Effect of high-fat, standard, and functional food meals on esophageal and gastric pH in patients with gastroesophageal reflux disease and healthy subjects

Wen Juan Fan1† | Yuan Tao Hou1† | Xiao Hong Sun1 | Xiao Qing Li1 | Zhi Feng Wang1 | Meng Guo2 | Li Ming Zhu1 | Ning Wang3 | Kang Yu4 | Jing Nan Li1 | Mei Yun Ke1 | Xiu Cai Fang1

1Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
2Beijing Wei Di Kang Tai Medical Equipment Ltd., Beijing, China
3Beijing Tongrentang Health Pharmaceutical Co., Ltd., Beijing, China
4Department of Clinical Nutrition, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Correspondence
Xiu Cai Fang, Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 1 Shuaifuyuan Road, Dongcheng District, Beijing 100730, China.
Email: fangxiucai2@aliyun.com

Funding information
National High Technology Research and Development Program of China, Grant/Award Number: 2010AA023007

Objectives: To investigate the effects of different test meals on esophageal and intragastric pH in patients with gastroesophageal reflux disease (GERD) and healthy subjects and to demonstrate the relationship between esophageal acid exposure (EAE) and gastric pH.

Methods: We enrolled patients with reflux esophagitis (RE; n = 15), nonerosive reflux disease (NERD; n = 12) and healthy subjects (n = 10). Four pH electrodes were used to monitor the pH of the distal esophagus, upper border of the lower esophageal sphincter, gastric fundus, and gastric body for 26 hours. Isocaloric and isovolumetric high-fat, standard, and functional meals were supplied randomly to the participants. The EAE and gastric acidity of each meal in fasting and postprandial states were compared.

Results: High-fat meals significantly increased postprandial EAE in patients with RE and NERD. EAE was higher after a high-fat meal than after a standard or functional food meals at the fourth hour postprandially in patients with RE (P < 0.05). Patients with NERD reported fewer symptoms after a functional food meal than after high-fat and standard meals (0 [interquartile range {IQR} 0–1] vs 1 [IQR 0–2] vs 3 [IQR 1–4], P = 0.014). Compared with high-fat and standard meals, functional food meal significantly decreased gastric acidity in patients with RE. EAE was significantly related to gastric acidity in patients with RE.

Conclusions: High-fat meals increased EAE in patients with RE and NERD. Functional food could serve as adjuvant therapy in GERD patients. EAE was related to gastric acidity in RE patients.

KEYWORDS
diet, functional food, gastric acid, gastroesophageal reflux, high-fat diet

1 | INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition in which gastroesophageal reflux causes bothersome symptoms or esophageal mucosal breakage. In recent years, the prevalence of GERD has rapidly increased in Asia. Reflux symptoms are usually aggravated after meals, especially those with greasy food. In Japan a higher intake of oil and fat (odds ratio {OR} 1.67) was one of the risk factors for nonerosive reflux disease (NERD) in women.
Diet modification is the basic treatment for patients with GERD, including decreasing the intake of fatty food, avoiding over-satiety, and avoiding meals within 3 hours before bedtime. However, the effects of meals of different volume, calorie, and fat content on esophageal acid exposure (EAE) are controversial. In both healthy controls and patients with GERD, EAE was more severe after the intake of a large-volume meal than small-volume meal when the fat content was controlled. In a group of patients with GERD, EAE was more severe after the intake of a high-calorie diet than a low-calorie diet with the same fat content. In contrast, the frequency of reflux symptoms, but not EAE, increased after the intake of the high-fat diet. Some of these discrepancies could be explained as follows. First, most studies did not classify patients with GERD into reflux esophagitis (RE) and NERD. The severity of EAE and response to different meals differed between patients with RE and NERD. The results of studies that enrolled healthy controls only cannot be extrapolated to patients with GERD. In addition, the components of the test meals were variable among the studies. Therefore, further rigorously designed studies are required to confirm the effects of fat content and other parameters of meals on EAE in patients with GERD.

The acidity of the reflux contents is significantly correlated with gastric acidity in GERD during a reflux episode, indicating a relationship between intragastric acidity and EAE. The main treatment for GERD is the administration of proton pump inhibitors (PPIs) to decrease acid secretion and reflux. In previous studies, 20–30% of the patients reported persistent symptoms despite standard treatment with PPIs. When receiving maintenance PPI therapy, 48.7% presented residual symptoms associated with a lower quality of life. Moreover, 47.8% with complete resolution of GERD experienced recurrent symptoms after the withdrawal of PPIs. Moreover, the long-term use of PPIs may result in food-borne infections. A feasible strategy for evaluating the effects of diet on patients with GERD and thus improving the use of dietary modifications, is to explore nonpharmacological treatments such as the intake of functional food to reduce the use of PPIs and to prevent against symptom relapse after the withdrawal of PPIs.

The aim of this study was to evaluate the effects of isocaloric and isovolumetric high-fat, standard, and functional food meals on esophageal and intragastric pH values in patients with both RE and NERD and healthy controls, thus to explore the relationship between gastric acidity and EAE and the therapeutic value of functional food in patients with GERD.

2 MATERIALS AND METHODS

2.1 Participants

2.1.1 Patients with GERD

Consecutive patients aged 18–65 years who had experienced troublesome heartburn and reflux symptoms for more than 3 months were enrolled in a tertiary Gastroenterology Clinic of the Peking Union Medical College Hospital (Beijing, China) from November 2012 to May 2013. All patients had experienced mild symptoms for at least 2 days per week or moderate-to-severe symptoms for more than one day per week during the previous month before their enrollment. Patients who had been diagnosed with mucosal erosive lesions under endoscopic examination during the previous month were enrolled in the RE group and those with normal endoscopic appearances were regarded as the NERD group. RE was graded using the Los Angeles classification.

2.1.2 Healthy subjects

Age-matched (18–65 years) healthy volunteers were recruited by advertisement during the study period. No healthy subjects reported reflux symptoms, any other discomfort or a previous diagnosis of GERD, and they had normal endoscopic findings during the previous month before their enrollment.

2.1.3 Exclusion criteria of both patients and healthy subjects

Patients with peptic ulcers, previous upper gastrointestinal (GI) surgery, suspicious or confirmed diagnosis of malignancies, major esophageal motor disorders, coronary heart disease, hypertension, bronchial asthma, systemic diseases, obvious depression and anxiety, and who were pregnant or lactation were excluded. Written informed consent was obtained from each participant before their enrollment. This study was approved by the Ethics Committee of Peking Union Medical College Hospital (no. S-481).

2.2 Esophageal manometry and pH monitoring

For GERD patients, acid-suppressive and prokinetic drugs were withdrawn at least one week before the study. Esophageal manometry was performed transnasally with a four-channel pneumohydraulic capillary infusion system (Medtronic, Minneapolis, MN, USA) according to the protocol in our previous study. The pH electrodes were calibrated at room temperature. Ambulatory esophageal pH monitoring was performed transnasally by using a portable four-electrode pH monitor (Medical Measurement Systems, Best, The Netherlands) and antimony electrodes (5-cm intervals between the adjacent electrodes), with the four sensors located at 5 cm above the lower esophageal sphincter (LES) (distal esophagus; channel 1 [C1]), immediately above the upper border of the LES (channel 2 [C2]), and at 5 and 10 cm below the upper border of the LES (gastric fundus, channel 3 [C3]; gastric body, channel 4 [C4]). The participants were required to be seated for 30 minutes before the pH monitoring procedure, and data recording was started in the fasting status and continued for 1 hour. The flowchart for the experiment is shown in Figure 1. To record the pH value of the fasting status before each meal for one hour and postprandial status for 4 hours for all the three meals, the total monitoring time was prolonged to 26 hours. Reflux symptoms, time periods of meals and sleepness were recorded by the participants during the monitoring. The participants were asked not to take a supine position during the 4-hour postprandial monitoring. The pH data of the overall 26 hours, and at the first, second, third and fourth postprandial hour were analyzed by Orion II software version 8.23 (Medical Measurement Systems).
spaces in patients with GERD.20 The functional food meal comprised finding of local tissue cell changes including dilated intercellular

Pharmaceutical Co., Ltd., Beijing, China) was developed based on the Table S2). The functional food (Beijing Tongrentang Health-

12.3%, 25.0%, and 62.6%, respectively (Supporting Information fat. The calorific percentages of carbohydrate, fat, and protein were

rice, radish, beef, vegetables and soup that contains a total of 22.2 g

ting is measured in the pretest. The high-fat meal comprised test meals were blended with food blenders for the

pared test meals were given the three test meals randomly according to their order (Supporting Information Table S4). Dining time was set at 15 minutes for each meal.

2.4 | Data analysis and definitions

The baseline reflux symptoms evaluated in this study were heartburn, acid reflux, and retrosternal pain. Baseline reflux symptom scores over the previous three months were calculated according to the formula from the study of Vigneri et al.21: reflux symptom score = severity score × frequency score. The number of reflux symptoms was recorded during monitoring.9

Fasting status was defined as the hour before the first meal, post-

prandial status was defined as the 4 hours after each meal, and night time was defined as 10 PM to 6 AM the next day. EAE of the distal esophagus and upper border of the LES was defined as a pH <4 and expressed as the percentage time of having a pH of <4, number of acid exposures, and number of long acid exposures (>5 minutes). Abnormal EAE in the distal esophagus was defined as a DeMeester score ≥14.72.12,22 Abnormal EAE in the upper border of the LES was defined as the percentage of the time when the pH <4 (over 10.6% according to the studies of Wenner et al.23 and Bansal et al.24). Intra-gastric pH data were collected at C3 and C4 and expressed as the percentage time when the pH was <4, and <2, as well as the mean pH values.

2.5 | Statistical analysis

All the statistical analyses were performed using SPSS software version 19.0 (IBM, Armonk, NY, USA). Before the analysis, the Kolmogorov-Smirnov test was used to detect a normal parametric distribution. Parametric and nonparametric data are presented as mean ± standard deviation or medians and interquartile range (IQR), respectively. For parametric data, a one-way ANOVA was used to compare the variables among the three groups. Whereas for nonparametric data, the Friedman test was used to compare the correlated sample differences among the three groups, such as the differences among three meals in the same group, and the Kruskal-Wallis test was used to compare independent sample differences among the three groups, such as differences among the three groups having the same meal. The Wilcoxon’s test and the Mann-Whitney U test were used to compare paired and independent nonparametric data in the two groups. For nonparametric correlations, Spearman’s test was used to assess the correlation between two quantitative variables. The χ² test was used for categorical variables, which are expressed as numbers and percentages. A P value of <0.05 was considered statistically significant.
3 | RESULTS

3.1 | Characteristics of the participants

A total of 29 GERD patients, including 15 with RE (nine with Los Angeles A and six with Los Angeles B) and 14 with NERD, and 10 healthy subjects were enrolled in the current study. Two patients with NERD were then eliminated due to the imperfect contact of the electrodes; therefore, and the number of eligible NERD patients was 12. Additionally, two patients with RE were found to have hiatal hernia. Substantial differences were found in terms of the participants’ age and body mass index (BMI) among the three groups, although the differences were not statistically significant (Table 1). The baseline reflux symptom scores were comparable between the RE and NERD groups during the previous 3 months (8.73 ± 3.47 vs 10.50 ± 3.83, P = 0.816).

During the 26-hour pH monitoring, the percentage time of pH value <4 in the distal esophagus in the RE group was significantly higher than in healthy subjects (7.7 [IQR 1.6–11.5] vs 1.2 [IQR 0.2–2.0], P = 0.01), although there was no significant difference between the RE and the NERD groups (7.7 [IQR 1.6–11.5] vs 2.0 [IQR 0.7–7.8], P > 0.05; Figure 2A). The DeMeester score for RE was significantly higher than that for healthy subjects (21.6 [IQR 5.8–38.3] vs 5.4 [IQR 1.0–7.1], P = 0.03), although it did not differ from that of NERD patients (7.2 [IQR 3.6–24.2]). The prevalence of abnormal EAE in the distal esophagus of patients with RE and NERD and that of healthy subjects was 60%, 25%, and 0%, respectively (P = 0.006), whereas the prevalence of abnormal EAE in the upper border of the LES of patients with RE and NERD was higher than that in the distal esophagus (100% vs 60%, 75% vs 25%, P < 0.05; Figure 2B). The score for long acid exposure (for over 5 minutes) was higher in patients with RE than in those with NERD and healthy subjects (Figure 2C). Of 15 patients with GERD who had normal EAE in the distal esophagus, including six patients with RE and nine with NERD, 80% showed abnormal EAE in the upper border of the LES. No significant difference in the number of symptoms was found between patients with RE and NERD (Figure 2D). None of the healthy subjects reported reflux symptoms. Representative tracings of the pH profiles of C1 and C2 when symptoms occurred are shown in Figures 2E,F.

3.2 | Effects of high-fat meal, standard meal and functional food on EAE

No significant increase in EAE was observed during the 4 hours after the standard meal in patients with RE and NERD compared with the EAE before meals. No abnormal EAE occurred in healthy subjects. In patients with RE, the postprandial EAE at the first, second, third and fourth hour in the distal esophagus after the high-fat meal was significantly higher than the preprandial EAE, particularly at the second hour (Figure 3A). Moreover, 4 hours after the high-fat meal EAE was more severe than after standard and functional food meals [5.2% [IQR 0.5–22.4%] vs 4.0% [IQR 0–10.5%] and 4.3% [IQR 0–26.5%], P = 0.047]. Similarly, in patients with NERD, the postprandial EAE at the first, second, third and fourth hour increased compared with the fasting EAE after the administration of high-fat diet (Figure 3B). While healthy subjects showed no increase in EAE after the high-fat meal (Figure 3C). After the functional food meal, the postprandial EAE showed no significant increase in patients with RE (Figure 3A), and at the first postprandial hour EAE was even a little lower than the preprandial EAE but without statistical significance (0.4% [IQR 0–3.48%] vs 0.8% [IQR 0–4.03%]). Postprandial EAE at the second, third and fourth hour after the functional food was not significantly different from the preprandial EAE.

After the high-fat meal, EAE in the upper border of the LES increased significantly at the second, third and fourth hour in patients with RE and NERD compared with those at their fasting status (Figures 4A,B). The EAE in the upper border of the LES also increased at the second hour after the standard meal in patients with NERD. Healthy subjects showed no significant increase after all three meals (Figure 4C). The functional food meal had no significant effect on EAE in the upper border of the LES.

Comparing the EAE of the patients in the three groups taking the same meal, we found that the EAE in the distal esophagus at the first (6.8% [IQR 2.3–18.3%] vs 2.7% [IQR 0–4.4%] vs 0.4% [IQR 0–4.8%], P = 0.025) and third (12.6% [IQR 4.7–21.1%] vs 1.0% [IQR 0–20.1%] vs 0.2% [IQR 0–4.6%], P = 0.013) postprandial hour after the high-fat meal was higher in patients with RE than in those with NERD and healthy subjects.

There was no significant difference in postprandial EAE at 4 hours after the same meal at lunch, dinner, and breakfast in C1 (Supporting Information Figure S1).

3.3 | Comparison of reflux symptoms after different test meals in patients with GERD

No significant difference in the number of postprandial reflux symptoms among the standard, high-fat, and functional food meals was found in patients with RE (1 [IQR 0–2] vs 1 [IQR 0–1] vs 1 [IQR 0–2], P = 0.537). However, the number of postprandial reflux symptoms was lower after the functional food meal than that after the high-fat
and standard meals in patients with NERD (0 [IQR 0–1] vs 1 [IQR 0–2] vs 3 [IQR 1–4], P = 0.014).

3.4 | Comparison of gastric acidity among different test meals

The percentage time of pH <4 and mean pH in the gastric fundus and gastric body were comparable before all the three kinds of test meals in patients with RE. And no significant difference in the percentage time of pH <4 was found in the gastric fundus after different meals (Figure 5A). The mean pH at the first and third postprandial hour in the gastric fundus was higher after the functional food meal than after the high-fat meal, and at the third postprandial hour it was also higher than that after the standard meal (Figure 5B). In the gastric body, the percentage time of pH <4 at the first postprandial hour was lower after the functional food meal than after the high-fat and standard meals (Figure 5C). In addition, the mean pH of the gastric body was higher after the functional food meal than after the high-fat meal at the first, second, third, and fourth postprandial hour (Figure 5D).
The percentage time of pH <4 and mean pH in the gastric fundus and gastric body of patients with NERD and healthy subjects showed no significant difference among the three test meals (P > 0.05).

3.5 | Correlation of EAE and gastric acidity in patients with GERD

The 26-hour monitoring data demonstrated that the number of acid exposures in the distal esophagus was negatively correlated with the mean pH of the gastric fundus in patients with RE (Figure 6A). The pH parameters of the upper border of the LES were also correlated with gastric acidity (Figures 6B–E). Even at night, the EAE and number of acid exposures in the distal esophagus were positively correlated with the percentage time of pH <4 in the gastric fundus (r = 0.81 and r = 0.70, both P < 0.05). No correlation was observed between EAE and gastric acidity in patients with NERD (data not shown).

4 | DISCUSSION

In the present study, we enrolled both patients with RE and NERD as well as healthy subjects, and isovolumetric and isocaloric high-fat, standard, and functional food meals were tested to eliminate the influence of diet volume and calorie content on EAE. The meals were randomly assigned to minimize the effects of test meals on the fasting status of the next meal. We found that a high-fat meal significantly increased postprandial EAE in patients with RE and NERD while a functional food meal reduced reflux symptoms in patients with NERD.

Reflux symptoms are usually triggered and aggravated by greasy foods; however, previous studies on the effects of high-fat meals on EAE have shown inconsistent results. Fox et al. found no difference in EAE between high-fat (50%) and low-fat (25%) diets in patients with GERD without classifying it into RE and NERD. The present study showed that EAE in the distal esophagus and upper border of the LES increased after a high-fat meal in patients with RE and NERD after controlling the meal volume and calorie content. EAE at the first and third postprandial hour was more severe in patients with RE than in those with NERD, indicating that patients with RE responded more strongly to the high-fat meal. The high-fat meal increased EAE in patients with RE compared with standard and functional food meals at 4 hours after the meal, but it had no effect on reflux symptoms during pH monitoring.

The 4-electrode pH monitoring system described in this study can record simultaneously the pH of the distal esophagus, the upper border of the LES, the gastric fundus, and the gastric body. The site of the electrode in the upper border of the LES in this study was quite close to the monitoring site for short-segment reflux. In patients with GERD, simultaneous monitoring of the pH in the upper border of the LES detected short-segment reflux in 80% of the patients with normal EAE in the distal esophagus, indicating that synchronous pH
monitoring of the very distal esophagus may enhance the diagnostic yield of acid exposure in patients with GERD.

The present study demonstrates that at night gastric acidity in the gastric fundus is significantly correlated with distal EAE in patients with RE, which may be related to the night-time symptoms. Additionally, the acidity in the gastric body influenced the number of acid exposures of the upper border of the LES. Thus, it can be concluded that gastric acidity is closely related to EAE, especially in patients with RE.

This novel study showed the effects of functional food on EAE of patients with GERD. The limitations of PPIs in the treatment of GERD and the potential risk of their long-term use enhance the importance of adjuvant therapies. One study revealed that the percentage of complete regression of symptoms after dietary supplementation with melatonin, multivitamins, and betaine for 40 days in patients with GERD was superior to that in patients undergoing treatment with omeprazole at 20 mg/day. In the present study, the functional food meal reduced the number of reflux symptoms in patients with NERD, although there was no significant decrease in EAE. The functional food meal reduced the percentage time of pH <4 in the gastric body and elevated the mean pH in the gastric fundus and gastric body compared with the high-fat and standard meals. The fat content of the functional food and standard meals was 25%, and the carbohydrate and protein content was similar. More importantly, the pH of the functional food meal was 6.5 and its effect on gastric pH lasted for ≥4 hours, suggesting that the effect resulted from the inhibition of acid secretion rather than a buffering effect. Functional foods are derived from natural substances and contain biological active components that are intended to be consumed as part of the normal diet and offer the potential of enhanced health or reduced risk of disease. It also contains several traditional Chinese medicines such as A. villosum and tangerine peel. The composition of the functional food used in this study was based on nutritional intervention and function modulation. Marine collagen peptides stimulate epithelial cells to synthesize collagen, which is an important component of the intercellular matrix. Studies have shown that marine collagen peptides may reduce vascular endothelial cell injury and improve healing in skin wounds following cesarean section in rats. The wheat oligopeptides help to maintain the structural integrity of gastrointestinal epithelial cells and may protect intestinal epithelial cells from oxidative stress.

FIGURE 5 Percentage time of pH <4 and mean pH before and after the intake of (■) the high-fat meal, (○) standard meal and (–) functional food meal in the (A,B) gastric fundus and (C,D) gastric body. Postprandial intragastric pH parameters with different meals in patients with reflux esophagitis. P < 0.05 compared with *high-fat meal and **standard meal.
Isomaltooligosaccharide may promote the intestinal bifidobacteria proliferation and improve intestinal excretory functions, as well as ameliorate visceral hyperalgesia with repairing damage to the ileal epithelial ultrastructure in irritable bowel syndrome rat models. A. villosum increases the release of prostaglandin E2 from the gastric mucosa, thus reducing acid secretion. Studies with large sample sizes are needed to verify the clinical adjuvant therapeutic effects of functional food.

This study had some limitations. Our sample size was relatively small, and inconsistencies in the demographic data might have influenced the results. Patients with RE had mild-to-moderate erosive lesions (Los Angeles A and B). In this study, we aimed to investigate...
the effects of three different test meals in 26-hour pH monitoring. In order to minimize the effects of test meals on the fasting status of the next meal, we randomized the order of meals in the participants. However, the effect of a high-fat meal may last for 4 hours after meal which may have an effect on the fasting status of the next meal. In addition, classic Chinese foods were selected for the test meals, which are seldom used in the studies abroad. Finally, we did not discuss the relationship between esophageal motility and the effects of different meals on EAE in this article since the relevant data have been published elsewhere.19

In conclusion, a high-fat meal significantly increased postprandial EAE in patients with RE and NERD. Synchronous monitoring of the pH in the upper border of the LES may enhance the diagnostic yield of acid exposure in patients with GERD. In patients with RE, EAE was closely related to gastric acidity in the gastric fundus and gastric body. Functional food may have adjuvant therapeutic effects in patients with GERD. The results of the present study may provide evidence for optimizing dietary modifications and developing functional food for patients with GERD.

ACKNOWLEDGMENTS

We thank Dr. Tao XU from the Department of Epidemiology and Statistics, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences & School of Basic Medicine, Peking Union Medical College (Beijing, China) for his statistical support. The authors also thank the postgraduate student Ming Wei SONG from Tianjin Medical University General Hospital for her helpful contributions to the test meals. Finally, the authors thank Angela MORBEN from the Edanz Group for language editing of this article. This work was supported by the National High Technology Research and Development Program of China (no. 2010AA023007).

CONFLICTS OF INTEREST

None.

REFERENCES

1. Vakil N, van Zanten SV, kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101(8):1900-1920.
2. Okimoto E, Ishimura N, Morito Y, et al. Prevalence of gastroesophageal reflux disease in children, adults, and elderly in the same community. J Gastroenterol Hepatol. 2015;30(7):1140-1146.
3. Matsuji N, Fujita T, Watanabe N, et al. Lifestyle factors associated with gastroesophageal reflux disease in the Japanese population. J Gastroenterol. 2013;48(3):340-349.
4. DeVault KR, Castell DO; American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol. 2005;100(1):190-200.
5. Sandhu DS, Fass R. Current trends in the management of gastroesophageal reflux disease. Gut Liver. 2018;12(1):7-16.
6. Iwakiri K, Kobayashi M, Kotoyori M, Yamada H, Sugitara T, Nakagawa Y. Relationship between postprandial esophageal acid exposure and meal volume and fat content. Dig Dis Sci. 1996;41(5):926-930.
7. Wu KL, Rayner CK, Chuah SK, et al. Effect of liquid meals with different volumes on gastroesophageal reflux disease. J Gastroenterol Hepatol. 2014;29(3):469-473.
8. Pehl C, Pfeiffer A, Waizenhoefer A, Wendl B, Schepp W. Effect of caloric density of a meal on lower oesophageal sphincter motility and gastro-esophageal reflux in healthy subjects. Aliment Pharmacol Ther. 2001;15(2):233-239.
9. Fox M, Barr C, Nolan S, Lomer M, Anggiansah A, Wong T. The effects of dietary fat and calorie density on esophageal acid exposure and reflux symptoms. Clin Gastroenterol Hepatol. 2007;5(4):439-444.
10. Sun XH, Ke MY, Wang ZF, Fang XC. Characteristics of esophageal motility in patients with non-erosive reflux disease and reflux esophagitis. Natl Med J China. 2014;9(42):1718-1721. (in Chinese).
11. Nam SY, Park BJ, Cho YA, et al. Different effects of dietary factors on reflux esophagitis and non-erosive reflux disease in 11,690 Korean subjects. J Gastroenterol. 2017;52(7):818-829.
12. Gardner JD, Sloan S, Minner PB, Robinson M. Meal-stimulated gastric acid secretion and integrated gastric acidity in gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2003;17(7):945-953.
13. El-Serag H, Becher A, Jones R. Systematic review: persistent reflux symptoms on proton pump inhibitor therapy in primary care and community studies. Aliment Pharmacol Ther. 2010;32(6):720-737.
14. Kawara F, Fujita T, Morita Y, et al. Factors associated with residual gastroesophageal reflux disease symptoms in patients receiving proton pump inhibitor maintenance therapy. World J Gastroenterol. 2017;23(11):2060-2067.
15. Min YW, Shin YW, Cheon GJ, et al. Recurrence and its impact on the health-related quality of life in patients with gastroesophageal reflux disease: a prospective follow-up analysis. J Neurogastroenterol Motil. 2016;22(1):86-93.
16. Kim YG, Graham DY, Jang BI. Proton pump inhibitor use and recurrent Clostridium difficile-associated disease: a case-control analysis matched by propensity score. J Clin Gastroenterol. 2012;46(5):397-400.
17. Armstrong D, Bennett JR, Blum AL, et al. The endoscopic assessment of esophagitis: a progress report on observer agreement. Gastroenterology. 1996;111(1):85-92.
18. Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. Gut. 2001;49(1):145-151.
19. Hou YT, Sun XH, Li QX, et al. Esophageal motility abnormalities and their impact on esophageal acid exposure in patients with gastroesophageal reflux disease. Chin J Intern Med. 2015;54(10):865-869. (in Chinese).
20. Xue Y, Zhou LY, Lin SR. Dilated intercellular spaces in gastroesophageal reflux disease patients and the change of intercellular spaces after omeprazole treatment. Chin Med J (Engl). 2008;121(14):1297-1301.
21. Vigneri S, Termini R, Leandro G, et al. A comparison of five maintenance therapies for reflux esophagitis. N Engl J Med. 1995;333(17):1106-1110.
22. Johnson LF, DeMeester TR. Development of the 24-hour intraesophageal pH monitoring composite scoring system. J Clin Gastroenterol. 1986;8(suppl):52-58.
23. Wenner J, Johansson F, Johansson J, Oberg S. Acid reflux immediately above the squamocolumnar junction and in the distal esophagus: simultaneous pH monitoring using the wireless capsule pH system. Am J Gastroenterol. 2006;101(8):1734-1741.
24. Bansal A, Wani S, Rastogi A, et al. Impact of measurement of esophageal acid exposure close to the gastroesophageal junction on diagnostic accuracy and event–symptom correlation: a prospective study using wireless dual pH monitoring. Am J Gastroenterol. 2009;104(12):2918-2925.
25. Fletcher J, Wirz A, Henry E, McCol KE. Studies of acid exposure immediately above the gastro-oesophageal squamocolumnar junction: evidence of short segment reflux. Gut. 2004;53(2):168-173.
26. Gawron AJ, Rothe J, Fought AJ, et al. Many patients continue using proton pump inhibitors after negative results from tests for reflux disease. Clinic Gastroenterol Hepatol. 2012;10(6):620-625.
27. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. Gastroenterology. 2017;152(4):706-715.
28. Pereira Rde S. Regression of gastroesophageal reflux disease symptoms using dietary supplementation with melatonin, vitamins and aminoacids comparison with omeprazole. J Pineal Res. 2006;41(3):195-200.
29. Serafini M, Stanzione A, Foddaí S. Functional foods: traditional use and European legislation. Int J Food Sci Nutr. 2012;63(suppl):7-9.
30. Yamada S, Nagaoka H, Terajima M, Tsuda N, Hayashi Y, Yamauchi M. Effects of fish collagen peptides on collagen post-translational modifications and mineralization in an osteoblastic cell culture system. Dent Mater J. 2013;32(1):88-95.

31. Itoh H, Aso Y, Furuse M, Noishiki Y, Miyata T. A honeycomb collagen carrier for cell culture as a tissue engineering scaffold. Artif Organs. 2001;25(3):213-217.

32. Zhu C, Zhang W, Liu J, et al. Marine collagen peptides reduce endothelial cell injury in diabetic rats by inhibiting apoptosis and the expression of coupling factor 6 and microparticles. Mol Med Rep. 2017;16(4):3947-3957.

33. Wang J, Xu M, Liang R, Zhao M, Zhang Z, Li Y. Oral administration of marine collagen peptides prepared from chum salmon (Oncorhynchus keta) improves wound healing following cesarean section in rats. Food Nutr Res. 2015;59:26411.

34. You X. Food additives and functional ingredients. China Food Additives. 2008;1:43-51. (in Chinese).

35. Zhang YZ, Jiang SM, Wei Y, et al. The protective effect of wheat oligopeptides on oxidative stress in intestinal epithelial cells in vitro. Food Fermentat Ind. 2015;41(1):46-50. (in Chinese).

36. Wang W, Xin H, Fang X, et al. Isomalt-oligosaccharides ameliorate visceral hyperalgesia with repair damage of ileal epithelial ultrastructure in rats. PLoS One. 2017;12(4):e0175276.

37. Chien MY, Lin YT, Peng FC, et al. Gastroprotective potential against indomethacin and safety assessment of the homology of medicine and food formula cuttlebone complex. Food Funct. 2015;6(8):2803-2812.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.