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【 ORIGINAL ARTICLE 】

Different Food Preferences in Patients with Gastrointestinal Disorders

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Abstract:

Objective Gastrointestinal (GI) disorders such as functional dyspepsia (FD), irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), and inflammatory bowel disease (IBD) can exhibit overlapping GI symptoms, including abdominal pain and alterations in bowel habits. The symptoms of GI disorders are commonly considered to be triggered and exacerbated by fatty food intake. Therefore, this study aimed to compare the food preferences of patients with GI disorders.

Methods Forty food images (including fatty and light foods) and 20 animal images were selected to evaluate food preferences. The preference score was assessed using a visual analog scale ranging from 1 to 100. GI symptoms were evaluated using the GI Symptom Rating Scale (GSRS), and correlations between the GSRS and preference scores were investigated.

Results Overall, 22 healthy controls and 23, 29, 27, and 20 patients with FD, IBS, GERD, and IBD, respectively, were enrolled. The preference score for all foods in patients with FD was significantly lower than that in healthy controls and those with IBS, GERD, and IBD (52.9 vs. 66.5 vs. 68.5 vs. 69.1 vs. 70.7, $p< 0.01$). The score of fatty foods was lower in patients with FD than in healthy controls and those with IBS, GERD, and IBD (43.8 vs. 72.3 vs. 77.5 vs. 77.4 vs. 80.7, $p<0.01$), whereas that of light foods and animal images was not different among the groups. No significant correlation was found between the preference score and symptom severity.

Conclusion Patients with FD had a negative preference for foods, particularly fatty foods, independent of the severity of GI symptoms.

Key words: functional dyspepsia, irritable bowel syndrome, gastroesophageal reflux disease, inflammatory bowel disease, food preference

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Introduction

Disorders of gut-brain interaction (DGBI) are clinically diagnosed as conditions with subjective gastrointestinal (GI) symptoms without organic abnormalities (1). Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are major entities of DGBIs (2, 3). In addition to abdominal pain, FD and IBS are characterized by postprandial abdominal discomfort and alterations in bowel habits, respectively. Food intake and DGBI symptoms are strongly correlated. Previous studies have shown that fatty food intake can result in

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symptom emergence and exacerbation in patients with FD (4) and IBS (5).

Gastroesophageal reflux disease (GERD) induces reflux symptoms through the backward flow of stomach contents to the esophagus (6). Food intake is uncontroversially associated with the GERD pathophysiology because it can lead to increased gastric acid secretion, thus resulting in an impairment of the esophageal epithelium. In particular, fat intake leads to a relaxation of the lower esophageal sphincter, which can trigger reflux of the gastric contents (7). Fat intake is a well-known risk factor for GERD; however, it remains unclear whether patients with GERD prefer fatty foods.

Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD), which mainly manifest as abdominal symptoms, such as abdominal pain and diarrhea (8). This disease entity is also strongly associated with food intake. Furthermore, eliminating fatty foods has been proven beneficial for symptom relief in patients with CD (9) and UC (10). However, whether or not such patients prefer fatty foods remains to be adequately investigated.

Although the symptoms of DGBI, GERD, and IBD overlap and food intake is associated with all disorders, food preferences can differ among disorders. A previous study revealed that the food preference score of patients with FD was lower than that of patients with IBS (11). However, the differences between FD, IBS, GERD, and IBD have not been sufficiently confirmed, and the relationship between symptom severity and food preference remains unclear.

Therefore, this study aimed to compare the food preferences of FD, GERD, IBS, and IBD patients and investigate the correlation between symptom severity and food preference. We hypothesized that only patients with FD would show a negative preference for fatty foods, as we observed numerous cases among those with GERD and IBD despite advising against excessive consumption of fatty foods. Furthermore, we assumed that the symptom scores were negatively correlated with the food preference scores.

Materials and Methods

Study design and participants

This prospective observational study was conducted in Kawasaki between July 2022 and November 2023. The Research Ethics Committee of Kawasaki Medical School and Hospital approved the study protocol (IRB No.: 5696-02), and informed consent was obtained from each participant.

This study was conducted in accordance with the principles of the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (12).

FD and IBS were diagnosed and classified using ROME IV criteria (2, 3). We enrolled participants with reflux symptoms with reflux esophagitis (RE) grade A or B according to the Los Angeles classification as patients with GERD (13, 14). IBD, including UC and CD, was diagnosed using the Japanese clinical practice guidelines (15). All patients with IBD were in the remission stage and did not experience exacerbation or require additional treatment in the last 1 month. Healthy controls were enrolled from among those who underwent routine medical checkups without any GI symptoms. The exclusion criteria were as follows: age < 18 or >70 years, active malignant disorders, severe depressive mental state, and use of medication associated with appetite. We excluded older adults because of physiological [including a decrease in saliva secretion (16) and loss of taste and smell sensation (17)] and psychological (such as an increase in dementia and depression prevalence) factors (18). Other comorbidities, including cardiac failure (19) and psychological factors such as an increase in dementia prevalence, were also considered to exclude older participants (20).

Age, sex, body mass index (BMI), alcohol drinking status, smoking status, subjective food hypersensitivity, and other comorbidities, including hypertension and diabetes mellitus, were investigated and compared among the groups. Patients were categorized as having disorders that induced the chief symptoms when they experienced the overlapping symptoms of FD, GERD, IBS, and IBD. Based on previous studies (11, 12), the appropriate sample size was set as at least 17 participants in each group, and statistical parameters α and 1-β were set as 0.05 and 0.81, respectively (21).

Questionnaire for GI symptoms

We used the GI Symptom Rating Scale (GSRS) because it can cover various symptoms such as pain, bloating, constipation, and diarrhea (22). Fifteen questions were scored on a scale of 1-7, and five major sub-scores (reflux, abdominal pain, indigestion, diarrhea, and constipation) were calculated.

Food image and categorization

Forty food and 20 animal images were included as a control task to assess food preference (Fig. 1). Subjective food fattiness was ranked by 40 healthy participants, and fat content was evaluated to categorize food images into fatty and light foods. Foods with at least 20 g of fat per 100 g were ranked in the top 10, and those with at most 4 g of fat per 100 g were ranked in the last 10 and were defined as fatty and light foods, respectively.

Evaluation of food preference

A visual analog scale (VAS) ranging from 1 (dislike) to 100 (like) was used to evaluate preference. Participants were instructed to indicate their liking for food on a scale from 1 (dislike) to 100 (like) (Supplementary material 1). All questionnaires were administered in a fasting state for at least 6 h from the last meal.

Statistical analysis

Continuous data (such as age and BMI) were expressed

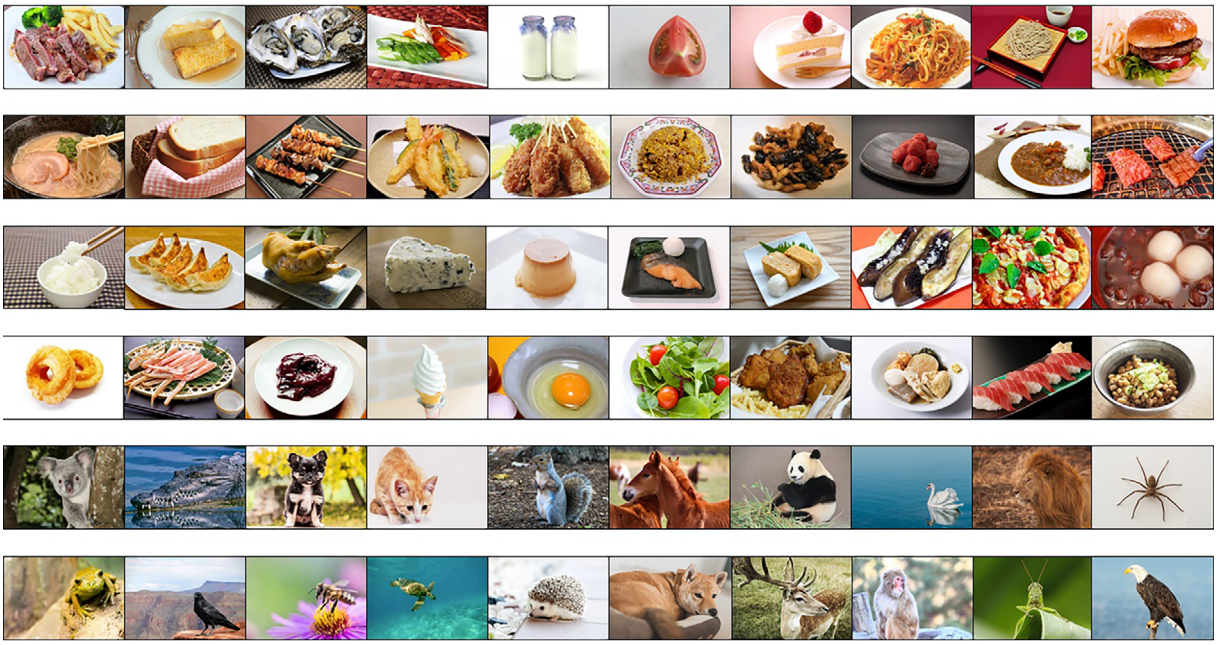

Figure 1. **Images used to evaluate preference. Forty different food images, including 10 fatty foods, 10 light food images, and 20 animal images were included. The rights to use all images were secured from the copyright owner for inclusion in this study.**

Table 1. **Comparison of Clinical Background among Healthy Controls and Patients with Functional Dyspepsia, Gastroesophageal Reflux Disease, Irritable Bowel Syndrome, and Inflammatory Bowel Disease.**

Variables	Control (n=22)	FD (n=23)	IBS (n=29)	GERD (n=27)	IBD (n=20)	p values
Age [mean (IQR), year]	46.5 (28-58)	40.3 (35-45)	43.1 (38-48)	49.1 (42-55)	45.6 (40-52)	0.11[a]
Male sex [n (%)]	9 (40.9)	4 (17.3)	7 (24.1)	9 (33.3)	9 (45.0)	0.18[b]
BMI [mean (SD), kg/m^2]	22.8 (2.6)	21.4 (2.5)	22.1 (3.4)	23.5 (2.7)	22.6 (3.0)	0.36[a]
Alcohol: current drinker [n (%)]	4 (18.1)	3 (13.0)	6 (20.6)	7 (25.9)	4 (20.0)	0.85[b]
Smoking [n (%)]	0 (0)	0 (0)	3 (10.3)	5 (18.5)	2 (10.0)	0.28[b]
Food allergy [n (%)]	3 (13.6)	6 (26.0)	8 (27.5)	4 (14.8)	1 (5.0)	0.28[b]
Disease duration [mean (SD), year]	0 (0)	8.9 (6.5)	11.2 (8.4)	14.1 (8.2)	9.5 (5.2)	0.14[a]

BMI: body mass index, IQR: interquartile range, FD: functional dyspepsia, GERD: gastroesophageal reflux disease, IBD: inflammatory bowel disease, IBS: irritable bowel syndrome, SD: standard deviation, n: number

p values were calculated using analysis of variance (ANOVA)[a] or chi-square test[b].

as the means, and categorical data (including sex and current smoking) were presented as counts and percentages. Interquartile ranges (IQRs) are calculated for age. An analysis of variance, chi-square test, and Kruskal-Wallis test were used to compare variables among the five groups. The correlation between the symptoms and preference scores was determined using Spearman's test. All statistical analyses were performed using the MATLAB software program (MathWorks, Natick, United States), and two-sided p values <0.05 were considered statistically significant.

Results

Background and GI symptoms

We enrolled 22 healthy controls and 23, 29, 27, and 20 patients with FD, IBS, GERD, or IBD, respectively. Table 1 presents the clinical characteristics of each group. The status was similar in all groups with respect to age, sex, BMI, drinking, smoking, and food allergy. Supplementary material 2 presents the comorbidities, disease subtypes, and overlapping diseases among the groups.

Table 2 shows the GSRS scores for each group. Reflux scores were significantly higher in patients with FD and GERD than in healthy controls and patients with IBS and IBD. Additionally, abdominal pain scores were significantly higher in patients with FD, IBS, GERD, and IBD than in the healthy controls. The indigestion scores of patients with FD, IBS, and IBD were significantly higher than those of healthy controls and individuals with GERD. Diarrhea scores were significantly higher in patients with IBS and IBD than in those with FD, GERD, and healthy controls. Furthermore, the constipation scores were significantly higher in patients with FD, IBS, and IBD than in those with

Table 2. Comparison of Gastrointestinal Symptom Scores among Healthy Controls and Patients with Functional Dyspepsia, Gastroesophageal Reflux Disease, Irritable Bowel Syndrome, and Inflammatory Bowel Disease.

Variables	Control (n=22)	FD (n=23)	IBS (n=29)	GERD (n=27)	IBD (n=20)	p values
GSRS score [mean (SD)]						
Reflux	1.10 (0.3)	2.54 (1.1)	1.67 (0.8)	3.20 (0.9)	1.60 (0.8)	<0.01
Abdominal pain	1.06 (0.2)	2.65 (0.9)	2.63 (1.0)	1.95 (0.4)	2.69 (0.7)	<0.01
Indigestion	1.12 (0.3)	2.64 (1.3)	2.56 (1.0)	1.74 (0.6)	2.05 (0.6)	<0.01
Diarrhea	1.06 (0.3)	2.24 (1.1)	3.61 (1.6)	1.66 (0.7)	3.86 (1.3)	<0.01
Constipation	1.32 (0.4)	2.25 (1.0)	2.75 (1.4)	1.36 (0.5)	2.12 (1.2)	<0.01
Average	1.14 (0.2)	2.49 (0.7)	2.64 (0.8)	1.92 (0.4)	2.49 (0.6)	<0.01

FD: functional dyspepsia, GERD: gastroesophageal reflux disease, GSRS: gastrointestinal symptom rating scale, IBD: inflammatory bowel disease, IBS: irritable bowel syndrome, SD: standard deviation
p values were calculated using analysis of variance.

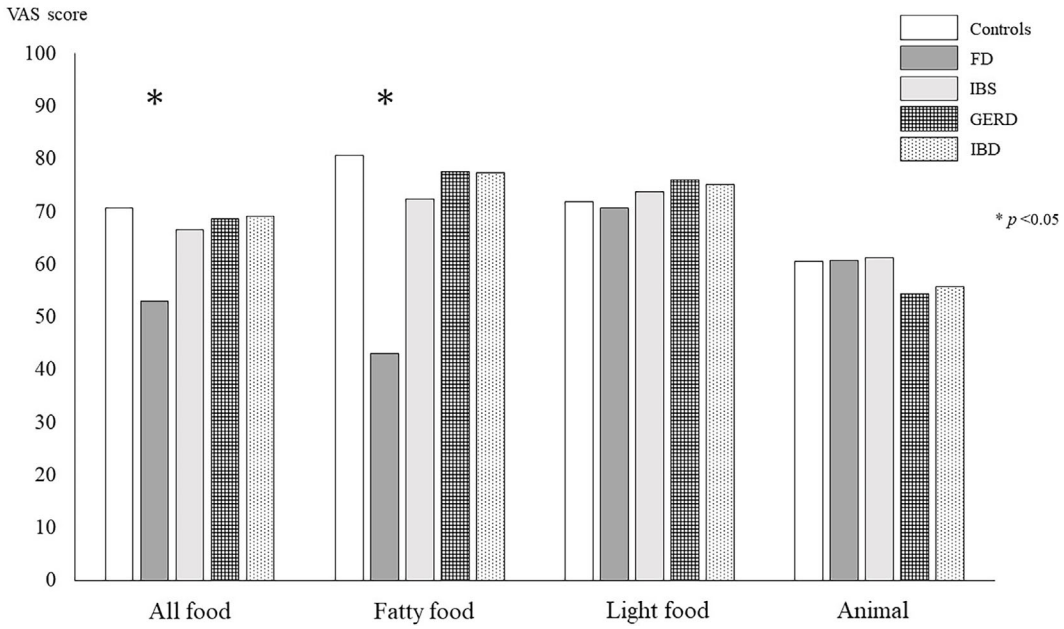

Figure 2. Comparison of the preference shown in the mean VAS scores. The bar plots and error bars indicate the mean VAS score and standard error in each group, respectively. The data were analyzed using ANOVA with the Tukey-Kramer post-hoc test. ANOVA: analysis of variance, FD: functional dyspepsia, GERD: gastroesophageal reflux disease, IBD: inflammatory bowel disease, VAS: visual analog scale

GERD and in healthy controls.

Food preference

Fig. 2 shows the mean VAS scores for each section. In all foods, the preference score was significantly lower in patients with FD than in healthy controls and those with IBS, GERD, and IBD (52.9 vs. 66.5 vs. 68.5 vs. 69.1 vs. 70.7, p <0.01). Similarly, the score of fatty foods was significantly lower in patients with FD than in healthy controls and those with IBS, GERD, and IBD (43.8 vs. 72.3 vs. 77.5 vs. 77.4 vs. 80.7, p<0.01). However, no significant differences in light-food and animal images were found among the five groups (Supplementary material 3).

Fig. 3 shows the correlation between the preference and total symptom scores. No significant correlation was found between each preference score in all categories (A: all food, B: fatty food, C: light food, and D: animal images) and the total symptom scores in patients with FD who had lower preference scores for foods. However, preference scores tended to be negatively correlated with GSRS scores for all foods and fatty foods. Moreover, in the other groups, no correlation was found among all the image groups (data not shown).

Discussion

To our knowledge, this is the first study to show differences in food preferences among various GI disorders. Although patients in all disease groups exhibited GI symptoms, including abdominal pain, their preferences for food differed. Patients with FD had lower scores for all foods and fatty foods than healthy controls, whereas those with GERD,

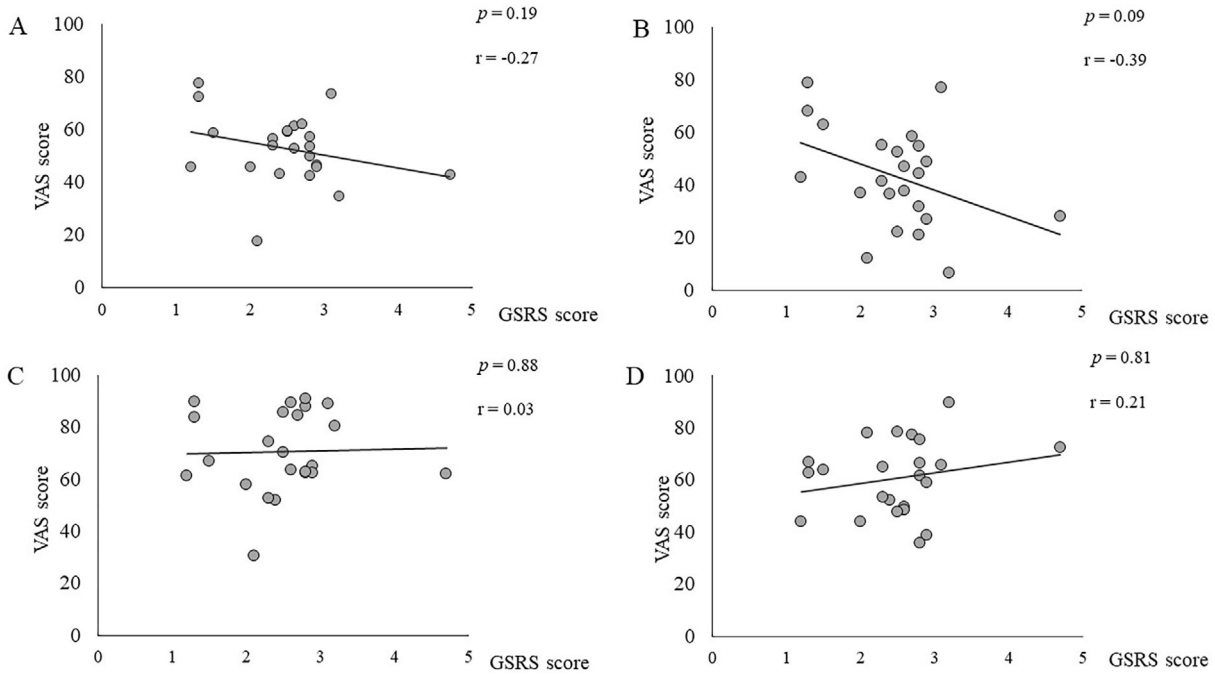

Figure 3. Correlations between preference and total symptom scores in patients with FD. A) Correlation between preference score of all foods and total GSRS score. B) Correlation between preference score of fatty foods and total GSRS score. C) Correlation between preference score of light foods and total GSRS score. D) Correlation between preference score of animal images and total GSRS score. The data were analyzed using the Spearman test, and "r" indicates the Pearson's correlation coefficient. FD: functional dyspepsia, GSRS: Gastrointestinal Symptom Rating Scale

IBS, and IBD exhibited preference scores similar to those of the healthy controls. Furthermore, no significant correlation was found between the food preference scores and symptom severity in patients with FD.

Patients with FD exhibited lower preferences for food than those with GERD, IBS, IBD, and healthy controls, which is partly consistent with a previous study (11). Additionally, the differences between FD, IBS, GERD, and IBD were confirmed in this study. The different duration from food intake to symptom emergence was suggested as the reason why patients with FD had lower preference scores than those with IBS (11). However, patients with GERD experience GI symptoms immediately after food intake. The reason why patients with GERD and IBD do not exhibit negative food preferences is not clearly understood. One possible explanation might be that the symptoms can be controlled to some extent using anti-acids (14, 23, 24) and immune modulators (15, 25, 26) in patients with GERD and IBD, respectively. In contrast, patients with FD tended to have difficulty controlling their abdominal symptoms. Only 30-50% of patients with FD can achieve symptom relief with first-line therapy (27). However, other factors, such as processing in the central nervous system and biological conditions (including differences in serum appetite hormones), should be assessed in future studies.

As expected, the preference scores for foods in patients with GERD and IBD were similar to those in healthy controls, even though they had abdominal symptoms triggered by food intake. A systematic review revealed that a high-fat diet is associated with exacerbation of GERD and is a crucial risk factor (28). We have experienced scenarios in clinical situations in which patients with GERD or IBD consume fatty foods that could worsen abdominal symptoms, thus leading to the exacerbation of their symptoms, despite their understanding that fatty food could trigger abdominal symptoms. Our study data confirmed that they did not have negative emotions about food, which can trigger abdominal symptoms, and this finding is consistent with the abovementioned episode. Therefore, based on our data, physicians should consider patients' emotions in clinical settings, and strict patient education should be provided, particularly for patients with GERD, IBD, and IBS. Exploring other GI disorders, such as non-erosive reflux disease and chronic constipation, can thus provide further understanding and findings for better clinical management of GI disorders.

Notably, no significant correlation was found between preference and total symptom scores, although a tendency was detected, indicating that negative food preference was related to more severe GI symptoms. Psychologically, fear conditioning can be long-lasting and difficult to extinguish once it is established (29, 30). However, GI symptoms can fluctuate in patients with FD (31). Therefore, patients with FD may have had fear conditioning to fatty foods, even though their GI symptoms were not severe. Based on our findings, once a negative preference for food has been established, it might become fixed and independent of the exis-

tence of GI symptoms in patients with FD. Therefore, a longitudinal assessment of the same population can provide further insight into our hypothesis.

This study is associated with some limitations. First, heterogeneous patients were included and they were not limited by age, treatment, severity or duration. This finding may be associated with several types of bias. However, it can also indicate that our results may reflect the situation of the entire general population. Second, the results were based only on subjective scores. Therefore, future assessments of all participants should include objective data, such as pulse rate and brain activity (32), to confirm the authenticity of the scores. Third, the task used in this study was our original creation and it was not internationally validated. Currently, there is no globally accepted image set for evaluating food preferences, including those for fatty and light foods. Therefore, we developed an original task to assess the food preferences tailored to the Japanese population. However, to ensure objectivity, we categorized the foods based on objective fat content and evaluated subjective fattiness using questionnaires for the general population other than the participants in this study.

In conclusion, patients with FD exhibited negative preferences for foods, particularly fatty foods, compared to those with other GI disorders such as GERD, IBS, and IBD. Furthermore, such preferences were not associated with the symptom severity in this study. Therefore, these results provide beneficial insights into the pathophysiology of GI disorders, and the clinical management and understanding of patients with GI disorders.

This study was reviewed and approved by the Research Ethics Committee of Kawasaki Medical School and Hospital, and written informed consent was obtained from all the patients.

The authors state that they have no Conflict of Interest (COI).

References

1. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology **150**: 1262-1279, 2016.
2. Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal disorders. Gastroenterology **150**: 1380-1392, 2016.
3. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. Gastroenterology **150**: 1393-1407, 2016.
4. Pilichiewicz AN, Feltrin KL, Horowitz M, et al. Functional dyspepsia is associated with a greater symptomatic response to fat but not carbohydrate, increased fasting and postprandial CCK, and diminished PYY. Am J Gastroenterol **103**: 2613-2623, 2008.
5. Simrén M, Månsson A, Langkilde AM, et al. Food-related gastrointestinal symptoms in the irritable bowel syndrome. Digestion **63**: 108-115, 2001.
6. Maret-Ouda J, Markar SR, Lagergren J. Gastroesophageal reflux disease: a review. JAMA **324**: 2536-2547, 2020.
7. Holloway RH, Lyrenas E, Ireland A, Dent J. Effect of intraduodenal fat on lower oesophageal sphincter function and gastro-oesophageal reflux. Gut **40**: 449-453, 1997.
8. Tavakoli P, Vollmer-Conna U, Hadzi-Pavlovic D, Grimm MC. A review of inflammatory bowel disease: a model of microbial, immune and neuropsychological integration. Public Health Rev **42**: 1603990, 2021.
9. Sakamoto N, Kono S, Wakai K, et al.; Epidemiology Group of the Research Committee on Inflammatory Bowel Disease in Japan. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. Inflamm Bowel Dis **11**: 154-163, 2005.
10. Fritsch J, Garces L, Quintero MA, et al. Low-fat, high-fiber diet reduces markers of inflammation and dysbiosis and improves quality of life in patients with ulcerative colitis. Clin Gastroenterol Hepatol **19**: 1189-1199.e30, 2021.
11. Katsumata R, Hosokawa T, Manabe N, et al. Brain activity in response to food images in patients with irritable bowel syndrome and functional dyspepsia. J Gastroenterol **58**: 1178-1187, 2023.
12. von Elm E, Altman DG, Egger M, et al.; the STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet **370**: 1453-1457, 2007.
13. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut **45**: 172-180, 1999.
14. Iwakiri K, Fujiwara Y, Manabe N, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2021. J Gastroenterol **57**: 267-285, 2022.
15. Nakase H, Uchino M, Shinzaki S, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease 2020. J Gastroenterol **56**: 489-526, 2020.
16. Ship JA, Pillemer SR, Baum BJ. Xerostomia and the geriatric patient. J Am Geriatr Soc **50**: 535-543, 2002.
17. Di Francesco V, Fantin F, Residori L, et al. Effect of age on the dynamics of acylated ghrelin in fasting conditions and in response to a meal. J Am Geriatr Soc **56**: 1369-1370, 2008.
18. Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. JAMA **288**: 2307-2312, 2002.
19. Pilgrim AL, Robinson SM, Sayer AA, Roberts HC. An overview of appetite decline in older people. Nurs Older People **27**: 29-35, 2015.
20. Goldberg SE, Whittamore KH, Harwood RH, et al. The prevalence of mental health problems among older adults admitted as an emergency to a general hospital. Age Ageing **41**: 80-86, 2012.
21. Fleiss JL, Tytun A, Ury HK. A simple approximation for calculating sample sizes for comparing independent proportions. Biometrics **36**: 343-346, 1980.
22. Svedlund J, Sjödin I, Dotevall G. GSRS - a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci **33**: 129-134, 1988.
23. Tran T, Lowry AM, El-Serag HB. Meta-analysis: the efficacy of over-the-counter gastro-oesophageal reflux disease therapies. Aliment Pharmacol Ther **25**: 143-153, 2007.
24. Oshima T, Arai E, Taki M, et al. Randomised clinical trial: vonoprazan versus lansoprazole for the initial relief of heartburn in patients with erosive oesophagitis. Aliment Pharmacol Ther **49**: 140-146, 2019.
25. Cai Z, Wang S, Li J. Treatment of inflammatory bowel disease: a comprehensive review. Front Med (Lausanne) **8**: 765474, 2021.
26. Peyrin-Biroulet L, Lémann M. Review article: remission rates achievable by current therapies for inflammatory bowel disease. Aliment Pharmacol Ther **33**: 870-879, 2011.
27. Miwa H, Nagahara A, Asakawa A, et al. Evidence-based clinical practice guidelines for functional dyspepsia 2021. J Gastroenterol **57**: 47-61, 2022.
28. Zhang M, Hou ZK, Huang ZB, Chen XL, Liu FB. Dietary and lifestyle factors related to gastroesophageal reflux disease: a systematic review. Ther Clin Risk Manag **17**: 305-323, 2021.

29. Chambers KC. Conditioned taste aversions. World J Otorhinolaryngol Head Neck Surg **4**: 92-100, 2018.
30. Garb JL, Stunkard AJ. Taste aversions in man. Am J Psychiatry **131**: 1204-1207, 1974.
31. Halder SL, Locke GR 3rd, Schleck CD, Zinsmeister AR, Melton LJ 3rd, Talley NJ. Natural history of functional gastrointestinal disorders: a 12-year longitudinal population-based study. Gastroenterology **133**: 799-807, 2007.
32. Ali MK, Chen JDZ. Roles of heart rate variability in assessing autonomic nervous system in functional gastrointestinal disorders: a systematic review. Diagnostics (Basel) **13**: 293, 2023.