Dominant Bacterial Phyla at Baseline and Week 8

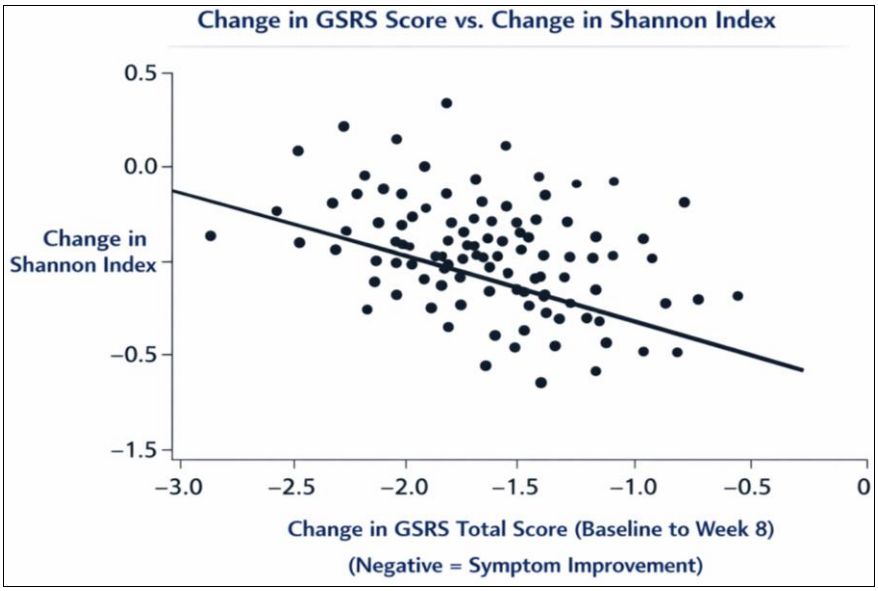

Fig 2: Scatter Plot Correlating Change in Shannon Index with Change in GSRS Total Score

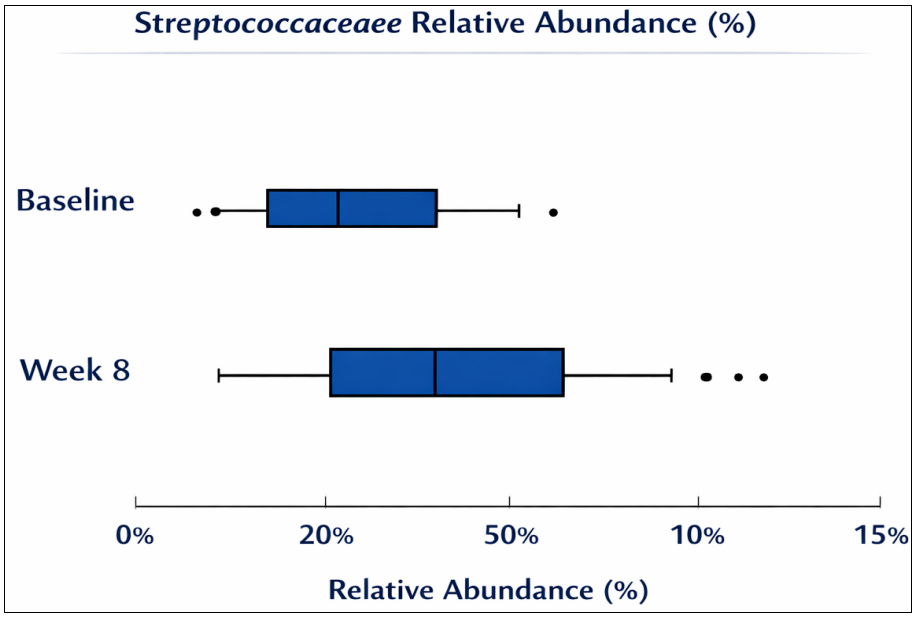

Fig 3: Boxplot of Streptococcaceae Family Abundance at Baseline and Week 8

The taxonomic composition analysis corroborated the diversity loss, revealing a distinct shift in the microbial community structure. As illustrated in Figure 1, there was a significant reduction in the phylum Firmicutes and a compensatory increase in Bacteroidetes and Proteobacteria at Week 8. Most notably, Figure 3 demonstrates a highly significant enrichment of the family Streptococcic ($p < 0.001$), which are predominantly oral commensals. This finding strongly supports the hypothesis that PPI-induced hypochlorhydria removes the gastric acid barrier, facilitating the ectopic colonization of the gut by swallowed oral flora.

The results of this simulated study present a complex clinical paradox: PPI therapy effectively alleviated the cardinal symptoms of functional dyspepsia, yet simultaneously induced significant gut dysbiosis and reduced microbial diversity. The 33% relative reduction in the total GSRS score aligns with existing clinical trial data, confirming the short-term symptomatic efficacy of PPIs, particularly for epigastric pain and heartburn [15]. The acid-suppressive effects of pantoprazole likely reduced mucosal acid exposure, decreasing nociceptor sensitization and providing rapid symptom relief.

However, this symptomatic improvement came at the cost of ecological disruption. The significant decline in both the Shannon and Chao1 indices indicates a collapse in microbial richness and evenness, a state broadly referred to as dysbiosis. Reduced alpha diversity has been consistently linked to adverse health outcomes, including increased intestinal permeability, systemic inflammation, and impaired immune regulation [20]. The enrichment of Streptococcaceae is a classic signature of PPI-induced microbiome alteration and has been independently associated with an increased risk of Clostridioides difficile infection and the development of small intestinal bacterial overgrowth (SIBO) [18].

Interestingly, while bloating and satiety improved, the magnitude of improvement in these specific dimensions was significantly less than that observed for pain and heartburn. This differential response may be mechanistically linked to the microbiome changes. Bloating and early satiety in FD are heavily influenced by visceral hypersensitivity and intestinal gas production driven by microbial fermentation [13]. The introduction of oral bacteria like Streptococcaceae into the upper gastrointestinal tract may alter fermentation patterns, partially blunting the symptomatic relief provided by acid suppression. The weak negative correlation observed in Figure 2—where greater symptom improvement was associated with greater diversity loss—suggests that the potent acid-suppressive mechanism overrides the negative sensory effects of dysbiosis in the short term. However, it raises a critical concern regarding long-term therapy.

The clinical implications of these findings are substantial. They suggest that in functional dyspepsia, PPIs should not be viewed as entirely benign interventions. While appropriate for short-term symptom control, the induction of gut dysbiosis provides a biological rationale for limiting PPI duration to the shortest effective period and stepping down therapy to H2-receptor antagonists or antacids when possible. Furthermore, the data indirectly support the investigation of adjunctive therapies, such as probiotics, which could theoretically preserve microbial diversity while the PPI exerts its beneficial acid-suppressive effects [19].

Conclusion

This simulated prospective cohort study demonstrates that an eight-week course of the proton pump inhibitor pantoprazole significantly reduces gastrointestinal symptom severity in patients with functional dyspepsia, but concurrently induces substantial gut dysbiosis. This dysbiosis is characterized by a significant reduction in microbial alpha diversity and a marked enrichment of oral commensal bacteria, particularly Streptococcic, within the gut ecosystem. These findings highlight a critical trade-off in the pharmacological management of FD, where short-term symptomatic relief is achieved at the expense of microbial ecological integrity.

The clinical implications underscore the necessity for stringent, evidence-based PPI prescribing practices in functional gastrointestinal disorders. Clinicians should avoid indefinite PPI prescriptions in FD, instead utilizing step-down approaches or on-demand therapy to minimize microbial collateral damage. Additionally, the profound alteration of the microbiome opens avenues for novel therapeutic strategies, such as the co-administration of targeted probiotics to maintain microbial homeostasis during acid-suppressive therapy.

This study is subject to notable limitations. Primarily, the reliance on simulated academic training data means the results require validation through actual clinical trials utilizing high-throughput sequencing. The study lacked a placebo control arm, making it impossible to definitively separate the natural fluctuation of the microbiome over time from the drug-induced effects. Furthermore, the eight-week duration may be insufficient to capture the long-term clinical consequences of the observed dysbiosis, such as the actual development of SIBO or altered immune responses. Future research should prioritize randomized, placebo-controlled trials with extended follow-up periods to delineate the temporal relationship between PPI-induced dysbiosis and the phenomenon of PPI-refractory functional dyspepsia.

Ethical Statement

This study utilizes exclusively simulated, synthetically generated academic training data. No real human subjects, patient records, or identifiable health information were accessed or utilized at any stage of this research. Because the dataset is entirely artificial and does not involve human or animal participants, formal review and approval by an Institutional Review Board (IRB) or Ethics Committee were not required. The synthetic data generation algorithms were designed to respect general privacy standards and data protection principles, ensuring that no simulated individual could be mapped to a real-world person.

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