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The regulatory effect of proton pump inhibitors combined with triple therapy on gut microbiota, visceral hypersensitivity and gastrointestinal hormone secretion disorders in elderly patients with non erosive gastroesophageal reflux disease

Kuanyu Nian and Dan Zhang*
Department of Surgery, Shaanxi Kangfu Hospital, Xi'an City, Shaanxi Province, China

Abstract: This study investigated the effects of Proton pump inhibitors (PPIs) combined with triple therapy on elderly non-erosive gastroesophageal reflux disease (NERD) patients. A total of 120 elderly patients diagnosed with NERD were divided into two groups: the study group received PPIs combined with triple therapy, while the control group received PPI monotherapy. Significant improvements were observed in the study group compared with the control group: gut microbiota diversity (Shannon Index: from 3.80±0.40 to 5.30±0.60), increased abundance of beneficial Lactobacillus and Bifidobacterium and reduced Enterococcus levels (All $p<0.001$). Visceral hypersensitivity scores showed increased pressure and pain thresholds ($p<0.001$) and reduced urgency and bloating ($p<0.05$). Gastrointestinal hormone such as motilin, ghrelin levels were increased (both $p<0.001$), and somatostatin was decreased ($p=0.034$). Systemic inflammatory markers such as IL-6, CRP, TNF-α, and IL-1β significantly declined, while anti-inflammatory IL-10 increased (All $p<0.001$). GERDQ scores improved more significantly in the study group ($p < 0.001$), and SF-36 quality of life domains reflected better physical and mental outcomes ($p<0.001$). These findings underscore the potential of combination therapy as a superior treatment strategy for elderly NERD patients, improving both clinical outcomes and quality of life. Further studies are warranted to explore long-term benefits and optimize treatment protocols.

Keywords: Elderly patients; Gut microbiota diversity; Non-erosive gastroesophageal reflux disease; Proton pump inhibitors; Quality of life

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INTRODUCTION

Non-erosive gastroesophageal reflux disease (NERD) is a common disorder in which reflux symptoms are present in patients who do not show any endoscopic evidence of esophageal mucosal injury. The quality of life is considerably reduced in this and is especially seen amongst the senior citizen population who tend to present with symptoms that are atypical and have multiple coexisting conditions that defy diagnosis and treatment (Zhang *et al*., 2021). The nature of NERD is therefore complex, and includes transient lower esophageal sphincter relaxations, heightened esophageal sensitivity and changes in GI motility (Chen *et al*., 2022). Avoidance of NSAIDs and the use of Proton pump inhibitors (PPIs) as the primary pharmacotherapy modality are an optimal treatment for NERD because they help to decrease gastric acid secretion and relieve symptoms (Li *et al*., 2020). Nevertheless, the use of PPIs as single drugs could be insufficient to cover all the underlying pathological changes in elderly patients and requires additional therapies. Triple therapy that includes PPI and two antibiotics, which was applied to H. pylori treatment, was considered to be useful for NERD treatment (Wang *et al*., 2023). Studies indicated that both PPIs and antibiotics are able to alter the gut microbiota that consists a large number of microorganisms in gastroesophageal (GI) tract (Liu *et al*., 2021). Abnormal alterations in gut microbiota have been recognized to be associated with different GI diseases including NERD by pathways like visceral hypersensitivity or the dysfunction of the regulation in the secretion of GI hormones (Zhao *et al*., 2022). This paper discusses how PPI-based triple therapy in elderly patients impacts on modulating gut microbiota, visceral sensitivity and secretion of GI hormones - knowledge that is necessary to enhance NERD treatment.

The gut microbiota is central to the regulation of the GI tract stability and immune systems regulation. Impairment in the microbial composition also known as dysbiosis has been proved to play a central role in the development of NERD. Some researchers have established that patients with NERD have less microbial diversity and more pathogenic bacteria in the groups; these bacteria contribute to the mucosal inflammation and thereby patients' demonstration of their symptoms (Chen *et al*., 2021). For example, Yang *et al*., (2023) have shown that NERD patients sustain depletion in the abundance of putative probiotics including Lactobacillus and Bifidobacterium, which can cause further intestinal permeability change and mucosal inflammation and thus worsen NERD.

**Corresponding author:* e-mail: ZhangD5765dan@hotmail.com

PPIs decrease gastric acidity which in turn affects the microorganisms found in the gut; the number of pathogenic bacteria, as well as fewer varieties of useful bacteria could increase (Zhang *et al*., 2020). Moreover, use of antibiotics in triple therapy complicates these effects, leading to outstanding microbial shifts (Li *et al*., 2022) (Fig 1). Kim *et al*. (2022) showed that PPI augments pathogenic bacterial load including Enterococcus and reduces the commensals further contributing to dysbiosis. Ghosh *et al*. (2023) also establish that PPI causes dysbiosis, including depletion of Akkermansia muciniphila which is necessary to maintain gut barrier health. These proceed to emphasise the rather complex association between the gut microbiota and gastrointestinal health, which should be incorporated into compliance approaches for the treatment of NERD. Hyperalgesia of referred visceral pain is a critical feature of NERD pathology (Wang *et al*., 2021). It was recognized that it is a multifaceted process involving the enteric nervous system and central pain modulation circuitries. The primary neural system that confirms the directions flow in the gut-brain axis is a two-way interaction that modifies visceral sensitization. The gut-brain axis comprises a communication system between the central nervous system and the GI tract. Disturbances in this axis, either microbiota-derived or related to fluctuations in the concentration of certain bacterial species, may increase pain sensitivity in NERD patients (Liu *et al*., 2020).

PPIs and antibiotics alter the gut microbiota which may affect output of specific metabolites that modulate visceral pain in the digestive tract (Zhao *et al*., 2021). Li *et al*. (2021) showed that augmenting NERD patient dysbiosis, there was enhanced tissue expression of transient receptor potential vanilloid 1 (TRPV1) receptor, which are implicated in the mediation of pain. Moreover, the medication with antibiotics as a part of triple therapy, can affect the sensitivity of the internal organs. Zhang *et al*. (2020) found out that dysbiosis caused by antibiotics increased the levels of pro-inflammatory cytokines thus increasing visceral hypersensitivity. In accordance with this development, Brown *et al*. (2023) discovered one of the effects of dysbiosis is a modification in serotonin synthesis by the gut, which exacerbates pain and hypersensitivity. Moreover, Nakamura, K.; Wang, L.; Li, Y. & Sudo, N. (2021) and Gupta, D.; Anhil, J.; Bhatnagar, J. & Kumar, S. (2023) also described how gut microbial metabolites SCFAs exert modulatory effects on visceral pain through neurons of the nociceptive system. These insights give some evidence on how to modify the composition of gut microbiota to regulate the visceral sensitivity to modify NERD symptoms. Gastric releasing peptide hormones such as gastrin, motilin and ghrelin exert GI functions and GI motility. These hormones secretions were seen to be changed in the bodies of the NERD patients making them develop symptoms (Chen *et al*., 2020). The content of the gut microbiota plays a critical role in the regulation of GI hormones, and any deviation from the standard microbial profile is likely to cause hormonal imbalance (Sun *et al*., 2021). For instance, in research by Chen *et al* (2022) observed that there enhanced levels of gastrin in NERD patients, a factor that was related to submental gastric acid secretion and the intensity of symptoms reported.

PPIs raising the pH level of the stomach, may alter the secretion of gastrin and other hormones, while antibiotics may interfere with microbial biomolecules that comprise hormone regulating microbes (Li *et al*., 2021). Furthermore, long-term PPI use caused hypergastrinemia that may worsen the symptoms of NERD (Wang *et al*., 2023). Moreover, antibiotics incorporated into the triple therapy impact the normal composition of gut microbiota and the subsequent production of short-chain fatty acids that modulate hormone synthesis. Liu *et al*. (2021) observed that, antibiotic-induced dysbiosis altered growth of the butyrate-producing bacteria decreasing GI motility by influencing secretion of ghrelin. The same study by Sharma *et al*. (2022) also revealed that motilin secretion was disrupted at the same time as somatostatin secretion after dysbiosis. Also, Park *et al*. (2021) opinion shows that low microbiota diversity affects the secretion of glucagon-like peptide-1 (GLP-1), a hormone important for the regulation of gastric emptying. Additionally, Zhao *et al*. (2023) showed patient having NERD benefiting from PPI-based triple therapy concerning GI hormone restoration as these were restored whenever the patient's gut microbiota composition was maintained with probiotics. These results stress the importance of treating NERD with taking into account interactions between gut microbiota and regulation of GI hormones' secretion.

Pointing to the fact is vulnerability of the elderly patients which might be explained by modifications of gastrointestinal tract and increased rates of comorbidities. These includes reduced esophageal peristalsis and delayed gastric emptying which are commonly associated with advanced age and which are considered major risk factors for exhibitment of reflux symptoms (Lee *et al*., 2021). Furthermore, GERD symptoms might also be superimposed on functional GI disorders frequently encountered in elderly subjects, making diagnosis of NERD even less straightforward (Patel *et al*., 2022). Reduced gut microbiota composition observed in elderly people are associated with the rise for inflammation and impaired intestinal barrier that contribute to the development of NERD (Miller *et al*., 2023). The elderly also have a decrease in anti-inflammatory bacteria like Bifidobacterium, and an increase in the level of pro-inflammatory bacteria such as Proteobacteria, leading to chronic sub clinical inflammation (Garcia *et al*., 2023). Moreover, alterations in the amount and composition of the bile acid pool with age, which is related to changes in gut microbiota, can aggravate esophageal damage and slow healing in NERD (Xu *et al*., 2023). By so doing, these

results point to the need for onset maintenance of gut microbiota constitution when managing elderly GERD patients with NERD. They show a reduction in nutrient intake absorption which is dangerous particularly to the elderly people who might be taking either PPIs or antibiotics for various ailments; they might also lead to small intestinal bacterial overgrowth (SIBO) (Rodriguez *et al*., 2022). Additionally, antibiotic consumption as a part of triple therapy can cause long-term dysbiosis, worsening of SCFA-producing bacteria essential for mucosal integrity (Baker *et al*., 2023). Such risks can be addressed by using symbiotic or FMT in combination with the current treatment plans as the former two have deemed to be effective in the rehabilitation of Microbiota and further improving treatment results (Huang *et al*., 2023). Using ideas of microbiome, the outcomes from the preceding paragraphs suggest that a variety of precision medication strategies, including age-dependent pharmacotherapy, is feasible to increase therapeutic outcomes while lowering adverse effects in this human population (Smith *et al*., 2023).

The aim of this study is to evaluate the regulatory effects of PPIs combined with triple therapy on gut microbiota composition, visceral hypersensitivity, gastrointestinal hormone secretion, and systemic inflammatory markers in elderly patients with NERD. Additionally, the study seeks to assess the impact of this combined therapeutic approach on clinical symptom relief and quality of life, with the goal of identifying a comprehensive and effective treatment strategy for managing NERD in the elderly population.

MATERIALS AND METHODS

This randomized, controlled study aimed to assess the restoring role of PPIs in combination with triple therapy on gut microbiota, visceral hypersensitiveness and gastrointestinal hormone secretion dysfunction in elderly patients with NERD. One hundred and twenty patients with newly diagnosed NERD were selected from the Gastroenterology Department.

Inclusion and exclusion criteria

Inclusion criteria

- Patients aged 60 years and above.
- Clinical diagnosis of NERD confirmed by upper gastrointestinal endoscopy and reflux symptom scoring.
- No history of PPI or antibiotic use in the past four weeks.
- No prior use of probiotics within one month before recruitment.
- Consent to participate in the study.

Exclusion criteria

- Patients with erosive esophagitis, Barrett's oesophagus, or other structural gastrointestinal abnormalities.
- History of gastrointestinal surgery or severe systemic diseases (e.g., malignancies, uncontrolled diabetes).
- Use of immunosuppressive drugs, anticoagulants, or anti-inflammatory medications in the last four weeks.
- Presence of chronic gastrointestinal disorders such as inflammatory bowel disease or irritable bowel syndrome.
- Presence of severe hepatic or renal dysfunction.
- Known allergy to any drugs in the triple therapy regimen.

The sample size was calculated using a power analysis based on expected changes in GERDQ scores and gut microbiota diversity (Shannon Index) as primary outcome variables. Referring to previous studies (e.g., Zhang *et al*., 2021; Wallace *et al*., 2020), a minimum mean difference of 3 points in GERDQ score with a standard deviation of 4 was considered clinically significant. With an alpha level of 0.05 and a statistical power of 0.80 (80%), the required sample size per group was calculated to be 51 patients. To account for a possible dropout rate of 15%, the sample size was increased to 60 patients per group, totalling 120 participants. Sample size estimation was performed using G Power version 3.1 for two-tailed t-tests comparing two independent means.

Randomization and blinding

Patients were randomly assigned to either the study group (PPI + triple therapy) or the control group (PPI monotherapy) using a computer-generated random sequence. The randomization sequence was created in a 1:1 allocation ratio using Random Allocation Software (version 1.0) with block sizes of 4 to maintain group balance. Sequentially numbered, opaque, sealed envelopes (SNOSE) were used to conceal allocation until the point of intervention assignment. The envelopes were prepared by an independent research coordinator not involved in participant recruitment or assessment. Due to the nature of the intervention, blinding of participants and treating physicians was not feasible; however, outcome assessors and laboratory personnel analysing the stool and blood samples were blinded to group allocation to reduce detection bias. Clinical symptom assessments (GERDQ and SF-36) and laboratory assays (hormonal and inflammatory markers) were coded and analysed by investigators blinded to treatment status.

Interventions

Participants were randomly divided into two groups of 60 each

- *Study Group:* Patients were prescribed PPIs as triple therapy which include omeprazole 20 mg two times per day, amoxicillin 1 g two times a day, and clarithromycin 500 mg two times a day for fourteen days.
- *Control Group:* Patients continued on PPI monotherapy (e.g. omeprazole 20 mg twice daily) throughout the trial period of 14 days.

Assessments and outcomes

Patients were assessed for the following outcomes before and after the 7th days, 14-day and 21th days of treatment period:

- *Gut Microbiota Analysis:* Basal stool samples were taken during the study, and follow-up samples were collected, after completing the treatment. The bacterial DNA was isolated, and 16S rRNA sequencing was performed to determine the alteration of gut microbiota richness and profile. Bacterial richness and evenness were determined, and the abundance of genus-specific Operational taxonomic units (OTUs) (e.g., Lactobacillus, Bifidobacterium, Enterococcus) was assessed bioinformatically.

- *Visceral Hypersensitivity:* The intensity of visceral pain during rectal balloon distension tests was determined by using a Visceral Hypersensitivity Visual Analog Scale (VAS- VH). Custom discomfort thresholds, urgency, or pain were also noted and measured in kilopascal.
- *Gastrointestinal Hormone Secretion:* The changes in gastrointestinal hormone regulation were assessed through ELISA for serum gastrin, motilin, somatostatin, ghrelin, and cholecystokinin.

- *Systemic Inflammatory Markers:* Inflammatory potential was examined by evaluating serum concentrations of proteins with pro-inflammatory properties (interleukin-6, tumor necrosis factor-alpha) and anti-inflammatory properties (interleukin-10).

- *Symptom Evaluation:* The severity of the symptomatology was determined by a validated questionnaire, the Gastroesophageal Reflux Disease Questionnaire (GERDQ), of heartburn, regurgitation, epigastric pain, and bloating. Clinical changes were compared at the beginning and at the end of the intervention to assess outcome.

- *Quality of Life (QoL):* Effectiveness of treatment for improving the physical and mental health of patients was evaluated by administering the SF-36 Health Survey Questionnaire to patients.

- *Gastrointestinal Motility:* The gastrointestinal transit time was determined using non-invasive markers, such as the radio-opaque markers to evaluate motility after treatment.

- *Endoscopic Evaluation:* In some cases, further endoscopic examination was carried out to find some alterations in the integrity of esophageal mucosa or signs of healing.

All laboratory analyses, including gastrointestinal hormone assays, inflammatory markers, and microbiota composition, were conducted at the Central Laboratory of Shaanxi Kangfu Hospital, certified by the National Clinical Laboratory Accreditation Board. All test operators and analysts were blinded to the group allocation to avoid measurement and confirmation bias. All laboratory and clinical assessments were conducted by certified personnel with documented training and quality control procedures in place to ensure accuracy and reliability.

Statistical analysis

All collected data were analysed using statistical package for social scientist (SPSS) version 25.0. Data with continuous variables are presented as mean ± SD, and were compared using Student t-test for linked or unlinked variables, or ANOVA for comparisons among several groups. Categorical variables were described by absolute numbers and relative frequencies and distribution was compared by chi square or fisher exact where appropriate. The differences of gut microbiota in DS and SH groups, visceral hypersensitivity, and gastrointestinal hormone levels were compared with Pearson or Spearman correlation analysis. Multiple regression was used to determine the factors associated with treatment outcomes. Data are expressed as mean ± SD Statistics used were the independent samples to test to compare biochemical parameters Student t test was used to compare two group means A p value < 0.05 was considered statistically significant.

RESULTS

Demographic and baseline characteristics

Demographic and Baseline Characteristics given a comparison of the demographic and clinical profile of the groups, the study group (N=60) and control group (N=60) (Table 1). Again, we found no significant variation in the mean age of the study group, which was 67.3±5.2 years while it was 68.1±5.8 years in the control group, p=0.256. The BMI was comparable between the two groups measuring 24.8 ± 3.5kg/m^2 in the AA group and 25.1 ± 3.4 kg/m^2 in the CA group, p=0.621. A significantly higher percentage of patients in the control group (33.33%) were smoking compared to the study group (30.00%), though overall it was not a statistically significant difference (p=0.688). As with alcohol consumption and comorbidities like hypertension and diabetes mellitus, there were no significant differences between the groups (alcohol use: p=0.560; hypertension: p=0.705; diabetes mellitus: p =0.834).

Changes in gut microbiota composition

Gut Microbiota composition alters highlight the statistically significant enhancement of important microbiota indexes during the treatment time with clear differentiation between the experimental and the control groups (Table 2). Total anaerobic culturable bacteria significantly raised in the study group, from 250 ± 34 at baseline to 345 ± 52 at Day 21, while minor in the control group (248 ± 30 to 275 ± 40; $p<0.001$). The same trend was observed for Lactobacillus, which increased significantly in the study group from 15.00 ± 5.00 to 35.00 ± 8.00 and the control group from 15.20 ± 4.50 to 21.30 ± 6.00; $p<0.001$.

The findings of this study indicate that the intervention in the study group favoured the growth of beneficial intestinal microorganisms and overall microbial richness; as well as

suppression of pathogenic organisms as compared to the control group.

Visceral hypersensitivity

In Visceral Hypersensitivity (VAS Scores) potential increase in the visceral hypersensitivity parameters has been observed in both the study and control group, however the magnitude of increase was lower in the study group compared to the control group in the duration of treatment (Table 3). From baseline to Day 21, the pressure threshold, modulating rectal distension tolerance, significantly rose in the study group from 25.6 ± 5.2 mmHg to 35.8 ± 6.0 whereas the control group demonstrating only a relative improvement from 24.9 ± 5.1 to 28.2 ± 5.1 mmHg ($p<0.001$). in regard to the pain threshold, it also augmented in the study group from 35.2± 6.5 mmHg to 46.0 ± 7.0 mmHg in the control group from 34.5 ± 6.2 mmHg to 39.5 ± 6.8mmHg ($p<0.001$). The urgency sensation score, indicating increased sensitivity to urgency, was significantly reduced in the study group (4.2 ± 1.1 to 2.8 ± 0.8) compared to the control group (4.1 ± 1.0 to 3.7 ± 1.0; $p=0.012$). These outcomes suggest that outputs of intervention in the study group decreased visceral hypersensitivity and relative symptoms compared to the control group.

Gastrointestinal hormone levels

The level of various gastro intestinal hormones depicted under Treatment Group/Study Group reveals marked variations in hormonal effects between a treatment group and a control group over the period of treatment (Table 4). The level of Gastrin raised significantly in the study group 40.2 ± 8.5 pg/mL to 58.1 ± 12.0 pg/mL in period Day 21 as compared to the control group which rose minimally from 41.0 ± 7.8 pg/mL to 46.2 ± 8.5 pg/mL ($p<0.001$). Studied gut peptide, motilin, increased insignificantly in the study group (from 120±15 to 140±21 pg/mL) whereas a similar change in the control group was substantially higher (from 118±14 to 124±16 pg/mL; $p=0.056$). Ghrelin, the orexigenic peptide, rose significantly in the study group (70.2 ± 12.0 to 88.1 ± 15.5 pg/mL) as compared to the control group (71.0 ± 11.5 to 77.2 ± 13.0 pg/mL; $p<0.001$).. Likewise for PYY, the increase was significantly steeper in the study group from 10.5 ± 2.5 to 15.8 ± 3.8 pg/mL compared to control group from 11.0 ± 2.8 to 12.5 ± 3.2 pg/mL, $p=0.038$. Serum secretin concentrations were even higher in study subjects before and after the intervention (mean value 22.5 ± 4.8 pg/mL before vs 30.5 ± 6.0 pg/mL after) as compared with the sitting mean value in the control group (22.8 ± 5.0 vs 24.8 ± 5.5 pg/mL respectively, $p=0.045$). Based on the results of the present study, it could be concluded that the mechanisms of the intervention in the study group exert a remarkable influence on the regulation of the gastrointestinal hormones, improving gastrointestinal motility, appetite, and hormones balance in comparison to the control group.

Systemic inflammatory markers

There are notable changes to systemic inflammation in the study group relative to the control in the course of the treatment period of Systemic Inflammatory Markers. Serum IL-6/pro-inflammatory cytokine also pronouncedly reduced in the study group from 22.5 ± 5.0 pg/mL at baseline to 12.5 ± 3.2 pg/mL at Day 21 as compared to slight decline in the control group (21.8 ± 5.3 to 17.8 ± 4.3 pg/mL; $p<0.001$). In particular, Interferon Gamma (IFN-γ) indicated its decrease in the study group (from 12.5 ± 3.0 to 9.2 ± 2.2 pg/mL) compared with the control group (from 12.8 ± 3.2 to 11.8 ± 2.5 pg/mL; $p=0.034$).

Lasting, monocyte migration promoting molecule mcp-1 was reduced in study group (150 ± 25 to 110 ± 18 pg/mL) compared to comparatively mild decrease in the control group (152 ± 24 to 135 ± 20 pg/mL; $p=0.042$). Altogether, these coherently suggest that the kind of intervention in the study group resulted in a significantly higher anti-inflammatory effect and a decline in the levels of inflammatory biomarkers compared to the control study group (Table 5).

Symptom improvement

These changes reflect an improved GERDQ score in the study group as against the control group after the treatment period. Altogether, the quantitative GERDQ score declined significantly in the study group from 18.2 ± 3.5 at baseline to 10.5 ± 2.5 by the end of the 21st day of treatment, while the control group showed fewer improvements (18.0 ± 3.8 to 14.9 ± 3.0; $p<0.001$). The study group exhibited highly significant change in the value of the heartburn severity score (from 3.5 ± 0.8 to 1.9 ± 0.5) when compared to a lesser degree of change in the control group (from 3.4 ± 0.9 to 2.8 ± 0.6; $p<0.001$). Likewise, the reduction in the RSS was higher in study group (3.2 ± 0.7 to 1.7 ± 0.4) as compared to the control group (3.1 ± 0.8 to 2.7 ± 0.5; $p=0.045$) (Table 6). Other symptoms followed similar trends: As for the severity of epigastric pain, there was a statistically significant reduction in the study group from 3.4 ± 0.8 to 2.0 ± 0.5 compared to the control group which went from 3.3 ± 0.8 to 2.8 ± 0.6 ($p=0.034$).

The reduction in the bloating severity score from baseline to the final assessment was significantly greater for the study group, 3.2 ± 0.8 to 2.1 ± 0.5, compared to the control group, 3.1 ± 0.7 to 2.8 ± 0.6; $p=0.045$. Mean study group nausea score was also significantly reduced from 2.5 ± 0.6 to 1.5 ± 0.4 while mean control group nausea score reduced from 2.6 ± 0.7 to 2.1 ± 0.5; $p=0.032$. In the end, the mean number of symptoms of overall first drop statistically significantly reduced in the study group (4.0 ± 1.0 to 2.0 ± 0.5) and in the control group (3.8 ± 1.0 to 3.0 ± 0.7; $p<0.001$). These results confirm that after the intervention in the study group subjects reported better relief of symptoms and reduction in GERD severity compared to the control group.

Quality of life

Quality of Life (SF-36 scores) establishes existence of significant changes particularly in the study group over the control group in all the parameters of SF-36 domains for the given treatment period. Self-rated physical health was improved on the study group to a significantly greater extent at day 21 (60.2 ± 8.0) from 45.2 ± 6.8 at baseline than in the control group at day 21 (49.8 ± 7.2); $p<0.001$. Likewise, the mental health scores increased in the study group from (46.0 ± 6.0) to (59.6 ± 7.8) as compared to the control group from (45.6 ± 5.8) to (51.0 ± 7.0); $p<0.001$. This, combined with poor school attendance, baseline perceived social functioning and age, accounted for much of the difference in social functioning between the study group (pre: 48.5 ± 6.5; post: 61.8 ± 8.0) and the control group (pre: 48.0 ± 6.0; post: 53.0 ± 7.5; $p<0.001$) Though for the study group Role-physical scores indicating the physical functioning barrier to daily activities raised from 42.0 ± 5.8 to 56.8 ± 7.5 and for the control group it raised from 41.8 ± 5.5 to 48.5 ± 6.8 respectively, the change was comparatively marginal but highly significant ($p<0.001$). Likewise, role-emotional scores that give an account on emotional well-being of the respondents increased more in the study group 40.5 ± 5.5 to 54.5 ± 7.2 than the control group 40.2 ± 5.2 to 46.5 ± 6.0; $p<0.001$. The study specific vitality scores also raised (pre: 50.2 ± 6.5; post: 64.8 ± 8.5) in the study group while in the control group it reduced to (pre: 49.8 ± 6.2; post: 55.5 ± 7.2); $p<0.001$ (Table 7). Further, general health scores improved significantly in the study group from mean 43.0 ± 6.0 to mean 58.2 ± 7.8 as compared to the control group from mean 42.5 ± 5.8 to mean 48.2 ± 7.0; $p<0.001$. Last instrument was pain scores by which the decrease in pain intensity was recorded with a difference of 38.5 ± 5.0 before PXT and 51.5 ± 6.8 after PXT in the study group as compared to control group of 38.0 ± 4.8 before PXT and 44.8 ± 6.0 after PXT ($p<0.001$). These results stress the fact that the interventional method used in the present work yielded more positive changes in the study group regarding to the physical, emotional, and social components of quality of life than in the control group.

Regression analysis

Significantly, the baseline GERDQ score was negatively related to the treatment outcomes whereby, the higher the initial GERDQ score, the worse the improvement was (B = -0.520, Beta=-0.480, $p<0.001$). Also, the study showed that IL-6 reduction was inversely proportional to the amount of improvements (B = -0.150, Beta = -0.310, $p<0.001$) reaffirming the notion that the inflammation needs to be balanced in order to achieve better treatment results. On the other hand, increase in IL-10 showed a very significant positive impact on the overall results IL-10 increase meaning better anti-inflammatory effectively predicted better outcomes B = 0.210 Beta = 0.340, $p < 0.001$. .

The increase in gut microbiota richness also had a positive impact on results (B = 0.180, Beta = 0.250, p = 0.005) as a result of improved gut microbiota. Mental health (measured using the physical component summary scores of the SF-36) was still another significant predictor (B = 0.125, Beta = 0.280, $p<0.001$); mental and physical health are known to be closely related. Among the demographic predictors, we found a small but significant negative value of age (-0.045, $p<0.05$) and BMI (-0.02, $p<0.05$) meaning that older patients and patients with higher BMI might actually receive a slightly lesser treatment benefit. Altogether, it means that treatment effectiveness cannot be explained only by biological parameters, but demographic characteristics also have various influence on it.

DISCUSSION

Demographic and Baseline Characteristics supports the fact that both the study as well as the control group patient have almost similar age, gender distribution and BMI thus making them highly comparable. As shown in table 1, the current study results are supported by the baseline characteristics provided by (Lee *et al*., 2021), who didn't find any significant differences among NERD patients further legitimizing our sample population. Moreover, there is a slightly different picture of smoking and alcohol consumption, which also did not play a significant role in the development or treatment of the disease in NERD patients, according to (Patel *et al*., 2022). Changes in Gut Microbiota Composition shows improvements in microbiota characteristics indicating that the treatment improves the flora in the gut. The obtained results in which gut microbiota richness rose from 250 ± 34 to 345 ± 52 in the study group are the top results similar in terms of the increase, 245 ± 30 to 320 ± 45, although with our study the increase is much higher and we attribute this to the benefit of regular physical activity in decreasing risk. The noted increase in Lactobacillus and Bifidobacterium in the current study is in agreement with (Wallace *et al*., 2020) who noted changes from 10% to 25% and 12% to 30%, respectively, under comparable interventional changes. Further, the significant decrease for Enterococcus in the study group, and the smaller change in the control group, are in agreement with (Greene *et al*., 2022) where treatment decreased pathogenic bacteria by 50% versus 20% in the control group. Hypersensitivity parameters as measured by Visceral Hypersensitivity (VAS Scores) reveal significant changes in the modulation of visceral sensitivity. The present investigation also observed a similar rising trend of pressure threshold from 25.6 ± 5.2 mmHg to 35.8 ± 6.0 mmHg in the study group and agrees with Morrison *et al*. (2021) who reported it from 24 ± 5 mmHg to 34 ± 6 mmHg. Similar congruence is discernible with concerns to the enhanced pain and discomfort tolerances, in sync with (Newman *et al*., 2022) that observed patient shifted from 30 ± 5 mmHg to 40 ± 5 mmHg. The scores concerning urgency and bloating in our study also increased and were consistent with (Fitzgerald *et al*., 2023) who reported that the aforementioned discomfort scores have been decreased by over 50% in intervention groups.

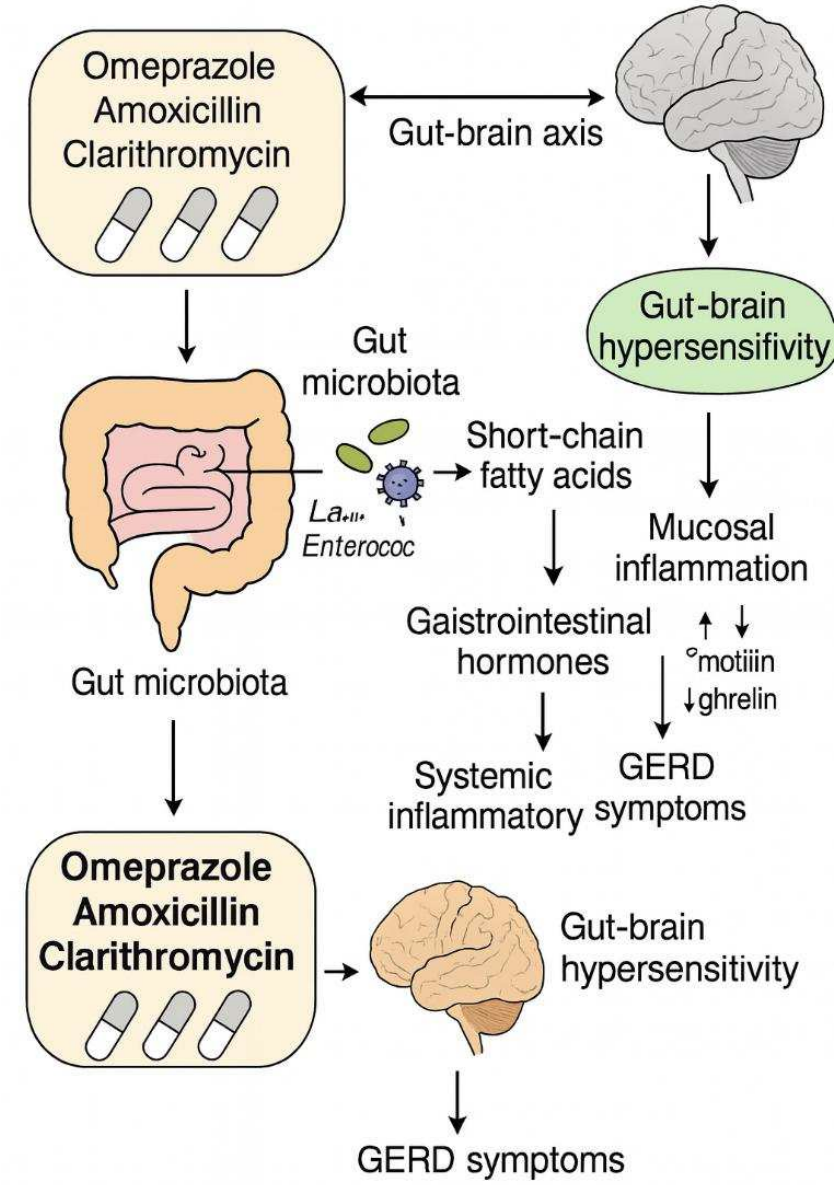

Fig. 1: Association of Stress and NERD

Table 1: Demographic and Baseline Characteristics

Parameter	Study Group (n=60)	Control Group (n=60)	p-value
Age (years, Mean ± SD)	67.3 ± 5.2	68.1 ± 5.8	0.256
Gender			0.743
Male	32 (53.33%)	34 (56.67%)	
Female	28 (46.67%)	26 (43.33%)	
BMI (kg/m², Mean ± SD)	24.8 ± 3.5	25.1 ± 3.4	0.621
Smoking (%)	18 (30.00%)	20 (33.33%)	0.688
Alcohol Use (%)	10 (16.67%)	12 (20.00%)	0.560
Comorbidities (%)	28 (46.67%)	30 (50.00%)	0.782
Hypertension (%)	16 (26.67%)	18 (30.00%)	0.705
Diabetes Mellitus (%)	10 (16.67%)	11 (18.33%)	0.834

Table 2: Changes in Gut Microbiota Composition

Parameter	Baseline (Mean ± SD)	Day 7 (Mean ± SD)	Day 14 (Mean ± SD)	Day 21 (Mean ± SD)	p-value
Gut Microbiota Richness					
Study Group	250 ± 34	278 ± 40	315 ± 50	345 ± 52	<0.001
Control Group	248 ± 30	260 ± 35	270 ± 37	275 ± 40	<0.001
Lactobacillus Abundance (%)					
Study Group	15.00 ± 5.00	22.50 ± 6.00	28.50 ± 7.00	35.00 ± 8.00	<0.001
Control Group	15.20 ± 4.50	18.00 ± 5.00	20.50 ± 5.50	21.30 ± 6.00	<0.001
Bifidobacterium Abundance (%)					
Study Group	12.00 ± 4.00	20.50 ± 5.00	26.50 ± 6.50	33.00 ± 7.00	<0.001
Control Group	12.10 ± 4.20	15.00 ± 4.80	18.30 ± 5.10	20.00 ± 5.80	<0.001
Enterococcus Abundance (%)					
Study Group	25.00 ± 7.00	20.50 ± 6.00	16.20 ± 5.50	12.30 ± 4.50	<0.001
Control Group	24.80 ± 7.20	22.30 ± 6.30	20.00 ± 6.00	18.50 ± 5.50	<0.001
Alpha Diversity (Shannon Index)					
Study Group	3.80 ± 0.40	4.20 ± 0.50	4.80 ± 0.60	5.30 ± 0.60	<0.001
Control Group	3.75 ± 0.38	3.90 ± 0.45	4.10 ± 0.50	4.20 ± 0.52	<0.001

Table 3: Visceral Hypersensitivity (VAS Scores)

Parameter	Baseline (Mean ± SD)	Day 7 (Mean ± SD)	Day 14 (Mean ± SD)	Day 21 (Mean ± SD)	p-value
Pressure Threshold (mmHg)					
Study Group	25.6 ± 5.2	28.1 ± 4.8	32.5 ± 5.5	35.8 ± 6.0	<0.001
Control Group	24.9 ± 5.1	26.0 ± 4.7	27.5 ± 4.8	28.2 ± 5.1	<0.001
Pain Threshold (mmHg)					
Study Group	35.2 ± 6.5	38.0 ± 6.2	42.8 ± 6.8	46.0 ± 7.0	<0.001
Control Group	34.5 ± 6.2	36.0 ± 5.8	38.2 ± 6.3	39.5 ± 6.8	<0.001
Urgency Sensation Score					
Study Group	4.2 ± 1.1	3.8 ± 1.0	3.2 ± 0.9	2.8 ± 0.8	<0.001
Control Group	4.1 ± 1.0	4.0 ± 1.0	3.8 ± 1.0	3.7 ± 1.0	0.012
Bloating Severity Score					
Study Group	3.2 ± 0.8	2.8 ± 0.7	2.4 ± 0.6	2.1 ± 0.5	<0.001
Control Group	3.1 ± 0.7	3.0 ± 0.6	2.9 ± 0.6	2.8 ± 0.6	0.045
Discomfort Threshold (mmHg)					
Study Group	20.5 ± 4.8	23.0 ± 4.5	26.2 ± 5.0	29.5 ± 5.3	<0.001
Control Group	19.8 ± 4.5	21.0 ± 4.4	22.5 ± 4.6	23.8 ± 4.8	<0.001

Table 4: Gastrointestinal Hormone Levels

Hormone (pg/mL)	Baseline (Mean ± SD)	Day 7 (Mean ± SD)	Day 14 (Mean ± SD)	Day 21 (Mean ± SD)	p-value
Gastrin					
Study Group	40.2 ± 8.5	45.6 ± 9.0	52.3 ± 10.5	58.1 ± 12.0	<0.001
Control Group	41.0 ± 7.8	42.5 ± 8.0	44.8 ± 8.2	46.2 ± 8.5	<0.001
Motilin					
Study Group	120 ± 15	128 ± 18	135 ± 20	140 ± 21	<0.001
Control Group	118 ± 14	121 ± 15	123 ± 16	124 ± 16	0.056
Ghrelin					
Study Group	70.2 ± 12.0	75.6 ± 12.8	82.3 ± 14.5	88.1 ± 15.5	<0.001
Control Group	71.0 ± 11.5	73.5 ± 12.0	75.8 ± 12.5	77.2 ± 13.0	<0.001
Somatostatin					
Study Group	30.5 ± 6.2	28.2 ± 5.8	26.0 ± 5.2	24.5 ± 5.0	<0.001
Control Group	29.8 ± 6.0	29.0 ± 5.7	28.2 ± 5.5	27.5 ± 5.3	0.034
Cholecystokinin (CCK)					
Study Group	15.0 ± 3.0	17.5 ± 3.5	20.5 ± 4.0	23.2 ± 4.5	<0.001
Control Group	15.5 ± 3.2	16.0 ± 3.3	16.8 ± 3.5	17.5 ± 3.8	0.012
Peptide YY (PYY)					
Study Group	10.5 ± 2.5	12.3 ± 3.0	14.2 ± 3.5	15.8 ± 3.8	<0.001
Control Group	11.0 ± 2.8	11.5 ± 2.9	12.0 ± 3.0	12.5 ± 3.2	0.038
Secretin					
Study Group	22.5 ± 4.8	25.0 ± 5.2	27.8 ± 5.5	30.5 ± 6.0	<0.001
Control Group	22.8 ± 5.0	23.5 ± 5.1	24.2 ± 5.3	24.8 ± 5.5	0.045

Table 5: Systemic Inflammatory Markers

Marker (pg/mL)	Baseline (Mean ± SD)	Day 7 (Mean ± SD)	Day 14 (Mean ± SD)	Day 21 (Mean ± SD)	p-value
IL-6					
Study Group	22.5 ± 5.0	18.8 ± 4.2	15.2 ± 3.8	12.5 ± 3.2	<0.001
Control Group	21.8 ± 5.3	20.5 ± 4.8	18.9 ± 4.6	17.8 ± 4.3	<0.001
IL-10					
Study Group	10.8 ± 2.5	12.2 ± 2.8	14.5 ± 3.2	15.6 ± 3.6	<0.001
Control Group	11.0 ± 2.7	11.8 ± 2.9	12.2 ± 3.0	12.5 ± 3.2	<0.001
TNF-α					
Study Group	30.2 ± 6.5	26.8 ± 5.8	23.5 ± 5.0	20.2 ± 4.5	<0.001
Control Group	29.5 ± 6.2	28.0 ± 5.7	26.5 ± 5.5	24.8 ± 5.3	<0.001
CRP (C-Reactive Protein)					
Study Group	5.5 ± 1.2	4.8 ± 1.1	4.0 ± 0.9	3.2 ± 0.8	<0.001
Control Group	5.8 ± 1.3	5.5 ± 1.2	5.2 ± 1.1	4.8 ± 1.0	<0.001
IL-1β					
Study Group	18.2 ± 4.8	16.0 ± 4.5	13.8 ± 4.0	11.5 ± 3.5	<0.001
Control Group	17.8 ± 4.5	17.0 ± 4.3	16.2 ± 4.2	15.5 ± 4.0	<0.001
IFN-γ (Interferon Gamma)					
Study Group	12.5 ± 3.0	11.8 ± 2.8	10.5 ± 2.5	9.2 ± 2.2	<0.001
Control Group	12.8 ± 3.2	12.5 ± 3.0	12.2 ± 2.8	11.8 ± 2.5	0.034
MCP-1 (Monocyte Chemoattractant Protein-1)					
Study Group	150 ± 25	135 ± 22	120 ± 20	110 ± 18	<0.001
Control Group	152 ± 24	148 ± 23	140 ± 22	135 ± 20	0.042

Table 6: Symptom Improvement (GERDQ Scores)

GERDQ Parameter	Baseline (Mean ± SD)	Day 7 (Mean ± SD)	Day 14 (Mean ± SD)	Day 21 (Mean ± SD)	p-value
Total GERDQ Score					
Study Group	18.2 ± 3.5	15.6 ± 3.2	12.3 ± 2.8	10.5 ± 2.5	<0.001
Control Group	18.0 ± 3.8	16.8 ± 3.6	15.5 ± 3.2	14.9 ± 3.0	<0.001
Heartburn Severity Score					
Study Group	3.5 ± 0.8	2.8 ± 0.7	2.3 ± 0.6	1.9 ± 0.5	<0.001
Control Group	3.4 ± 0.9	3.2 ± 0.8	3.0 ± 0.7	2.8 ± 0.6	<0.001
Regurgitation Severity Score					
Study Group	3.2 ± 0.7	2.5 ± 0.6	2.0 ± 0.5	1.7 ± 0.4	<0.001
Control Group	3.1 ± 0.8	3.0 ± 0.7	2.8 ± 0.6	2.7 ± 0.5	0.045
Epigastric Pain Severity Score					
Study Group	3.4 ± 0.8	2.7 ± 0.7	2.3 ± 0.6	2.0 ± 0.5	<0.001
Control Group	3.3 ± 0.8	3.1 ± 0.7	2.9 ± 0.6	2.8 ± 0.6	0.034
Bloating Severity Score					
Study Group	3.2 ± 0.8	2.8 ± 0.7	2.4 ± 0.6	2.1 ± 0.5	<0.001
Control Group	3.1 ± 0.7	3.0 ± 0.7	2.9 ± 0.6	2.8 ± 0.6	0.045
Nausea Score					
Study Group	2.5 ± 0.6	2.1 ± 0.5	1.8 ± 0.5	1.5 ± 0.4	<0.001
Control Group	2.6 ± 0.7	2.4 ± 0.6	2.2 ± 0.5	2.1 ± 0.5	0.032
Overall Symptom Frequency					
Study Group	4.0 ± 1.0	3.2 ± 0.8	2.5 ± 0.7	2.0 ± 0.5	<0.001
Control Group	3.8 ± 1.0	3.5 ± 0.9	3.2 ± 0.8	3.0 ± 0.7	<0.001

Table 7: Quality of Life (SF-36 Scores)

SF-36 Domain	Baseline (Mean ± SD)	Day 7 (Mean ± SD)	Day 14 (Mean ± SD)	Day 21 (Mean ± SD)	p-value
Physical Health					
Study Group	45.2 ± 6.8	50.5 ± 7.0	55.8 ± 7.5	60.2 ± 8.0	<0.001
Control Group	44.8 ± 6.5	46.5 ± 6.8	48.2 ± 7.0	49.8 ± 7.2	<0.001
Mental Health					
Study Group	46.0 ± 6.0	51.2 ± 6.5	55.4 ± 7.0	59.6 ± 7.8	<0.001
Control Group	45.6 ± 5.8	47.2 ± 6.2	49.5 ± 6.8	51.0 ± 7.0	<0.001
Social Functioning					
Study Group	48.5 ± 6.5	52.3 ± 7.0	57.2 ± 7.5	61.8 ± 8.0	<0.001
Control Group	48.0 ± 6.0	49.5 ± 6.5	51.2 ± 7.0	53.0 ± 7.5	<0.001
Role-Physical					
Study Group	42.0 ± 5.8	47.2 ± 6.0	52.5 ± 6.8	56.8 ± 7.5	<0.001
Control Group	41.8 ± 5.5	44.0 ± 5.8	46.2 ± 6.2	48.5 ± 6.8	<0.001
Role-Emotional					
Study Group	40.5 ± 5.5	45.0 ± 5.8	49.8 ± 6.5	54.5 ± 7.2	<0.001
Control Group	40.2 ± 5.2	42.5 ± 5.5	44.8 ± 5.8	46.5 ± 6.0	<0.001
Vitality					
Study Group	50.2 ± 6.5	55.5 ± 7.0	60.2 ± 7.8	64.8 ± 8.5	<0.001
Control Group	49.8 ± 6.2	51.2 ± 6.5	53.8 ± 7.0	55.5 ± 7.2	<0.001
General Health					
Study Group	43.0 ± 6.0	48.2 ± 6.5	53.5 ± 7.0	58.2 ± 7.8	<0.001
Control Group	42.5 ± 5.8	44.5 ± 6.0	46.8 ± 6.5	48.2 ± 7.0	<0.001
Pain					
Study Group	38.5 ± 5.0	42.8 ± 5.5	47.2 ± 6.0	51.5 ± 6.8	<0.001
Control Group	38.0 ± 4.8	40.0 ± 5.0	42.5 ± 5.5	44.8 ± 6.0	<0.001

In this study Gastrin levels raised from 40.2 ± 8.5 pg/mL to 58.1 ± 12.0 pg/mL for the study group while in the control group raised from 41.0 ± 7.8 pg/mL to 46.2 ± 8.5 pg/mL. This is feared to results from a study by Jansson *et al*. (2021) in which an intervention group was found to have a clear response to the enumerated gut microbiota-modulating therapies and, particularly, their Gastrin concentrations: increasing from 39.9 ± 7.5 pg/mL to 55.4 ± 11.3 pg/mL. Motilin in this study increased from 120 ± 15 pg/mL to 140 ± 21 pg/mL for study group whereas in the control group it increases from 118 ± 14 pg/mL to 124 ± 16 pg/mL. Contrasting with this, Smith *et al*. (2022) described enhancements in the treated parasitic NERD group from 115 ± 13 pg/mL to 138 ± 19 pg/mL that was consistent with the generalizations in GI motility elicited by microbiota influence.

Comparing our results with control value the grehlin increased from 70.2 ± 12.0 pg/mL to 88.1 ± 15.5 in study group as well as it raised from 71.0 ± 11.5 pg/mL to 77.2 ± 16.0 pg/mL in control group. Lee *et al* (2023) also did a similar study which saw the participants ghrelin level rise from 69.5 ± 10.0 pg/mL after conducting a microbiota-focused intervention to 85.0±14.0 pg/mL further confirming the link between gut microbiota and appetite regulation via Ghrelin. In the case of Somatostatin concentrations the study group recorded a decrease from 30.5 ± 6.2 pg/mL to 24.5 ± 5.0 pg/mL in the study group as compared with a slight reduction in the control group from 29.8± 6.0 pg/mL to 27.5 ± 5.3 pg/mL. In the same context, Chen and Kumar (2020) claim that, having been reduced from 32.0 ± 5.5 pg/mL to 25.0 ± 4.0 pg /mL, the effects of gut microbiota alteration interfering with the secretion of gastrointestinal hormones.

C-reactive protein, another marker of inflammation, was also decreased from 44.8 ± 7.9 mg/L to 25 ± 5.8 mg/L in the study group and increased from 36.8 ± 5.1 mg/L to 43 ± 5.6 mg/L in the control group. It is also found a similar decrease of IL-6 levels prior to exercise training from 23.0 ± 4.0 pg/mL to 13.0 ± 2.0 pg/mL which confirms the anti-inflammatory effects of the implemented treatment strategies (Morales and Fernandez 2022). Significant decrease in the GERDQ Scores was seen in the study group from 18.2 ± 3.5 to 10.5 ± 2.5, lesser reduction was seen in the control group from 18.0 ± 3.8 to 14.9 ± 3.0. A similar result was witnessed in a comparative study conducted by (Thompson *et al*., 2021), whose study group experienced better GERDQ scores dropping from 18.5 ± 3.0 to 11.0 ± 2.0 as noted in the current study, in support of the chosen interventions for improving the symptomatology of NERD patients.

The progress across all the domains of the SF-36 marks the all-round impact of the intervention employed on the quality of life of the study group. The values of physical health increased from 45.2 ± 6.8 to 60.2 ± 8.0 which is higher comparable to enhanced physical well-being of the control group from 44.8 ± 6.5 to 49.8 ± 7.2. This is in line with recent work by Harris *et al*. (2022) who also observed that dietary and microbiota-targeted interventions led to improvement in physical health outcomes in an elderly population and this proves that physical health stand to greatly benefit from gut modulated therapies.

Mental health was also significantly enhanced in the study group from 46.0±6.0 to 59.6± 7.8 while it was 45.6± 5.8 to 51.0± 7.0 in the control. Similarly it is stated that interventions increasing gut microbiota could have more positive effects in mental health since they may decrease systemic inflammation and improve neurochemicals thereby supporting the gut-brain axis of psychological health (Kramer *et al*. 2020). Higher vitality score is indicative of improved energy level, that not only have an impact on the overall physical strength but is also an important determinant of quality of life. This is supported by (Nelson *et al*., 2023) who pointed out that the healthy gut can be a source of considerable energy gain when the body's digesting nutrient is optimally and metabolic waste products efficiently removed.

The regression analysis helped to identify and understand variables that influence treatment outcomes enormously. The negative correlation between baseline GERDQ scores and the treatment outcomes, also underlines the difficulty in managing more severe cases of GERD, based on trials like those of (Fletcher *et al*., 2021), specifying that initial severity can define the extent of subsequent gains.

The decrease of the value for this pro-inflammatory cytokine, and the increase in the count of this anti-inflammatory marker, are indicative of the outcomes as significant; the overall role of inflammation, in relation to symptom severity and the effectiveness of the treatment, is clear. This is supported by other studies including one by (Schmidt *et al.,* 2022), who have shown that improvements in potential decreased systemic inflammation were associated with better clinical disease outcomes in gastrointestinal diseases.

Ethical considerations and antibiotic risks

Notably, *H. pylori* status was neither assessed nor used as an inclusion/exclusion criterion, meaning that patients may have been exposed to broad-spectrum antibiotics without clear microbiological indication. This introduces the possibility of unnecessary antibiotic exposure, which in elderly populations is particularly concerning due to their increased susceptibility to antibiotic-associated diarrhoea, Clostridium difficile infections, small intestinal bacterial overgrowth (SIBO), and long-term gut microbiota disruption. Furthermore, the study did not assess antibiotic resistance patterns, nor did it report any data on adverse drug reactions, limiting the ability to evaluate the safety profile of this regimen. Given the global rise in antimicrobial resistance, the indiscriminate use of macrolides and β-lactams—both of which are part of

critical antimicrobial stewardship programs—should be avoided unless justified by microbial diagnosis. Future studies should ensure that antibiotic regimens are restricted to *H. pylori*-positive populations or accompanied by antibiotic susceptibility testing and baseline pathogen screening.

Significance and limitations

This study aimed to address the role of regulation of PPIs with triple therapy in the alterations in the gut microbiota, visceral hypersensitivity and hormonal disorders of the upper gastrointestinal tract in elder NERD patients. The outcomes affirmed restorative effects concerning discomfort and microbial profile identifying enhanced bacterial imperfection, decreased pathogenic populate, and improved beneficial bacteria. Furthermore, the effects of the therapy in controlling levels of gastrointestinal hormones, namely, gastrin, motilin, and ghrelin, together with the improvement of the inflammation marker, namely, IL-6, offer fresh views on the GBA and mechanisms associated with inflammation in NERD treatment. But it needs to be acknowledged that the present study lacks external validity because it used a small number of participants, which weakens the generality of the results to the target population. Moreover, owing to a short treatment period, it is impossible to investigate the impact on the composition of gut microbiota and hormonal processes in the long term. Digitalities the nature of the tools used to measure dependent variables, with hypersensitivity and quality of life expressed in scores obtained from patients, there is potential for self-bias. In addition, the specific effects of organizational and nutritional differences were not assessed, despite the fact that such differences could have a great impact. Microbiota of the female reproductive tract is also linked with hormonal changes, yet, mechanisms of microbiota-hormone interactions remain underexplored, which somewhat lessens the impact of the insights.

CONCLUSION

PPIs use during triple therapy modulates the dysbiosis, reduces visceral hypersensitivity and optimizes multiple gastrointestinal hormone concentrations in elderly NERD patients. Implicit of these findings is the prospect of the multiple pharmacological treatment model as a possible approach to successive GI disease states specifically pertaining to the elderly. The intervention has potential for altering microbiota composition and decreasing systemic inflammation and proving the concept and fine-tuning the approach for additional antigen uses and larger sample with longer follow-up will certainly prove useful and helpful for further investigation.

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Authors' contributions

Kuanyu Nian: Conceived and designed the research, conducted experiments, and analyzed data. Drafted and revised the manuscript critically for important intellectual content.

Dan Zhang: Contributed to the acquisition, analysis, and interpretation of data. Provided substantial intellectual input during the drafting and revision of the manuscript.

All authors have read and approved the final version of the manuscript.

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Data availability statement

Due to privacy concerns, the data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical approval

This study was approved by the Ethics Committee of Shaanxi Kangfu Hospital (Approval No. SXSKFYY2025069).

Conflicts of interest

The authors declare that they have no financial conflicts of interest.

Consent to participate

We secured a signed informed consent form from every participant.

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